Potansiyel Antibiyotik ve Antitümör Özelliklere Sahip Yeni Ferrosen Türevlerinin Tasarım ve Sentezi

Proje No: 104T202

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ÖNSÖZ

Türkiye Bilimsel ve Teknik Araştırma Kurumu (TÜBİTAK) tarafından desteklenen bu çalışma Orta Doğu Teknik Üniversitesi, Fen-Edebiyat Fakültesi, Kimya Bölümü'nde gerçekleştirilmiştir. Sağladıkları maddi destekten dolayı TÜBİTAK yetkililerine sonsuz teşekkürlerimi sunarım. Sağladıkları her türlü altyapı desteği ile bu projeyi mümkün kılan Orta Doğu Teknik Üniversitesi, Fen-Edebiyat Fakültesi, Kimya Bölümü yetkililerine de çok teşekkür ederim.

Bu projede görev alan veya çalışmaları ile projeye destek olan ODTÜ Kimya Bölümü Doktora öğrencisi *Arif Kıvrak*'a ve Yüksek Lisans öğrencileri *Mustafa Köktürk*, *Tuğçe Eralp*, *Tülay Aslı Tumay*, *Canet Açıkgöz*, *Meral Görmen*, *Ayşe Nur Pinar*, *Özlem Velioğlu* ve *Ceyda Yazıcı*'ya da sonsuz teşekkürlerimi sunarım.

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İÇİNDEKİLER

TABLO LİSTESİ

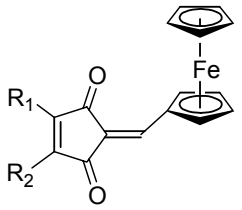
Sayfa

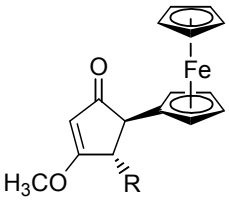
ŞEMA LİSTESİ

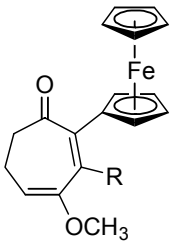
Sayfa

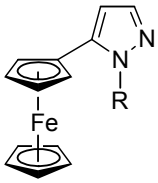
ÖZ

Ferrosen ve ferrosenyum tuzlarının son yapılan çalışmalarda antitümör aktivite göstermesinden sonra yapılarında ferrosen grubu ihtiva eden biyoaktif yapılar büyük önem kazanmıştır çünkü ferrosen grubu bu bileşiklerin sahip oldukları antitümör ve antibiyotik etkileri dahada artırmaktadır. Dolayısıyla daha etkili antitümör maddelerinin bulunması ve geliştirilmesi kanser gibi hastalıkların tedavisinde yeni umutlar olabilir. Organik ve organometalik bileşiklerin biyolojik aktiviteleri hakkında bazı tahminler yapılabilmekle beraber aktivitelerin kesin olarak belirlenmesi ancak biyolojik aktivite testleri ile mümkündür. Bu da genellikle bu bileşiklerin önce eldesini yani laboratuvarda sentezini gerektirmektedir. Bir ferrosenil grubunun antitümör ve antibiyotik gibi önemli biyolojik aktivitelere sahip alkilidensiklopentendion (**1**), siklopentenon (**2**), sikloheptadienon (**3**) ve pirazol (**4**) yapılarına direk bağlı olduğu bu tür türevler literatürde hemen hemen bilinmemekte ve bunların sentezine yönelik herhangi bir çalışmada yoktur. Bu projede yeni ve uygulanabilir yöntemler geliştirilerek yapıları aşağıda gösterilen literatürde bilinmeyen bu yeni ferrosenii türevlerinin sentezi gerçekleştirilmiştir. Ferrosenil grubunun bu maddelerin sahip oldukları biyolojik aktiviteyi dahada artırması beklenmektedir. Sentezlenen bu bileşiklerden bir veya bir kaçının istenilen düzeyde biyolojik aktivite göstermesi halinde bu bileşikler kanser gibi hastalıkların tedavisinde umut verici yeni ilaç maddeleri olabileceklerdir.







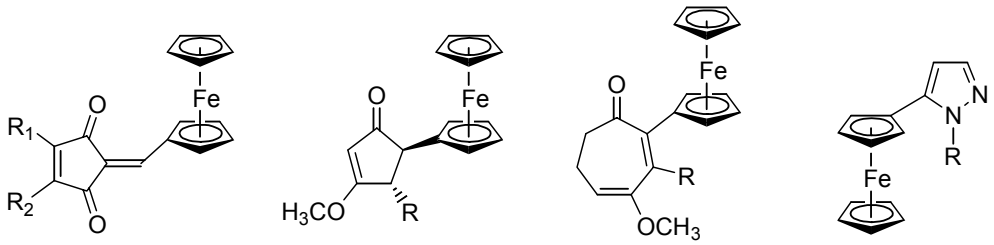


1A ($R_1 = R_2 =$ *i*-PrO)	**2A** (R = H)	**3A** (R = H)	**4A** (R = H)
1B (R_1 = Me, R_2 = *i*-PrO)	**2B** (R = Me)	**3B** (R = Me)	**4B** (R = Ph)
1C ($R_1 = R_2$ = Me)	**2C** (R = Bn)	**3C** (R = Bn)	**4C** (R = CH_2-CH_2-OH)
1D (R_1 = Ph, R_2 = *i*-PrO)	**2D** (R = Ph)	**3D** (R = Ph)	**4D** (R = CH_2-Ph)
1E ($R_1 = R_2$ = Ph)	**2E** (R = Fc)	**3E** (R = Fc)	**4E** (R = p-C_6H_4-CO_2H)

Anahtar Kelimeler: Ferrosen; ferrosenil sübstitüe alkilidensiklopentendion, siklopentenon, sikloheptadienon, pirazol; sentez; biyolojik aktivite; antibiyotik; antitümör.

ABSTRACT

After ferrocene and ferrocenium salts have shown antitumor activities in recent studies, biologically active compounds containing a ferrocene moiety have gained more importance since the ferrocene group increases their antitumor and antibiotic activities more and more. Development of new potential antitumor compounds is likely to provide new promising drug substances for curing the cancer type diseases. Although the biological activities of organic and organometallic compounds/complexes can be predicted to some extent, the certain activities can be determined only by their biological activity tests, which would require first the laboratory synthesis of such compounds/complexes. The examples of ferrocenyl-substituted alkylidenecyclopentenediones (**1**), cyclopentenones (**2**), cycloheptadienones (**3**) and pyrazoles (**4**), as well as general methods for their syntheses, are almost unknown, but these compounds should be medicinally very important compounds. In this project, the synthesis of these new compounds, which are unknown in literature, was achieved by developing new and applicable methods. It is expected that ferrocenyl moiety will increase their current biological activity more and more. If one or few of them shows the expected biological activity, then such compounds can be promising drug candidates to cure the cancer type diseases.



1A (R_1 = R_2 = *i*-PrO)	**2A** (R = H)	**3A** (R = H)	**4A** (R = H)
1B (R_1 = Me, R_2 = *i*-PrO)	**2B** (R = Me)	**3B** (R = Me)	**4B** (R = Ph)
1C (R_1 = R_2 = Me)	**2C** (R = Bn)	**3C** (R = Bn)	**4C** (R = CH_2-CH_2-OH)
1D (R_1 = Ph, R_2 = *i*-PrO)	**2D** (R = Ph)	**3D** (R = Ph)	**4D** (R = CH_2-Ph)
1E (R_1 = R_2 = Ph)	**2E** (R = Fc)	**3E** (R = Fc)	**4E** (R = p-C_6H_4-CO_2H)

Key Words: Ferrocene; ferrocenyl-substituted alkylidenecyclopentenedione, cyclopentenone, cycloheptadienone, pyrazole; synthesis; biological activity; antibiotic; antitumor.

POTANSİYEL ANTİBİYOTİK VE ANTİTÜMÖR ÖZELLİKLERE SAHİP YENİ FERROSEN TÜREVLERİNİN TASARIM VE SENTEZİ

TÜBİTAK-104T202 ARAŞTIRMA PROJESİ SONUÇ RAPORU

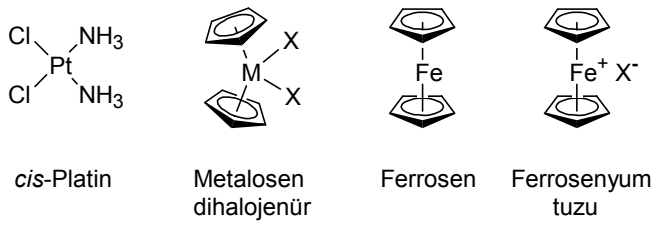
Proje Yürütücüsü: Prof. Dr. Metin ZORA
ODTÜ Kimya Bölümü, 06531 ANKARA

1.0 GİRİŞ

cis-Platin (*cis*-[$PtCl_2(NH_3)_2$]) olarak bilinen organometalik bileşiğin antitümör ilacı olarak büyük başarı kazanmasından sonra tıp ve biyoloji alanlarında organometalik bileşiklere olan ilgi hızla artmıştır (Şema 1) (Rosenberg, 1969). Çalışılan türevler arasında *cis*-platin'den sonra $Cp_2M(IV)X_2$ (M = Ti, Mo, X = Cl, Br, I) yapısındaki metalosen dihalojenürlerin birçok tümere karşı aktif olduğu bulunmuştur (Şema 1) (Kopt-Maier, 1987 ve 1994; Keptler 1993). Son zamanlarda Köpf-Maier tarafından yapılan çalışmalarda bazı ferrosenyum tuzlarının ($Cp_2Fe^+X^-$, X = PF_6, $FeCl_4$, 2,4,6-$(NO_2)_3C_6H_2O$, $Cl_3CCO_2.2Cl_3CCO_2H$) klasik antitümör ilaçlarına karşı direnç gösteren *Ehrlich ascites* tümörlerine karşı *antineoplastic* aktivite gösterdiği saptanmıştır (Şema 1) (Kopt-Maier, 1984 ve 1985; Osella, 2000). İlginç olarak ferrosen ve ferrosenyum türevleri *cis*-platin ve metalosen dihalojenürlere göre yapısal farklılıklar göstermektedir. Ferrosen'de demir atomu +2, ferrosenyum iyonunda ise +3 değerlikli iken bu bileşiklerde *cis* posizyonunda kolay ayrılabilir halojen ligandı yoktur. Ayrıca bu bileşiklerde demir atomu iki siklopentadienil halkasına kuvvetlice bağlandığından bu demir atomunun daha fazla koordinasyona girmesi çok zordur. Ferrosenin kendisi suda çözünür olmadığından herhangi bir biyolojik aktivite göstermemektedir. Fakat hücre içinde kolayca ferrosenyum iyonuna yükseltgenmekte, böylece çözünür olmakta ve biyolojik aktivite gösterebilmektedir (Osella, 2000). Çok kesin olmamakla beraber ferrosenyum iyonlarının veya tuzlarının antitümör aktivitelerinin demir atomunun +3 değerliğine bağlı olduğu

sanılmaktadır (Osella, 2000). Sonuç olarak ferrosen/ferrosenyum redoks sistemi biyolojik sistemlerde büyük rol oynamaktadır.

Şema 1

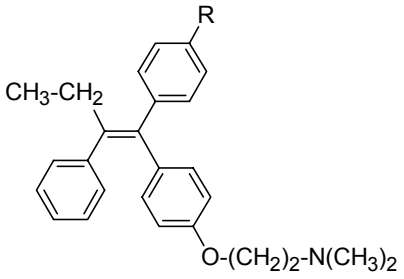


Göğüs kanseri kadınlar arasında en yaygın kanser türü olup her sekiz kadının birinde bu hastalık görülmektedir. Günümüzde bu hastalığı tedavi etmek için kullanılan en temel ilaçlar *tamoksifen* ve türevleridir (Şema 2) (Dagani, 2002). Faydalarının yanısıra bu ilaçların istenmeyen yan etkileride vardır. Örneğin uzun süren terapi dönemlerinde vücutun bu ilaçlara karşı direnç gösterdiği bulunmuştur. Ayrıca bu ilaçların rahim kanseri olma riskini artırdığı ve ciğerlerde kan pıhtılaşmasına neden olduğu da gözlenmiştir (Dagani, 2002). En önemlisi bu ilaçların sadece hormona bağlı göğüs kanseri türlerinde etkili olduğu, hormona bağlı olmayan türlerde ise hiç bir etki göstermediği anlaşılmıştır (Dagani, 2002). Jaouen ve çalışma arkadaşları *tamoksifen* bazlı ilaçlara alternatif olarak *ferrosifen* türevlerini geliştirmişlerdir, yani tamoksifen'lerdeki bir fenil grubunu ferrosen ile yer değiştirmişlerdir (Şema 2) (Top, 1997 ve 2001). İlk yapılan klinik çalışmalarda *ferrosifen* türevlerinin *tamoksifen* türevlerine göre daha etkili ve en önemlisi bu bileşiklerin hormona bağlı olmayan göğüs kanseri türlerinde de etkili olduğu görülmüştür (Dagani, 2002). Ferrosifen türevlerine ait klinik çalışmalar tam anlamıyla bitmemiş olmakla beraber şu ana kadar alınan sonuçlar bu türevlerin göğüs kanseri tedavisinde ilaç olabileceğini göstermiştir.

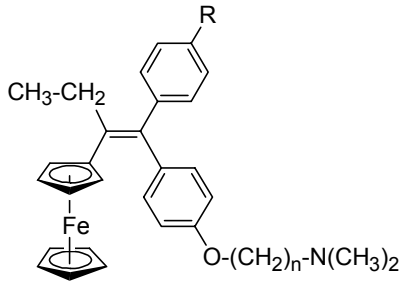
Bu çalışmalardan sonra yapılarında ferrosen içeren biyoaktif organik yapılar büyük önem kazan-mıştır çünkü bu tür bileşikler potansiyel antitümör maddelerdir (LaLonde, 1997; Patt, 1997 ve 1999; Hakimelahi, 2001). Dolayısıyla son yıllarda bu tür yapıları üretecek

sentetik metotlara büyük bir gereksinim doğmuştur. Bizde çalışmalarımızı bu konu üzerine yoğunlaştırmış ve ferrosenil grubu içeren siklobutenon, furan, ketoester, siklopentendion, alkiliden-furanon ve kinon türevlerinin sentezini başarı ile gerçekleştirmiş bulunmaktayız (Zora, 2001, 2002 ve 2003).

Şema 2



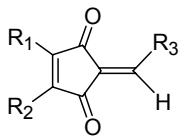
Tamoksifen (R = H)
Hidroksitamoksifen (R = OH)



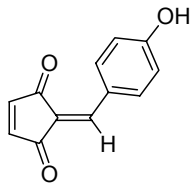
Hidroksiferrosifen (R = OH, n = 2-5, 8)

2-Alkiliden- veya 2-benziliden-4-siklopenten-1,3-dion sistemi doğal ve biyoaktif ürünlerde çok sık rastlanan yapılardan biridir (Şema 3). Bu tür yapılar genelde antitümör (Inayama, 1976) özelliklere sahip olup *klavulone* (*klaviridenon*) (Kikuchi, 1982 ve 1983; Kobayashi, 1982 ve 1983; Iguchi, 1983; Corey, 1984; Shibasaki, 1985), *klorovulon* (Iguchi, 1985 ve 1986; Nagaoka, 1986) ve *punaglandin* (Baker, 1985; Nagaoka, 1986; Sasai, 1987) gibi antitümör antibiyotiklerinin yapılarında bulunmaktadır. Son zamanlarda yapılan çalışmalarda benzilidensiklopentendion yapısı içeren bir seri KIH ve TX türevleri (Şema 3) biyolojik aktiviteleri açısından detaylı olarak incelenmiş ve bunlar arasında en çok TX-1123 ve TX-1925 bileşiklerinin antitümör özellik gösterdiği bulunmuştur (Hori, 2002 ve 2003). Hatta bu iki bileşiğin antitümor ajanı olarak bilinen *trifostin* AG-17 [2-(3,5-Di-*tert*-butil-4-hidroksi-benziliden)malononitril] bileşiğinden daha çok antitümor aktivite gösterdiği de gözlenmiştir (Hori, 2002 ve 2003).

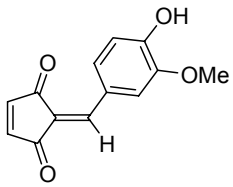
Şema 3



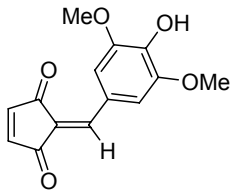
Alkilidensiklopentendion (R_3 = Alkil)
Benzilidensiklopentendion (R_3 = Aril)



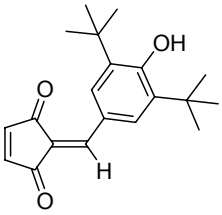
KIH-200



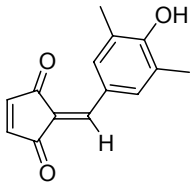
KIH-201



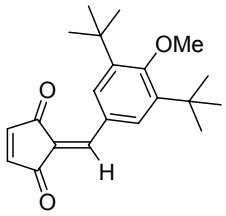
KIH-202



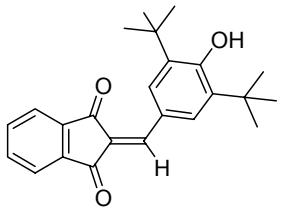
TX-1123



TX-1918



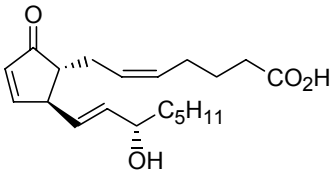
TX-1925



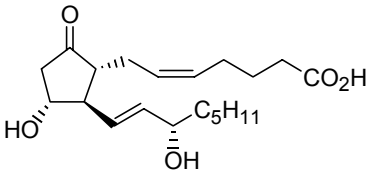
TX-1926

Hemen hemen bütün dokularda bulunan ve yapılarında karbosiklik beşli halka sistemi içeren *prostaglandin* ve türevleri (Şema 4) tıbbi olarak çok büyük öneme sahip olup damarda kanın pıhtılaşmasını önleyerek kalp atışını ve kan basıncını düzenleyip kalp krizi riskini büyük ölçüde azaltmaktadır (Johnson, 1985; Degen, 2004). Ayrıca bu bileşiklerin gebelik ve doğurganlık üzerine de olumlu etkileri vardır (Johnson, 1985; Degen, 2004).

Şema 4



PGA_2

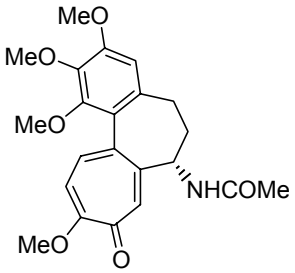


PGE_2

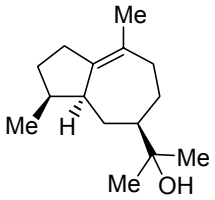
Karbosiklik yedili halka sistemleri; *tiglian*, *dafnan* ve *ingenan* diterpenleri (Evans, 1986; Wender, 1989 ve 1990), *kolkisin* ve türevleri (Boger, 1985; Muzaffar, 1991), *guaiazulen*, *hidroazulen* ve *guaianolid* seskiterpenleri (Goldsmith, 1983; Heathcock, 1983; Martin 1990) gibi bir çok doğal ürünün yapısında bulunur ve bu ürünlerin hepsi tıbbi olarak büyük öneme

sahiptirler. Örneğin damla hastalıklarının tedavisinde yıllardır kullanılan *kolkisin* ve türevleri son zamanlarda bulaşıcı ateşli hastalıkların tedavisinde ilaç olarak seçilmiştir (Şema 5) (Boger, 1985; Muzaffar, 1991). *Kolkisin* türevlerinin, *tubulin* proteiniyle olan etkileşiminin antimitotik etkiler gösterdiğide saptanmıştır. Bitki özü veya aroması olarak bilinen *bulnesol*, *dausen* ve *dihydroarbiklovin*'de yıllardır ilaç ve parfüm yapımında kullanılmaktadır (Şema 5) (Goldsmith, 1983; Heathcock, 1983; Martin 1990).

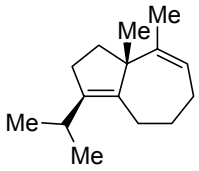
Şema 5



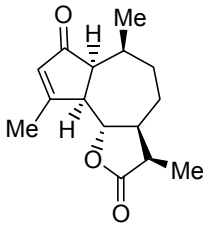
Kolkisin



Bulnesol



Dausen

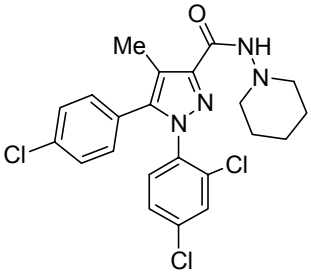


Dihydroarbiklovin

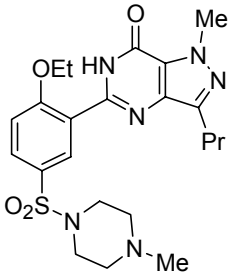
Yapısında iki azot atomu bulunduran ve aromatik bir bileşik olan pirazol ve türevleri antitümör özelliklerinin yanısıra değişik biyolojik aktivitelerde göstermektedir (Şema 6) (Komeda, 2000 ve 2002; Nakamura, 2003). Örneğin SR141716A bir cannabinoid receptor antagonist'dir (Lan, 1999; Francisco, 2002). Viagra ticari adı ile bilinen sildenafil ise erkeklik gücünü artırıcı bir ilaç olup, bugüne kadar bütün zamanların en hızlı satan ilacı olmuştur (Şema 6) (Dale, 2000).

Şema 6

Pirazol



SR141716A



Sildenafil (Viagra)

Tecrübelerimizin ve bilgilerimizin ışığı altında, yukarıda bahsedilen, antitümör ve antibiyotik gibi önemli biyolojik aktivitelere sahip alkiliden veya benzilidensiklopentendion yapıları (Şema 3), karbosiklik beşli (Şema 4) ve yedili halka sistemleri (Şema 5), ve pirazol türevleri (Şema 6) eğer yapılarındaki ferrosenil grubu ihtiva ederlerse bu bileşiklerin sahip oldukları antitümör ve antibiyotik özelliklerinin daha da artması beklenmektedir. Bir ferrosenil grubunun bu yapı taşlarına direk bağlı olduğu bu türevler maalesef literatürde bilinmemekte veya çok az bilinmekte olup, bunların sentezine yönelik herhangi bir kapsamlı çalışmaya da rastlanmamıştır. Yeni ve daha etkili antitümör reaktiflerin bulunması ve geliştirilmesi kanser gibi hastalıkların tedavisinde yeni umutlar oluşturacaktır. Bu reaktiflerin geliştirilmeside önce bu maddelerin laboratuvarlarda sentezini gerektirmektedir. Bu projede bu tür bileşiklerin sentezine yönelik yeni ve uygulanabilir yöntemler geliştirilecektir.

2.0 PROJENİN AMACI

Bu projenin amacı Şema 7'de yapıları gösterildiği üzere potansiyel antitümör ve antibiyotik özellik göstermeleri beklenen

(i) 2-ferroseniliden-4-siklopenten-1,3-dion türevleri **1A**/**B**/**C**/**D**/**E**'yi,

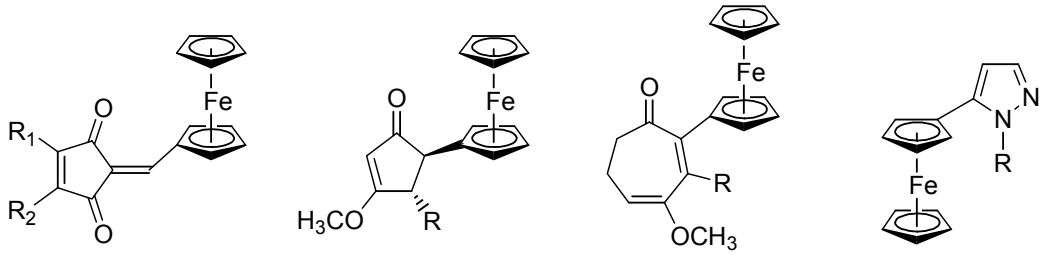
(ii) 5-ferrosenil-3-metoksi-2-siklopentenon türevleri **2A**/**B**/**C**/**D**/**E**'yi,

(iii) 2-ferrosenil-4-metoksi-2,4-sikloheptadienon türevleri **3A**/**B**/**C**/**D**/**E**'yi ve

(iv) 1-alkyl/aryl-5-ferrosenilpirazol türevleri **4A**/**B**/**C**/**D**/**E**'yi sentezlemektir.

Ayrıca bu bileşiklerin sentezi için gerekli olan başlangıç maddelerini hazırlamak, sentez için önerilen yöntemleri test edip tepkime şartlarını optimize etmek yani çözücü, konsantrasyon, zaman ve sıcaklığın ürün verimleri üzerine olan etkilerini araştırmak ve oluşan ürünleri spektroskopik yöntemlerle karakterize etmek bu projenin araştırma hedeflerini oluşturmaktadır.

Şema 7



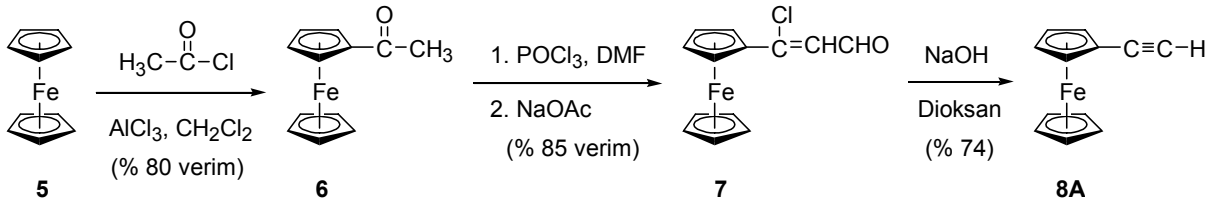
1A (R_1 = R_2 = *i*-PrO)	**2A** (R = H)	**3A** (R = H)	**4A** (R = H)
1B (R_1 = Me, R_2 = *i*-PrO)	**2B** (R = Me)	**3B** (R = Me)	**4B** (R = Ph)
1C (R_1 = R_2 = Me)	**2C** (R = Bn)	**3C** (R = Bn)	**4C** (R = CH_2-CH_2-OH)
1D (R_1 = Ph, R_2 = *i*-PrO)	**2D** (R = Ph)	**3D** (R = Ph)	**4D** (R = CH_2-Ph)
1E (R_1 = R_2 = Ph)	**2E** (R = Fc)	**3E** (R = Fc)	**4E** (R = p-C_6H_4-CO_2H)

3.0 BULGULAR VE TARTIŞMA

3.1 2-Ferroseniliden-4-siklopenten-1,3-dion (**1**) türevlerinin sentezi

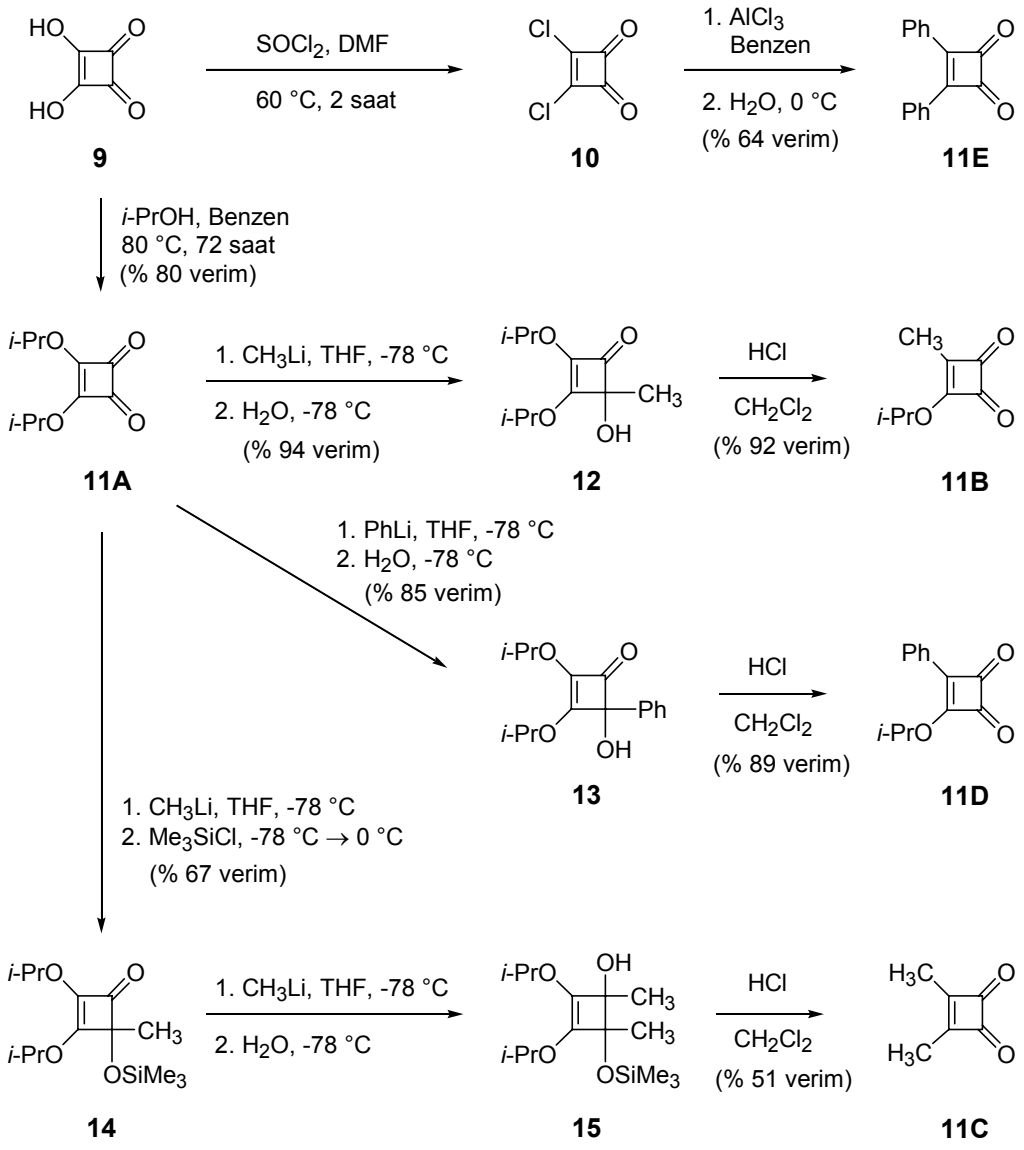
Proje kapsamında önce gerekli olan başlangıç maddeleri **8A**, **11A/B/C/D/E** ve **17A/B/C/D/E** hazırlanmıştır (Şema 8, 9 ve Tablo 1). Bu amaçla etinilferrosen (**8A**) bileşiği ilk olarak sentezlenmiştir (Şema 8). Ferrosen (**5**) bileşiğinin aluminyum klorür varlığında asetil klorür ile Friedel-Crafts tepkimesi asetilferrosen (**6**) bileşiğini vermiştir (Gibson, 1997). Daha sonra bu bileşik sırasıyla fosfor oksiklorür ve sodyum asetat ile tepkimeye sokularak 2-formil-1-klorvinil)ferrosen (**7**) bileşiğine dönüştürülmüştür (Polin, 1996). Son olarak bileşik **7**'nin dioksan çözücüsü içerisinde sodyum hidroksit ile ısıtılması etinilferrosen (**8A**) bileşiğini üretmiştir (Şema 8) (Polin, 1996).

Şema 8



Siklobutendion türevleri **11A**/**B**/**C**/**D**/**E**'nin sentezleri Şema 9'da gösterilen yöntem ve tepkimelere göre gerçekleştirilmiştir.

Şema 9

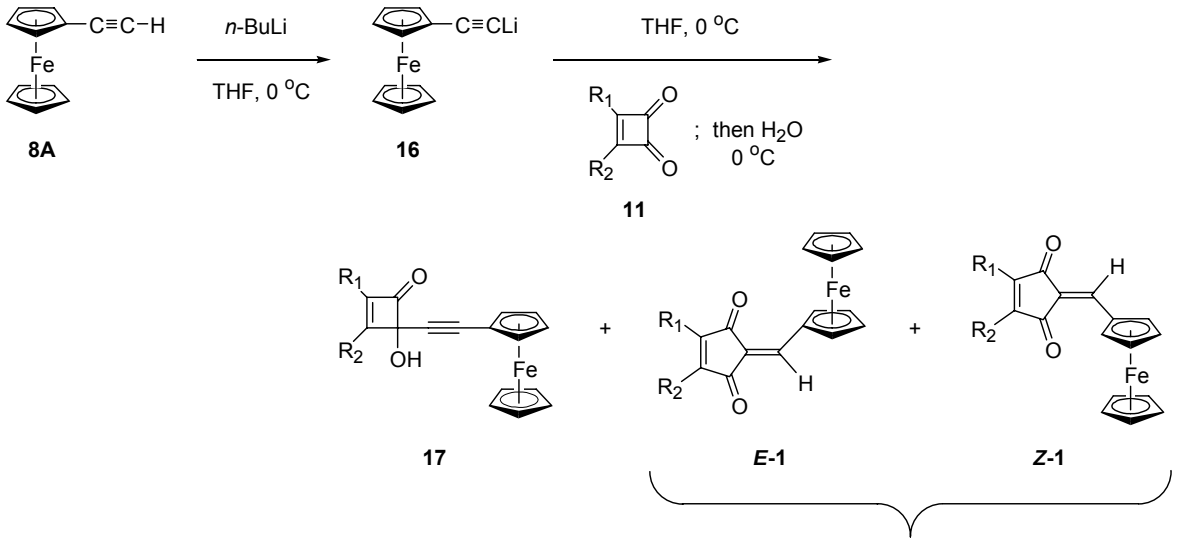


İlk olarak skuarik asit (**9**) tiyonil klorür ile tepkimeye sokularak skuaril diklorür (**10**) bileşiği hazırlanmıştır (De Selma, 1970). Daha sonra bu bileşik aluminyum klorür varlığında benzen ile Friedel-Crafts tepkimesi (Olah, 1963-1965, 1973 ve 1991; Roberts, 1984) olarak bilinen elektrofilik aromatik yer değiştirme tepkimesine sokularak difenilsiklobutendion bileşiği

11E sentezlenmiştir. Diğer siklobutendion türevlerinin sentezi için skuarik asit (**9**) önce benzen çözücüsü içersinde izopropil alkol ile ısıtılarak diizopropil skuarat (**11A**) bileşiği sentezlenmiştir (Şema 9) (Liebeskind, 1988). Daha sonra bu bileşik metillityum ile tepkimesi siklobutenon **12** bileşiğini vermiştir. Bu bileşiğinde metilen klorür çözücüsü içersinde HCl ile hidrolizi siklobutendion bileşiği **11B**'yi üretmiştir (Liebeskind, 1988). Benzer şekilde diizopropil skuarat (**11A**) bileşiği önce fenillityum ile tepkimeye sokulmuş ve bu tepkimeden oluşan siklobutenon **13** bileşiği HCl ile hidroliz edilerek siklobutendion bileşiği **11D** hazırlanmıştır (Şema 9) (Liebeskind, 1988). Siklobutenon türevi **11C**'nin sentezi için diizopropil skuarat (**11A**) sırasıyla metillityum ve trimetilsilil klorür ile tepkimeye sokularak önce siklobutenon bileşiği **14** sentezlenmiştir. Bu bileşiğin de metillityum ile tepkimesi siklobuten bileşiği **15**'i vermiştir. Bununda HCl ile hidrolizi siklobutendion bileşiği **11C**'yi üretmiştir (Şema 9) (Liebeskind, 1988).

Son safhada 4-(ferroseniletinil)-2-siklobutenon (**17A**/**B**/**C**/**D**/**E**) bileşiklerinin sentezi Tablo 1'de gösterildiği gibi 2-etinilferrosen (**8A**) ve siklobutenon türevleri **11A**/**B**/**C**/**D**/**E**'den gerçekleştirilmiştir. Bu amaçla ferrosen **8A** bileşiği *n*-butillityum ile muamele edilerek tepkime ortamında önce 2-(lityumetinil)ferrosen (**16**) bileşiği oluşturulmuştur. Daha sonra bu bileşiğin siklobutendion **11A**/**B**/**C**/**D**/**E** türevleri ile olan tepkimesi başlangıç maddeleri olan siklobutenon **17A**/**B**/**C**/**D**/**E** bileşiklerini veya bunların düzenlenme ürünlerini üretmiştir. Tablo 1'den görüldüğü üzere özellikle fenil sübstitüye siklobutenon **17D**/**E** bileşiklerinin çok reaktif olduğu ve dolayısıyla saflaştırma esnasında kısmen ferrosenilidensiklopentendion türevleri **1D** ve **1E**'ye dönüştüğü ve de kısmen bozunduğu gözlenmiştir. Bu nedenle bu reaktif siklobutenon **17** bileşiklerinin bundan sonraki termoliz tepkimeleri için bu bileşikler sentezlendikten sonra saflaştırılmadan ham ürün olarak izole edilmesine ve derhal termoliz tepkimelerine sokulmalarına karar verilmiştir. Böylece saflaştırma esnasında bozunmalardan gelebilecek ürün kayıplarının minumuma inmesi beklenmiştir. Tablo 1'de yapıları gösterilen bütün siklobutenon **17** ve ferrosenilidensiklopentenedion **1**, ***E*-1** ve ***Z*-1** bileşikleri literatürde ilk kez sentezlenmiştir.

Tablo 1: 4-(Ferroseniletinil)-2-siklobutenon türevleri 17'nin sentezi.



			Ürün Verimleri (%)			
Deneme [a]	**R_1**	**R_2**	**17**	**1**	***E*-1**	***Z*-1**
A	*i*-PrO	*i*-PrO	65	5	–	–
B	Me	*i*-PrO	34	–	19	9
C	Me	Me	38	22	–	–
D	Ph	*i*-PrO	[b]	–	35	–
E	Ph	Ph	[c]	37	–	–

[a] Deneme harfleri **1**, ***E*-1**, ***Z*-1**, **11** ve **17** nolu bileşikler için R_1 ve R_2 gruplarını tanımlar.

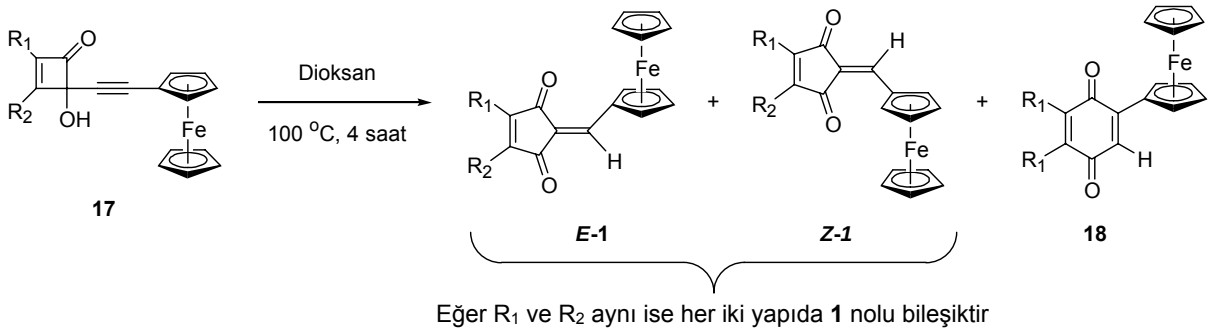
[b] Bileşik **17D** çok reaktif olduğundan saflaştırma esnasında bileşik ***E*-1D**'ye dönüştüğü ve/veya kısmen bozunduğu gözlenmiştir.

[c] Bileşik **17E** çok reaktif olduğundan saflaştırma esnasında bileşik **1E**'ye dönüştüğü ve/veya kısmen bozunduğu gözlenmiştir.

Gerekli başlangıç maddeleri hazırlandıktan sonra 2-ferroseniliden-4-siklopenten-1,3-dion (**1A/B/C/D/E**) bileşiklerinin sentezi gerçekleştirilmiştir. Bu bileşiklerin sentezi Tablo 2, 3 ve 4'de gösterildiği üzere siklobutenon **17A/B/C/D/E** bileşiklerinin termoliz veya düzenlenme tepkimeleriyle sentezlenmiştir.

İlk olarak siklobutenon **17** türevlerinin termoliz tepkimeleri incelenmiştir (Tablo 2). Bu amaçla siklobutenon **17** bileşikleri dioksan içersinde 100 ^{o}C'de 4 saat süre ile ısıtılmıştır. Tablo 2'den görüldüğü üzere bütün tepkimelerde 2-ferroseniliden-4-siklopenten-1,3-dion (**1**) türevleri tek ve/veya ana ürün olarak oluşmuştur. Farklı sübstitüent taşıyan siklobutenon **17B**/**D** bileşikleri termoliz sonucunda ferrosenilidensiklopentendion **1D**/**E** türevlerini *E* ve/veya *Z* izomerler olarak üretmiştir. Bu tepkimelerde *E*-izomer tek ve/veya ana izomer olarak oluşmuştur. Tablo 2'den görüldüğü üzere bazı termoliz tepkimelerinde ferrosenilkinon türevleri **18A**/**B**/**C** düşük verimlerle yan ürün olarak oluşmuştur.

Tablo 2: Metot A ile 2-ferroseniliden-4-siklopenten-1,3-dion (1) türevlerinin sentezi.



Eğer R_1 ve R_2 aynı ise her iki yapıda **1** nolu bileşiktir

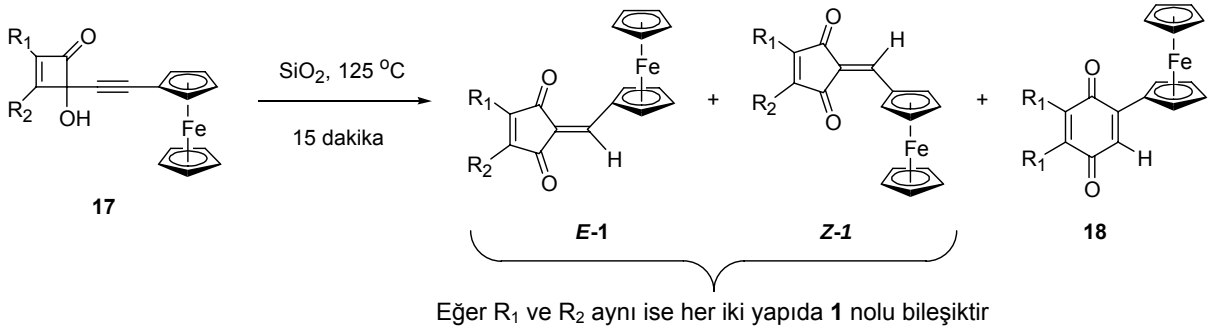
			Ürün Verimleri (%)			
Deneme [a]	**R_1**	**R_2**	**1**	***E*-1**	***Z*-1**	**18**
A	*i*-PrO	*i*-PrO	70	–	–	2
B	Me	*i*-PrO	–	61	3	4
C	Me	Me	55	–	–	8
D	Ph	*i*-PrO	–	53	–	–
E	Ph	Ph	58	–	–	–

[a] Deneme harfleri **1**, ***E*-1**, ***Z*-1**, **17** ve **18** nolu bileşikler için R_1 ve R_2 gruplarını tanımlar.

Önceden bahsedildiği üzere fenil sübstitüye siklobutenon **17D**/**E** bileşiklerinin çok reaktif olduğu ve dolayısıyla bu türevlerin saflaştırma esnasında kısmen ferroseniliden-siklopentendion (**1**) türevlerine dönüştüğü ve de kısmen bozunduğu gözlenmiştir. Bu nedenle bu reaktif siklobutenon **17D**/**E** bileşikleri sentezlendikten sonra saflaştırılmadan ham ürün olarak izole edilmiş ve derhal termoliz tepkimelerine tabi tutulmuşlardır. Böylece bu maddelerin saflaştırma esnasındaki bozunmalarından kaynaklanabilecek ürün kayıplarının minumuma inmesi sağlanmıştır.

Çalışmalarımız esnasında gördük ki başlangıç siklobutenonlar **17** bileşikleri bir miktar silika jel (SiO_2) ile karıştırılıp bir saat camı üzerinde 125 ^oC'de bir etüv içinde 15 dakika kadar ısıtıldığında kolaylıkla ferrosenilidensiklopentendion (**1**) türevlerine dönüşmektedirler (Tablo 3). Farklı sübstitüent taşıyan siklobutenon **17B** bileşiğinin düzenlenme tepkimesi sonucunda ferrosenilidensiklopentendion **1B** türevi 1.4:1 oranında *E* ve *Z* izomerler olarak oluştuğu göz-

Tablo 3: Metot B ile 2-ferroseniliden-4-siklopenten-1,3-dion (1) türevlerinin sentezi.



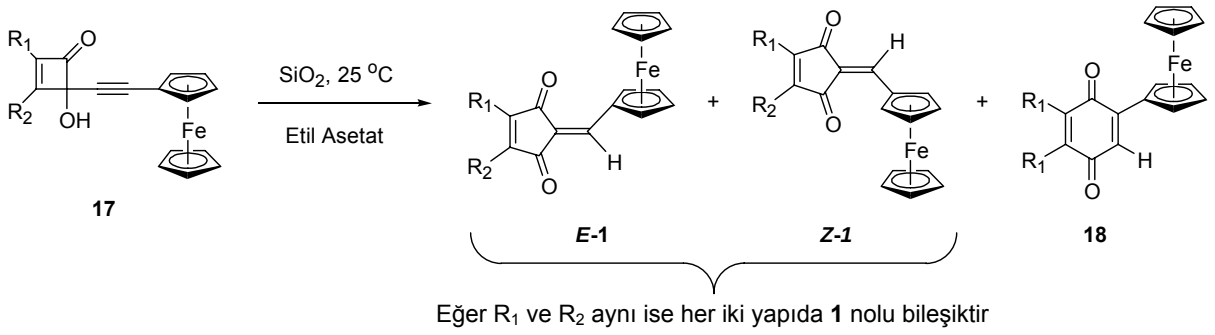
			Ürün Verimleri (%)			
Deneme [a]	**R_1**	**R_2**	**1**	***E*-1**	***Z*-1**	**18**
A	*i*-PrO	*i*-PrO	67	~	~	~
B	Me	*i*-PrO	~	45	32	~
C	Me	Me	71	~	~	5

[a] Deneme harfleri **1**, ***E*-1**, ***Z*-1**, **17** ve **18** nolu bileşikler için R_1 ve R_2 gruplarını tanımlar.

lenmiştir (Tablo 3, Deneme B). Bu sonuç Tablo 2 Deneme B'deki sonuç ile kıyaslandığında *Z* izomer miktarının arttığı görülür. Bu da muhtemelen tepkime ortamında önce oluşan *E* izomerin silika jel'in Lewis asit etkisiyle Z izomere dönüşmesiyle olmaktadır. Fenil sübstitüye siklobutenon **17D**/**E** bileşikleri çok reaktif olduğundan ve çok çabuk bozunduğundan ötürü bu ısıtma tepkimelerinde denenmemiştir.

Siklobutenon **17** bileşikleri sentezlendikten sonra kolon kromatografisi ile silika jel üzerinden saflaştırılmaları esnasında kısmen ferrosenilidensiklopentendion **1** türevlerine dönüşmektedirler. Dolayısıyla bu başlangıç bileşiklerinin oda sıcaklığında etil asetat gibi bir organik çözücü içerisinde silika jel ile karıştırıldığında ferrosenilidensiklopentendion **1** türevleri üretmesi beklenmiştir. Bu tepkimelerden elde edilen sonuçlar Tablo 4'de özetlen-

Tablo 4: Metot C ile 2-ferroseniliden-4-siklopenten-1,3-dion (1) türevlerinin sentezi.



			Ürün Verimleri (%)			
Deneme [a]	**R_1**	**R_2**	**1**	***E*-1**	***Z*-1**	**18**
A	*i*-PrO	*i*-PrO	34	–	–	–
B	Me	*i*-PrO	–	51	6	–
C	Me	Me	74	–	–	8
D	Ph	*i*-PrO	–	56	–	–
E	Ph	Ph	45	–	–	–

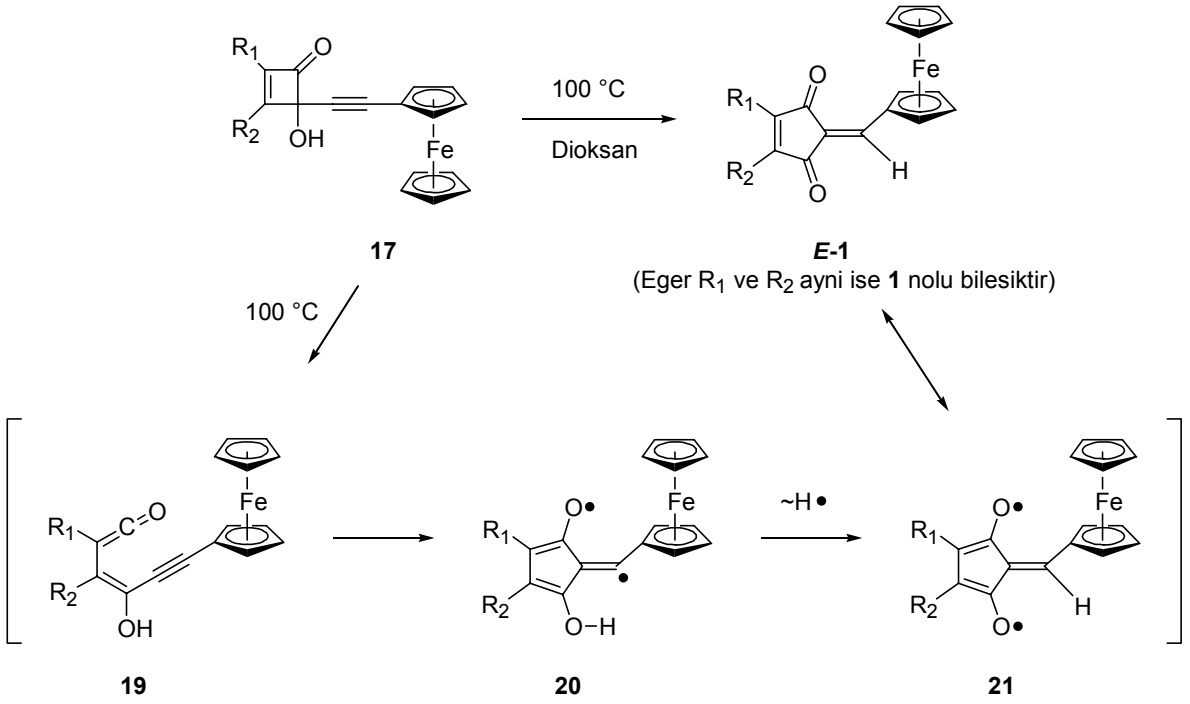
[a] Deneme harfleri **1**, ***E*-1**, ***Z*-1**, **17** ve **18** nolu bileşikler için R_1 ve R_2 gruplarını tanımlar.

mektedir. Beklenildiği üzere siklobutenon **17** bileşiklerinin oldukça reaktif olduğu ve oda sıcaklığında silika jel varlığında kolayca ferrosenilidensiklopentendion **1** türevlerine dönüştüğü gözlenmiştir.

Sonuçta siklobutenon **17** türevleri üç farklı metotla ferrosenilidensiklopentendion **1** bileşiklerine dönüştürülmüştür (Tablo 2-4). Herbir metot hemen hemen benzer verimlerle sonuç bileşiklerini üretmiştir. Dolayısıyla bu metotların birbirine kıyasla fazla bir üstünlük arzetmediği görülmüştür.

Ferrosenilidensiklopentendion **1** türevlerinin oluşum mekanizmaları Şema 10 ve 11'de verilmiştir (Karlsson, 1985; Foland, 1989; Moore, 1992). Siklobutenon bileşiği **17** dioksan gibi bir çözücü içinde 100 ^{o}C'de ısıtıldığında elektrosiklik halka açılması ile önce alkinil sübstitüe vinilketen ara ürünü **19**'u vermiştir (Şema 10). Bu ara ürün beşli halka kapanması ile diradikal ara ürünü **20**'yi oluşturmuştur ki bu da bir hidrojen kayması ile dioksijen radikali **21**'e dönüşmüştür. Bu da resonans ile sonuç bileşiği **1**'i üretmiştir. Bu tepkimelerde beşli halka kapanmasının olabilmesi ara ürün **20**'de karbon radikaline komşu "radikal kararlılığını artırıcı"

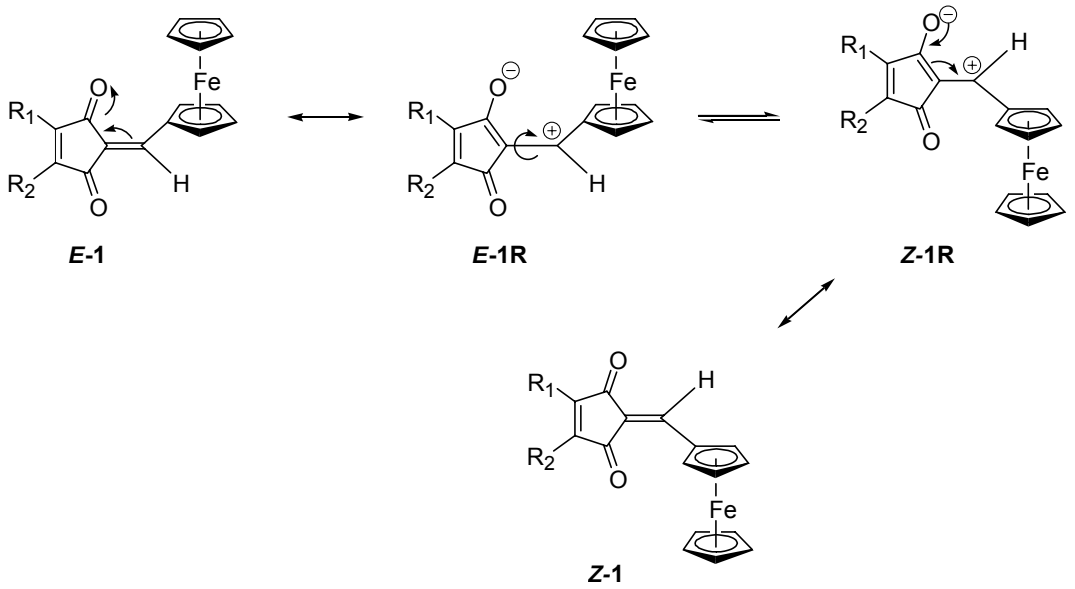
Şema 10



bir grubun olmasına bağlıdır (Moore, 1992). Elde edilen sonuçlar göstermiştir ki bu tür tepkimelerde ferrosen grubunun kendisine komşu bir radikali kararlı kıldığı (Creary, 1989 ve 2000), dolayısıyla beşli halka kapanmasının sorunsuz olarak gerçekleştiği gözlenmiştir.

Şema 10'de görüldüğü üzere eğer R_1 ve R_2 grupları farklı ise bu tepkimelerde ferrosenilidensiklopentendion **1** sonuç bileşiğinin *E* izomeri tek ve/veya ana ürün olarak oluşmaktadır. Fakat bazı tepkimelerde düşük miktarlarda da olsa Z izomerin oluştuğu gözlenmiştir. Aslında *Z* izomer tepkimenin ikincil ürünü olup *E* izomerin tepkime ortamında *Z* izomere dönüşmesiyle oluşmaktadır. *E* izomerin *Z* izomere dönüşüm mekanizması Şema 11'de verilmiştir. ***E*-1** izomeri resonans ile önce ***E*-1R** izomerine dönüşmektedir. Bu dönüşüm silika jel (SiO_2) gibi bir Lewis asit varlığında çok daha kolay olmaktadır. Oluşan bu ***E*-1R** izomeri daha sonra C–C bağı etrafındaki bir serbest dönme ile ***Z*-1R** izomerine dönüşmekte, bu da resonans ile ***Z*-1** izomerini üretmektedir (Şema 11).

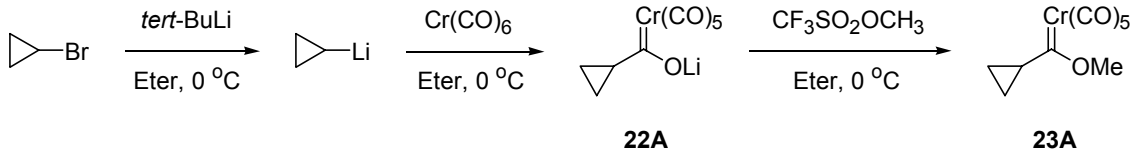
Şema 11



3.2 5-Ferrosenil-3-metoksi-2-siklopentenon (**2**) türevlerinin sentezi

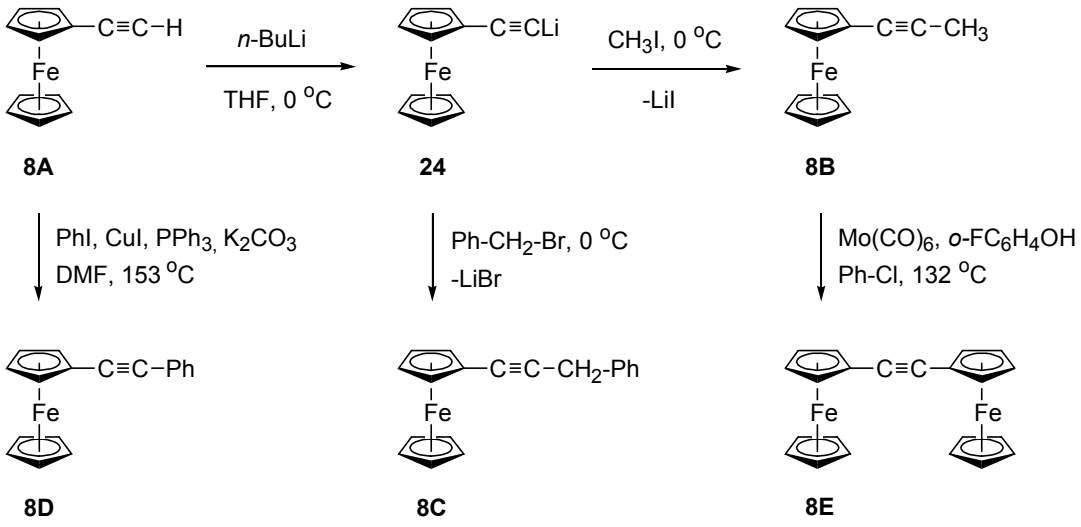
Bu kısımda 5-ferrosenil-3-metoksi-2-siklopentenon türevleri **2A/B/C/D/E**'nin sentezi için gerekli başlangıç maddeleri olan metal karben kompleksi **23A** (Şema 12) ile ferrosenilalkin bileşikleri **8A/B/C/D/E** (Şema 13) bilinen literatür yöntemlerine göre hazırlanmıştır. İlk olarak metal karben kompleksi **23A**'nın sentezi için siklopropilbromür *tert*-BuLi ile tepkimeye sokularak tepkime ortamında önce siklopropillityum hazırlanmıştır (Şema 12) (Herndon 1988; Tumer 1992). Daha sonra bunun kromhekzakarbonil ile muamelesi önce tepkime ortamında kompleks **22A**'yı oluşturmuştur ki bu ara kompleksinde izole edilmeden doğrudan metil triflat ($CF_3SO_2OCH_3$) ile tepkimesi krom karben kompleksi **23A**'yı üretmiştir (Şema 12) (Herndon 1988; Tumer 1992).

Şema 12



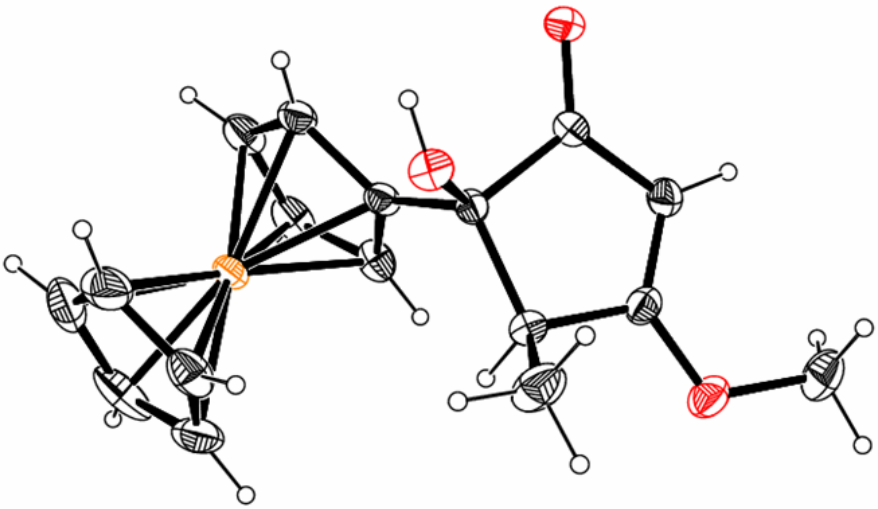
İkinci safhada ferrosenilalkin bileşikleri **8A/B/C/D/E**'nin sentezleri gerçekleştirilmiştir (Etinilferrosen (**8A**) bileşiği Şema 8'de gösterildiği üzere daha önce hazırlanmıştı). Bu amaçla ferrosen **8A** bileşiği *n*-butillityum ile muamele edilerek tepkime ortamında önce 2-(lityumetinil)ferrosen (**24**) bileşiği oluşturulmuştur (Şema 13) (Doisneau, 1992). Daha sonra bu bileşiğin metil iyodür ve benzil bromür ile tepkimeleri propinilferrosen (**8B**) ve (3-fenilpropinil)ferrosen (**8C**) bileşiklerini üretmiştir (Doisneau, 1992). Diğer taraftan ferroseniletinil (**11A**) bileşiğinin iyodobenzen ile bakır iyodür, trifenilfosfin ve potasyum karbonat varlığında DMF içersindeki tepkimesi (feniletinil)ferrosen (**8D**) bileşiğini vermiştir (Zora, 2006; Okuro, 1993). Diferroseniletin (**8E**), propinilferrosen (**8B**) bileşiğinin molibdenhekzakarbonil ve *o*-florofenol varlığında klorobenzen içersindeki metatez tepkimesiyle sentezlenmiştir (Sashuk, 2004; Kotora, 2003).

Şema 13

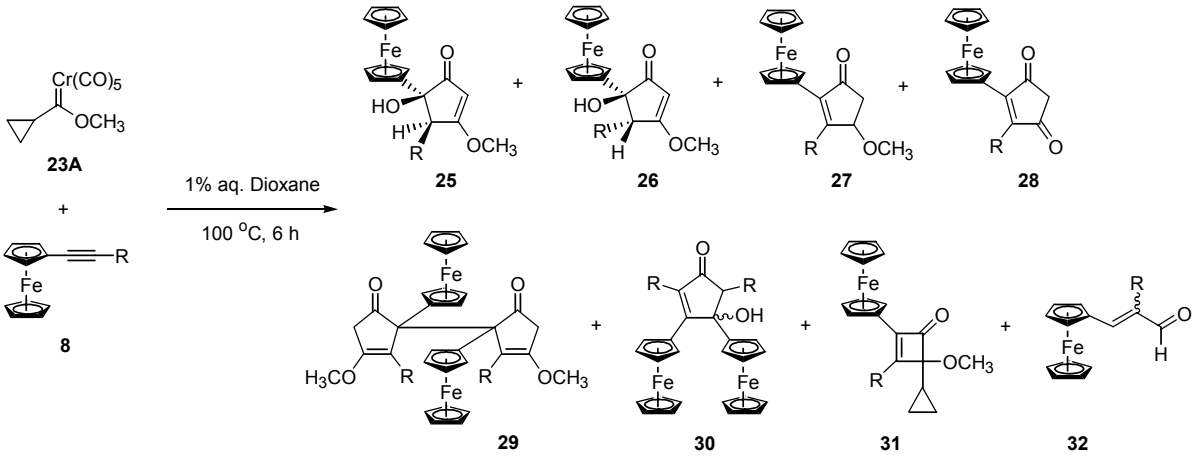


Son safhada metal karben kompleksi **23A**'nın ferrosenil alkin bileşikleri **8A/B/C/D/E** ile olan tepkimeleri incelenmiştir. Sonuçlar Tablo 5'de verilmiştir. Çok ilginç olarak bu tepkimelerde 5-hidroksi-2-siklopentenon türevleri **25** ve/veya **26** oluşmuştur (Tablo 5). Bilgilerimize göre bu hidroksi sübstitüe siklopentenon türevleri bu tür tepkimelerden ilk defa izole edilmişlerdir. Bu yeni bileşiklerden **25B**'nin yapısı X-ışını analiz yöntemiyle belirlenmiştir (Şema 14).

Şema 14. (4*R*(*S*),5*R*(*S*))-5-Ferrosenil-5-hidroksi-3-metoksi-4-metil-2-siklopentenon (**25B**) bileşiğinin ORTEP diagramı



Tablo 5: Metal karben kompleksi 23A'nın ferrosenil alkin bileşikleri 8 ile tepkimesi.



Deneme[a]	Alkin	R	Ürünler (Verim, %)
A	**8A**	H	**25A** (45) + **30A** (6)
B	**8B**	CH_3	**25B** (36) + **26B** (16) + **27B** (17) + **28B** (17) + **29B**[b] (4) + **32B**[c] (6)
C	**8C**	CH_2-Ph	**25C** (16) + **28C** (57)
D	**8D**	$Si(CH_3)_3$	**25A** (26)
E	**8E**	Ph	**25E** (31) + **27E** (5) + **28E** (55)
F	**8F**	Fc	**25F** (18) + **27F** (9) + **28F** (32) + **31F** (7)

[a] Deneme harfleri **8**, **25**-**32** nolu bileşikler için R grubunu tanımlar.

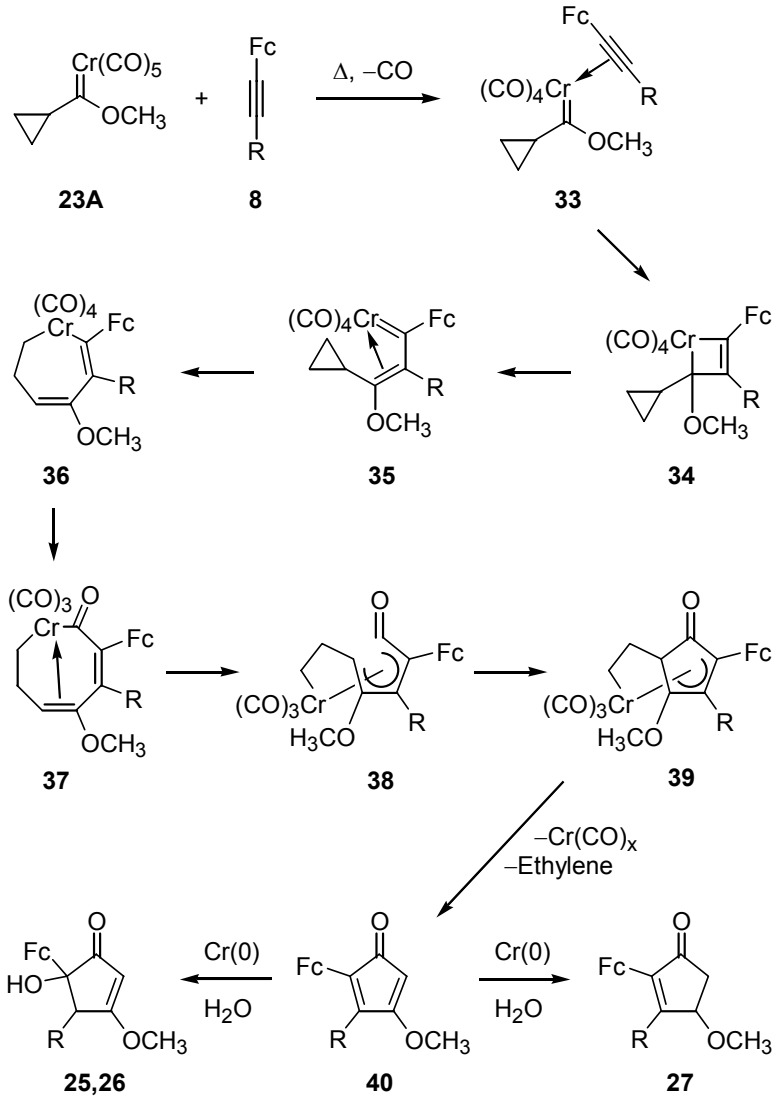
[b] Bu ürünün stereokimyası yani mezo veya rasemik karışım (DL-isomerler) olup olmadığı tanımlanmadı.

[c] Bu üründeki çifte bağın konfigürasyonu tanımlanmadı.

Siklopentenon **25**, **26** ve **27**'nin önerilen oluşum mekanizması Şema 15'de verilmiştir (Dotz 1984; Wulff, 1985, 1989 ve 1991; Herndon 1988, 1989 ve 1990; Tumer 1992). Krom karben kompleksi **23A** 100 °C'de ferrosenil alkin **8** varlığında ısıtıldığında metalden bir CO ligandı ayrılır ve alkin bileşiği **8** metale koordine olarak ara kompleks **33**'ü oluşturmuştur. Bu

da [2+2] siklokatılmasıyla kompleks **34**'e dönüşmüştür. Elektrosiklik halka açılması kompleks **35**'i üretmiş ve bu kompleksde 1,5-alkil kayması ile kompleks **36**'yı vermiştir. CO inzersiyonu kompleks **37**'yi oluşturmuştur ki bu kompleksde düzenlenme ile önce kompleks **38**'i sonra da kompleks **39**'u üretmştir. Bu kompleksten bir etilen molekülünün ayrılması ile siklopentadienon **40** oluşmuştur. Bu tür tepkimelerde siklopentadienon tipi bileşiklerin oluşumu daha önce Herndon araştırma grubu tarafından ispatlanmıştı (Herndon, 1989). Daha sonra siklopentadienon **40**'a su katılması siklopentenon bileşiği **25** ve/veya **26**'yı üretmiştir. Bu bileşikte çifte bağ indirgenmesi ise bileşik **27**'yi vermiştir (Şema 15).

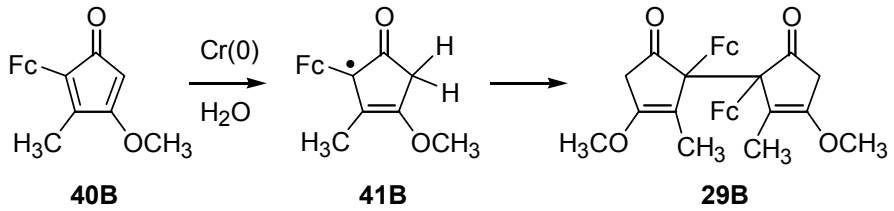
Şema 15



Siklopentadienon bileşiklerinin indirgenmesi bilindiği halde bu bileşiklere bu tür tepkimelerde su katılması ilk defa bu çalışmada bizim tarafımızdan gözlenmiştir. Su katılmasına aşağıda bahsedileceği üzere ferrosenil grubu etki etmektedir. Su katılma basamağında hidroksi grubu karbonile göre α posizyonunda eklenmektedir çünkü tepkime esnasında oluşan karbokatyon bu posizyonda oluşmaktadır. Bu aslında karbonil grubunu biraz kararsız kılsa da bu pozisyonundaki ferrosenil grubu bu karbokatyonu oldukça kararlı yapmaktadır çünkü genelde ferrosenil grubu α posizyonundaki karbokatyonu çok kararlı kılan çok iyi bir gruptur (Traylor, 1967; Watts, 1977; Harrington, 2003). α-Posizyonundaki bir karbokatyonu kararlı kılmada fenil grubu ile kıyaslandığında ferrosenil grubu karbokatyonları çok daha kararlı kılan bir gruptur (Traylor, 1967; Watts, 1977; Harrington, 2003).

İlginç olarak bu tepkimelerden dimerik siklopentenon türevi **29B**'de izole edilmiştir (Tablo 5). Bu bileşik için önerilen oluşum mekanızması Şema 16'da verilmiştir. Tepkime esnasında siklopentadienon **40B** Cr(0) yan ürünleri ve H_2O varlığında radikal **41B**'ye ingirgenir. Ferrosenil grubu karbokatyonlarda olduğu gibi α posizyonundaki radikalleride oldukça kararlı kılan bir gruptur (Creary, 1989 ve 2000). Radikal **40B**'nin dimerleşmesi sonucu bileşik **29B** oluşmuştur.

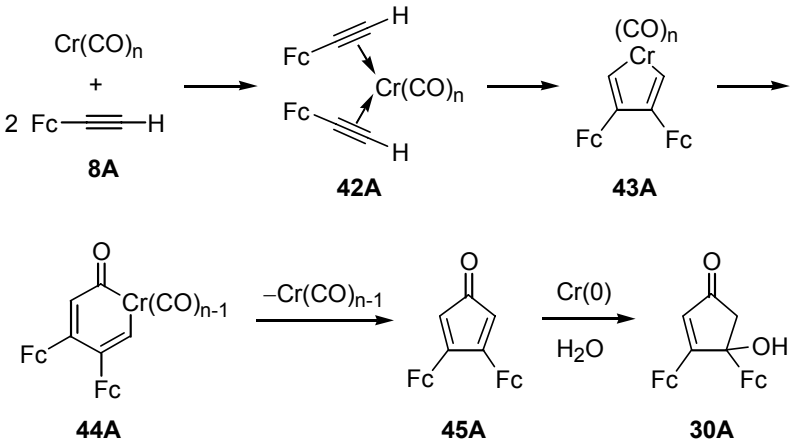
Şema 16



Bu tepkimelerden siklopentenon **30A** bileşiğide izole edilmiştir (Tablo 5). Bileşik **30A** için önerilen oluşum mekanızması Şema 17'de verilmiştir. İki mol etinilferrosen (**8A**) bileşiğinin tepkime esnasında oluşan bir $Cr(CO)_n$ kompleksine koordinasyonu alkin kompleksi **42A**'yı oluşturur ki bu da Reppe tipi bir bağlanma (Straub, 2004) ile kompleks **43A**'ya

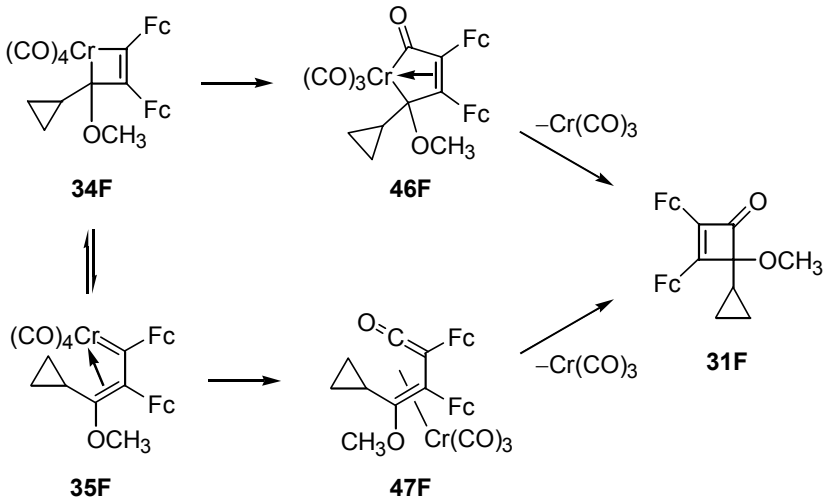
dönüşmektedir. Bu kompleksde CO inzersiyonu ile kompleks **44A**'yı oluşturur ki bu da indirgeyi çıkarma/ayrılma (reductive elimination) tepkimesi ile siklopentadienon **45A** bileşiğini vermektedir. Bu bileşiğe su katılması sonucu siklopentenon **30A** bileşiği oluşmaktadır (Şema 17). Yukarıda bahsedildiği üzere bu su katılma basamağında hidroksil grubu beklenildiği üzere ferrosenin α pozisyonuna eklenmektedir.

Şema 17



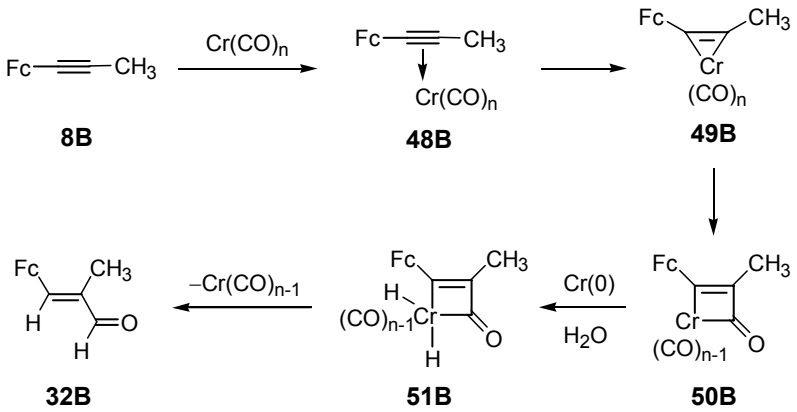
Siklobutenon **31F** bileşiği için önerilen oluşum mekanizmaları Şema 18'de verilmiştir (Chan, 1987; Tumer, 1992). İlk olarak metalasiklobuten **34F** CO inzersiyonu vererek kompleks **46F**'i verir ki bu da indirgeyici ayrılma ile siklobutenon **31F**'yi oluşturmaktadır. Alternatif olarak kompleks **35F** CO inzersiyonu ile kompleks **47F**'e dönüşebilmekte bu da elektrosiklik halka kapanması ile siklobutenon **31F**'yi üretmektedir (Şema 18). Kompleks **34F** ve **35F** tepkime ortamında kolayca birbirine dönüşebildiğinden siklobutenon **31F** bileşiğinin her iki mekanizma ile oluşma olasılığı vardır (kompleks **34F** ve **35F**'in oluşum mekanizmaları daha önce Şema 15'de verilmişti).

Şema 18



İlginç olarak bu tepkimelerden α,β-doymamış bir aldehit bileşiği yani **32F**'de izole edilmişitr. Bu bileşik için önerilen oluşum mekanizması Şema 19'da gösterilmiştir. Bu bileşik muhtemelen bir hidroformilasyon tepkimesi ile oluşmuştur (Bhaduri, 2000). Ferrosenil alkin **8B** bileşiğinin tepkime ortamında oluşan doymamış bir Cr(CO)n kompleksine koordinasyonu alkin kompleksi **48B**'yi verir ki bu da kompleks **49B**'ye dönüşmektedir. Daha sonra CO inzersiyonu kompleks **50B**'yi üretir. Bu kompleksde yükseltgeyici katılma (oxidative addition) ile kompleks **51B**'ye dönüşmektedir ki bu da arka arkaya iki defa indirgeyici ayrılma (reductive elimination) tepkimesi ile doymamış aldehit bileşiği **32B**'yi vermektedir (Şema 19).

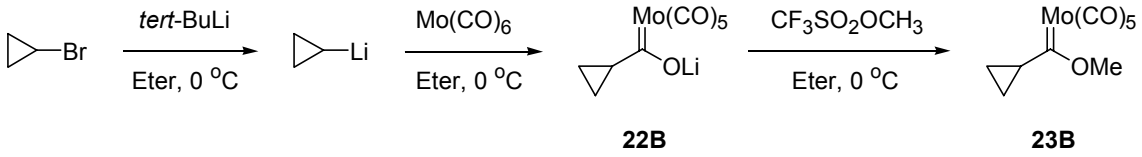
Şema 19



3.3 2-Ferrosenil-4-metoksi-2,4-sikloheptadienon (**3**) türevlerinin sentezi

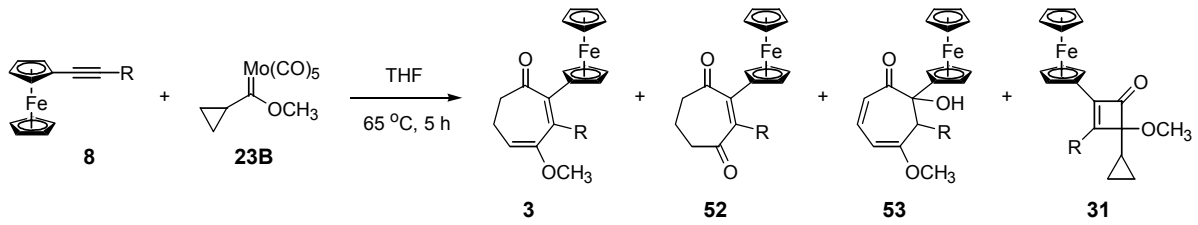
Bu kısımda öncelikle 2-ferrosenil-4-metoksi-2,4-sikloheptadienon (**3**) türevlerinin sentezi için gerekli metal karben kompleksi **23B** (Şema 20) hazırlanmıştır (Gerekli ferrosenilalkin bileşikleri **8A**/**B**/**C**/**D**/**E** ise Şema 8 ve 13'de gösterildiği üzere daha önce bilinen literatür yöntemlerine göre sentezlenmişti). İlk olarak metal karben kompleksi **23B**'nin sentezi için siklopropilbromür *tert*-BuLi ile tepkimeye sokularak tepkime ortamında önce siklopropillityum hazırlanmıştır (Şema 20) (Herndon 1993). Daha sonra bunun molibden hekzakarbonil ile muamelesi önce tepkime ortamında kompleks **22B**'yi oluşturmuştur ki bu ara kompleksinde izole edilmeden doğrudan metil triflat ($CF_3SO_2OCH_3$) ile tepkimesi molibden karben kompleksi **23B**'yi üretmiştir (Şema 20) (Herndon 1993).

Şema 20



Projenin ikinci safhasında metal karben kompleksi **23B**'nin ferrosenil alkin bileşikleri **8** ile olan tepkimeleri çalışılmıştır. Sonuçlar Tablo 6'da verilmiştir. Tablo 6'dan görüleceği üzere bu tepkimelerden sikloheptadienon bileşikleri **3** ve **53**, sikloheptendion **52** ve siklobutenon **31** bileşikleri izole edilmiştir. Molibden karben kompleksi **23B** krom karben kompleksi **23A**'ya kıyasla daha reaktif olduğundan karben **23B**'nin tepkimeleri daha düşük sıcaklıkta (yani 65 ^{o}C'de) gerçekleştirilmiştir. Oluşan ürünlerden sikloheptadienon **3C**'nin yapısı X-ışını analiz yöntemiyle belirlenmiştir (Şema 21).

Tablo 6: Metal karben kompleksi 23B'nin ferrosenil alkin bileşikleri 8 ile tepkimesi.

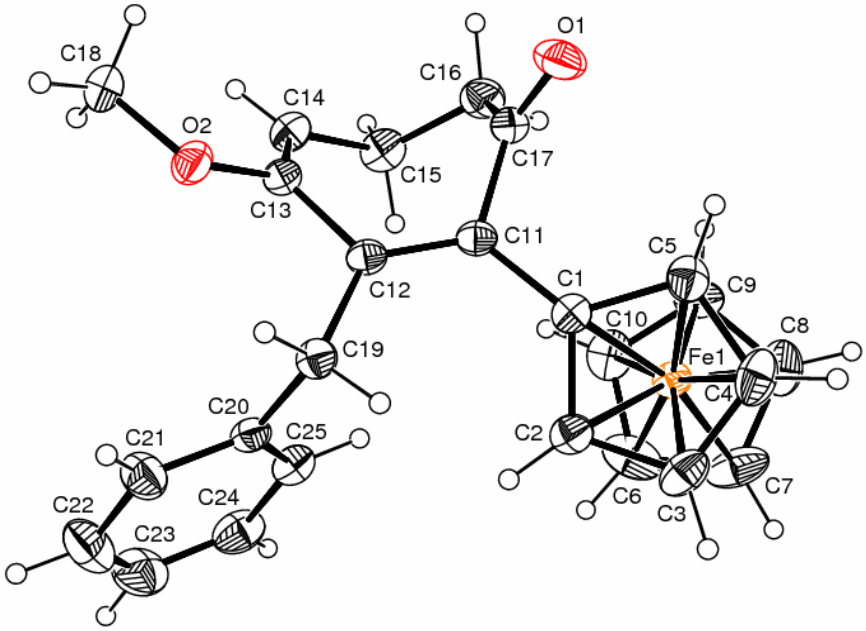


Deneme[a]	Alkin	R	Ürünler (Verim, %)
B	**8B**	CH_3	**3B** (47) + **52B** (12) + **53B**[b] (12)
C	**8C**	CH_2Ph	**3C** (70) + **52C** (13)
E	**8E**	Ph	**3E** (72) + **52E** (10)
F	**8F**	Fc	**3F** (15) + **31F** (8)

[a] Deneme harfleri **3**, **8**, **31**, **52** ve **53** nolu bileşikler için R grubunu tanımlar.

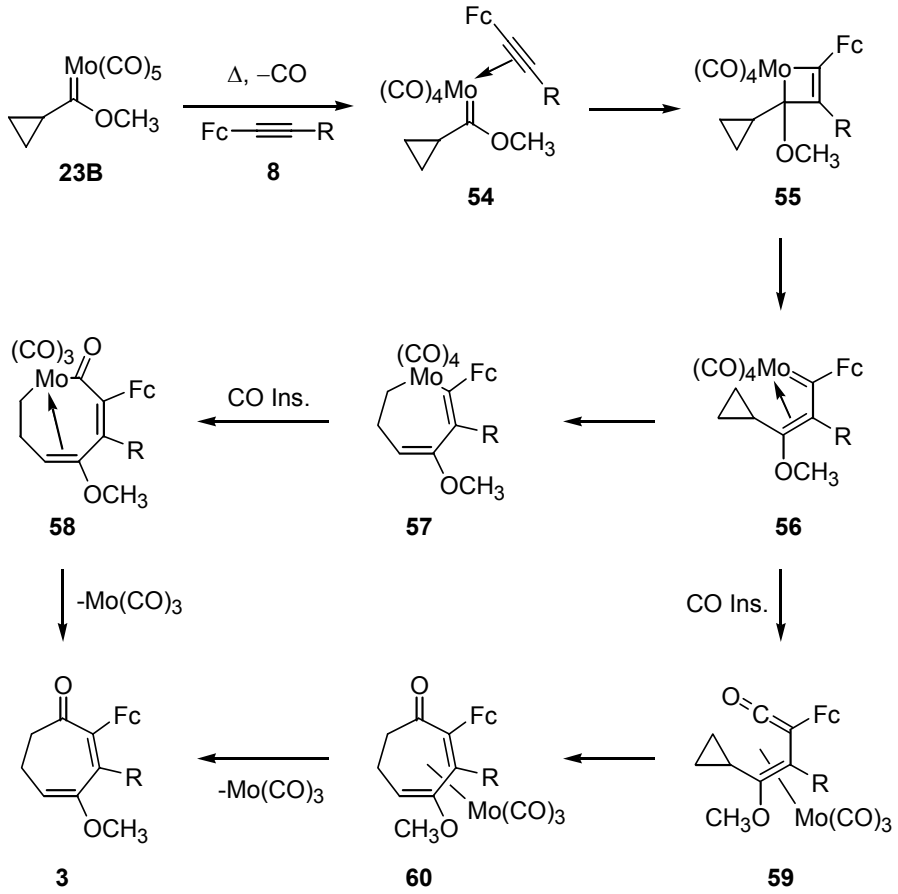
[b] Bu ürünün 6 ve 7 nolu karbonlarındaki sübstitüentlerin göreceli sterokimyası tanımlanmadı.

Şema 21. 3-Benzil-2-ferrosenil-4-metoksi-2,4-sikloheptadienon (**3C**) bileşiğinin ORTEP diagramı



Sikloheptadienon **3** bileşikleri için önerilen oluşum mekanizması Şema 22'de verilmiştir (Herndon, 1991 ve 1993). Molibden karben kompleksi **23B** 65 ^{o}C'de ferrosenil alkin bileşiği **8** varlığında ısıtıldığında metalden bir CO ligandı ayrılır ve alkin bileşiği **8** metale koordine olarak ara kompleks **54**'ü oluşturmuştur. Bu da [2+2] siklokatılmasıyla kompleks **55**'e dönüşmüştür. Elektrosiklik halka açılması kompleks **56**'yı üretmiş ve bu kompleksde 1,5-alkil kayması ile kompleks **57**'yi vermiştir. CO inzersiyonu kompleks **58**'i üretmiştir ki bu da indirgeyici ayrılma tepkimesi ile sikloheptadienon **3**'ü vermiştir. Alternatif olarak kompleks **56** CO inzersiyonu ile kompleks **59**'a dönüşmekte bu da 1,5-alkil kayması ile kompleks **60**'ı üretmektedir. Son olarak dekomplekszasyon (decomplexation) sikloheptadienon **3**'ü üretmiştir (Şema 22) (Herndon, 1991 ve 1993).

Şema 22



Sikloheptendion **52** bileşiği aslında tepkimenin ikincil ürünü olup tepkime esnasında oluşan sikloheptadienon **3** bileşiğindeki enol ether fonksiyonel grubunun hidroliz olmasıyla oluşmaktadır (Herndon, 1991 ve 1993).

Bu tepkimelerde önceden bilinmeyen 7-hidroksi-2,4-sikloheptadienon bileşiği **53B**'de oluşmuştur. Genelde 4-metoksi-2,4-sikloheptadienon türevlerinin ısıtıldıklarında arka arkaya iki defa 1,5-H kayması ile daha kararlı olan 5-metoksi-2,4-sikloheptadienon türevlerine dönüştüğü çok iyi bilinmektedir (Herndon, 1991 ve 1993). Şu anda oluşum mekanizması bizim için çok net olmasada tepkime ortamında sikloheptadienon **3B** bileşiği daha kararlı izomerine dönüşürken muhtemelen su katılması olmakta ve sikloheptadienon **53B** oluşmaktadır.

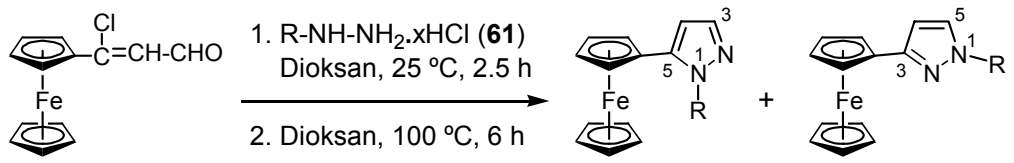
Siklobutenon **31F** bileşiği, krom karben kompleksi **23A**'nın ferrosenil alkin **8F** ile olan tepkimesindede oluşmuştu (Tablo 5) ve bu madde için önerilen oluşum mekanizması Şema 18'de verilmişti. Aynı bileşik molibden karben kompleksi **23B** ile olan tepkimedede muhtemelen benzer bir mekanizma ile oluşmaktadır.

Ferrosenil alkin bileşikleri **8A** ve **8D** bileşikleri Molibden karben kompleksi **23B** ile olan tepkimelerde maalesef çok kompleks tepkime karışımları üretmiş ve beklenen ürünler bu karışımlardan izole edilememişlerdir.

3.4 1-Akyl/aryl-5-ferrosenilpirazol (**4**) türevlerinin sentezi

Bu son kısımda ilk olarak 2-formil-1-klorvinil)ferrosen (3-klor-3-ferrosenilpropenal, **7**) bileşiğinin hidrazin **61** türevleri ile olan tepkimeleri incelenmiştir. Sonuçlar Tablo 7'de özetlenmiştir. Tepkimeler önce farklı koşullarda denenerek tepkime şartları optimize edilmiştir. Buna göre 1 ekuvalent 2-formil-1-klorvinil)ferrosen (**7**) 3 ekuvalent hidrazin veya hidrazin tuzu (**8**) ile oda sıcaklığında dioksan çözücüsü içinde muamele edilmiş daha sonra oluşan tepkime karışımı 100 ^{o}C'de geri soğutucu altında kaynatılmıştır. Bu tepkimelerde varsa hidrazin türevleri yerine bunların tuzları tercih edilmiştir çünkü hidrazin tuzları pirazol türevlerini daha yüksek verimlerle üretmiştir.

Tablo 7: (2-Formil-1-klorvinil)ferrosen (7) bileşiğinin hidrazin 61 türevleriyle tepkimesi



7 **4** (1,5-izomer) **62** (1,3-izomer)

Deneme[a]	R	x	Ürünler (Verim, %)
A	H	2	**4A** (51)
B	Ph	1	**4B** (67) + **62B** (4)
C	CH_2-CH_2-OH	2	**4C** (3) + **62C** (34)
D	CH_2-Ph	2	**4D** (55)
E	*p*-C_6H_4-CO_2H	1	**4E** (47)
F	*o*-C_5H_4N	0	**4F** (60)
G	CO-*p*-C_6H_4-OH	0	**4A** (50) + **62G** (43)

[a] Deneme harfleri **4**, **61** ve **62** nolu bileşikler için R grubu ile **61** nolu bileşik için **x**'i tanımlar.

Tablo 7'den görüldüğü üzere bu tepkimeler 1-alkll/aril-5-ferrosenilpirazol (**4**) ve/veya 1-alkil/aril-3-ferrosenilpirazol (**62**) türevlerini üretmiştir ki bu bileşikler yaygın olarak 1,5- ve 1,3-pirazol izomerleri olarak tanımlanmaktadır. Bu izomerler ^{13}C-NMR spektrumlarına bakılarak çok kolay olarak birbirlerinden ayırt edilebilmektedir. Genelde 1,5-izomerde C5 karbonu yukarı alana kaymakta ve yaklaşık olarak 140 ppm'de resonans olmaktadır. Diğer taraftan 1,3-izomerde bu karbona karşılık gelen C3 karbonu aşağı alana kaymakta ve yaklaşık olarak 150 ppm civarında pik vermektedir. Ayrıca 1,5-izomerde C5 ve C3 karbonları arasındaki kimyasal kayma farkının mutlak değeri 1,3-izomerde bu karbonlara karşılık gelen C3 ve C5 karbonları arasındaki kimyasal kayma farkının mutlak değerinden genellikle daha küçüktür, yani $|\Delta\delta(C5\text{-}C3)_{1,5\text{-isomer}}| < |\Delta\delta(C3\text{-}C5)_{1,3\text{-isomer}}|$'dir.

Ferrocenylpropenal **7** bileşiğinin hydrazin dihidroklorür (**61A**) ile tepkimesi bir pirazol türevi oluşturmuştur ki bu bileşik geçiçi olarak 5-ferrosenilpirazol (**4A**) olarak tanımlanmıştır (Tablo 7, Deneme A). Pirazol türevleri "annular" tautomerizme bağlı olarak **4A** ve **62A** tautomerleri gibi farklı tautomerik yapıda bulunabilmektedir (Elguero, 1974; Aguilar-Parrilla, 1992; De Paz, 1997; Garcia, 2002). Aslında pirazol bileşiklerindeki proton transferi 1,5-hidrojen kayması olup bu tür prosesler için sıvı ve katı fazda rapor edilen aktivasyon barierleri yaklaşık olarak 10-14 kkal/mol civarındadır (De Paz, 1997). Beklenildiği üzere **4A** ve **62A** tautomerleri birbiriyle dengede olabilmekte veya kısmen birbirlerine dönüşebilmektedir. Bu bileşiğin tautomerik formunu belirleyebilmek için gerek 25 ^{o}C'de gerekse -15 ^{o}C'de iyi çözümlenmiş bir ^{13}C-NMR spektrumunu almayı maalesef başaramadık. Aslında pirazol **4A** bileşiği bilinen bir madde olmasına rağmen bu bileşiğin tautomerik formunun belirlenmesi için gerekli olan ^{13}C-NMR datası literatürde rapor edilmemiştir (Shvekhgeimer, 1992). **4A** ve **62A** tautomerlerini spektroskopik olarak tanımlayabilmek için çalışmalarımız devam etmektedir.

Gaussian 98 program (Frisch, 1998) paketini kullanarak bu tautomerlerin DFT (B3LYP/6-31G*) (Becke, 1993; Lee, 1988) seviyesinde relatif enerjilerinide hesapladık. Hesaplamalarımıza göre gaz fazda **62A** tautomeri **4A** tautomerinden 0.3 kkal/mol daha kararlıdır. Elguero ve çalışma arkadaşları tarafından gösterildiği üzere pirazol bileşikleri farklı fazlarda farklı tautomerik yapılarda olabilmektedir (Garcia, 2002). Örneğin gaz ve sıvı fazda 3-fenilpirazol daha karalı iken katı fazda 5-fenilpirazol daha kararlı olmaktadır.

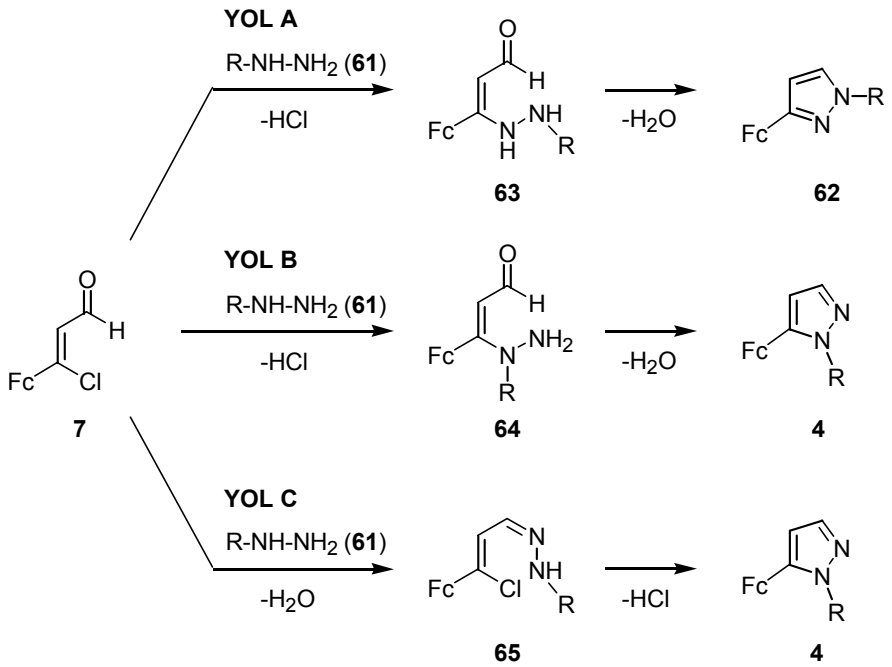
Ferrosenilpropenal **7** bileşiğinin fenilhidrazin dihidroklorür (**61B**) ile tepkimesi ana ürün olarak 5-ferrosenil-1-fenilpirazol (**4B**) bileşiğini oluşturmuştur, çok azda 3-ferrosenil-1-fenilpirazol (**62B**) bileşiğini vermiştir (Tablo7, Deneme B). İlginç olarak ferrosenilpropenal **7** ve (2-hidroksietil)hidrazinyum diklorür (**61C**) (Turgut, 2005) arasındaki tepkimeden ana ürün olarak 2-(3-ferrosenilpirazol-1-il)etanol (**62C**) alınmış, 2-(5-ferrosenil-pirazol-1-il)etanol (**4C**) yan ürün olarak alınmıştır (Tablo7, Deneme C). Diğer taraftan ferrosenilpropenal **7** bileşiğinin benzilhidrazin dihidroklorür (**61D**) ile tepkimesi sadece 1-benzil-5-ferrosenilpirazol (**4D**)

bileşiğini vermiştir (Tablo 7, Deneme D). Yukarıda bahsedildiği üzere **4B-D** ve **62B-C** bileşiklerinin spektroskopik tanımlanmaları bu bileşiklerdeki C5 ve/veya C3 karbonlarının kimyasal kayma değerlerine göre ve bu karbonlar arasındaki kimyasal kayma farkı değerlerine göre yapılmıştır.

Ferrosenilpropenal **7** ile 4-hidrazinobenzoik asit (**61E**) arasındaki tepkime 4-(5-ferrosenilpirazol-1-il)benzoik asit (**4E**) bileşiğini üretmiştir (Tablo 7, Deneme E). Benzer olarak ferrosenilpropenal **7** ile 2-piridinohidrazinyum diklorür (**61F**) (Zora, 2006) arasındaki tepkimeden 2-(5-ferrosenilpirazol-1-il)piridin (**4F**) bileşiği izole edilmiştir (Deneme F). Diğer taraftan ferrosenilpropenal **7** bileşiğinin 4-hidroksibenzhidrazid (**61G**) ile tepkimesi (3-ferrosenilpirazol-1-il)(4-hidroksifenil)metanon (**62G**) ve 5-ferrosenilpirazol (**4A**) ürünlerini oluşturmuştur (Tablo 7, Deneme G).

Pirazol **4** (1,5-izomer) ve **62** (1,3-izomer) bileşiklerinin oluşumu için üç mekanistik yol önerilmiştir (Şema 23). Yol A ve B'de tepkime hidrazin **61** bileşiğinin ferrosenilpropenal **7** bileşiğine konjuge katılmasıyla başlar ve oluşan β-hidrazinoenon **63** and **64** bileşiklerinin kalaşmasıyla ve/veya kondenzasyonu ile sona erer. Yol C'de ise tepkime hidrazin **61** bileşiği-

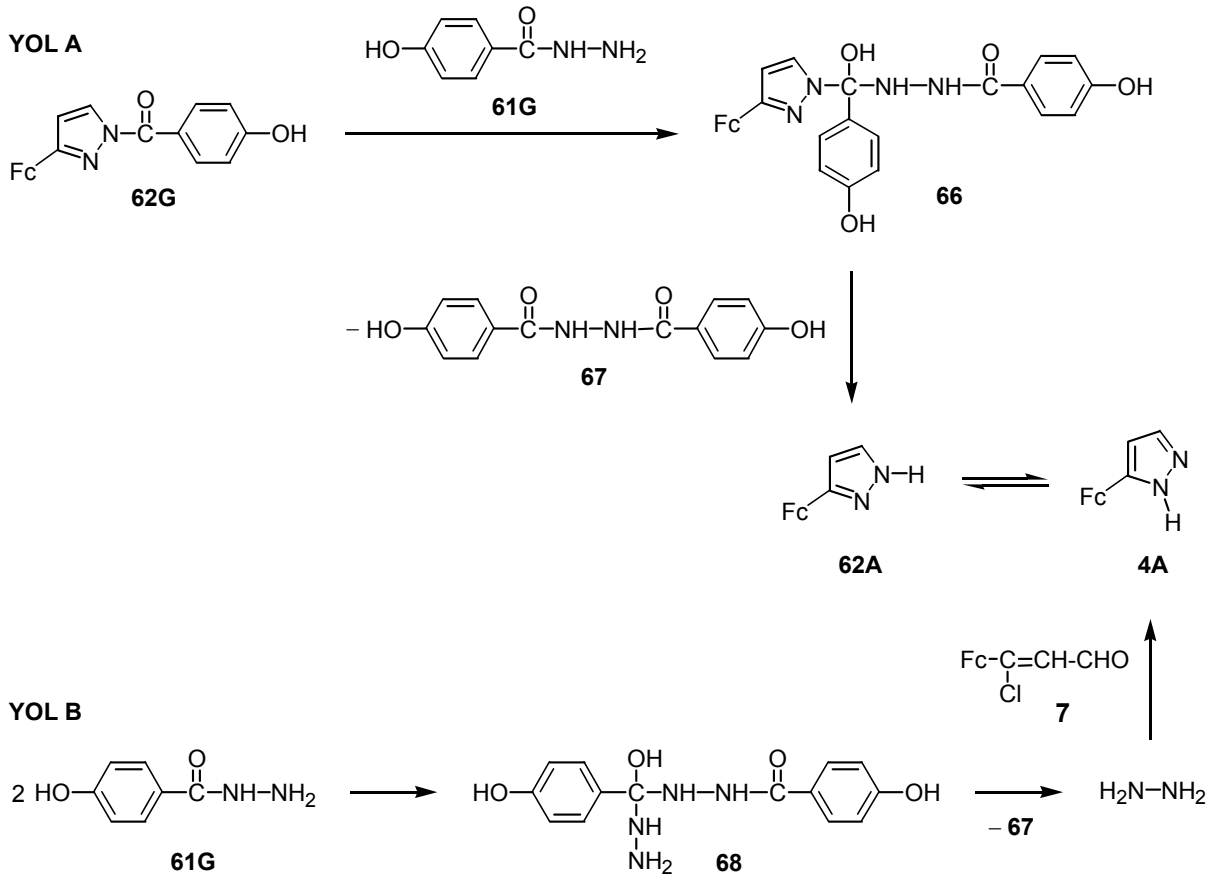
Şema 23



nin ferrosenilpropenal **7** bileşiğine kondenzasyonu ile başlar ve oluşan α,β-doymamış hidrazon **65** bileşiğinde katılma-eliminasyon ile son bulur. Şema 23'den görüldüğü üzere yol A'daki tepkime 1,3-pirazol izomeri **62**'yi üretirken yol B ve C'deki tepkimeler 1,5-pirazol izomeri **4**'ü üretmektedir. Sonuçlar göstermiştir ki tepkimeler esnasında hidrazin bileşiğinin sübstitüentine bağlı olarak bu yollardan biri veya bir kaçı etkili olmaktadır.

İlginç olarak ferrosenilpropenal **7** bileşiğinin 4-hidroksibenzhidrazid (**61G**) ile tepkimesinden (3-ferrosenilpirazol-1-il)(4-hidroksifenil)metanon (**62G**) ürününe ilave olarak 5-ferrosenilpirazol (**4A**) bileşiğide ürün olarak alınmıştır (Tablo 7, Deneme G). Bu tepkimede 5-ferrosenilpirazol (**4A**) bileşiğinin oluşumuna dair önerilen iki mekanistik yol Şema 24'de gösterilmiştir. Yol A'ya göre **4A** bileşiğinin oluşumu yeni bir tepkimeden değil, tepkime esnasında oluşan pirazol **62G** bileşiğinin hidrolizi sonucu oluşan ikincil bir üründür. Benzhid-

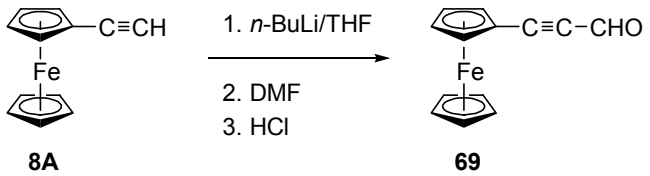
Şema 24



razid **61G** bileşiğinin pirazol **62G**'ye nükleofilik katılması hidrazid **66**'yı verir ki bu da genelde çok kararlı olmayıp benzoik asit hidrazit **67**'yi elimine ederek pirazol **62A**'yı oluşturmaktadır. Önceden bahsedildiği üzere bu bileşikte tautomeri **4A** ile dengede olabilir veya kısmen ona dönüşebilmektedir. Alternatif olarak yol B'de gösterildiği üzere benzhidrazid **61G** nükleofilik katılma yolu ile kendisi ile tepkimeye girerek hidrazid **68** ara ürününü oluşturmaktadır (Şema 24). Bu ara üründe benzoik asit hidrazit **67**'yi elimine ederek tepkime ortamında hidrazin oluşturmaktadır. Bu da ferrosenilpropenal **7** bileşiği ile tepkimeye girerek pirazol **4A** bileşiğini üretmektedir. Şu anda pirazol **4A** bileşiğinin hangi yolla oluştuğu bilinmemekle beraber önerilen her iki yoldaki tepkimelerin olabilirliği hakkında literatür mevcuttur (Mitkidou, 1993; Ali, 2006; Sailu, 2006).

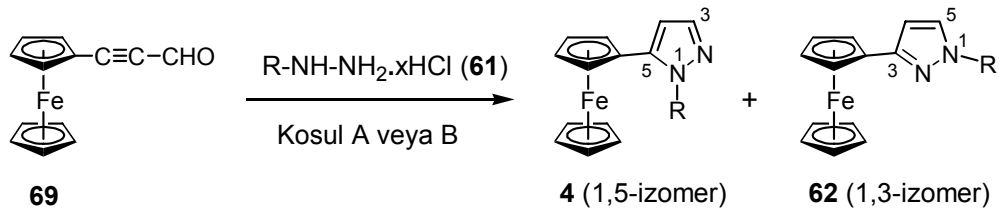
İkinci kısımda 3-ferrosenilpropinal (**69**) bileşiğinin hidrazinyum tuzları **61** ile olan tepkimeleriyle ferrosenil pirazol türevleri **4** ve/veya **62**'nin sentezleri gerçekleştirilmiştir. Bu amaçla ilk olarak etinilferrosen (**8A**) bileşiğinden 3-ferrosenilpropinal (**69**) başlangıç bileşiği hazırlanmıştır. Bileşik **8A**'nın *n*-butillityum ile muamele edilmesinden sonra DMF ile formilasyon tepkimesi 3-ferrosenilpropinal (**69**) bileşiğini oluşturmuştur (Şema 25) (Doisneau, 1992).

Şema 25



Daha sonra 3-ferrosenilpropinal (**9**) bileşiğinin hidrazinyum tuzları **10** ile olan tepkimeleri çalışılmıştır. Tepkimeler argon atmosferi ortamında geri soğutucu altında kaynayan dioksan (Koşul A) veya metanol (Koşul B) çözücüsü içerisinde 1:1.5 mol oranında 3-ferrosenilpropinal (**9**) ve hidrazinyum tuzu (**10**) kullanılarak gerçekleştirilmiş ve oluşan ürünler flaş kolon kromatografisi yardımı ile izole edilmiştir. Sonuçlar Tablo 8'de verilmiştir.

Tablo 8: 3-Ferrosenilpropinal (69) bileşiğinin hidrazinyum tuzları 61 ile tepkimesi.



Deneme[a]	R	x	Ürünler (Verim, %)	
			Koşul A[b]	Koşul B[c]
A	H	2	**4A** (47)	**4A** (70)
B	Ph	1	**4B** (45) + **62B** (14)	**4B** (70) + **62B** (20)
C	CH_2-CH_2-OH	2	**4C** (6) + **62C** (19)	**4C** (31) + **62C** (25)
D	CH_2-Ph	2	**4D** (63)	**4D** (46) + **62D** (30)

[a] Deneme harfleri **4**, **61** ve **62** nolu bileşikler için R grubu ile **10** nolu bileşik için **x**'i tanımlar.
[b] Koşul A: Dioksan, 100 ^{o}C, 8 saat.
[c] Koşul B: CH_3OH, 65 ^{o}C, 5 saat.

Bu tepkimelerde hidrazin türevleri yerine bunların tuzları tercih edilmiştir çünkü bu tuzlar pirazol türevlerini daha yüksek verimlerle oluşturmuştur. Tablo 7'de bahsedildiği üzere (2-formil-1-klorvinil)ferrosen (**7**) bileşiğinin hidrazin türevleri ile tepkimeleri pirazol türevlerini dioksan çözücü içerisinde daha yüksek verimlerle ürettiğinden 3-ferrosenilpropinal (**69**) bileşiğinin hidrazinyum tuzları **61** ile olan tepkimeleride önce dioksan çözücüsünde (Koşul A) denenmiştir. Fakat bu tepkimelerde bu çözücü kullanıldığında pirazol türevleri nispeten düşük verimlerle oluşmuştur. Daha sonra aynı tepkimeler farklı çözücülerde incelendiğinde görülmüştür ki metanol çözücüsü (Koşul B) beklenen pirazol türevlerini daha kısa sürede daha yüksek verimlerle üretmiştir (Tablo 8).

Tablo 8'den görüldüğü üzere bu tepkimeler 1-alkll/aril-5-ferrosenilpirazol (**4**) (1,5-izomer) ve/veya 1-alkil/aril-3-ferrosenilpirazol (**62**) (1,3-izomer) türevlerini üretmiştir. Önceden

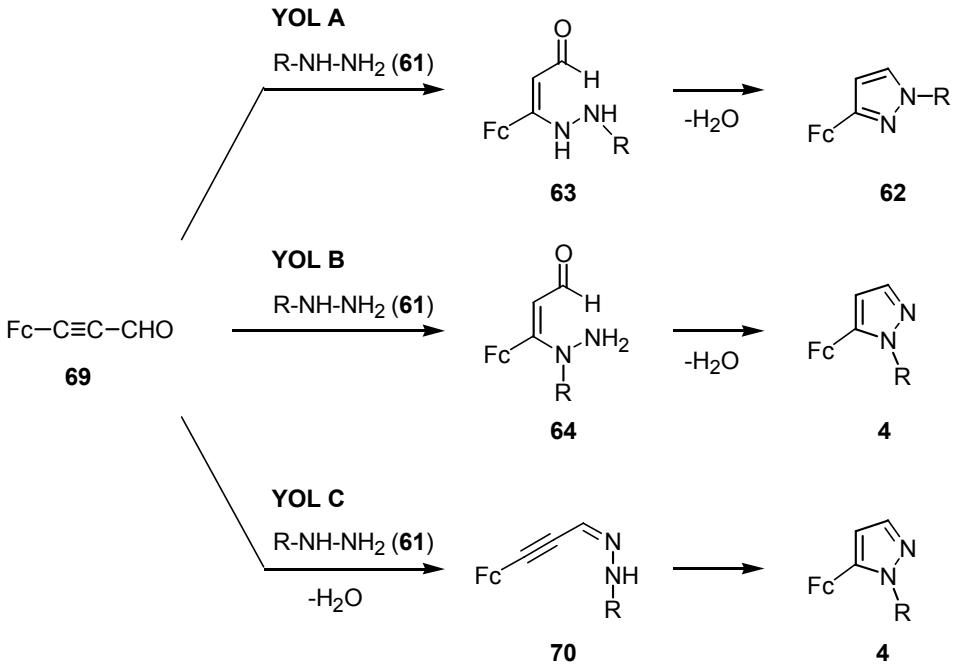
bahsedildiği üzere bu pirazol izomerleri ^{13}C-NMR spektrumlarından kolayca birbirlerinden ayırt edilebilmektedir. 3-Ferrosenilpropinal (**69**) bileşiğinin hydrazin dihidroklorür (**61A**) ile her iki koşuldada tepkimesi bir pirazol türevi oluşturmuştur ki bu bileşik geçiçi olarak 5-ferrosenilpirazol (**4A**) olarak tanımlanmıştır (Tablo 8, Deneme A). Bilindiği üzere pirazol türevleri "annular" tautomerizme bağlı olarak **4A** ve **62A** izomerleri gibi farklı tautomerik yapıda bulunabilmektedir (Elguero, 1974; Aguilar-Parrilla, 1992; De Paz, 1997; Garcia, 2002). Önceden bahsedildiği üzere bu bileşiğin tautomerik formunu belirleyebilmek için gerek 25 ^{o}C'de gerekse -15 ^{o}C'de iyi çözümlenmiş bir ^{13}C-NMR spektrumunu almayı maalesef başaramadık ama **4A** ve **62A** tautomerlerini spektroskopik olarak tanımlayabilmek için deneysel çalışmalarımız devam etmektedir.

3-Ferrosenilpropinal (**69**) bileşiğinin fenilhidrazin dihidroklorür (**61B**) ile tepkimesi her iki koşuldada 5-ferrosenil-1-fenilpirazol (**4B**) bileşiğini ana ürün, 3-ferrosenil-1-fenilpirazol (**62B**) bileşiğinide yan ürün olarak oluşturmuştur (Tablo 8, Deneme B). İlginç olarak 3-ferrosenilpropinal (**69**) ve (2-hidroksietil)hidrazinyum diklorür (**61C**) (Turgut, 2005) arasındaki tepkimelerden her iki üründe yani 2-(3-ferrosenilpirazol-1-il)etanol (**62C**) ve 2-(5-ferrosenil-pirazol-1-il)etanol (**4C**) ürünleri alınmasına rağmen Koşul A'da 1,5-pirazol izomer **4C** ana ürün olarak oluşurken Koşul B'de 1,3-pirazol izomeri **62C** ana ürün olarak oluşmuştur (Tablo 8, Deneme C). Diğer taraftan 3-ferrosenilpropinal (**69**) bileşiğinin benzilhidrazin dihidroklorür (**61D**) ile tepkimesi Koşul A'da sadece 1-benzil-5-ferrosenilpirazol (**4D**) ürününü verirken Koşul B'de ana ürün olarak **4D** bileşiğini, yan ürün olarakta 1-benzil-3-ferrosenilpirazol (**62D**) bileşiğini üretmiştir (Tablo 8, Deneme D). Bundan önceki çalışmada bahsedildiği üzere **4B-D** ve **62B-D** bileşiklerinin spektroskopik tanımlanmaları bu bileşiklerdeki C5 ve C3 karbonlarının kimyasal kayma değerlerine göre ve bu karbonlar arasındaki kimyasal kayma farkı değerlerine göre yapılmıştır.

Şema 26'da gösterildiği üzere pirazol **4** (1,5-izomer) ve **62** (1,3-izomer) bileşiklerinin oluşumu için üç mekanistik yol önerilmiştir. Yol A ve B'deki tepkimeler hidrazin **61** bileşiğinin 3-ferrosenilpropinal (**69**) bileşiğine konjuge katılmasıyla başlar ve oluşan β-hidrazinoenon **63**

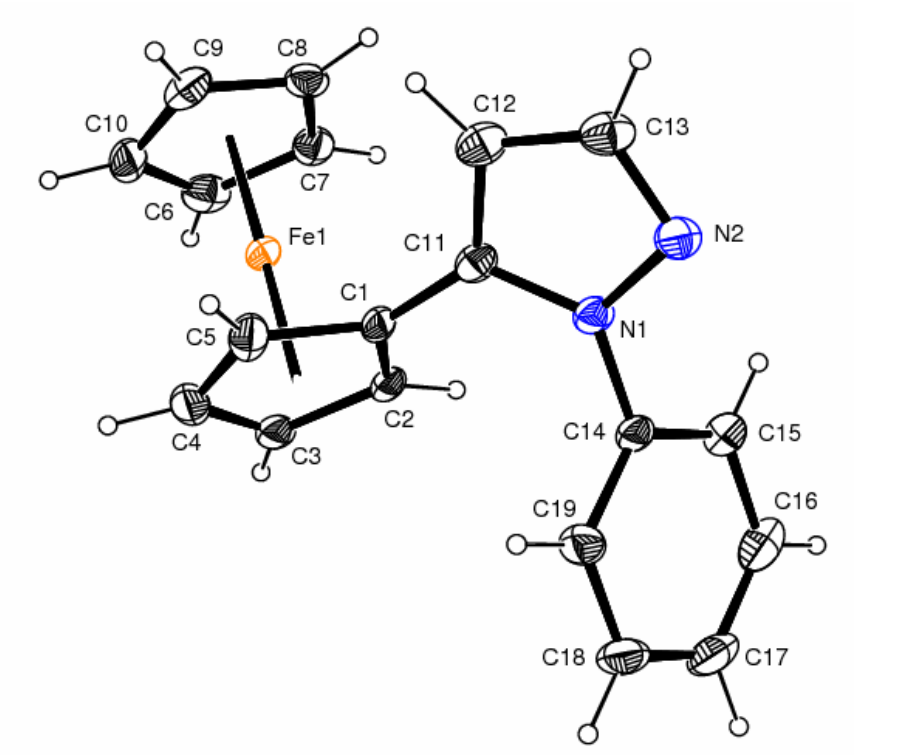
and **64** bileşiklerinin halkalaşması ve/veya kondenzasyonu ile sona erer. Yol C'de ise tepkime hidrazin **61** bileşiğinin 3-ferrosenilpropinal (**69**) bileşiğine kondenzasyonu ile başlar ve oluşan α,β-doymamış hidrazon **70** bileşiğinin halkalaşması ile son bulur. Şema 26'dan görüldüğü üzere yol A'daki tepkime 1,3-pirazol izomeri **62**'yi üretirken yol B ve C'deki tepkimeler 1,5-pirazol izomeri **4**'ü üretmektedir. Sonuçlar göstermiştir ki tepkimeler esnasında hidrazin bileşiğinin sübstitüentine bağlı olarak bu yollardan biri veya bir kaçı etkili olmaktadır.

Şema 26

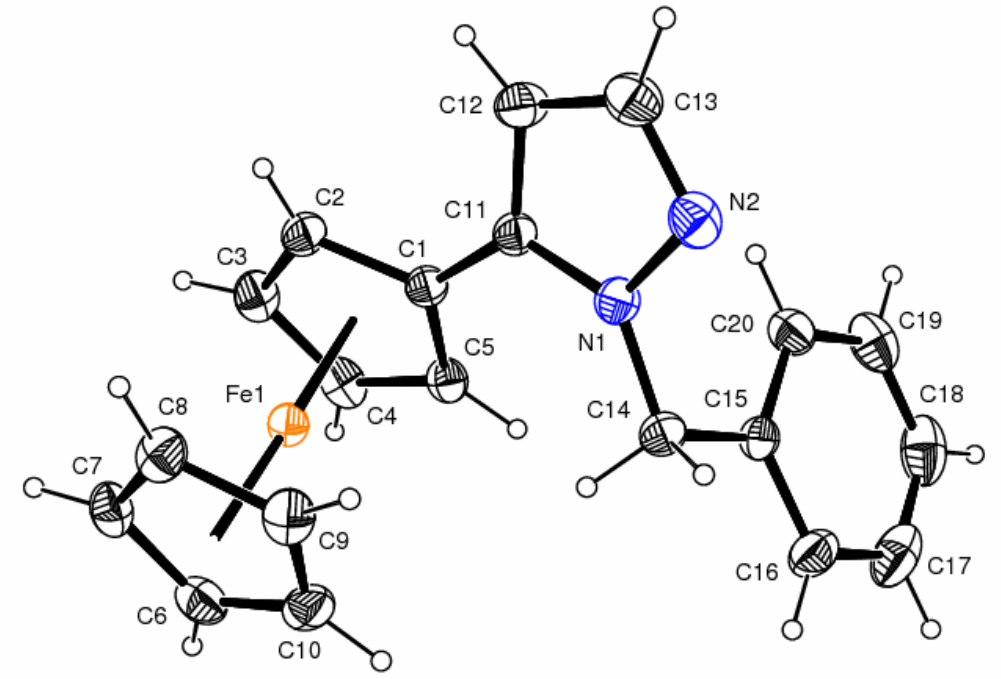


Pirazol bileşikleri **4B**, **4D** ve **62C**'nin yapıları X-ışını tek kristal analizi ile de aydınlatılmıştır. Bu bileşiklere ait ORTEP diagramları sırasıyla Şema 27, 28 ve 29'da gösterilmiştir. Bileşik **4D**'nin asimetrik biriminde iki molekül bulunmasına rağmen yapının daha iyi görünebilmesi için Şema 28'de sadece bir molekül gösterilmiştir.

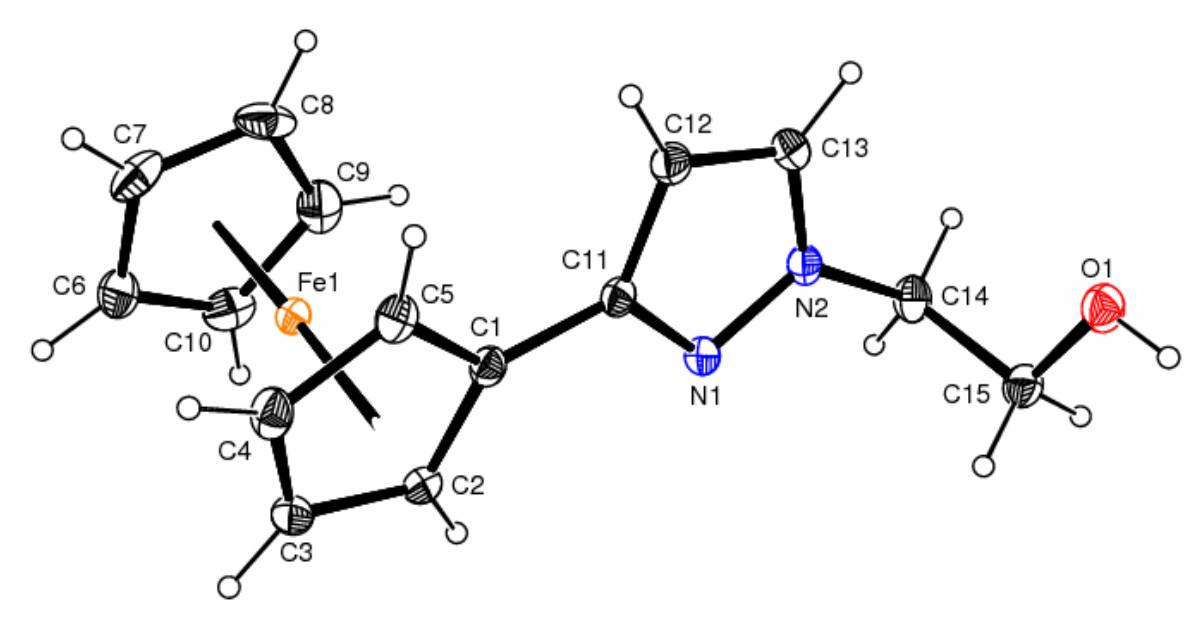
Şema 27. 5-Ferrosenil-1-fenil-1*H*-pirazol (**4B**) bileşiğinin ORTEP diagramı.



Şema 28. 1-Benzil-5-ferrosenil-1*H*-pirazol (**4D**) bileşiğinin ORTEP diagramı.



Şema 29. 2-(3-Ferrosenilpirazol-1-il)etanol (**62C**) bileşiğinin ORTEP diagramı.



Bu bileşiklere ait birim hücre, X-ışını data toplama ve yapı çözümüne ait detaylar Tablo 9'da verilmektedir. Bu yapılara ilişkin şeçilmiş bağ uzunlukları, bağ açıları ve dihedral açılarda Tablo 10'da gösterilmiştir.

Bu kristal yapılarında gözlenen en önemli yapısal özellik sterik etkilere bağlı olarak pirazol ve sübstitüye siklopentadienil halkalarının düzlemsellikten ayrılmasıdır ki bu da konjugasyonun bir ölçüde azalmasına neden olmaktadır. Bu aromatic yapıların düzlemsellikten sapma açısı bileşik **4B**'de 45.36(2)^{o} (Şema 27), bileşik **4D**'de 26.85(11)^{o} ve 33.52(6)^{o} (Şema 28), ve bileşik **62C**'de 11.87(12)^{o} (Şema 29) olarak belirlenmiştir. Kısacası ferrosen grubu ile pirazol halkasındaki azot (N1 veya N2) atomu üzerindeki 2-hidroksietil, benzil veya fenil grubu arasındaki sterik etkiye bağlı olarak bu sapma açısı **62C** < **4D** < **4B** şeklinde artmaktadır. Maksimum sterik etkileşim **4B**'de Fc and Ph grupları arasında görülür (Şema 28). Bunun sonucu Fc grubu gibi Ph grubuda pirazol halka düzleminden 64.95(2)^{o}'lik bir sapma gösterir, bu da ciddi olarak konjugasyonun durmasına neden olur.

Bir diğer önemli yapısal özellikte **62C** bileşiğinde C14 ve C15 atomları "staggered" konformasyonunda olmasına rağmen bu atomlar üzerindeki pirazol ve hidroksil grupları "gauche" konformasyonunda bulunmaktadırlar çünkü N2-C14-C15-O1 dihedral açısı yaklaşık

Tablo 9: Bileşik 4B, 4D ve 62C için kristalografik data ve yapı çözüm parametreleri			
	4B	**4D**	**62C**
Empirical formula	$C_{19}H_{16}FeN_2$	$C_{20}H_{18}FeN_2$	$C_{15}H_{16}FeN_2O$
Formula weight	328.19	342.21	296.15
Crystal size (mm)	0.470 x 0.380 x 0.260	0.640 x 0.570 x 0.440	0.780 x 0.423 x 0.210
Temperature (K)	293(2)	293(2)	296(2)
Crystal system	Orthorhombic	Triclinic	Monoclinic
Space group	P c a 21	P -1	P 21/c
a (Å)	21.999(2)	9.2923(5)	9.3038(17)
b (Å)	5.9827(6)	10.7911(6)	14.0340(3)
c (Å)	11.4051(9)	16.9299(9)	10.6563(16)
α (°)	90.000(0)	75.493(4)	90.000(0)
β (°)	90.000(0)	89.605(4)	110.482(13)
γ (°)	90.000(0)	75.870(4)	90.000(0)
V (Å^3)	1501.1(2)	1591.12(15)	1303.4(4)
Z	4	4	4
D_x (g cm^{-3})	1.452	1.429	1.509
μ (Mo K_α) (mm^{-1})	1.001	0.948	1.149
Radiation/wavelength (Å)	Mo K_α/0.71073	Mo K_α/0.71073	Mo K_α/0.71073
θ_{max} (°)	27.06	27.90	26.00
Index range (hkl)	-22/27, -7/7, -14/14	-12/12, -14/14, -22/22	-11/11, -17/17, -13/13
Reflections measured	7738	30561	15701
Independent reflections (R_{int})	3217	7544	2563
Reflections with $I > 2\sigma(I)$	2645	6232	2270
Number of parameters	199	415	172
Number of restraints	1	0	0
$R[F^2 > 2\sigma(F^2)]$	0.0399	0.028	0.0251
$wR(F^2)$	0.1236	0.0759	0.0660
Goodness-of-fit (F^2)	1.201	1.050	1.046
Max, min $\Delta\rho$ (e/Å^3)	0.882, -0.750	0.198, -0.351	0.217, -0.268

Tablo 10: Bileşik 4B, 4D ve 62C için seçilmiş bağ uzunlukları (Å), bağ açıları (°) ve dihedral açılar (°).

	4B	4D	62C
C1-Fe1	2.064(4)	2.0460(14)	2.0449(16)
C1-C2	1.413(6)	1.425(2)	1.427(2)
C1-C5	1.448(6)	1.425(2)	1.428(2)
C1-C11	1.444(6)	1.464(2)	1.462(2)
C2-C3	1.427(6)	1.415(2)	1.418(3)
C3-C4	1.405(7)	1.408(3)	1.416(3)
C4-C5	1.402(7)	1.421(2)	1.418(3)
C6-Fe1	2.028(4)	2.0484(17)	2.0393(19)
C11-N1	1.358(4)	1.3552(19)	1.337(2)
C11-C12	1.385(5)	1.375(2)	1.404(2)
C12-C13	1.385(6)	1.384(3)	1.364(3)
C13-N2	1.321(6)	1.313(2)	1.336(2)
C14-N1	1.422(4)	1.4414(19)	–
C15-O1	–	–	1.410(2)
N1-N2	1.365(4)	1.3637(18)	1.3585(19)
C2-C1-C11	128.8(4)	122.48(14)	128.43(15)
C11-C1-Fe1	129.3(3)	130.41(10)	125.43(11)
C11-N1-N2	112.5(3)	112.26(13)	104.84(13)
C12-C11-C1	132.1(3)	128.49(14)	127.37(16)
C13-N2-N1	104.1(3)	104.21(14)	111.87(14)
C13-C12-C11	105.7(3)	105.76(15)	105.22(15)
C14-C15-O1	–	–	109.05(15)
C15-C14-N1	119.3(3)	113.90(12)	–
N1-C11-C1	122.6(3)	126.00(13)	122.07(15)
C1-C11-N1-C14	-1.5(6)	3.7(2)	–
C2-C1-C11-N1	-43.8(6)	156.31(15)	-12.9(3)
C5-C1-C11-C12	-46.9(7)	148.51(17)	-10.7(3)
C5-C1-C11-N1	133.1(4)	-29.5(2)	168.70(15)
C15-C14-N1-C11	117.3(4)	89.17(18)	–
C15-C14-N2-C13	–	–	94.4(2)
C15-C14-N1-C11	117.3(4)	89.17(18)	–
C15-C14-N1-N2	-64.7(5)	-84.20 (17)	–
C15-C14-N2-N1	–	–	-81.4(2)
C2-C1-C11-N1	-43.8(6)	156.31(15)	-12.9(3)
C5-C1-C11-N1	133.1(4)	-29.5(2)	168.70(15)
N1-C14-C15-C16	179.9(4)	175.42(14)	–
N2-C14-C15-O1	–	–	-69.0(2)

olarak -69.0(2)^{o}'dir (Şema 29).

Katı fazdaki yapıları incelenen her bir bileşiğin kristal yapısı farklı bir düzenlenme göstermektedir. Genel olarak bu yapılar C–H. . .N veya O–H. . .N intermoleküler hidrojen bağlarıyla, ve/veya C–H. . .π etkileşimleriyle kararlı olmaktadırlar.

4.0 SONUÇ

Bu projede gerekli başlangıç maddeleri hazırlanarak potansiyel tıbbi ve biyolojik aktivete gösterebilecek

(i) 2-ferroseniliden-4-siklopenten-1,3-dion türevleri **1A**/**B**/**C/D/E**,

(ii) 5-ferrosenil-3-metoksi-2-siklopentenon türevleri **2A**/**B**/**C/D/E**,

(iii) 2-ferrosenil-4-metoksi-2,4-sikloheptadienon türevleri **3A**/**B**/**C/D/E** ve

(iv) 1-alkyl/aryl-5-ferrosenilpirazol türevleri **4A**/**B**/**C/D/E**

proje çalışma takvimine göre başarıyla sentezlemiştir. Çalışılan bütün tepkimeler beklenen reaksiyonları vermiş ve istenen ürünleri üretmiştir. Sentezlenen yeni maddelerin yapıları NMR (^{1}H- ve ^{13}C-NMR), IR, MS ve HRMS spektroskopik yöntemleri ve/veya X-ışını tek kristal analizi ile aydınlatılmıştır. Sezlenen maddelerin biyolojik aktivite testleri konusunda uzman ilgili gruplarla ortak bir çalışmaya gidilerek yapılması planlanmaktadır.

Proje kapsamında elde edilen deneysel sonuçlarla SCI indeksine giren uluslararası dergilerde 9 yurtdışı makale yayınlanmıştır. Deneysel sonuçlar ayrıca ilgili kongrelerde 7 bildiri veya poster olarak sunulmuştur.

Ülkemizin çok ihtiyaç duyduğu yarının genç ve yetenekli bilim adamlarının yetiştirilmesinde onların lisansüstü eğitimlerine katkı sağlamak amacıyla bu projenin tamamı Yüksek Lisans tez çalışması şeklinde yürütülmüştür. 9 öğrencinin Yüksek Lisans tez çalışması bu projenin olanaklarından faydalanılarak gerçekleştirilmiştir.

5.0 DENEYSEL KISIM

Bu projede tanımlanan maddelerin ^{1}H- ve ^{13}C-NMR spektrumları Bruker DPX 400 FT-NMR (400 MHz) spektrometresi ile çekilmiş olup kimyasal kayma değerleri (δ) tetrametilsilan (TMS) referansına göre verilmiştir. Spin-spin etkileşme sabitleri (*J*) Hertz (Hz) olarak, spin-spin yarılmaları ise s (singlet), d (dublet), t (triplet), q (kuartet) ve m (multiplet) sembolleriyle gösterilmiştir. DEPT ^{13}C-NMR sonuçları parentez içersinde C, CH, CH_2 and CH_3 olarak verilmiştir. İnfrared spektrumları Perkin Elmer 1600 FT-IR spektrometresi veya Bruker Vertex 70 Spekrometresi ile ATR tekniği kullanılarak çekilmiş olup pik yerleri cm^{-1} olarak ifade edilmiştir. Pik büyüklükleri birbirlerine göre göreceli olarak g (geniş), çk (çok kuvvetli), k (kuvvetli), o (orta), z (zayıf) ve çz (çok zayıf) sembolleriyle verilmiştir. Kütle spektrumları (MS) Finnigan MAT 95, Bruker Daltonics veya Agilent 1100 Serisi LC MSD spektrometre ile Elektron İyonlaşma (EI) veya Elektrosprey İyonlaşma (ESI) tekniği kullanılarak alınmıştır. Yüksek hassasiyetli kütle spektrumları (HRMS) Finnigan MAT 95 veya Bruker Daltonics spektrometre ile Elektron İyonlaşma (EI) veya Elektrosprey İyonlaşma (ESI) tekniği kullanılarak alınmıştır. Elementel analizler LECO CHNS-932 cihazı ile yapılmıştır.

Flaş kolon kromatografileri Merck (grade 9385, 230-400 mesh, 60 Å) marka silika ile gerçekleştirilmiştir. Rutin ince tabaka kromatografi (TLC) analizleri için Merck marka (Silica gel 60 F254, 0.25 mm) silika kaplı aluminyum plakalar kullanılmıştır. İnce tabaka kromatografisindeki (İTK) R_f (alıkoyma faktörü) değerleri için verilen karışık çözücü sistemleri hacim-hacim ilişkisine göre hazırlanmıştır.

Reaktif kalitesindeki kimyasallar Aldrich, Merck, Acros, Carlo-Erba veya Lab-Scan firmalarından, teknik kalitedeki çözücüler ise Birpa, Delta ve Atabay firmalarından satın alınmıştır. Teknik kalitedeki bütün çözücüler damıtılarak saflaştırılmıştır. Reaktif kalitedeki dietil eter, tetrahidrofuran (THF) ve dioksan çözücüleri sodyum üzerinden, diklormetan çözücüsü ise fosfor pentoksit üzerinden damıtılarak kurutulmuştur. Bu çalışmadaki bütün tepkimeler son derece kuru cam düzeneklerle argon gazı (0.1 psi) ile yaratılan inert bir atmosferde gerçekleştirilmiştir.

Asetilferrosen (6): Ferrosen (**5**) (10.0 g, 0.054 mol) 45 mL susuz diklorometan içinde çözüldü. Oluşan koyu turuncu/kırmızı solüsyona asetilklorür (4.63 g, 0.059 mol) eklendi ve buz banyosu içinde 0˚C'ye soğutuldu. Daha sonra susuz aluminyum klorür (7.2 g, 0.054 mol) kapaklı bir örnek kabının içine tartıldı ve reaksiyon karışımına yaklaşık olarak 10 parça halinde eklendi. Her bir eklemeden sonra 2 dakika beklendi ve eklendikçe reaksiyon karışımının gözle görülür bir şekilde koyulaştığı görüldü. Ekleme işi tamamlandıktan sonra reaksiyon 2 saat boyunca karıştırıldı. Bu süre içerisinde buzlu suyun oda sıcaklığına gelmesine izin verildi. Sonra solüsyon tekrar buzlu suya konularak soğutuldu ve 4 x 2.5 mL soğuk suyun yavaşça eklenmesiyle hidroliz edildi. Ardından daha hızlı bir biçimde 15 mL soğuk su eklendi. Daha sonra karışım diklorometan ile birkaç defa ekstraksiyon edildi Toplanan organik fazların %5'lik NaOH çözeltisiyle yıkanıp, $MgSO_4$ üzerinde kurutulup, süzülüp, uçurulmasından sonra elde edilen kırmızı/turuncu katı flaş kolon kromatografi yöntemiyle silika jel üzerinde 19:1 hekzan/etil asetat elüenti kullanılarak saflaştırıldı. Sonuç olarak 9.8 g asetilferrosen (**6**) bileşiği % 80 verimle elde edildi.

Bileşik 6 için spektroskopik data: ^{1}H-NMR ($CDCl_3$) δ: 4.78 (br s, 2H), 4.51 (br s, 2H), 4.21 (s, 5H), 2.40 (s, 3H). Bu spektroskopik data literatürde bu madde için verilen değerlerle uyum içersindedir (Gibson, 1997).

(2-Formil-1-klorvinil)ferrosen (7): Asetilferrosen (**6**) (4.56 g, 0.02 mol) ve *N,N*-dimetilformamit (DMF) (5 mL, 0.064 mol) bir ağzına damlatma hunisi takılmış 2-ağızlı bir balonda argon gazı altında 0˚C'ye soğutularak birkaç dakika karıştırıldı. Diğer taraftan argon gazı geçirilmiş ayrı bir balona DMF (5 mL, 0.064 mol) eklendi ve 0˚C'ye soğutuldu. Daha sonra üzerine dikkatli bir şekilde fosfor oksiklorür (5 mL, 0.054 mol) eklendi. Oluşan viskoz kompleks damlatma hunisine transfer edildi ve asetilferrosen-DMF karışımına 30 dakika boyunca damla damla eklendi. Ekleme işlemi bittikten sonra reaksiyon karışımı 2 saat 0˚C'de karıştırıldı. Bu süre zarfında karışımın rengi kahverenginden önce koyu yeşile sonra da koyu maviye dönüştü. Daha sonra karışımı nötürlemek amacıyla 15 mL dietil eter eklendi ve

karışımın iyice karışması sağlandı. Yine 0˚C'de sodyum asetat trihidrat (23.2 g, 0.170 mol) bir seferde karışıma eklendi. Bunu 1 mL suyun dikkatli bir biçimde eklenmesi takip etti. Sonra buz banyosu kaldırılıp karışımın oda sıcaklığına gelmesi beklendi. Bu sıcaklık değişimi sırasında koyu mavi olan rengin kırmızıya dönüştüğü gözlendi. 1 saatlik karışımın ardından 1 mL eter daha eklenip reaksiyon 3 saatlik bir karışım sürecine daha bırakıldı. Bu süre sonunda karışım birkaç defa eter ile ekstrakte edildi. Ayrılan organik fazlar birleştirildi ve doymuş sodyum bikarbonat solüsyonu ile yıkandı. Daha sonra organik fazın $MgSO_4$ üzerinde kurutulup, süzülüp, rotavapta konsantre edilip, yüksek vakumda kurutulmasından sonra 4.68 g (2-formil-1-klorvinil)ferrosen (**7**) bileşiği % 85 verimle mor kristaller halinde elde edildi.

Bileşik 7 için spektroskopik data: ^{1}H-NMR ($CDCl_3$) δ: 10.09 (d, 1H, *J* = 6.7), 6.40 (d, 1H, *J* = 6.7), 4.75 (s, 2H), 4.57 (s, 2H), 4.24 (s, 5H). Bu spektroskopik data literatürde bu madde için verilen değerlerle uyum içersindedir (Polin, 1996).

Etinilferrosen (8A): Ucuna geri-soğutucu takılmış bir balonun içerisine argon gazı altında (2-formil-1-klorvinil)ferrosen (**7**) (2.6 g, 47.5 mmol) ve 30 mL susuz 1,4-dioksan konuldu. Sonra bu karışım dioksanın kaynama noktasına kadar ısıtılıp 5 dakika geri soğutucu altında kaynatıldı. Bu sürenin sonunda 25 mL kaynar 1 N'lik sodium hidroksit solüsyonu dikkatli bir biçimde hızlıca reaksiyon karışımına eklendi. Daha sonra karışım tekrar 25 dakika geri-soğutucu altında kaynatıldı ve bu süre sonunda tepkime karışımının oda sıcaklığına gelmesi beklendi. Oda sıcaklığına ulaşan karışım bir beherin içindeki buzun üzerine döküldü ve 1 N'lik hidroklorik asit ile nötralize edildi. Daha sonra sulu karışım birkaç defa hekzan ile ekstrakte edildi. Toplanan organik fazların doymuş sodyum bikarbonat solüsyonu ile yıkanıp, $MgSO_4$ üzerinde kurutulup, süzülüp, uçurulmasıyla elde edilen turuncu madde flaş kolon kromatografi yöntemiyle silika jel'de hekzan elüenti kullanılarak saflaştırıldı. Sonuç olarak 1.48 g etinilferrosen (**8A**) bileşiği % 74 verimle turuncu kristaller halinde elde edildi.

Bileşik 8A için spektroskopik data: ^{1}H-NMR ($CDCl_3$) δ: 4.46 (m, 2H), 4.21 (s, 5H), 4.19 (m, 2H), 2.71 (s, 1H). Bu spektroskopik data literatürde bu madde için verilen değerlerle uyum içersindedir (Polin, 1996).

3,4-Diizopropoksi-3-siklobuten-1,2-dion (Diizopropil skuarat, 11A): Dean-Stark düzeneğine takılı dibi yuvarlak 100 mL lik bir balona sırasıyla 3,4-diisopropoksi-3-siklobuten-1,2-dion (skuarik acid, **9**) (10.00 g, 88 mmol) ve 100 mL 1:1 oranında benzen/2-propanol çözücüsü konuldu. Oluşan süspansiyon manyetik karıştırıcı ile karıştırılarak 72 saat geri soğutucu altında kaynatılmıştır. Bu esnada tepkime çözücüsü ve oluşan azeotrop devamlı olarak 1:1 oranında benzen/2-propanol çözücüsü ile yenilendi (Yaklaşık olarak 500 mL 1:1 oranında benzen/2-propanol çözücüsü kullanıldı). 72 saat sonunda organik faz düşük vakum altında uçuruldu ve oluşan yağımsı ham ürün 500 mL reaktif kalitesindeki dietil eter çözücüsü içinde çözüldü. Bu organik faz sırasıyla iki kere 20 mL doymuş $NaHCO_3$ ve bir kere de 20 mL doymuş NaCl çözeltisi ile yıkandı. Daha sonra Na_2SO_4 üzerinde kurutulan organik faz düşük vakum altında uçuruldu. Oluşan altın renkli ve argon altında muhafaza edilen viskoz yağ argon altında buzdolabında katılaştı. Bu katı madde parçalanıp yüksek vakuma takılarak içerebileceği eser miktardaki organik çözücüsü de tamamen uçuruldu ve bu işlem sonunda 13.90 g diizopropil skuarat (**11A**) elde edildi (% 80 verim, e.n. 43-44 °C). ^{1}H NMR, IR ve TLC (R_f = 0.30, 4:1 hekzan-etil acetat içinde) ile yapılan kontrollerde maddenin saf olduğu ve başlangıç maddesi skuarik acid (**9**) içermediği görülmüştür.

Bileşik 11A için spektroskopik data: ^{1}H-NMR ($CDCl_3$): □ 5.35 (m, 2H), 1.48 (d, 12H); IR (CH_2Cl_2): 2989 (z), 1813 (o), 1731 (k), 1595 (çk), 1407 (k), 1325 (o), 1266 (çk) cm^{-1}. Bu spektroskopik data literatürde bu madde için verilen değerlerle uyum içersindedir (Liebeskind, 1988).

4-Hidroksi-2,3-diizopropoksi-4-metil-2-siklobuten-1-on (12): Devamlı argon altında tutulan ve ağzı septumla kapatılmış tek ağızlı 250 mL lik dibi yuvarlak bir balona sırasıyla

diizopropil skuarat (**11A**) (5.0 g, 25.30 mmol) ve THF (125 mL) konulup balon karışımı -78 °C ye soğutuldu ve tepkime sonuna kadar da bu sıcaklık muhafaza edildi. Bu karışıma sonra uygun metillityum (17.9 mL 1.69 M dietil eter çözeltisi, 30.30 mmol) 15 dakikalık bir süre içersinde şırınga ile damla damla ilave edildi ve tepkime karışımı -78 °C de 3 saat kadar karıştırıldı. Bu süre sonunda 50 ml doymuş sulu amonyum klorür çozeltisi -78 °C de tepkime karışımına ilave edildi. Daha sonra kendi kendine oda sıcaklığına gelmesi sağlanan tepkime karışımı eter çözücüsü ile (3 x 200 mL) ekstrakte edilip toplanan organik fazlar bir kere 50 mL su ile yıkanıp sodyum sülfat üzerinde kurutuldu. Organik fazların düşük vakum altında uçurulmasından sonra alınan yağımsı ham ürün elüent olarak 9:1 hekzan-etil asetat çözücü sistemi kullanılarak flaş kolon kromatografisi ile saflaştırıldı ve siklobutenon **12** izole edildi (5.10 g, % 94 verim).

Bileşik 12 için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ 4.89 (septet, 1H, *J* = 6.0 Hz), 4.87 (septet, 1H, *J* = 6.0 Hz), 2.60 (s, 1H), 1.50 (s, 3H), 1.41 (d, 3H, *J* = 6.0 Hz), 1.39 (d, 3H, *J* = 6.0 Hz), 1.29 (d, 3H, *J* = 6.0 Hz), 1.26 (d, 3H, *J* = 6.0 Hz); IR (neat): 3400 (g), 2990 (o), 1770 (k), 1625 (çk), 1390 (o), 1340 (o). Bu spektroskopik data literatürde bu madde için verilen değerlerle uyum içersindedir (Liebeskind, 1988).

3-İzopropoksi-4-metil-3-siklobuten-1,2-dion (11B): Siklobutenon **12** (5.10 g, 23.70 mmol) 150 mL CH_2Cl_2 içinde çözülüp bu karışıma 8 damla derişik HCl ilave edildi ve oluşan tepkime karışımı oda sıcaklığında yaklaşık olarak 20-30 dakika kadar karıştırıldı (Tepkime rutin TLC ile takip edilip siklobutenon **3**'ün TLC deki spotunun kaybolmasından sonra karıştırma işlemine son verildi). Tepkime karışımı sonra içinde 50 mL doymuş sulu sodyum bikarbonat bulunan bir ayırma hunisine döküldü ve organik ürün CH_2Cl_2 (3 x 200 mL) ile ekstrakte edildi. Toplanan organik fazlar sodyum sülfat üzerinde kurutulup düşük vakumda uçuruldu. Oluşan viskoz yağımsı ürün flaş kolon kromatografisinde elüent olarak 9:1 hekzan-etil asetat çözücü sistemi kullanılarak saflaştırıldı ve siklobutendion **11B** (R_f = 0.26, 4:1 hekzan-etil asetat içinde) izole edildi (3.36 g, % 92 verim).

Bileşik 11B için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ 5.40 (septet, 1H, *J* = 6.0 Hz), 2.22 (s, 3 H), 1.48 (d, 6H, *J* = 6.0 Hz); IR (neat): 2985 (çz), 2359 (z), 1799 (çk), 1750 (çk), 1597 (çk), 1399 (k), 1331 (o), 1098 (o), 1072 (z), 977 (çz), 897 (çz), 730 (z) cm^{-1}. Bu spektroskopik data literatürde bu madde için verilen değerlerle uyum içersindedir (Liebeskind, 1988).

4-Hidroksi-2,3-diizopropoksi-4-fenil-2-siklobuten-1-on (13): Devamlı argon altında tutulan ve ağzı septumla kapatılmış tek ağızlı 250 mL lik dibi yuvarlak bir balona sırasıyla diizopropil skuarat (**11A**) (5.0 g, 25.30 mmol) ve THF (125 mL) konulup balon karışımı -78 °C ye soğutuldu ve tepkime sonuna kadar da bu sıcaklık muhafaza edildi. Bu karışıma sonra uygun fenillityum (16.8 mL 1.8 M siklohekzan-dietil eter çözeltisi, 30.30 mmol) 15 dakikalık bir süre içersinde şırınga ile damla damla ilave edildi ve tepkime karışımı -78 °C de 3 saat kadar karıştırıldı. Bu süre sonunda 50 ml doymuş sulu amonyum klorür çozeltisi -78 °C de tepkime karışımına ilave edildi. Daha sonra kendi kendine oda sıcaklığına gelmesi sağlanan tepkime karışımı eter çözücüsü ile (3 x 200 mL) ekstrakte edilip toplanan organik fazlar bir kere 50 mL su ile yıkanıp sodyum sülfat üzerinde kurutuldu. Organik fazların düşük vakum altında uçurulmasından sonra alınan yağımsı ham ürün elüent olarak 9:1 hekzan-etil asetat çözücü sistemi kullanılarak flaş kolon kromatografisi ile saflaştırıldı ve siklobutenon **13** izole edildi (5.90 g, % 85 verim).

Bileşik 13 için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ 7.56-7.51 (m, 2H), 7.40-7.29 (m, 3H), 4.96 (septet, 1H, *J* = 6.0 Hz), 4.91 (septet, 1H, *J* = 6.0 Hz), 2.81 (s, 1H), 1.41 (d, 3H, *J* = 6.0 Hz), 1.35 (d, 3H, *J* = 6.0 Hz), 1.34 (d, 3H, *J* = 6.0 Hz), 1.30 (d, 3H, *J* = 6.0 Hz); IR (neat): 3570 (g), 2980 (o), 1768 (çk), 1620 (çk), 1318 (o) cm^{-1}. Bu spektroskopik data literatürde bu madde için verilen değerlerle uyum içersindedir (Liebeskind, 1988).

4-İzopropoxy-3-fenil-3-siklobuten-1,2-dion (11D): Siklobutenon **13** (5.90 g, 21.50 mmol) 150 mL CH_2Cl_2 içinde çözülüp bu karışıma 8 damla derişik HCl ilave edildi ve oluşan

tepkime karışımı oda sıcaklığında yaklaşık olarak 20-30 dakika kadar karıştırıldı (Tepkime rutin TLC ile takip edilip siklobutenon **3**'ün TLC deki spotunun kaybolmasından sonra karıştırma işlemine son verildi). Tepkime karışımı sonra içinde 50 mL doymuş sulu sodyum bikarbonat bulunan bir ayırma hunisine döküldü ve organik ürün CH_2Cl_2 (3 x 200 mL) ile ekstrakte edildi. Toplanan organik fazlar sodyum sülfat üzerinde kurutulup düşük vakumda uçuruldu. Oluşan viskoz yağımsı ürün flaş kolon kromatografisinde elüent olarak 9:1 hekzan-etil asetat çözücü sistemi kullanılarak saflaştırıldı ve siklobutendion **11B** (R_f = 0.26, 4:1 hekzan-etil asetat içinde) izole edildi (4.12 g, % 89 verim).

Bileşik 11D için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ 8.10-8.00 (m, 2H), 7.60-7.45 (m, 3H), 5.63 (septet, 1H, *J* = 6.0 Hz), 1.57 (d, 6H, *J* = 6.0 Hz); IR (CH_2Cl_2): 2986 (o), 1781 (çk), 1749 (çk), 1603 (çk), 1586 (çk), 1494 (s), 1397 (çk), 1342 (k), 1268 (k), 1086 (çk), 1016 (k), 905 (k), 777 (o), 692 (k) cm^{-1}. Bu spektroskopik data literatürde bu madde için verilen değerlerle uyum içersindedir (Liebeskind, 1988).

4-(Trimethylsiloxy)-2,3-diizopropoksi-4-metil-2-siklobuten-1-on (14): Devamlı argon altında tutulan ve ağzı septumla kapatılmış tek ağızlı 250 mL lik dibi yuvarlak bir balona sırasıyla diizopropil skuarat (**11A**) (2.5 g, 12.62 mmol) ve THF (25 mL) konulup balon karışımı -78 °C ye soğutuldu. Bu karışıma sonra metillityum ((10.1 ml 1.5 M diethyl ether solution, 15.15 mmol) 15 dakikalık bir süre içersinde şırınga ile damla damla ilave edildi ve tepkime karışımı -78 °C de 3 saat kadar karıştırıldı. Daha sonra oda sıcaklığına gelmesi sağlanan karışıma trimetilsilil klorür (3.2 ml, 25.24 mmol) ilave edildi ve oda sıcaklğında 1 saat süre ile karıştırıldı. Bu süre sonunda tepkime karışımına eter (150 mL) ilave edildi. Oluşan fazlar ayrıldı ve su fazı eter çözücüsü ile (3 x 50 mL) ekstrakte edildi. Toplanan organik fazlar Na_2SO_4 üzerinde kurutulup süzülüpdü ve rotavapta konsantre edildi. Elde edilen ham ürün aluminyum oksit ve elüent olarak 9:1 hekzan-etil asetat çözücü sistemi kullanılarak flaş kolon kromatografisi yardımı ile saflaştırıldı ve siklobutenon **14** (R_f = 0.43 in 9:1 hekzan/etil asetat) izole edildi (2.41 g, % 67 verim).

Bileşik 14 için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ 4.79 (septet, 1H, *J* = 6.1 Hz), 1.36 (s, 3H), 1.34 (d, 3H, *J* = 6.3 Hz), 1.32 (d, 3H, *J* = 6.3 Hz), 1.21 (d, 3H, *J* = 6.1 Hz) d, 1.18 (3H, *J* = 6.1 Hz), 0.07 (s, 9H); ^{13}C-NMR ($CDCl_3$): δ 185.8 (C), 167.5 (C), 129.1 (C), 83.1 (C), 75.2 (CH), 71.7 (CH), 21.5 (CH_3), 21.4 (CH_3), 21.1 (CH_3), 21.0 (CH_3), 19.5 (CH_3), 0.29 (CH_3); IR (CH_2Cl_2): 2980 (m), 2933 (w), 1768 (m), 1625 (vs), 1465 (w), 1385 (m), 1322 (s), 1251 (m), 1142 (m), 1100 (m), 1036 (w), 995 (s), 924 (m), 910 (m), 865 (w), 845 (w) cm^{-1}. Bu spektroskopik data literatürde bu madde için verilen değerlerle uyum içersindedir (Liebeskind, 1988).

3,4-Dimetil-3-siklobuten-1,2-dion (11C): Argon altında tutulan ve ağzı septumla kapatılmış tek ağızlı dibi yuvarlak bir balona sırasıyla 4-(trimethylsiloxy)-2,3-diizopropoksi-4-metil-2-siklobuten-1-on (**14**) (2.41 g, 8.42 mmol) ve THF (25 mL) konulup balon karışımı -78 °C ye soğutuldu. Bu karışıma sonra metillityum (6.73 mL 1.5 M dietil eter çözücüsü, 10.1 mmol) 15 dakikalık bir süre içersinde şırınga ile damla damla ilave edildi ve tepkime karışımı -78 °C de 3 saat kadar karıştırıldı. Daha sonra tepkime karışımına su (25 mL) ilave edildi ve karışımın oda sıcaklığına gelmesi sağlandı. Karışım eter çözücüsü ile (3 x 50 mL) ekstrakte edilip toplanan organik fazlar Na_2SO_4 üzerinde kurutulup süzüldü ve rotavapta konsantre edildi. Elde edilen ham ürün **15** 20 mL CH_2Cl_2 içinde çözülüp bu karışıma 4 damla derişik HCl ilave edildi ve oluşan tepkime karışımı oda sıcaklığında yaklaşık olarak 20-30 dakika kadar karıştırıldı (Tepkime rutin TLC ile takip edilip siklobuten **15**'in TLC deki spotunun kaybolmasından sonra karıştırma işlemine son verildi). Tepkime karışımı sonra içinde 20 mL doymuş sulu sodyum bikarbonat bulunan bir ayırma hunisine döküldü ve organik ürün CH_2Cl_2 (2 x 50 mL) ile ekstrakte edildi. Toplanan organik fazlar sodyum sülfat üzerinde kurutulup düşük vakumda uçuruldu. Oluşan ham ürün silika jel kullanılarak flaş kolon kromatografisi ile elüent olarak 9:1 hekzan-etil asetat çözücü sistemi kullanılarak saflaştırıldı ve siklobutendion **11C** (R_f = 0.23, 4:1 hekzan-etil asetat içinde) izole edildi (0.47 g, % 51 verim).

Bileşik 11C için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ 2.31 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 200.2 (C), 199.7 (C), 11.3 (CH_3); IR (CH_2Cl_2): 1774 (vs), 1606 (vs), 1428 (w), 1383 (m), 1307 (m), 1179 (w), 1106 (w), 1017 (m), 908 (w), 682 (w) cm^{-1}. Bu spektroskopik data literatürde bu madde için verilen değerlerle uyum içersindedir (Liebeskind, 1988).

3,4-Difenil-3-siklobuten-1,2-dion (11E): Bir geri soğutucuya bağlanmış dibi yuvarlak bir balona sırasıyla skuarik asit (**9**) (3.0 g, 26 mmol), tiyonil klorür (6.42 g, 54 mmol) ve DMF (katalitik miktarda, 1-2 damla) konuldu ve oluşan karışım 2.5 saat süre ile 65 ^{o}C'de ısıtıldı. Daha sonra 3,4-diklor-3-siklobuten-1,2-dion (**10**) bileşiğinin oluştuğu tepkime karışımı oda sıcaklığına soğutuldu ve bunun üzerine 20 mL benzen ve aluminyum klorür (8.50 g, 63.8 mmol) konuldu ve oluşan karışım oda sıcaklığında 24 saat süre karıştırıldı. Bu süre sonunda balon karışımı yavaşca bir beher içerisindeki buzlu suya ilave edildi. Daha sonra karışım eter çözücüsü (3 x 100 mL) ile ekstrakte edilip toplanan organik fazlar Na_2SO_4 üzerinde kurutulup süzüldü ve düşük vakumda konsantre edildi. Elde edilen ham ürün silika jel kullanılarak flaş kolon kromatografisi ile elüent olarak 9:1 hekzan-etil asetat çözücü sistemi kullanılarak saflaştırıldı ve siklobutendion **11E** (R_f = 0.35, 9:1 hekzan-etil asetat içinde) izole edildi (3.99 g, % 64 verim).

Bileşik 11E için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ 8.02 (d, 4H, *J* = 7.5 Hz), 7.56-7.47 (m, 6H). Bu spektroskopik data literatürde bu madde için verilen değerlerle uyum içersindedir (Yang, 1999).

Genel Prosedür 1: 4-(Ferroseniletinil)-2-siklobutenon türevleri 17A/B/C/D/E'nin sentezi (Tablo 1): Etinilferrosen (**8A**) bileşiğinin (1.2 mmol) -78 ^{o}C'de ve argon altındaki THF (15 mL) çözeltisine *n*-butillityum (1.1 mmol) 15 dakikalık bir süre içinde şırınga ile eklendi ve bu sıcaklıkta 30 dakika karıştırıldı. Bu süre sonunda tepkime ortamında oluşan ferroseniletinillityum kanula vasıtasıyla argon altında ve -78 ^{o}C'deki uygun siklobutendion (**11A**/**B**/**C**/**D**/**E**) (1 mmol) bileşiğinin THF (15 mL) çözeltisine transfer edildi. Oluşan karışım

aynı sıcaklıkta 3 saat daha karıştırıldı ve bu karışıma su (10 mL) eklendi. Tepkime karışımı oda sıcaklığına geldikten sonra eterle (3 x 50 mL) ektrakte edildi. Toplanan organik fazlar Na_2SO_4 üzerinde kurutulup düşük vakumda uçurulmasından sonra flaş kolon kromatografi yöntemiyle silika jel'de sırasıyla 9:1 ve 4:1 hekzan/etil asetat elüenti kullanılarak saflaştırıldı.

4-Ferroseniletinil-4-hidroksi-2,3-diizopropoksi-2-siklobutenon (17A): Etinilferrosen (**8A**) (0.25 g, 1.2 mmol), *n*-butillityum (0.45 mL 2.5 M hekzan-eter çözücüsü, 1.1 mmol) ve siklobutenon **11A** (200 mg, 1 mmol) kullanılarak Genel Prosedür 1'e göre sentezlendi. Tepkime sonunda elde edilen ham ürün flaş kolon kromatografi ile saflaştırıldı ve iki fraksiyon izole edildi. Birinci fraksiyon (R_f = 0.40 in 9:1 hekzan-etil asetat içinde) 2-ferroseniliden-4,5-diizopropoksi-4-siklopenten-1,3-dion (**1A**) olarak tanımlandı (20 mg, % 5 verim). İkinci fraksiyon (R_f = 0.30, 4:1 hekzan-etil asetat içinde) 4-ferroseniletinil-4-hidroksi-2,3-diizopropoksi-2-siklobutenon (**17A**) olarak tanımlandı (265 mg, % 65 verim).

Bileşik 1A için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ 7.22 (s, 1H), 4.91, 5.50 (septet, 1H, *J*=6.2 Hz), 5.44 (septet, 1H, *J*=6.2 Hz), 5.14 (pseudo t, 2H), 4.56 (pseudo t, 2H), 4.13 (s, 5H), 1.36 (d, 6H, *J*=6.2 Hz), 1.34 (d, 6H, *J*=6.2 Hz); ^{13}C-NMR ($CDCl_3$): δ 187.7 (C), 186.1 (C), 150.9 (C), 147.1 (C), 139.0 (CH), 121.6 (C), 76.2 (C), 75.1 (CH), 74.9 (CH), 74.2 (CH), 73.4 (CH), 70.4 (CH), 23.4 (CH_3), 23.4 (CH_3); IR (CH_2Cl_2): 2982 (w), 2933 (vw), 1668 (vs), 1620 (vs), 1461 (vw), 1377 (m), 1305 (s), 1102 (s), 1029 (s) cm^{-1}; MS (FAB): 409 ($[M+1]^+$, 36), 408 ($[M]^+$, 75), 367 (12), 366 (9), 324 (41), 301 (27), 259 (100), 186 (9), 135 (10), 121 (8), 103 (18), 85 (18), 45 (34); HRMS (FAB): Calc. for $C_{22}H_{24}FeO_4$: 408.1024. Found: 408.1035.

Bileşik 17A için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ 5.01 (septet, 1H, *J*=6.1 Hz), 4.87 (septet, 1H, *J*=6.1 Hz), 4.41 (s, 2H), 4.17 (s, 7H), 3.10 (br s, 1H), 1.45 (d, 3H, *J*=6.1 Hz), 1.43 (d, 3H, *J*=6.1 Hz), 1.29 (d, 3H, *J*=6.1 Hz), 1.28 (d, 3H, *J*=6.1 Hz); ^{13}C-NMR ($CDCl_3$): δ 181.0 (C), 164.8 (C), 134.3 (C), 88.3 (C), 80.0 (C), 79.7 (C), 78.2 (CH), 74.5 (CH), 72.0 (CH), 70.4 (CH), 69.3 (CH), 63.9(C), 23.1(CH_3), 22.9(CH_3); IR (CH_2Cl_2): 3358 (w), 3323 (br), 2975

(m), 2928 (m), 2223 (w), 1773 (s), 1627 (vs), 1458 (w), 1388 (s), 1322 (s), 1261 (s), 1096 (s) cm^{-1}; MS (FAB): 409 ($[M+1]^+$, 55), 408 ($[M]^+$, 100), 395 (11), 324 (19), 311 (6), 213 (18), 199 (7), 137 (17), 136 (16), 43 (11), 41 (9); HRMS (FAB): Calc. for $C_{22}H_{24}FeO_4$: 408.1034. Found: 408.1024.

4-Ferroseniletinil-4-hidroksi-3-izopropoksi-2-metil-2-siklobutenon (17B): Etinil-ferrosen (**8A**) (0.25 g, 1.2 mmol), *n*-butillityum (0.45 mL 2.5 M hekzan-eter çözücüsü, 1.1 mmol) ve siklobutenon **11B** (155 mg, 1 mmol) kullanılarak Genel Prosedür 1'e göre sentezlendi. Tepkime sonunda elde edilen ham ürün flaş kolon kromatografi ile saflaştırıldı ve üç fraksiyon izole edildi. Birinci fraksiyon (R_f = 0.58 in 9:1 hekzan-etil asetat içinde) *E*-2-ferroseniliden-4-izopropoksi-5-metil-4-siklopenten-1,3-dion (***E*-1B**) olarak tanımlandı (69 mg, % 19 verim). İkinci fraksiyon (R_f = 0.45 in 9:1 hekzan-etil asetat içinde) *Z*-2-ferroseniliden-4-izopropoksi-5-metil-4-siklopenten-1,3-dion (***Z*-1B**) olarak tanımlandı (33 mg, % 9 verim). Üçüncü fraksiyon (R_f = 0.25, 4:1 hekzan-etil asetat içinde) 4-ferroseniletinil-4-hidroksi-2-metil-3-izopropoksi-2-siklobutenon (**17B**) olarak tanımlandı (124 mg, % 34 verim).

Bileşik *E*-1B için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ 7.25 (s, 1H), 5.61 (septet, 1H, *J*=6.1 Hz), 5.21 (s, 2H), 4.60 (s, 2 H), 4.15 (s, 5H), 1.93 (s, 3H), 1.36 (d, 6H, *J*=6.1 Hz); ^{13}C-NMR ($CDCl_3$): δ 191.0 (C), 189.5 (C), 163.8 (C), 140.7 (CH), 134.7 (C), 122.6 (C), 76.1 (C), 74.5 (CH)(Fc CH and isopropoxy CH overlaps), 73.8 (CH), 70.5 (CH), 23.7 (CH_3), 7.6 (CH_3); IR (CH_2Cl_2): 2980(vw) , 1712 (w), 1668 (vs), 1605 (vs), 1492 (w), 1376 (vs), 1319 (m), 1247 (w), 1127 (m), 1088 (s), 1024 (s) cm^{-1}; MS (FAB): 365 ($[M+1]^+$, 73), 364 ($[M]^+$, 100), 322 (35), 299 (16), 257 (100), 155 (12), 119 (26), 85 (30); HRMS (FAB): Calc. for $C_{20}H_{20}FeO_3$: 364.0762. Found: 364.0775

Bileşik *Z*-1B için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ 7.39 (s, 1H), 5.58 (septet, 1H, *J*=6.1 Hz), 5.20 (s, 2H), 4.64 (s, 2H), 4.18 (s, 5H), 1.97 (s, 3H), 1.40 (d, 6H, *J*=6.1 Hz); ^{13}C-NMR ($CDCl_3$): δ 192.3 (C), 188.0 (C), 166.3 (C), 141.0 (CH), 130.0 (C), 122.2 (C), 76.2 (C), 74.6 (CH), 74.4 (CH), 73.8 (CH), 70.5 (CH), 23.6 (CH_3), 7.5 (CH_3).

Bileşik 17B için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ 5.08 (septet, 1H, *J*=6.1 Hz), 4.40 (s, 2H), 4.17 (s, 7H), 3.34 (s, 1H), 1.68 (s, 3H), 1.50 (d, 3H, *J*=6.1 Hz), 1.46 (d, 3H, *J*=6.1 Hz); ^{13}C-NMR ($CDCl_3$): δ 187.6 (C), 180.3 (C), 124.9 (C), 89.4 (C), 84.2 (C), 79.9 (C), 77.7 (CH), 72.0 (CH), 70.4 (CH), 69.4 (CH), 63.8 (C), 23.4 (CH_3), 23.1 (CH_3), 7.0 (CH_3); IR (CH_2Cl_2): 3559 (w), 3308 (br), 2976 (w), 2926 (vw), 2223 (w), 1764 (s), 1623 (vs), 1463 (vw), 1397 (s), 1312 (s), 1097 (s) cm^{-1}; MS (FAB): 365 ($[M+1]^+$, 81), 364 ($[M]^+$, 87), 347 (82), 322 (100), 305 (25), 295 (16), 257 (96), 255 (13), 210 (11), 183 (6), 157 (8), 121 (20), 85 (9); HRMS (FAB): Calc. for $C_{20}H_{20}FeO_3$: 364.0762. Found: 364.0775.

4-Ferroseniletinil-4-hidroksi-2,3-dimetil-2-siklobutenon (17C): Etinilferrosen (**8A**) (0.25 g, 1.2 mmol), *n*-butillityum (0.45 mL 2.5 M hekzan-eter çözücüsü, 1.1 mmol) ve siklobutenon **11C** (110 mg, 1 mmol) kullanılarak Genel Prosedür 1'e göre sentezlendi. Tepkime sonunda elde edilen ham ürün flaş kolon kromatografi ile saflaştırıldı ve iki fraksiyon izole edildi. Birinci fraksiyon (R_f = 0.49 in 9:1 hekzan-etil asetat içinde) 2-ferroseniliden-4,5-dimetil-4-siklopenten-1,3-dion (**1C**) olarak tanımlandı (70 mg, % 22 verim). İkinci fraksiyon (R_f = 0.17, 4:1 hekzan-etil asetat içinde) 4-ferroseniletinil-4-hidroksi-2,3-dimetil-2-siklobutenon (**17C**) olarak tanımlandı (112 mg, % 38 verim).

Bileşik 1C için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ 7.40 (s, 1H), 5.24 (pseudo t, 2H, *J* = 1.7 Hz), 4.64 (pseudo t, 2H, *J* = 1.7 Hz), 4.13 (s, 5H), 2.02 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 194.7 (C), 193.5 (C), 154.0 (C), 150.2 (C), 142.8 (CH), 121.1 (C), 76.0 (C), 74.6 (CH), 74.1 (CH), 70.6 (CH), 9.6 (CH_3), 9.6 (CH_3); IR (CH_2Cl_2): 2982 (w), 2933 (vw), 1712 (w), 1668 (vs), 1604 (vs), 1492 (w), 1376 (vs), 1326 (s), 1248 (m), 1126 (s), 1088 (s), 1023 (s) cm^{-1}; MS (FAB): 321 ($[M+1]^+$, 51), 320 ($[M]^+$, 100), 256 (23), 255 (84), 149 (14), 121(9), 85 (9), 69 (6); HRMS (FAB): Calc. for $C_{18}H_{16}FeO_2$: 320.0500. Found: 320.0514

Bileşik 17C için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ 4.39 (s, 2H), 4.18 (s, 2H), 4.16 (s, 5H), 2.58(s,1H), 2.20 (s, 3H), 1.75 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 189.8 (C), 177.2 (C), 151.1 (C), 89.2 (C), 87.1 (C), 80.4 (C), 72.0 (CH), 70.6 (CH), 69.4 (CH), 63.9 (C), 10.9 (CH_3),

8.4 (CH_3); IR (CH_2Cl_2): 3568 (w), 3392 (br), 3099 (vw), 2960 (vw), 2219 (m), 1765 (vs), 1637 (s), 1432 (w), 1380 (w), 1303 (w), 1259 (w), 1176 (w), 1099 (m) cm^{-1}; MS (FAB): 321 ($[M+1]^+$, 68), 320 ($[M]^+$, 100), 303 (76), 275 (50), 255 (90), 253 (11), 183 (10), 155 (14), 121 (13), 115 (4), 85 (5); HRMS (FAB): Calc. for $C_{18}H_{16}FeO_2$: 320.0500. Found: 320.0489.

2-Fenil-4-ferroseniletinil-4-hidroksi-3-izopropoksi-2-siklobutenon (17D): Etinil-ferrosen (**8A**) (0.25 g, 1.2 mmol), *n*-butillityum (0.45 mL 2.5 M hekzan-eter çözücüsü, 1.1 mmol) ve siklobutenon **11D** (216 mg, 1 mmol) kullanılarak Genel Prosedür 1'e göre sentezlendi. Tepkime sonunda elde edilen ham ürün flaş kolon kromatografi ile saflaştırıldı. Tek fraksiyon (R_f = 0.48 in 4:1 hekzan-etil asetat içinde) izole edildi ve siklobutenon **17D**'nin düzenlenme ürünü olan *E*-2-ferroseniliden-4-fenil-5-izopropoksi-4-siklopenten-1,3-dion (***E*-1D**) olarak tanımlandı (149 mg, % 35 verim).

Bileşik *E*-1D için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ 7.97 (d, 2H, *J* = 7.2 Hz), 7.45-7.35 (m, 4H), 5.91 (septet, 1H, *J* = 6.1 Hz), 5.27 (pseudo t, 2H, *J* = 1.7 Hz), 4.65 (pseudo t, 2H, *J* = 1.7 Hz), 4.15 (s, 5H), 1.41 (d, 6H, *J* = 6.1 Hz); ^{13}C-NMR ($CDCl_3$): δ 189.6 (C), 189.4 (C), 162.7 (C), 142.3 (CH), 132.1 (C), 130.0 (CH), 129.4 (CH), 128.5 (CH), 122.7 (C), 76.1 (C), 75.7 (CH), 74.9 (CH), 74.1 (CH), 70.6 (CH), 23.8 (CH_3) two of the tertiary carbons match with each other; IR (CH_2Cl_2): 2982 (vw), 1712 (w), 1668 (vs), 1617 (s), 1593 (m), 1491 (vw), 1376 (m), 1322 (w), 1268 (m), 1126 (w), 1088 (w), 1023 (m) cm^{-1}; MS (FAB): 427 ($[M+1]^+$, 87), 426 ($[M]^+$, 100), 384 (47), 361 (12), 320 (30), 319 (91), 245 (4), 189 (4), 149 (4), 121 (5), 85 (4); HRMS (FAB): Calc. for $C_{25}H_{22}FeO_3$: 426.0918. Found: 426.0908.

2,3-Difenil-4-ferroseniletinil-4-hidroksi-2-siklobutenon (17E): Etinilferrosen (**8A**) (0.25 g, 1.2 mmol), *n*-butillityum (0.45 mL 2.5 M hekzan-eter çözücüsü, 1.1 mmol) ve siklobutenon **11E** (234 mg, 1 mmol) kullanılarak Genel Prosedür 1'e göre sentezlendi. Tepkime sonunda elde edilen ham ürün flaş kolon kromatografi ile saflaştırıldı. Tek fraksiyon (R_f = 0.42 in 4:1 hekzan-etil asetat içinde) izole edildi ve siklobutenon **17E**'nin düzenlenme

ürünü olan 2-ferroseniliden-4,5-difenil-4-siklopenten-1,3-dion (**1E**) olarak tanımlandı (165 mg, % 37 verim).

Bileşik 1E için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ 7.69 (s, 1H), 7.46-7.40 (m, 4H), 7.38-7.31 (m, 6H), 5.34 (s, 2H), 4.72 (s, 2H), 4.21 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 193.2 (C), 192.0 (C), 151.0 (C), 147.5 (C), 146.2 (CH), 130.6 (CH), 130.5 (CH), 130.3 (C), 130.1 (C), 130.0 (CH), 128.8 (CH), 76.2 (C), 75.1 (CH), 74.8 (CH), 70.8 (CH); IR (CH_2Cl_2): 2982 (w), 2933 (vw), 1712 (w), 1668 (vs), 1616 (vs), 1606 (vs), 1492 (w), 1376 (vs), 1326 (m), 1248 (w), 1127 (m), 1088 (s), 1024 (s) cm^{-1}; MS (FAB): 446 ($[M+2]^+$, 39), 445 ($[M+1]^+$, 100), 444 ($[M]^+$, 81), 379 (67), 377 (9), 323 (6), 279 (5), 202 (5), 135 (8), 119 (15), 85 (13); HRMS (FAB, $[M]^+$): Calc. for $C_{28}H_{20}FeO_2$: 444.0813. Found: 444.0825; HRMS (FAB, $[M+1]^+$): Calc. for $C_{28}H_{21}FeO_2$: 445.0891. Found: 445.0914.

Genel Prosedür 2: 2-Ferroseniliden-4-siklopenten-1,3-dion (1A/B/C/D/E) bileşiklerinin Metot A'ya göre sentezi (Tablo 2): Siklobutenon bileşiği **17** (0.5 mmol) 15 mL dioksan içerisinde çözüldü ve oluşan karışım argon altında geri soğutucu altında 4 saat süre ile kaynatıldı. Daha sonra karışım oda sıcaklığına soğutuldu ve organik çözücü düşük vakumda uçuruldu. Elde edilen ham ürün karışımı flaş kolon kromatografi yöntemi ile silika jel üzerinden 9:1 hekzan/etil asetat elüenti kullanılarak saflaştırıldı. Bu tepkimelerden Tablo 2'de verilen ürünler izole edildi (ürün verimleri için Tablo 2'ye bakınız).

Genel Prosedür 3: 2-Ferroseniliden-4-siklopenten-1,3-dion (1A/B/C/D/E) bileşiklerinin Metot B'ye göre sentezi (Tablo 3): Siklobutenon bileşiği **17** (0.1 mmol) 0.5 g silika jel ile karıştırılıp bir saat camı üzerinde etüv içerisinde 125 ^{o}C'de 15 dakika süre ile ısıtıldı. Daha sonra karışım oda sıcaklığına soğutuldu ve elde edilen ham ürün karışımı flaş kolon kromatografi yöntemi ile silika jel üzerinden 9:1 hekzan/etil asetat elüenti kullanılarak saflaştırıldı. Bu tepkimelerden Tablo 3'te verilen ürünler izole edildi (ürün verimleri için Tablo 3'e bakınız).

Genel Prosedür 4: 2-Ferroseniliden-4-siklopenten-1,3-dion (1A/B/C/D/E) bileşiklerinin Metot C'ye göre sentezi (Tablo 4): Siklobutenon bileşiği **17** (0.5 mmol) ve silika jel (0.5 g) 10 mL etil asetat içerisine konuldu ve oluşan karışım oda sıcaklığında argon altında 24 saat süre ile karıştırıldı. Daha sonra organik çözücü düşük vakumda uçuruldu ve elde edilen ham ürün karışımı flaş kolon kromatografi yöntemi ile silika jel üzerinden 9:1 hekzan/etil asetat elüenti kullanılarak saflaştırıldı. Bu tepkimelerden Tablo 4'de verilen ürünler izole edildi (ürün verimleri için Tablo 4'e bakınız).

2-Ferroseniliden-4,5-diizopropoksi-4-siklopenten-1,3-dion (1A) için spektroskopik data: (R_f = 0.40, 9:1 hekzan-etil asetat içinde); ^{1}H-NMR ($CDCl_3$): δ 7.22 (s, 1H), 4.91, 5.50 (septet, 1H, *J*=6.2 Hz), 5.44 (septet, 1H, *J*=6.2 Hz), 5.14 (pseudo t, 2H), 4.56 (pseudo t, 2H), 4.13 (s, 5H), 1.36 (d, 6H, *J*=6.2 Hz), 1.34 (d, 6H, *J*=6.2 Hz); ^{13}C-NMR ($CDCl_3$): δ 187.7 (C), 186.1 (C), 150.9 (C), 147.1 (C), 139.0 (CH), 121.6 (C), 76.2 (C), 75.1 (CH), 74.9 (CH), 74.2 (CH), 73.4 (CH), 70.4 (CH), 23.4 (CH_3), 23.4 (CH_3); IR (CH_2Cl_2): 2982 (w), 2933 (vw), 1668 (vs), 1620 (vs), 1461 (vw), 1377 (m), 1305 (s), 1102 (s), 1029 (s) cm^{-1}; MS (FAB): 409 ($[M+1]^+$, 36), 408 ($[M]^+$, 75), 367 (12), 366 (9), 324 (41), 301 (27), 259 (100), 186 (9), 135 (10), 121 (8), 103 (18), 85 (18), 45 (34); HRMS (FAB): Calc. for $C_{22}H_{24}FeO_4$: 408.1024. Found: 408.1035.

(2*E*)-2-Ferroseniliden-4-izopropoksi-5-metil-4-siklopenten-1,3-dion (*E*-1B) için spektroskopik data: (R_f = 0.58, 9:1 hekzan-etil asetat içinde); ^{1}H-NMR ($CDCl_3$): δ 7.25 (s, 1H), 5.61 (septet, 1H, *J*=6.1 Hz), 5.21 (s, 2H), 4.60 (s, 2 H), 4.15 (s, 5H), 1.93 (s, 3H), 1.36 (d, 6H, *J*=6.1 Hz); ^{13}C-NMR ($CDCl_3$): δ 191.0 (C), 189.5 (C), 163.8 (C), 140.7 (CH), 134.7 (C), 122.6 (C), 76.1 (C), 74.5 (CH)(Fc CH and isopropoxy CH overlaps), 73.8 (CH), 70.5 (CH), 23.7 (CH_3), 7.6 (CH_3); IR (CH_2Cl_2): 2980(vw) , 1712 (w), 1668 (vs), 1605 (vs), 1492 (w), 1376 (vs), 1319 (m), 1247 (w), 1127 (m), 1088 (s), 1024 (s) cm^{-1}; MS (FAB): 365 ($[M+1]^+$,

73), 364 ($[M]^+$, 100), 322 (35), 299 (16), 257 (100), 155 (12), 119 (26), 85 (30); HRMS (FAB): Calc. for $C_{20}H_{20}FeO_3$: 364.0762. Found: 364.0775

(2*Z*)-2-Ferroseniliden-4-izopropoksi-5-metil-4-siklopenten-1,3-dion (*Z*-1B) için spektroskopik data: (R_f = 0.45, 9:1 hekzan-etil asetat içinde); ^{1}H-NMR ($CDCl_3$): δ 7.39 (s, 1H), 5.58 (septet, 1H, *J*=6.1 Hz), 5.20 (s, 2H), 4.64 (s, 2H), 4.18 (s, 5H), 1.97 (s, 3H), 1.40 (d, 6H, *J*=6.1 Hz); ^{13}C-NMR ($CDCl_3$): δ 192.3 (C), 188.0 (C), 166.3 (C), 141.0 (CH), 130.0 (C), 122.2 (C), 76.2 (C), 74.6 (CH), 74.4 (CH), 73.8 (CH), 70.5 (CH), 23.6 (CH_3), 7.5 (CH_3).

2-Ferroseniliden-4,5-dimetil-4-siklopenten-1,3-dion (1C) için spektroskopik data: (R_f = 0.49, 4:1 hekzan-etil asetat içinde); ^{1}H-NMR ($CDCl_3$): δ 7.40 (s, 1H), 5.24 (pseudo t, 2H, *J* = 1.7 Hz), 4.64 (pseudo t, 2H, *J* = 1.7 Hz), 4.13 (s, 5H), 2.02 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 194.7 (C), 193.5 (C), 154.0 (C), 150.2 (C), 142.8 (CH), 121.1 (C), 76.0 (C), 74.6 (CH), 74.1 (CH), 70.6 (CH), 9.6 (CH_3), 9.6 (CH_3); IR (CH_2Cl_2): 2982 (w), 2933 (vw), 1712 (w), 1668 (vs), 1604 (vs), 1492 (w), 1376 (vs), 1326 (s), 1248 (m), 1126 (s), 1088 (s), 1023 (s) cm^{-1}; MS (FAB): 321 ($[M+1]^+$, 51), 320 ($[M]^+$, 100), 256 (23), 255 (84), 149 (14), 121(9), 85 (9), 69 (6); HRMS (FAB): Calc. for $C_{18}H_{16}FeO_2$: 320.0500. Found: 320.0514

(2*E*)-2-Ferroseniliden-4-izopropoksi-5-fenil-4-siklopenten-1,3-dione (*E*-1D) için spektroskopik data: (R_f = 0.48, 4:1 hekzan-etil asetat içinde); ^{1}H-NMR ($CDCl_3$): δ 7.97 (d, 2H, *J* = 7.2 Hz), 7.45-7.35 (m, 4H), 5.91 (s, 1H, *J* = 6.1 Hz), 5.27 (pseudo t, 2H, *J* = 1.7 Hz), 4.65 (pseudo t, 2H, *J* = 1.7 Hz), 4.15 (s, 5H), 1.41 (d, 6H, *J* = 6.1 Hz); ^{13}C-NMR ($CDCl_3$): δ 189.6 (C), 189.4 (C), 162.7 (C), 142.3 (CH), 132.1 (C), 130.0 (CH), 129.4 (CH), 128.5 (CH), 122.7 (C), 76.1 (C), 75.7 (CH), 74.9 (CH), 74.1 (CH), 70.6 (CH), 23.8 (CH_3) two of the tertiary carbons match with each other; IR (CH_2Cl_2): 2982 (vw), 1712 (w), 1668 (vs), 1617 (s), 1593 (m), 1491 (vw), 1376 (m), 1322 (w), 1268 (m), 1126 (w), 1088 (w), 1023 (m) cm^{-1}; MS (FAB):

427 ([M+1]$^+$, 87), 426 ([M]$^+$, 100), 384 (47), 361 (12), 320 (30), 319 (91), 245 (4), 189 (4), 149 (4), 121 (5), 85 (4); HRMS (FAB): Calc. for $C_{25}H_{22}FeO_3$: 426.0918. Found: 426.0908.

(2*E*)-2Ferroseniliden-4,5-difenil-4-siklopenten-1,3-dion (1E) için spektroskopik data: (R_f = 0.42, 4:1 hekzan-etil asetat içinde); ^{1}H-NMR ($CDCl_3$): δ 7.69 (s, 1H), 7.46-7.40 (m, 4H), 7.38-7.31 (m, 6H), 5.34 (s, 2H), 4.72 (s, 2H), 4.21 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 193.2 (C), 192.0 (C), 151.0 (C), 147.5 (C), 146.2 (CH), 130.6 (CH), 130.5 (CH), 130.3 (C), 130.1 (C), 130.0 (CH), 128.8 (CH), 76.2 (C), 75.1 (CH), 74.8 (CH), 70.8 (CH); IR (CH_2Cl_2): 2982 (w), 2933 (vw), 1712 (w), 1668 (vs), 1616 (vs), 1606 (vs), 1492 (w), 1376 (vs), 1326 (m), 1248 (w), 1127 (m), 1088 (s), 1024 (s) cm^{-1}; MS (FAB): 446 ([M+2]$^+$, 39), 445 ([M+1]$^+$, 100), 444 ([M]$^+$, 81), 379 (67), 377 (9), 323 (6), 279 (5), 202 (5), 135 (8), 119 (15), 85 (13); HRMS (FAB, [M]$^+$): Calc. for $C_{28}H_{20}FeO_2$: 444.0813. Found: 444.0825; HRMS (FAB, [M+1]$^+$): Calc. for $C_{28}H_{21}FeO_2$: 445.0891. Found: 445.0914.

2,3-Diizopropoksi-5-ferrosenil-[1,4]-benzokinon (18A) için spektroskopik data: (R_f = 0.41, 9:1 hekzan-etil asetat içinde); ^{1}H-NMR ($CDCl_3$): δ 6.67 (s, 1H), 4.91 (s, 2H), 4.89 (septet, 1 H, *J* = 6.2 Hz), 4.74 (septet, 1 H, *J* = 6.2 Hz), 4.57 (s, 2H), 4.13 (s, 5H), 1.33 (d, 6H, *J* = 6.2 Hz), 1.31 (d, 6H, *J* = 6.2 Hz); ^{13}C-NMR ($CDCl_3$): δ 184.8 (C), 184.0 (C), 147.2 (C), 145.8 (C), 125.5 (CH), 76.3 (C), 76.2(CH), 72.5(CH), 70.9 (CH), 70.1 (CH), 23.1 (CH_3), 23.0 (CH_3) two tertiary carbons match with each other; IR (CH_2Cl_2): 2975 (w), 2928 (vw), 1637 (s), 1567 (s), 1453 (w), 1378 (w), 1261 (vs), 1181(m), 1101 (s), 1049 (w) cm^{-1}; MS (FAB): 410 ([M+2H]$^+$, 100), 409 ([M+1H]$^+$, 14), 408 ([M]$^+$, 16), 368 (18), 325 (23), 291 (29), 259 (24), 213 (17), 186 (8), 121 (8); HRMS (FAB, [M]$^+$): Calc. for $C_{22}H_{24}FeO_4$: 408.1024. Found: 408.1015; HRMS (FAB, [M+2H]$^+$): Calc. for $C_{22}H_{26}FeO_4$: 410.1180. Found: 410.1199.

2-İzopropoksi-3-metil-5-ferrosenil-[1,4]-benzokinon (18B) için spektroskopik data: (R_f = 0.59, 9:1 hekzan-etil asetat içinde); ^{1}H NMR ($CDCl_3$): δ 6.67 (s, 1H), 4.92 (s, 2H), 4.92

(septet, 1 H, *J*=6.1 Hz), 4.58 (s, 2 H), 4.12 (s, 5H), 1.96 (s, 3H), 1.31 (d, 6H, *J*=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 187.7 (C), 183.5 (C), 154.8 (C), 148.8 (C), 131.0 (C), 126.0 (CH), 76.6 (C), 76.3 (CH), 72.5 (CH), 70.9 (CH), 70.30 (CH), 23.4 (CH_3), 9.9 (CH_3); IR (CH_2Cl_2):2975 (vw), 2928 (vw), 1646 (vs), 1580 (vs), 1453 (vw), 1378 (w), 1317 (vw), 1256 (s), 1181 (vs), 1096 (s), 1016 (m) cm^{-1}; MS (FAB): 366 ($[M+2H]^+$, 75), 365 ($[M+1H]^+$, 68), 364 ($[M]^+$, 100), 323 (27), 322 (19), 257 (45), 229 (9), 186 (3), 149 (6), 121 (6), 85 (4); HRMS (FAB, $[M]^+$): Calc. for $C_{20}H_{20}FeO_3$: 364.0762. Found: 364.0775; HRMS (FAB, $[M+2H]^+$): Calc. for $C_{20}H_{22}FeO_3$: 366.0918. Found: 366.0912.

2,3-Dimetil-5-ferrosenil-[1,4]-benzokinon (18C) için spektroskopik data: (R_f = 0.53, 9:1 hekzan-etil asetat içinde); ^1H NMR ($CDCl_3$): δ 6.80 (s, 1H), 4.91 (s, 2H), 4.55 (s, 2H), 4.11 (s, 5H), 1.94 (s, 3H), 1.93 (s, 3H); IR (CH_2Cl_2): 3680 (w), 3586 (vw), 2919 (w), 1641 (vs), 1623 (s), 1585 (s), 1453 (w), 1378 (w), 1317 (m), 1247 (s), 1030 (m) cm^{-1}; MS (FAB): 322 ($[M+2H]^+$, 72), 321 ($[M+1H]^+$, 88), 320 ($[M]^+$, 100), 287 (5), 255 (42), 253 (4), 209 (4), 177 (4), 155 (14), 119 (24), 85 (23); HRMS (FAB, $[M]^+$): Calc. for $C_{18}H_{16}FeO_2$: 320.0500. Found: 320.0489; HRMS (FAB, $[M+2H]^+$): Calc. for $C_{18}H_{18}FeO_2$: 322.0656. Found: 322.0667.

Pentakarbonil[(siklopropil)metoksimetilen]krom (23A). Ağzı septumla kapatılmış, argon altında tutulan ve -78 °C ye soğutulmuş tek ağızlı dibi yuvarlak 100 ml lik bir balon içinde dietil eter (25 mL) içinde bulunan siklopropil bromür (0.8 mL, 10 mmol) üzerine *tert*-butillityum reaktifi (9.1 mL 2.2 M çözeltisi, 20 mmol) 15 dakikalık bir süre içersinde şırınga ile damla damla ilave edildi ve oluşan karışım aynı sıcaklıkta 30 dakika süre ile karıştırıldı. Daha sonra bu karışım ağzı septumla kapatılmış tek ağızlı dibi yuvarlak 250 ml lik bir balon içinde bulunan, devamlı argon altında tutulan ve 0 °C ye soğutulmuş krom hekzakarbonilin (2.2 g, 10 mmol) dietil eter (50 ml) içindeki süspansiyonuna kanula yardımıyla transfer edildi. Oluşan tepkime karışımının oda sıcaklığına gelmesi beklenildikten sonra bu sıcaklıkta 2 saat süre ile karıştırıldı. Bu süre sonunda tepkime karışımı tekrar 0 °C ye soğutuldu ve bu karışıma metil

triflormetansulfonat (metil triflat) (3.4 mL, 30 mmol) eklendi. Bu karışım tekrar oda sıcaklığında 20 dakika karıştırıldı. Tepkime karışımı içerisinde 50 ml doymuş sulu sodyum bikarbonat çözeltisi bulunan ayırma hunisine aktarıldıktan sonra hekzan çözücüsü (3 x 100 ml) ile ekstrakte edildi. Toplanan organik faz ayırma hunisi içersinde önce 50 ml su ile sonra da 50 ml doymuş sulu sodyum klorür çözeltisi ile yıkandı. Yıkanan organik faz sodyum sülfat üzerinde kurutulduktan sonra düşük vakum altında uçuruldu. Elde edilen ham ürün elüent olarak hekzanın kullanıldığı flaş kolon kromatoğrafisi ile saflaştırıldı. Toplanan sarı fraksiyon uçurulduktan sonra krom karben kompleksi **23A** % 74 verim ile elde edilmiştir.

Kompleks 23A için spektroskopik data: ^{1}H NMR ($CDCl_3$): □ 4.65 (s, 3 H); 3.46 (m, 1 H), 1.36 (m, 2 H), 1.18 (m, 2 H). Bu spektroskopik data bu karben kompleksi için literatürdeki verilerle uyum içerisindedir (Tumer, 1992).

Propinilferrosen (8B): –78 °C de argon altında 30 mL THF içindeki etinilferrosen (**8A**) (400 mg, 1.9 mmol) bileşiğinin çözeltisine *n*-BuLi (1.3 mL 1.6 M hekzan çözeltisi, 2.0 mmol) eklendi. Elde edilen karışım 30 dk –78 °C de karıştırıldı ve bu süre sonunda metil iyodür (0.5 mL, 8 mmol) ortama eklendi. Daha sonra tepkime karışımı oda sıcaklığına getirildi ve 1 saat süre ile karıştırıldı. Karışım 0 °C de su ile hidrolize edildikten sonra CH_2Cl_2 ile ekstraksiyon yapıldı. Su ile yıkandıktan ve kurutulduktan sonra çözücü uçuruldu ve kalan kısım flaş kromatoğrafi ile hekzan kullanılarak saflaştırıldı. Oluşan turuncu renkli propinilferrosen (**8B**) % 96 verimle izole edildi.

Bileşik 8B için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ4.35 (s, 2 H), 4.25 (s, 2H), 4.20 (s, 5H), 1.95 (s, 3H). Bu spektroskopik data literatürde bu madde için verilen değerlerle uyum içersindedir (Doisneau, 1992).

(3-Fenilpropinil)ferrosen (8C): –78 °C de argon altında 30 mL THF içindeki etinilferrosen (**8A**) (400 mg, 1.9 mmol) bileşiğinin çözeltisine *n*-BuLi (1.3 mL 1.6 M hekzan çözeltisi, 2.0 mmol) eklendi. Elde edilen karışım 30 dk –78 °C de karıştırıldı ve bu süre

sonunda benzil bromür (0.9 mL, 8 mmol) ortama eklendi. Daha sonra tepkime karışımı oda sıcaklığına getirildi ve 1 saat süre ile karıştırıldı. Karışım 0 °C de su ile hidrolize edildikten sonra CH_2Cl_2 ile ekstraksiyon yapıldı. Su ile yıkandıktan ve kurutulduktan sonra çözücü uçuruldu ve kalan kısım flaş kromatoğrafi ile hekzan kullanılarak saflaştırıldı. Oluşan turuncu renkli (3-fenilpropinil)ferrosen (**8C**) % 56 verimle izole edildi.

Bileşik 8C için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ7.40-7.38 (m, 2H), 7.34-7.30 (m, 3H), 4.39 (s, 2H), 4.19 (s, 5H), 4.15 (s, 2H), 3.71 (s, 2H). Bu spektroskopik data literatürde bu madde için verilen değerlerle uyum içersindedir (Doisneau, 1992).

(Feniletinil)ferrosen (**8D**): Argon altındaki CuI (23 mg, 0.12 mmol), PPh_3 (62 mg, 0.24 mmol), K_2CO_3 (493 mg, 3.57 mmol) ve DMF (4.8 mL) karışımına iodobenzene (0.3 mL, 2.38 mmol) ve etinilferrosen (**8A**) (500 mg, 2.38 mmol) eklendi. Oluşan karışım 120 °C de 16 saat süre ile geri soğutucu altında kaynatıldı. Oluşan tepkim ekarışımı oda sıcaklığına getirildikten sonra eter ve su kullanılarak ekstraksiyon yapıldı. Organik kısım magnezyum sülfat ile kurutuldu. Elde edilen ham ürün silika jel üzerinden flaş kolon kromatografisi ile hekzan kullanılarak saflaştırıldı. Oluşan turuncu renkteki (feniletinil)ferrosen (**8D**) % 47 verimle izole edildi.

Bileşik 8D için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ7.46-7.40 (m, 2H), 7.26-7.19 (m, 3H), 4.43 (s, 2H), 4.16 (s, 5H), 4.14 (s, 2H). Bu spektroskopik data literatürde bu madde için verilen değerlerle uyum içersindedir (Zora, 2006; Okuro, 1993).

Diferroseniletin (8E): 35 mL klorbenzen içindeki propinilferrosen (**8B**) (430 mg, 1.920 mmol), $Mo(CO)_6$ (25 mg, 0.096 mmol) ve 2-florofenol (0.176 mL, 1.920 mmol) karışımı argon altında ısıtıcı kullanılarak 2 saat süre ile geri soğutucu altında kaynatıldı. Çözücü uçurulduktan sonra kalan kısım silika jel üzerinden flaş kromatografisi ile hekzan kullanılarak saflaştırıldı. Oluşan turuncu renkteki diferroseniletin (**8E**) % 26 verimle izole edildi.

Bileşik 8E için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ4.43 (s, 2H), 4.20 (s, 5H), 4.18 (s, 2H). Bu spektroskopik data literatürde bu madde için verilen değerlerle uyum içersindedir (Sashuk, 2004; Kotora, 2003).

Genel Prosedür 5: Metal karben kompleksi 23A'nın ferrosenil alkin bileşikleri 8 ile tepkimesi (Tablo 5): Bir ucuna geri soğutucu diğerine septum takılmış ve argon altında bulunan iki ağızlı dibi yuvarlak bir balona 20 mL of %1 sulu dioksan çözücü konuldu ve bu çözücü geri soğutucu altında kaynatılmaya başlandı. Daha sonra kaynayan bu çözücü üzerine metal karben kompleksi **23A** (0.5 mmol) ve ferrosenil alkin **8** (0.75 mmol) bileşiğinin 10 mL dioksan içindeki çözeltisi bir şırında pompası yardımı damla damla 2 saatlik bir süre içersinde ilave edildi. İlave sonunda oluşan tepkime karışımı 6 saat daha ısıtıldı. Bu süre sonunda tepkime karışımı oda sıcaklığına soğutuldu ve organik çözücü düşük vakum altında döner bir buharlaştırıcıda uçuruldu. Daha sonra ham ürün 50 mL etil asetat içinde çözüldü ve selit (celite) üzerinden süzüldü. Organik çözücü tekrar düşük vakum altında döner bir buharlaştırıcıda uçuruldu. Elde edilen ham ürün flaş kolon kromatografi yöntemiyle silika jel üzerinde sırasıyla 19:1'den 1:1 oranına kadar hekzan/etil asetat elüenti kullanılarak saflaştırıldı. Bu tepkimelerden Tablo 5'de verilen ürünler izole edildi (ürün verimleri için Tablo 5'e bakınız).

5-Ferrocenyl-5-hydroxy-3-methoxy-2-cyclopentenone (25A): ^{1}H-NMR ($CDCl_3$): δ 5.29 (s, 1H), 4.28 (s, 1H), 4.19 (br s, 8H), 3.89 (s, 3H), 3.08 (d, 1H, *J*=17.4 Hz), 2.97 (d, 1H, *J*=17.4 Hz), 2.82 (s, 1H); IR (CH_2Cl_2): 3053 (s), 2982 (m), 2682 (vw), 2302 (w), 1692 (w), 1599 (w), 1402 (s), 1270 (vs), 896 (s), 733 (vs) cm^{-1}; MS (EI): 312 (M^+, 100), 294, 247, 229, 213, 185, 169, 145, 129, 121, 56; HRMS: calcd for $C_{16}H_{16}FeO_3$: 312.0449. Found 312.0452. Anal. Calcd for $C_{16}H_{16}FeO_3$: C, 61.57; H, 5.17. Found: C, 61.21; H, 5.42.

(4*R*(*S*),5*R*(*S*))-5-Ferrocenyl-5-hydroxy-3-methoxy-4-methyl-2-cyclopentenone (25B): ^{1}H-NMR ($CDCl_3$): δ 5.21 (s, 1H), 4.20 (s, 1H), 4.18 (s, 5H), 4.14 (br s, 3H), 3.87 (s, 3H), 3.13 (q, 1H, *J*=7.3 Hz), 2.76 (s, 1H), 1.27 (d, 3H, *J*=7.3 Hz); ^{13}C-NMR ($CDCl_3$): δ 203.7 (C), 192.4 (C), 99.1 (CH), 92.7 (C), 77.2 (C), 68.9 (CH), 68.4 (CH), 68.3 (CH), 66.2 (CH), 65.9 (CH), 58.7 (CH_3), 48.0 (CH), 13.7 (CH_3); IR (CH_2Cl_2): 3056 (s), 2983 (w), 2298 (vw), 1691 (w), 1582 (s), 1418 (w), 1270 (vs), 892 (w), 744 (vs) cm^{-1}; MS (EI): 326 (M^+, 100), 308, 261, 243, 213, 186, 185, 149, 129, 84; HRMS: calcd for $C_{17}H_{18}FeO_3$: 326.0605. Found 326.0602.

(4*R*(*S*),5*R*(*S*))-4-Benzyl-5-ferrocenyl-5-hydroxy-3-methoxy-2-cyclopentenone (25C): ^{1}H-NMR ($CDCl_3$): δ 7.36-7.26 (m, 3H), 7.22-7.10 (m, 2H), 5.20 (s, 1H), 4.13 (s, 3H), 4.10 (s, 5H), 4.01 (s, 1H), 3.82 (s, 3H), 3.36 (dd, 1H, *J*=7.8, 4.4 Hz), 3.12 (dd, 1H, *J*=13.8, 7.8 Hz), 2.97 (dd, 1H, *J*=13.8, 4.4 Hz), 2.76 (s, 1H); IR (CH_2Cl_2): 3050 (s), 2977 (m), 2685 (vw), 2303 (w), 1699 (w), 1591 (m), 1420 (s), 1267 (vs), 898 (s), 746 (vs) cm^{-1}; MS (EI): 402 (M^+, 100), 384, 337, 319, 311, 246, 228, 213, 189, 170, 121, 91; HRMS: calcd for $C_{23}H_{22}FeO_3$: 402.0918. Found 402.0916.

(4*R*(*S*),5*R*(*S*))-5-Ferrocenyl-5-hydroxy-3-methoxy-4-phenyl-2-cyclopentenone (25E): ^{1}H-NMR ($CDCl_3$): δ 7.11-6.99 (m, 3H), 6.71 (d, 2H, *J*=6.7 Hz), 5.55 (s, 1H), 4.30 (s, 1H), 4.24 (s, 5H), 3.96 (s, 1H), 3.83 (s, 3H), 3.76 (s, 1H), 3.73 (s, 1H), 3.50 (s, 1H), 3.12 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 203.0 (C), 186.8 (C), 135.3 (C), 129.4 (CH), 127.6 (CH), 126.9 (CH), 102.8 (CH), 91.1 (C), 81.9 (C), 68.8 (CH), 68.4 (CH), 67.6 (CH), 67.3 (CH), 66.3 (CH), 58.9 (CH), 58.6 (CH_3); IR (CH_2Cl_2): 3056 (s), 2987 (m), 2681 (w), 2303 (w), 1704 (s), 1597 (vs), 1421 (m), 1354 (m), 1267 (vs), 1171 (m), 1020 (m), 902 (m), 825 (m), 748 (vs) cm^{-1}; MS (EI): 388 (M^+, 100), 372, 323, 305, 234, 213, 178, 175, 165, 121, 93; HRMS: calcd for $C_{22}H_{20}FeO_3$: 388.0762. Found 388.0761. Anal. Calcd for $C_{22}H_{20}FeO_3$: C, 67.82; H, 5.19. Found: C, 68.06; H, 5.43.

(4*R*(*S*),5*R*(*S*))-4,5-Diferrocenyl-5-hydroxy-3-methoxy-2-cyclopentenone (25F): ^{1}H-NMR ($CDCl_3$): δ 5.37 (s, 1H), 4.30 (s, 1H), 4.25 (s, 7H), 4.20 (s, 7H), 4.14 (s, 1H), 3.99 (s, 1H), 3.98 (s, 3H), 3.88 (s, 1H), 2.74 (s, 1H), 2.13 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 202.6 (C), 187.8 (C), 101.2 (CH), 93.4 (C), 84.5 (C), 78.9 (C), 69.5 (CH), 69.4 (CH), 69.2 (CH), 68.6 (CH), 68.5 (CH), 68.4 (CH), 68.0 (CH), 66.9 (CH), 66.7 (CH), 66.1 (CH), 58.6 (CH_3), 54.6 (CH); IR (CH_2Cl_2): 3055 (s), 2983 (m), 2682 (vw), 2301 (w), 1698 (w), 1596 (w), 1423 (m), 1270 (vs), 898 (m), 762 (vs) cm^{-1}; MS (EI): 496 (M^+, 100), 478, 358, 293, 283, 248, 213, 199, 129, 121; HRMS: calcd for $C_{26}H_{24}Fe_2O_3$: 496.0424. Found 496.0426.

(4*S*(*R*),5*R*(*S*))-5-Ferrocenyl-5-hydroxy-3-methoxy-4-methyl-2-cyclopentenone (26B): ^{1}H-NMR ($CDCl_3$): δ 5.30 (s, 1H), 4.33 (s, 5H), 4.30 (s, 1H), 4.18 (s, 1H), 4.16 (s, 1H), 3.81 (s, 3H), 3.75 (s, 1H), 3.06 (q, 1H, *J*=7.3 Hz), 2.98 (s, 1H), 0.74 (d, 3H, *J*=7.3 Hz); ^{13}C-NMR ($CDCl_3$): δ 203.5 (C), 189.3 (C), 100.5 (CH), 80.4 (C), 77.2 (C), 69.6 (CH), 69.4 (CH), 67.9 (CH), 67.8 (CH), 66.4 (CH), 58.5 (CH_3), 46.8 (CH), 12.0 (CH_3); IR (CH_2Cl_2): 3052 (m), 2981 (w), 1700 (m), 1591 (s), 1463 (vw), 1354 (w), 1268 (vs), 1104 (vw), 896 (vw), 819 (vw), 746 (vs) cm^{-1}; MS (EI): 326 (M^+, 100), 308, 262, 261, 243, 213, 185, 131, 113, 78; HRMS: calcd for $C_{17}H_{18}FeO_3$: 326.0605. Found 326.0607.

2-Ferrocenyl-4-methoxy-3-methyl-2-cyclopentenone (27B): ^{1}H-NMR ($CDCl_3$): δ 4.79 (s, 1H), 4.69 (s, 1H), 4.30 (s, 2H), 4.27 (dd, 1H, *J* = 6.0, 2.1 Hz), 4.08 (s, 5H), 3.40 (s, 3H), 2.69 (dd, 1H, *J*=18.0, 6.0 Hz), 2.39 (dd, 1H, *J*=18.0, 2.1 Hz), 2.21 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 202.9 (C), 164.3 (C), 139.0 (C), 79.9 (CH), 74.8 (C), 69.4 (CH), 68.9 (CH), 68.8 (CH), 68.6 (CH), 56.9 (CH_3), 41.1 (CH_2), 15.6 (CH_3); IR (CH_2Cl_2): 3053 (s), 2981 (m), 2683 (vw), 2300 (w), 1703 (w), 1414 (m), 1267 (vs), 1097 (vw), 896 (m), 755 (vs) cm^{-1}; MS (EI): 310 (M^+, 100), 279, 258, 227, 212, 186, 163, 129, 121, 91, 55; HRMS: calcd for $C_{17}H_{18}FeO_2$: 310.0656. Found 310.0659.

2-Ferrocenyl-4-methoxy-3-phenyl-2-cyclopentenone (27E): ^{1}H-NMR ($CDCl_3$): δ 7.45-7.35 (m, 5H), 4.89 (dd, 1H, *J*=5.9, 1.5 Hz), 4.58 (s, 1H), 4.39 (s, 1H), 4.34 (s, 1H), 4.26 (s, 1H), 4.09 (s, 5H), 3.47 (s, 3H), 2.80 (dd, 1H, *J*=18.2, 5.9 Hz), 2.57 (dd, 1H, *J*=18.2, 1.5 Hz); IR (CH_2Cl_2): 3050 (s), 2982 (m), 2679 (vw), 2307 (w), 1701 (w), 1420 (m), 1273 (vs), 901 (m), 751 (vs); MS (EI): 372 (M^+, 100), 356, 342, 291, 277, 249, 191, 165, 149, 121; HRMS: calcd for $C_{22}H_{20}FeO_2$: 372.0813. Found 372.0816.

2,3-Diferrocenyl-4-methoxy-2-cyclopentenone (27F): ^{1}H-NMR ($CDCl_3$): δ 4.90 (s, 2H), 4.85 (d, 1H, *J*=5.5 Hz), 4.55 (s, 1H), 4.46 (s, 2H), 4.43 (s, 1H), 4.37 (s, 1H), 4.25 (s, 1H), 4.14 (s, 5H), 4.08 (s, 5H), 3.45 (s, 3H), 2.69 (dd, 1H, *J*=5.5, 18.2 Hz), 2.51 (d, 1H, *J*=18.2 Hz); IR (CH_2Cl_2): 3051 (s), 2983 (m), 2683 (vw), 2306 (w), 1702 (w), 1420 (m), 1270 (vs), 899 (m), 748 (vs) cm^{-1}; MS (EI): 480 (M^+, 100), 478, 415, 355, 328, 300, 263, 240, 235, 178, 121; HRMS: calcd for $C_{26}H_{24}Fe_2O_2$: 480.0475. Found 480.0474.

4-Ferrocenyl-5-methyl-4-cyclopentene-1,3-dione (28B): ^{1}H-NMR ($CDCl_3$): δ 5.03 (s, 2H), 4.57 (s, 2H), 4.12 (s, 5H), 2.93 (s, 2H), 2.11 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 199.5 (C), 199.1 (C), 156.2 (C), 150.3 (C), 72.1 (C), 71.7 (CH), 70.5 (CH), 70.0 (CH), 41.8 (CH_2), 10.5 (CH_3); IR (KBr): 3131 (vw), 3096 (w), 2919 (w), 1732 (s), 1687 (vs), 1596 (vs), 1457 (s), 1332 (s), 1271 (vs), 1189 (s); MS (MALDI-TOF): 294 (M^+, 100), 292, 264, 242, 220, 219; HRMS: calcd for $C_{16}H_{14}FeO_2$: 294.0343. Found 294.0341.

4-Benzyl-5-ferrocenyl-4-cyclopentene-1,3-dione (28C): ^{1}H-NMR ($CDCl_3$): δ 7.33-7.27 (m, 2H), 7.25-7.10 (m, 3H), 4.98 (s, 2H), 4.56 (s, 2H), 4.03 (s, 5H), 3.97 (s, 2H), 3.02 (s, 2H); ^{13}C-NMR ($CDCl_3$): δ 199.4 (C), 199.2 (C), 157.7 (C), 151.2 (C), 136.8 (C), 128.8 (CH), 128.2 (CH), 126.7 (CH), 72.2 (CH), 71.7 (C), 70.8 (CH), 70.2 (CH), 42.1 (CH_2), 29.9 (CH_2); IR (KBr) 3134 (vw), 3096 (w), 2958 (vw), 1736 (m), 1694 (vs), 1594 (s), 1496 (m), 1455 (m), 1349 (m), 1352 (s), 1267 (s); MS (MALDI-TOF): 370 (M^+, 100), 368, 316, 301, 251, 250, 235, 195; HRMS: calcd for $C_{22}H_{18}FeO_2$: 370.0656. Found 370.0659.

4-Ferrocenyl-5-phenyl-4-cyclopentene-1,3-dione (28E): ^{1}H-NMR ($CDCl_3$): δ 7.45-7.33 (m, 3H), 7.31-7.22 (m, 2H), 4.66 (s, 2H), 4.48 (s, 2H), 4.08 (s, 5H), 3.11 (s, 2H); ^{13}C-NMR ($CDCl_3$): δ 199.1 (C), 197.8 (C), 156.5 (C), 150.2 (C), 130.7 (C), 129.3 (CH), 128.9 (CH), 128.6 (CH), 72.1 (CH), 71.5 (C), 71.2 (CH), 70.5 (CH), 42.6 (CH_2); IR (KBr) 3139 (vw), 3094 (w), 3078 (w), 2956 (vw), 1731 (s), 1696 (vs), 1582 (s), 1489 (m), 1440 (m), 1382 (m), 1352 (s), 1257 (s), 1186 (m); MS (MALDI-TOF): 356 (M^+, 100), 354, 294, 250, 242; HRMS: calcd for $C_{21}H_{16}FeO_2$: 356.0500. Found 356.0503.

4,5-Diferrocenyl-4-cyclopentene-1,3-dione (28F): ^{1}H-NMR ($CDCl_3$): δ 4.79 (s, 4H), 4.47 (s, 4H), 4.06 (s, 10H), 3.03 (s, 2H); ^{13}C-NMR ($CDCl_3$): δ 197.6 (C), 152.2 (C), 73.5 (C), 71.1 (CH), 70.5 (CH), 70.3 (CH), 43.2 (CH_2); IR (CH_2Cl_2): 3050 (s), 2985 (m), 2301 (w), 1725 (m), 1690 (vs), 1574 (w), 1475 (m), 1417 (m), 1381 (w), 1311 (w), 1275 (vs), 1211 (w), 1156 (vw), 1108 (w), 902 (m), 825 (w), 748 (vs) cm^{-1}; MS (EI): 464 (M^+, 100), 399, 396, 341, 277, 232, 186, 165, 152, 121; HRMS: calcd for $C_{25}H_{20}Fe_2O_2$: 464.0162. Found 464.0159.

1,1'-Diferrocenyl-4,4'-dimethoxy-5,5'-dimethylbicyclopentyl-3,3'-diene-2,2'-dione (29B): ^{1}H-NMR ($CDCl_3$): δ 4.78 (s, 1H), 4.75 (s, 1H), 4.35 (s, 1H), 4.34 (s, 1H), 4.11 (s, 5H), 3.16 (s, 3H), 2.62 (d, 1H, *J*=18.9 Hz), 2.40 (d, 1H, *J*=18.9 Hz), 2.20 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 202.0 (C), 163.9 (C), 142.2 (C), 87.6 (C), 74.1 (C), 69.8 (CH), 69.4 (CH), 69.3 (CH), 69.2 (CH), 68.4 (CH), 50.9 (CH_3), 40.8 (CH_2), 15.6 (CH_3); IR (CH_2Cl_2): 3054 (m), 2989 (vw), 2365 (vw), 1704 (w), 1423 (vw), 1273 (vs), 1105 (vw), 896 (vw), 749 (vs) cm^{-1}; MS (EI): 618 (M^+, 100), 556, 492, 310, 309, 294, 229, 199, 159, 121, 77; HRMS: calcd for $C_{34}H_{34}Fe_2O_4$: 618.1156. Found 618.1153.

3,4-Diferrocenyl-4-hydroxy-2-cyclopentenone (30A): ^{1}H-NMR ($CDCl_3$): δ 6.07 (s, 1H), 4.70 (s, 1H), 4.69 (s, 1H), 4.61 (s, 1H), 4.46 (s, 1H), 4.43 (s, 1H), 4.25 (s, 7H), 4.00 (s, 1H), 3.96 (s, 5H), 3.37 (d, 1H, *J*=17.7 Hz), 2.99 (d, 1H, *J*=17.7 Hz), 2.67 (s, 1H); IR (CH_2Cl_2):

3052 (s), 2981 (m), 2685 (vw), 2306 (w), 1686 (w), 1583 (w), 1426 (m), 1268 (vs), 899 (m), 741 (vs) cm^{-1}; MS (EI): 466 (M^+, 100), 450, 383, 328, 300, 233, 186, 178, 152, 121; HRMS: calcd for $C_{25}H_{22}Fe_2O_2$: 466.0319. Found 466.0320.

4-Cyclopropyl-2,3-diferrocenyl-4-methoxy-2-cyclobutenone (31F): ^{1}H-NMR ($CDCl_3$): δ 5.02 (s, 1H), 4.92 (s, 1H), 4.89 (s, 1H), 4.64 (s, 1H), 4.62 (s, 1H), 4.40 (s, 1H), 4.39 (s, 1H), 4.30 (s, 5H), 4.18 (s, 5H), 4.06 (s, 1H), 3.28 (s, 3H), 1.44 (m, 1H), 0.85 (m, 1H), 0.71 (m, 1H), 0.63 (m, 1H), 0.39 (m, 1H); IR (CH_2Cl_2): 3054 (m), 1743 (s), 1695 (m), 1606 (m), 1483 (m), 1261 (vs), 1103 (m), 916 (m), 821 (m), 755 (vs) cm^{-1}; MS (EI): 506.1 (M^+), 478.2, 464.1, 394.1, 328.0, 273.1, 215.1, 197.0, 186.0, 149.0; HRMS (EI): calcd for $C_{28}H_{26}Fe_2O_2$: 506.0632. Found 506.0634.

3-Ferrocenyl-2-methylpropenal (32B): ^{1}H-NMR ($CDCl_3$): δ 9.44 (s, 1H), 7.07 (s, 1H), 4.59 (t, 2H, *J*=1.8 Hz), 4.48 (t, 2H, *J*=1.8 Hz), 4.14 (s, 5H), 1.91 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 194.5 (C), 151.4 (CH), 134.8 (C), 72.0 (C), 71.4 (CH), 71.1 (CH), 69.7 (CH), 10.6 (CH_3); IR (CH_2Cl_2): 3052 (s), 2976 (m), 2682 (vw), 2411 (vw), 2307 (w), 1669 (vs), 1616 (vs), 1420 (m), 1259 (vs), 896 (m), 751 (vs) cm^{-1}; MS (EI): 254 (M^+, 100), 242, 226, 213, 189, 185, 160, 134, 121, 81; HRMS: calcd for $C_{14}H_{14}FeO$: 254.0394. Found 254.0392.

Pentakarbonil[(siklopropil)metoksimetilen]molibden (23B). Ağzı septumla kapatılmış, argon altında tutulan ve -78 °C ye soğutulmuş tek ağızlı dibi yuvarlak 100 ml lik bir balon içinde dietil eter (25 mL) içinde bulunan siklopropil bromür (0.8 mL, 10 mmol) üzerine *tert*-butillityum reaktifi (9.1 mL 2.2 M çözeltisi, 20 mmol) 15 dakikalık bir süre içersinde şırınga ile damla damla ilave edildi ve oluşan karışım aynı sıcaklıkta 30 dakika süre ile karıştırıldı. Daha sonra bu karışım ağzı septumla kapatılmış tek ağızlı dibi yuvarlak 250 ml lik bir balon içinde bulunan, devamlı argon altında tutulan ve 0 °C ye soğutulmuş molibden hekzakarbonilin (2.6 g, 10 mmol) dietil eter (50 ml) içindeki süspansiyonuna kanula

yardımıyla transfer edildi. Oluşan tepkime karışımının oda sıcaklığına gelmesi beklenildikten sonra bu sıcaklıkta 2 saat süre ile karıştırıldı. Bu süre sonunda tepkime karışımı tekrar 0 °C ye soğutuldu ve bu karışıma metil triflormetansulfonat (metil triflat) (3.4 mL, 30 mmol) eklendi. Bu karışım tekrar oda sıcaklığında 20 dakika karıştırıldı. Tepkime karışımı içerisinde 50 ml doymuş sulu sodyum bikarbonat çözeltisi bulunan ayırma hunisine aktarıldıktan sonra hekzan çözücüsü (3 x 100 ml) ile ekstrakte edildi. Toplanan organik faz ayırma hunisi içersinde önce 50 ml su ile sonra da 50 ml doymuş sulu sodyum klorür çözeltisi ile yıkandı. Yıkanan organik faz sodyum sülfat üzerinde kurutulduktan sonra düşük vakum altında uçuruldu. Elde edilen ham ürün elüent olarak hekzanın kullanıldığı flaş kolon kromatoğrafisi ile saflaştırıldı. Toplanan sarı fraksiyon uçurulduktan sonra molibden karben kompleksi **23B** % 70 verim ile elde edilmiştir.

Kompleks 23B için spektroskopik data: ^{1}H NMR ($CDCl_3$): □ 4.54 (s, 3 H); 3.45 (m, 1 H), 1.39 (m, 2 H), 1.19 (m, 2 H). Bu spektroskopik data bu karben kompleksi için literatürdeki verilerle uyum içerisindedir (Herndon, 1993).

Genel Prosedür 6: Metal karben kompleksi 23B'nin ferrosenil alkin bileşikleri 8A/B/C/D/E ile tepkimesi (Tablo 6): Metal karben kompleksi **23B** (0.5 mmol) ile ferrosenil alkin **8** (0.75 mmol) bileşiğinin 30 mL THF içindeki çözeltisi üzerine geri soğutucu takılmış ve argon altında bulunan dibi yuvarlak bir balon içerisinde 5 saat süre ile kaynatıldı. Bu süre sonunda tepkime karışımı oda sıcaklığına soğutuldu ve organik çözücü düşük vakum altında döner bir buharlaştırıcıda uçuruldu. Elde edilen ham ürün flaş kolon kromatografi yöntemiyle silika jel üzerinde sırasıyla 19:1'den 9:1 oranına kadar hekzan/etil asetat elüenti kullanılarak saflaştırıldı. Bu tepkimelerden Tablo 6'da verilen ürünler izole edildi (ürün verimleri için Tablo 6'ya bakınız).

2-Ferrocenyl-4-methoxy-3-methyl-2,4-cycloheptadienone (3B): ^{1}H-NMR ($CDCl_3$): δ 5.13 (t, 1H, *J*=7.3 Hz), 4.41 (s, 2H), 4.28 (s, 2H), 4.08 (s, 5H), 3.49 (s, 3H), 2.86 (pseudo t,

2H, *J*=6.4 Hz), 2.36 (pseudo q, 2H, *J*=6.8), 1.93 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 206.1 (C), 158.1 (C), 137.7 (C), 132.2 (C), 98.5 (CH), 79.3 (C), 69.9 (CH), 69.6 (CH), 68.9 (CH), 54.6 (CH_3), 51.6 (CH_2), 20.1 (CH_2), 16.5 (CH_3); IR (CH_2Cl_2): 3052 (s) 1683 (s), 1629 (m), 1422 (m), 1362 (m), 1272 (vs), 1258 (vs), 1203 (m), 1130 (m), 1105 (m) cm^{-1}; MS (EI): 336.2 (M^+), 334.2, 308.2, 293.1, 255.0, 227.0, 199.1, 186.0, 153.1, 129.1, 121.0, 115.1; HRMS (EI): calcd for $C_{19}H_{20}FeO_2$: 336.0813. Found: 336.0816.

3-Benzyl-2-ferrocenyl-4-methoxy-2,4-cycloheptadienone (3C): ^{1}H-NMR ($CDCl_3$): δ 7.34-7.28 (m, 3H), 7.19 (m, 2H), 5.13 (t, 1H, *J*=7.3 Hz), 4.41 (t, 2H, *J*=1.8 Hz), 4.25 (t, 2H, *J*=1.8 Hz), 4.08 (s, 5H), 3.80 (s, 2H), 3.36 (s, 3H), 2.98 (pseudo t, 2H, *J*=6.7 Hz), 2.45 (pseudo q, 2H, *J*=7.0 Hz); ^{13}C-NMR ($CDCl_3$): δ 205.7 (C), 157.1 (C), 139.8 (C), 139.5 (C), 133.5 (C), 128.4 (CH), 128.1 (CH), 125.9 (CH), 99.8 (CH), 78.3 (C), 69.6 (CH), 69.3 (CH), 69.1 (CH), 54.6 (CH_3), 51.7 (CH_2), 35.2 (CH_2), 20.3 (CH_2); IR (CH_2Cl_2): 3056 (vs), 2981 (m), 2682 (w), 2301 (m), 1688 (s), 1627 (m), 1424 (vs), 1260 (vs), 1049 (m), 902 (s) cm^{-1}; MS (EI): 412.2 (M^+), 398.2, 384.2, 370.2, 331.1, 318.1, 303.1, 275.1, 253.1, 217.1, 213.0, 186.1, 151.2, 137.1, 121.0; HRMS (EI): calcd for $C_{25}H_{24}FeO_2$: 412.1126. Found: 412.1130.

2-Ferrocenyl-4-methoxy-3-phenyl-2,4-cycloheptadienone (3E): ^{1}H-NMR (acetone-d_6): δ 7.25 (m, 3H), 7.05 (m, 2H), 5.46 (t, 3H, *J*=7.3 Hz), 4.16 (t, 2H, *J*=1.8 Hz), 4.09 (s, 5H), 3.87 (t, 2H, *J*=1.8 Hz), 3.38 (s, 3H), 3.03 (pseudo t, 2H, *J*=6.5 Hz), 2.64 (pseudo q, 2H, *J*=6.5 Hz); ^{13}C-NMR (acetone-d_6): δ 204.6 (C), 157.6 (C), 139.1 (C), 138.7 (C), 133.7 (C), 129.5 (CH), 127.9 (CH), 127.1 (CH), 100.4 (CH), 77.5 (C), 69.3 (CH), 69.2 (CH), 69.0 (CH), 54.1 (CH_3), 51.5 (CH_2), 20.4 (CH_2); IR (CH_2Cl_2): 3049 (vs), 2988 (s), 2680 (m), 2521 (w), 2407 (w), 2298 (s), 1682 (s), 1418 (m), 1259 (vs), 1158 (w), 900 (vs) cm^{-1}; MS (EI): 398.2 (M^+), 370.2, 339.2, 317.1, 303.1, 261.1, 226.1, 202.1, 186.1, 165.1, 127.2, 119.1; HRMS (EI): calcd for $C_{24}H_{22}FeO_2$: 398.0969. Found: 398.0972.

2,3-Diferrocenyl-4-methoxy-2,4-cycloheptadienone (3F): ^{1}H-NMR ($CDCl_3$): δ 5.09 (t, 1H, *J*=7.4 Hz), 4.21 (s, 2H), 4.17 (s, 2H), 4.12 (s, 2H), 4.11 (s, 5H), 4.08 (s, 5H), 3.98 (s, 2H), 3.64 (s, 3H), 2.91 (pseudo t, 2H, *J*=6.4 Hz), 2.44 (q, 2H, *J*=6.9 Hz); IR (CH_2Cl_2): 3054 (vs), 2989 (s), 2682 (m), 2406 (w), 2304 (m), 1700 (s), 1418 (s), 1266 (vs), 1102 (w), 897 (s) cm^{-1}; MS (EI): 506.2 (M^+), 438.1, 394.1, 362.2, 308.1, 242.1, 186.0, 113.1; HRMS (EI): calcd for $C_{28}H_{26}Fe_2O_2$: 506.0632. Found: 506.0635.

2-Ferrocenyl-3-methyl-2-cycloheptene-1,4-dione (52B): ^{1}H-NMR ($CDCl_3$): δ 4.49 (s, 2H), 4.43 (s, 2H), 4.16 (s, 5H), 2.83 (t, 2H, *J*=6.8 Hz), 2.61 (pseudo t, 2H, *J*=6.0 Hz), 2.04 (pseudo p, 2H, *J*=6.3 Hz), 2.01 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 204.2 (C), 203.4 (C), 148.6 (C), 134.8 (C), 77.3 (C), 70.7 (CH), 70.4 (CH), 69.7 (CH), 43.3 (CH_2), 41.7 (CH_2), 17.2 (CH_2), 16.4 (CH_3); IR (CH_2Cl_2): 3052 (s), 2985 (m), 1696 (s), 1663 (s), 1420 (m), 1272 (vs), 1260 (vs) 1108 (w), 895 (m) cm^{-1}; MS (EI): 322.1 (M^+), 320.1, 294.1, 277.1, 258.0, 257.0, 229.0, 199.0, 167.1, 149.1, 121.0; HRMS (EI): calcd for $C_{18}H_{18}FeO_2$: 322.0656. Found: 322.0659.

2-Benzyl-3-ferrocenyl-2-cycloheptene-1,4-dione (52C): ^{1}H-NMR ($CDCl_3$): δ 7.25 (t, *J*=7.2 Hz, 2H), 7.19-7.10 (m, 3H), 4.47 (s, 2H), 4.38 (s, 2H), 4.17 (s, 5H), 3.94 (s, 2H), 2.81 (t, 2H, *J*=5.8 Hz), 2.49 (pseudo t, 2H, *J*=5.3 Hz), 2.06 (pseudo p, 2H, *J*=5.3 Hz); IR (neat): 3104 (w), 2937 (w), 1696 (vs), 1664 (vs), 1578 (m), 1497 (w), 1259 (m), 1213 (s), 1107 (m), 1053 (m), 1004 (m) cm^{-1}; MS (EI): 398.2 (M+), 370.2, 333.1, 305.1, 275.1, 248.1, 234.1, 191.1, 178.1, 165.1, 121.0; HRMS (EI): calcd for $C_{24}H_{22}FeO_2$: 398.0969. Found: 398.0966.

2-Ferrocenyl-3-phenyl-2-cycloheptene-1,4-dione (52E): ^{1}H-NMR ($CDCl_3$): δ 7.36-7.29 (m, 3H), 7.02 (dd, 2H, *J*=7.8, 1.3 Hz), 4.19 (t, 2H, *J*=1.8 Hz), 4.08 (s, 5H), 3.80 (t, 3H, *J*=1.8 Hz), 2.90 (t, 2H, *J*=6.0 Hz), 2.58 (pseudo t, 2H, *J*=6.6 Hz), 2.15 (pseudo p, 2H, *J*=6.4 Hz); ^{13}C-NMR ($CDCl_3$): δ 197.6 (C), 156.3 (C), 137.8 (C), 135.3 (C), 130.2 (CH), 128.3 (CH), 127.1 (CH), 81.7 (C), 70.5 (CH), 70.2 (CH), 69.6 (CH), 38.2 (CH_2), 30.7 (CH_2), 22.7 (CH_2); IR

(CH_2Cl_2): 3048 (vs), 2985 (s), 2680 (w), 2305 (m), 1650 (s), 1578 (m), 1422 (s), 1358 (m), 1265 (vs), 1175 (m), 891 (s) cm^{-1}; MS (EI): 384.2 (M^+), 357.2, 356.2, 300.2, 291.1, 263.1, 235.1, 202.1, 178.1, 165.1, 152.1, 112.0; HRMS (EI): calcd for $C_{23}H_{20}FeO_2$: 384.0813. Found: 384.0816.

7-Ferrocenyl-7-hydroxy-5-methoxy-6-methyl-2,4-cycloheptadienone (53B): ^{1}H-NMR ($CDCl_3$): δ 6.58 (dd, 1H, *J*=12.4, 8.7 Hz), 5.99 (d, 1H, *J*=12.4 Hz), 4.94 (d, 1H, *J*=8.7 Hz), 4.39 (s, 1H), 4.23 (s, 1H), 4.13 (s, 1H), 4.07 (s, 6H), 3.92 (s, 1H), 3.42 (s, 3H), 2.53 (q, 1H, *J*=7.3 Hz), 1.12 (d, 3H, *J*=7.3 Hz); ^{13}C-NMR ($CDCl_3$): δ 198.2 (C), 174.2 (C), 140.4 (CH), 120.9 (CH), 95.4 (CH), 89.9 (C), 69.4 (C), 68.7 (CH), 67.6 (CH), 67.1 (CH), 66.9 (CH), 66.3 (CH), 55.6 (CH_3), 48.5 (CH), 11.1 (CH_3); MS (EI): 352.2 (M^+), 336.2, 322.1, 287.1, 269.1, 243.1, 242.1, 214.1, 213.0, 186.1, 139.1, 121.0, 115.1; HRMS (EI): calcd for $C_{19}H_{20}FeO_3$: 352.0762. Found: 352.0759.

Genel Prosedür 7: Ferrosenil pirazol türevleri 4 ve 62'nin sentezi (Tablo 7): Bir ucuna geri soğutucu diğerine septum takılmış ve argon altında bulunan iki ağızlı dibi yuvarlak bir balona 25 mL of dioksan çözücü konuldu ve bunun üzerine sırasıyla (2-formil-1-klorvinil)ferrosen (**7**) (340 mg, 1.0 mmol) ve hydrazin türevi veya tuzu (**61**) (3.0 mmol) ilave edildi. İlave sonunda oluşan tepkime karışımı önce 2.5 saat oda sıcaklığında karıştırıldıktan sonra 6 saat süre ile geri soğutucu altında 100 ^oC'de kaynatıldı. Bu süre sonunda tepkime karışımı oda sıcaklığına soğutuldu ve organik çözücü düşük vakum altında döner bir buharlaştırıcıda uçuruldu. Daha sonra ham ürün 20 mL su içinde çözüldü ve kloroform (3 x 30 mL) ile ekstrakte edildi. Toplanan kloroform fazı magnezyum sülfat üzerinde kurutulduktan sonra düşük vakum altında döner bir buharlaştırıcıda uçuruldu. Elde edilen ham ürün flaş kolon kromatografi yöntemiyle silika jel üzerinde sırasıyla 19:1'den 1:1 oranına kadar hekzan/etil asetat elüenti kullanılarak saflaştırıldı. Bu tepkimelerden Tablo 7'de verilen ürünler izole edildi (ürün verimleri için Tablo 7'ye bakınız).

5-Ferrosenil-1*H*-pirazol (4A): ^{1}H NMR ($CDCl_3$): δ 7.52 (s, 1H), 6.33 (s, 1H), 4.58 (s, 2H), 4.28 (s, 2H), 4.04 (s, 5H), NH piki H/D değişmesine ve/veya tautomerizme bağlı olarak gözlenmedi; IR (neat): 3115, 3026, 2875, 2840, 2816, 1598, 1565, 1463, 1415, 1289, 1102, 1053, 999, 937, 810, 764 cm^{-1}; MS (EI): 252 (M^+), 250, 224, 187, 166, 158, 133, 121, 103, 77; HRMS (EI): calcd. for $C_{13}H_{12}FeN_2$: 252.0350. Found: 252.0352.

1-Fenil-5-ferrosenil-1*H*-pirazol (4B): ^{1}H NMR ($CDCl_3$): δ 7.62 (s, 1H), 7.40 (m, 5H), 6.50 (s, 1H), 4.17 (s, 2H), 4.14 (s, 2H), 4.05 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 141.5 (C), 140.4 (C), 140.0 (CH), 128.8 (CH), 128.0 (CH), 126.1 (CH), 106.8 (CH), 75.1 (C), 69.9 (CH), 68.8 (CH), 68.6 (CH); IR (CH_2Cl_2): 3089, 3036, 1665, 1597, 1557, 1498, 1402, 1259, 1145, 971, 923, 870 cm^{-1}; MS (EI): 328 (M^+), 326, 263, 235, 207, 170, 153, 121, 77, 56; HRMS (EI): calcd. for $C_{19}H_{16}FeN_2$: 328.0663. Found: 328.0661.

1-Fenil-3-ferrosenil-1*H*-pirazol (62B): ^{1}H NMR ($CDCl_3$): δ 7.84 (d, 1H, *J* = 2.4 Hz), 7.71 (d, 2H, *J* = 7.8 Hz), 7.44 (t, 2H, *J* = 7.8 Hz), 7.25 (t, 1H, *J* = 7.8 Hz), 6.48 (d, 1H, *J* = 2.4 Hz), 4.76 (s, 2H), 4.29 (s, 2H), 4.07 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 152.5 (C), 140.3 (C), 129.4 (CH), 127.4 (CH), 126.0 (CH), 119.0 (CH), 105.6 (CH), 78.4 (C), 69.6 (CH), 68.7 (CH), 66.9 (CH); IR (CH_2Cl_2): 3090, 3030, 2959, 2865, 1681, 1649, 1598, 1557, 1506, 1458, 1257, 1129, 1043, 868, 820 cm^{-1}; MS (EI): 328 (M^+), 326, 263, 246, 206, 178, 149, 121, 91, 77, 56; HRMS (EI): calcd. for $C_{19}H_{16}FeN_2$: 328.0663. Found: 328.0665.

2-(5-Ferrosenilpirazol-1-il)etanol (4C): ^{1}H NMR ($CDCl_3$): δ 7.46 (d, 1H, *J* = 1.8 Hz), 6.30 (d, 1H, *J* = 1.8 Hz), 4.49 (s, 2H), 4.36 (s, 2H), 4.33 (t, 2H, *J* = 4.5 Hz), 4.18 (s, 5H), 4.02 (t, 2H, *J* = 4.5 Hz), 3.09 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 141.4 (C), 138.7 (CH), 106.0 (CH), 74.9 (C), 69.6 (CH), 68.9 (CH), 68.8 (CH), 61.8 (CH_2), 51.0 (CH_2); IR (neat): 3331, 2965,

2937, 1562, 1460, 1331, 1070, 1043, 824, 800 cm^{-1}; MS (EI): 296 (M^+), 294, 265, 252, 231, 200, 187, 146, 121, 103; HRMS (EI): calcd. for $C_{15}H_{16}FeN_2O$: 296.0612. Found: 296.0610.

2-(3-Ferrosenilpirazol-1-il)etanol (62C): ^1H NMR ($CDCl_3$): δ 7.31 (s, 1H), 6.22 (s, 1H), 4.76 (s, 2H), 4.35 (s, 2H), 4.21 (t, 2H, *J* = 4.3 Hz), 4.12 (s, 5H), 3.97 (t, 2H, *J* = 4.3 Hz), 3.52 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 151.3 (C), 130.8 (CH), 103.0 (CH), 78.3 (C), 69.4 (CH), 68.3 (CH), 66.6 (CH), 62.1 (CH_2), 53.5 (CH_2); IR (neat): 3229, 3142, 2950, 2869, 1556, 1502, 1408, 1349, 1230, 1067, 824, 764 cm^{-1}; MS (EI): 296 (M^+), 294, 278, 264, 231, 213, 199, 173, 148, 121, 103, 81; HRMS (EI): calcd. for $C_{15}H_{16}FeN_2O$: 296.0612. Found: 296.0614.

1-Benzil-5-ferrosenil-1*H*-pirazol (4D): ^1H NMR ($CDCl_3$): δ 7.44 (s, 1H), 7.23 (t, 2H, *J* = 7.28 Hz), 7.15 (t, 1H, *J* = 7.28 Hz), 6.96 (d, 2H, *J* = 7.28 Hz), 6.35 (s, 1H), 5.42 (s, 2H), 4.29 (s, 2H), 4.17 (s, 2H), 4.00 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 141.7 (C), 139.1 (C), 137.7 (CH), 128.6 (CH), 127.3 (CH), 126.2 (CH), 106.0 (CH), 74.9 (C), 70.5 (CH), 68.8 (CH), 68.4 (CH), 53.3 (CH_2); IR (neat): 3142, 3109, 2950, 2896, 1556, 1502, 1409, 1321, 1231, 1071, 873, 825, 765 cm^{-1}; MS (EI): 342 (M^+), 277, 252, 223, 185, 157, 121, 91, 65, 56; HRMS (EI): calcd. for $C_{20}H_{18}FeN_2$: 342.0819. Found: 342.0817.

4-(5-Ferrosenilpirazol-1-il)benzoik asit (4E): ^1H NMR ($CDCl_3$): δ 8.00 (d, 2H, *J* = 7.5 Hz), 7.86 (d, 1H, *J* = 8.5 Hz), 7.05 (d, 2H, *J* = 7.5 Hz), 6.68 (d, 1H, *J* = 8.5 Hz), 4.63 (t, 2H, *J* = 1.7 Hz), 4.37 (t, 2H, *J* = 1.7 Hz), 4.19 (s, 5H), karboksilik asit piki H/D değişmesine bağlı olarak gözlenmedi; ^{13}C NMR ($CDCl_3$): δ 170.5 (C), 139.1 (CH), 137.8 (C), 137.0 (C), 132.3 (CH), 120.3 (C), 117.8 (CH), 111.9 (CH), 83.0 (C), 70.2 (CH), 70.1 (CH), 67.4 (CH); IR (CH_2Cl_2): 3057, 2928, 2851, 2671, 2542, 1727, 1694, 1603, 1451, 1417, 1316, 1286, 1262, 1171, 1127, 1070, 746, 733, 719 cm^{-1}; MS (EI): 372 (M^+), 370, 329, 307, 251, 234, 205, 178, 137, 120, 65, 56; HRMS (EI): calcd. for $C_{20}H_{16}FeN_2O_2$: 372.0561. Found: 372.0559.

2-(5-Ferrosenilpirazol-1-il)piridin (4F): ^{1}H NMR ($CDCl_3$): δ 8.11 (ddd, 1H, *J* = 8.6, 7.5, 1.8 Hz), 7.87 (d, 1H, *J* = 9.0 Hz), 7.58 (ddd, 1H, *J* = 8.6, 7.5, 1.8 Hz), 7.22 (d, 1H, *J* = 8.5 Hz), 6.77 (ddd, 1H, *J* = 8.6, 7.5, 1.8 Hz), 6.65 (d, 1H, *J* = 9.0 Hz), 4.58 (t, 2H, *J* = 1.9 Hz), 4.35 (t, 2H, *J* = 1.9 Hz), 4.18 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 155.9 (C), 146.9 (CH), 139.1 (CH), 138.5 (CH), 136.7 (C), 118.1 (CH), 115.8 (CH), 107.6 (CH), 83.4 (C), 70.1 (CH), 70.0 (CH), 67.3 (CH); IR (neat): 3178, 3142, 3048, 2951, 1561, 1535, 1435, 1301, 1141, 1088, 867, 805, 769 cm^{-1}; MS (EI): 329 (M^+), 302, 300, 271, 264, 237, 210, 184, 156, 149, 120, 89, 67; HRMS (EI): calcd. for $C_{18}H_{15}FeN_3$: 329.0615. Found: 329.0613.

(3-Ferrosenilpirazol-1-il)(4-hidroksifenil)metanon (62G): ^{1}H NMR ($CDCl_3$): δ 8.33 (s, 1H), 8.21 (d, 2H, *J* = 7.95 Hz), 6.89 (d, 2H, *J* = 7.95 Hz), 6.51 (s, 1H), 5.87 (s, OH), 4.81 (s, 2H), 4.40 (s, 2H), 4.14 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 165.1 (C), 160.3 (C), 156.6 (C), 134.5 (CH), 131.5 (CH), 123.6 (C), 115.3 (CH), 107.9 (CH), 78.2 (C), 71.2 (CH), 71.1 (CH), 68.6 (CH); IR (neat): 3353, 3149, 1699, 1606, 1558, 1417, 1384, 1357, 1311, 1271, 1231, 1190, 1057, 895, 821, 756 cm^{-1}; MS (EI): 372 (M^+), 370, 307, 252, 224, 187, 158, 141, 121, 93, 84; HRMS (EI): calcd. for $C_{20}H_{16}FeN_2O_2$: 372.0561. Found: 372.0563.

3-Ferrosenilpropinal (ferrocenyl(formyl)acetylene, 69). Argon atmosferi altında bulunan etinilferrosen (**8**) (1.0 g, 4.8 mmol)bileşiğinin 30 mL THF içerisinde -78 °C soğutulmuş çözeltisine n-BuLi (3.2 mL, 1.6 M, 5 mmol) reaktifi damla damla ilave edilmiş ve oluşan karışım bu sıcaklıkta 30 dakika karıştırıldıktan sonra DMF (1.0 mL, 13 mmol) ilave edilmiştir. Daha sonra karışım -78 °C'de 1 saat daha karıştırıldıktan sonra yavaş yavaş oda sıcaklığına getirilmiş ve içinde bulunan 50 mL buzlu su ile 5 mL konsantre HCl bulunan behere aktarılmıştır. Daha sonra $NaHCO_3$ ile nötralize edilen karışım eter çözücüsü ile ekstrakte edilmiştir. Organic çözücülerin uçurulmasından sonra elde edilen ham ürün flaş kolon kromatografisi ile saflaştırılarak 3-ferrosenilpropinal (ferrocenyl(formyl)acetylene, **69**) bileşiği % 93 verim ile elde edilmiştir.

Bileşik 69 için spektroskopik data: ^{1}H-NMR ($CDCl_3$): δ 9.27 (s, 1H), 4.60 (s, 2H), 4.41 (s, 2H), 4.25 (s, 5H). Bu spektroskopik data literatürde bu madde için verilen değerlerle uyum içersindedir (Doisneau, 1992).

Genel Prosedür 8: Ferrosenil pirazol türevleri 4 ve 62'nin sentezi (Tablo 8): Bir ucuna geri soğutucu diğerine septum takılmış ve argon altında bulunan iki ağızlı dibi yuvarlak bir balona 10 mL of dioksan (Koşul A) veya 10 mL of metanol (Koşul B) çözücü konuldu ve daha sonra sırasıyla 3-ferrosenilpropinal (**69**) (100 mg, 0.420 mmol) ve hydrazin tuzu (**61**) (1.260 mmol) ilave edildi. Oluşan tepkime karışımı geri soğutucu altında 100 ^{o}C'de 8 saat (Koşul A) veya 64.5 ^{o}C'de 5 saat (Koşul B) kaynatıldı. Bu süre sonunda tepkime karışımı oda sıcaklığına soğutuldu ve organik çözücü düşük vakum altında döner bir buharlaştırıcıda uçuruldu. Daha sonra ham ürün 20 mL su içinde çözüldü ve kloroform (3 x 30 mL) ile ekstrakte edildi. Toplanan kloroform fazı magnezyum sülfat üzerinde kurutulduktan sonra düşük vakum altında döner bir buharlaştırıcıda uçuruldu. Elde edilen ham ürün flaş kolon kromatografi yöntemiyle silika jel üzerinde sırasıyla 19:1'den 1:1 oranına kadar hekzan/etil asetat elüenti kullanılarak saflaştırıldı. Bu tepkimelerden Tablo 8'de verilen ürünler izole edildi (ürün verimleri için Tablo 8'e bakınız).

1-Benzil-3-ferrosenil-1*H*-pirazol (62D): ^{1}H-NMR ($CDCl_3$): δ 7.40-7.31 (m, 3H), 7.28 (s, 1H), 7.23 (d, 2H, *J* = 7.2 Hz), 6.32 (s, 1H), 5.34 (s, 2H), 4.77 (s, 2H), 4.34 (s, 2H), 4.14 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 150.8 (C), 137.0 (C), 130.1 (CH), 128.7 (CH), 127.9 (CH), 127.5 (CH), 103.7 (CH), 79.0 (C), 69.6 (CH), 68.5 (CH), 66.7 (CH), 55.8 (CH_2); IR (KBr): 3108, 3079, 3030, 2941, 1556, 1497, 1435, 1404, 1303, 1230, 1102, 1060, 1000, 874, 833, 813, 761, 716 cm^{-1}; MS (ESI, *m/z*): 343.1 $[M+H]^+$, 252.0; Anal. Calcd for $C_{20}H_{18}FeN_2$ with 0.263 mol $CHCl_3$ incorporation: C, 65.14; H, 4.93; N, 7.50. Found: C, 65.14; H, 5.62; N, 7.50%.

6.0 KAYNAKLAR

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7.0 PROJE KAPSAMINDA YAPILAN YURTDIŞI YAYINLAR

Proje kapsamında aşağıda gösterilen yayınlar yapılmıştır:

1. **Metin Zora**, Mustafa Kokturk, Tugce Eralp, "*Synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-diones*," Tetrahedron 62, 10344-10351 (2006).

2. **Metin Zora**, Canet Açıkgöz, Tülay Aslı Tumay, Mustafa Odabaşoğlu, Orhan Büyükgüngör, "*Propynylferrocene and (phenylethynyl)ferrocene*," Acta Crystalographica C: Crystal Structure Communications C62, m327-m330 (2006).

3. **Metin Zora**, Günseli Turgut, Mustafa Odabaşoğlu, Orhan Büyükgüngör, "*2-Pyridiniohydrazinium dichloride*," Acta Crystalographica E: Structure Reports Online E62, o2677-o2679 (2006).

4. **Metin Zora**, Tülay Aslı Tumay, Orhan Büyükgüngör, "*Coupling of cyclopropylcarbene-chromium complex with ferrocenyl alkynes: Synthesis of 5-ferrocenyl-5-hydroxy-2-cyclopentenones and 4-ferrocenyl-4-cyclopentene-1,3-diones*," Tetrahedron 63, 4018-4026 (2007).

5. **Metin Zora**, Canet Açıkgöz, Mustafa Odabaşoğlu, Orhan Büyükgüngör, "*Coupling of pentacarbonyl[(cyclopropyl)methoxymethylene]molybdenum complex with ferrocenyl alkynes: Synthesis of ferrocenyl-substituted cycloheptadienones and cycloheptene-diones*," Journal of Organometallic Chemistry 692, 1571-1578 (2007).

6. Arif Kıvrak, **Metin Zora**, "*Efficient one-pot synthesis of cyanoferrocene from ferrocenecarboxaldehyde using* $NH_2OH.HCl/KI/ZnO/CH_3OH$ *system*," Journal of Organometallic Chemistry 692, 2346-2349 (2007).

7. **Metin Zora**, Meral Görmen, "*Synthesis of ferrocenyl pyrazoles by the reaction of (2-formyl-1-chlorovinyl)ferrocene with hydrazines*," Journal of Organometallic Chemistry 692, 5026-5032 (2007).

8. **Metin Zora**, Ayşe Nur Pinar, Mustafa Odabaşoğlu, Orhan Büyükgüngör, Günseli Turgut, "*Synthesis of ferrocenyl pyrazoles by the reaction of 3-ferrocenylpropynal with hydrazinium salts*," Journal of Organometallic Chemistry, 693, 145-154 (2008).

9. **Metin Zora**, Özlem Velioğlu, "*Synthesis of ferrocenyl quinolines*," Journal of Organometallic Chemistry, 693, 2159–2162 (2008).

8.0 PROJE KAPSAMINDA KONGRELERDE SUNULAN TEBLİĞLER VE POSTERLER

Proje kapsamında ilgili kongrelerde aşağıda gösterilen tebliğler ve posterler sunulmuştur:

1. Canet Açıkgöz, **Metin Zora**, "*Reaction of Ferrocenyl Alkynes with Cyclopropylcarbene-Molybdenum Complex: Synthesis of Ferrocenyl Cycloheptadienones*," OMCOS 13-IUPAC Symposium on Organometallic Chemistry Directed Towards Organic Synthesis, Geneva, Switzerland; July 17-21, 2005; P-460.

2. Tülay Aslı Tümay, **Metin Zora**, "*Reaction of Ferrocenyl Alkynes with Cyclopropylcarbene-Chromium Complex: Synthesis of Ferrocenyl Cyclopentenones*," OMCOS 13-IUPAC Symposium on Organometallic Chemistry Directed Towards Organic Synthesis, Geneva, Switzerland; July 17-21, 2005; P-463.

3. **Metin Zora**, Günseli Turgut, Meral Görmen, "*Synthesis of ferrocenyl substituted pyrazoles as potential antitumor substances*," 230th National Meeting of American Chemical Society, Washington, DC, USA; August 28-September 1, 2005; ORGN 138.

4. **Metin Zora**, Mustafa Köktürk, Tuğçe Eralp, "*Synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-diones as potential antitumor substances*," 230th National Meeting of American Chemical Society, Washington, DC, USA; August 28-September 1, 2005; ORGN 536.

5. **Metin Zora**, Arif Kivrak, "*Efficient one-pot synthesis of cyanoferrocene from ferrocenecarboxaldehyde using* $NH_2OH.HCl/KI/ZnO/CH_3CN$ *system*," 1st European Chemistry Congress, Budapest, Hungary; August 27-31, 2006; N-PO-178, pp 347-348.

6. **Metin Zora**, Arif Kivrak, "*KI/ZnO: Ferrosenilnitril sentezi için yeni ve etkili katalizör sistemi*," XX. Ulusal Kimya Kongresi, Erciyes Üniversitesi, Kayseri; 4-8 Eylül 2006; OKP-112.

7. **Metin Zora**, Tülay Aslı Tumay, "*Synthesis of 5-ferrocenyl-5-hydroxy-2-cyclopentenones and 4-ferrocenyl-4-cyclopentene-1,3-diones*," International Conference on Organic Chemistry, Erzurum, Turkey; June 5-9, 2007; OP-28, p 47.

9.0 PROJE KAPSAMINDA YAPILAN TEZLER

Proje olanaklarından yararlanılarak proje kapsamında aşağıdaki tezler yapılmıştır:

1. **Meral Görmen**, Yüksek Lisans Tezi: "*Synthesis of ferrocenyl substituted pyrazoles*," (Danışman: Prof. Dr. Metin Zora); Orta Doğu Teknik Üniversitesi, Kimya Bölümü, Temmuz 2005.

2. **Mustafa Köktürk**, Yüksek Lisans Tezi: "*Synthesis of ferrocenylidene cyclopentenediones*," (Danışman: Prof. Dr. Metin Zora); Orta Doğu Teknik Üniversitesi, Kimya Bölümü, Ağustos 2005.

3. **Canet Açıkgöz**, Yüksek Lisans Tezi: "*Synthesis of ferrocenyl cycloheptadienones*," (Danışman: Prof. Dr. Metin Zora); Orta Doğu Teknik Üniversitesi, Kimya Bölümü, Ağustos 2005.

4. **Tülay Aslı Tümay**, Yüksek Lisans Tezi: "*Synthesis of ferrocenyl cyclopentenones*," (Danışman: Prof. Dr. Metin Zora); Orta Doğu Teknik Üniversitesi, Kimya Bölümü, Ağustos 2005.

5. **Ayşe Nur Pinar**, Yüksek Lisans Tezi: "*Reaction of propgargyl aldehydes with hydrazinium salts: Synthesis of ferrocenyl and phenyl substituted pyrazoles*," (Danışman: Prof. Dr. Metin Zora); Orta Doğu Teknik Üniversitesi, Kimya Bölümü, Ağustos 2008.

6. **Özlem Velioğlu**, Yüksek Lisans Tezi: "*Synthesis of ferrocenyl substituted quinolines*," (Danışman: Prof. Dr. Metin Zora); Orta Doğu Teknik Üniversitesi, Kimya Bölümü, Ağustos 2008.

7. **Ceyda Yazıcı**, Yüksek Lisans Tezi: "*Synthesis of 4-iodopyrazole derivatives*," (Danışman: Prof. Dr. Metin Zora); Orta Doğu Teknik Üniversitesi, Kimya Bölümü, Ağustos 2008.

PROJE ÖZET BİLGİ FORMU

Proje Kodu: 104T202

Projenin Başlığı: Potansiyel antibiyotik ve antitümör özellikleri olan ferrosenilkinon türevlerinin sentezi

Proje Yürütücüsü ve Araştırıcılar:

Prof. Dr. Metin Zora (Proje Yürütücüsü)
Tülay Aslı Tümay (Yüksek Lisans Öğrencisi)
Canet Açıkgöz (Yüksek Lisans Öğrencisi)
Meral Görmen (Yüksek Lisans Öğrencisi)
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Özlem Velioğlu (Yüksek Lisans Öğrencisi)
Ceyda Yazıcı (Yüksek Lisans Öğrencisi)

Projenin Yürütüldüğü Kuruluş ve Adresi:

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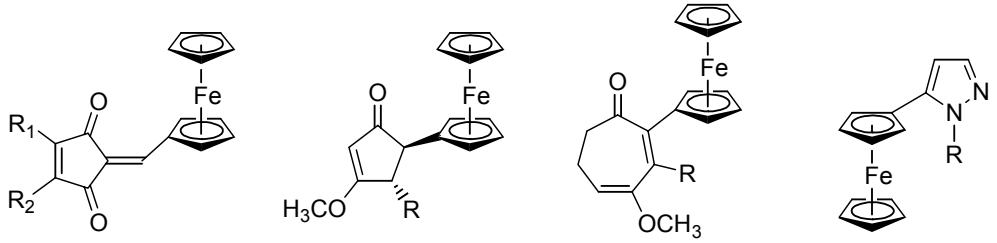
Destekleyen Kuruluş(ların) Adı ve Adresi:

TÜBİTAK, Atatürk Bulvarı, No: 221, Kavaklıdere, 06100 Ankara

Projenin Başlangıç ve Bitiş Tarihleri: 1 Nisan 2005-1 Ekim 2008

Öz:

Ferrosen ve ferrosenyum tuzlarının son yapılan çalışmalarda antitümör aktivite göstermesinden sonra yapılarında ferrosen grubu ihtiva eden biyoaktif yapılar büyük önem kazanmıştır çünkü ferrosen grubu bu bileşiklerin sahip oldukları antitümör ve antibiyotik etkileri dahada artırmaktadır. Dolayısıyla daha etkili antitümör maddelerinin bulunması ve geliştirilmesi kanser gibi hastalıkların tedavisinde yeni umutlar olabilir. Organik ve organometalik bileşiklerin biyolojik aktiviteleri hakkında bazı tahminler yapılabilmekle beraber aktivitelerin kesin olarak belirlenmesi ancak biyolojik aktivite testleri ile mümkündür. Bu da genellikle bu bileşiklerin önce eldesini yani laboratuvarda sentezini gerektirmektedir. Bir ferrosenil grubunun antitümör ve antibiyotik gibi önemli biyolojik aktivitelere sahip alkilidensiklopentendion (**1**), siklopentenon (**2**), sikloheptadienon (**3**) ve pirazol (**4**) yapılarına direk bağlı olduğu bu tür türevler literatürde hemen hemen bilinmemekte ve bunların sentezine yönelik herhangi bir çalışmada yoktur. Bu projede yeni ve uygulanabilir yöntemler geliştirilerek yapıları aşağıda gösterilen literatürde bilinmeyen bu yeni ferrosenii türevlerinin sentezi gerçekleştirilmiştir. Ferrosenil grubunun bu maddelerin sahip oldukları biyolojik aktiviteyi dahada artırması beklenmektedir. Sentezlenen bu bileşiklerden bir veya bir kaçının istenilen düzeyde biyolojik aktivite göstermesi halinde bu bileşikler kanser gibi hastalıkların tedavisinde umut verici yeni ilaç maddeleri olabileceklerdir.



1A ($R_1 = R_2 =$ *i*-PrO)	**2A** (R = H)	**3A** (R = H)	**4A** (R = H)
1B (R_1 = Me, R_2 = *i*-PrO)	**2B** (R = Me)	**3B** (R = Me)	**4B** (R = Ph)
1C ($R_1 = R_2$ = Me)	**2C** (R = Bn)	**3C** (R = Bn)	**4C** (R = CH_2-CH_2-OH)
1D (R_1 = Ph, R_2 = *i*-PrO)	**2D** (R = Ph)	**3D** (R = Ph)	**4D** (R = CH_2-Ph)
1E ($R_1 = R_2$ = Ph)	**2E** (R = Fc)	**3E** (R = Fc)	**4E** (R = p-C_6H_4-CO_2H)

Anahtar Kelimeler:

Ferrosen; ferrosenil sübstitüe alkilidensiklopentendion, siklopentenon, sikloheptadienon, pirazol; sentez; biyolojik aktivite; antibiyotik; antitümör.

Projeden sonuçlanan Yayınlar:

1. **Metin Zora**, Mustafa Kokturk, Tugce Eralp, "*Synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-diones*," Tetrahedron 62, 10344-10351 (2006).
2. **Metin Zora**, Canet Açıkgöz, Tülay Aslı Tumay, Mustafa Odabaşoğlu, Orhan Büyükgüngör, "*Propynylferrocene and (phenylethynyl)ferrocene*," Acta Crystalographica C: Crystal Structure Communications C62, m327-m330 (2006).
3. **Metin Zora**, Günseli Turgut, Mustafa Odabaşoğlu, Orhan Büyükgüngör, "*2-Pyridiniohydrazinium dichloride*," Acta Crystalographica E: Structure Reports Online E62, o2677-o2679 (2006).
4. **Metin Zora**, Tülay Aslı Tumay, Orhan Büyükgüngör, "*Coupling of cyclopropylcarbene-chromium complex with ferrocenyl alkynes: Synthesis of 5-ferrocenyl-5-hydroxy-2-cyclopentenones and 4-ferrocenyl-4-cyclopentene-1,3-diones*," Tetrahedron 63, 4018-4026 (2007).
5. **Metin Zora**, Canet Açıkgöz, Mustafa Odabaşoğlu, Orhan Büyükgüngör, "*Coupling of pentacarbonyl[(cyclopropyl)methoxymethylene]molybdenum complex with ferrocenyl alkynes: Synthesis of ferrocenyl-substituted cycloheptadienones and cycloheptene-diones*," Journal of Organometallic Chemistry 692, 1571-1578 (2007).
6. Arif Kıvrak, **Metin Zora**, "*Efficient one-pot synthesis of cyanoferrocene from ferrocenecarboxaldehyde using* $NH_2OH.HCl/KI/ZnO/CH_3OH$ *system*," Journal of Organometallic Chemistry 692, 2346-2349 (2007).
7. **Metin Zora**, Meral Görmen, "*Synthesis of ferrocenyl pyrazoles by the reaction of (2-formyl-1-chlorovinyl)ferrocene with hydrazines*," Journal of Organometallic Chemistry 692, 5026-5032 (2007).
8. **Metin Zora**, Ayşe Nur Pinar, Mustafa Odabaşoğlu, Orhan Büyükgüngör, Günseli Turgut, "*Synthesis of ferrocenyl pyrazoles by the reaction of 3-ferrocenylpropynal with hydrazinium salts*," Journal of Organometallic Chemistry, 693, 145-154 (2008).
9. **Metin Zora**, Özlem Velioğlu, "*Synthesis of ferrocenyl quinolines*," Journal of Organometallic Chemistry, 693, 2159–2162 (2008).

EKLER

PROJE KAPSAMINDA YAPILAN YURTDIŞI YAYINLAR

Potansiyel Antibiyotik ve Antitümör Özelliklere Sahip Yeni Ferrosen Türevlerinin Tasarım ve Sentezi

Proje No: 104T202

Proje Yürütücüsü: Prof.Dr. Metin ZORA

EKİM 2008
ANKARA

PROJE KAPSAMINDA YAPILAN YURTDIŞI YAYINLAR

1. **Metin Zora**, Mustafa Kokturk, Tugce Eralp, "*Synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-diones*," Tetrahedron 62, 10344-10351 (2006).

2. **Metin Zora**, Canet Açıkgöz, Tülay Aslı Tumay, Mustafa Odabaşoğlu, Orhan Büyükgüngör, "*Propynylferrocene and (phenylethynyl)ferrocene*," Acta Crystalographica C: Crystal Structure Communications C62, m327-m330 (2006).

3. **Metin Zora**, Günseli Turgut, Mustafa Odabaşoğlu, Orhan Büyükgüngör, "*2-Pyridiniohydrazinium dichloride*," Acta Crystalographica E: Structure Reports Online E62, o2677-o2679 (2006).

4. **Metin Zora**, Tülay Aslı Tumay, Orhan Büyükgüngör, "*Coupling of cyclopropylcarbene-chromium complex with ferrocenyl alkynes: Synthesis of 5-ferrocenyl-5-hydroxy-2-cyclopentenones and 4-ferrocenyl-4-cyclopentene-1,3-diones*," Tetrahedron 63, 4018-4026 (2007).

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7. **Metin Zora**, Meral Görmen, "*Synthesis of ferrocenyl pyrazoles by the reaction of (2-formyl-1-chlorovinyl)ferrocene with hydrazines*," Journal of Organometallic Chemistry 692, 5026-5032 (2007).

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Tetrahedron

Synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-diones

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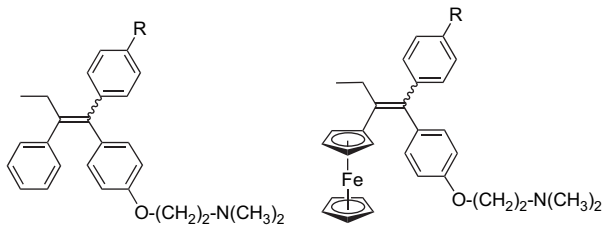
Abstract—A squarate-based synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-diones is described. When refluxed in dioxane at 100 °C, heated with silica gel as a solvent free grinded solid mixture at 125 °C or stirred with silica gel in ethyl acetate at room temperature, 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenones, prepared from ethynylferrocene and 3-cyclobutene-1,2-diones, afforded 2-ferrocenylidene-4-cyclopentene-1,3-diones as the major or single product of the reaction. In some cases, ferrocenyl quinones also resulted from these reactions as the minor products. The major or exclusive formation of 2-ferrocenylidene-4-cyclopentene-1,3-diones is attributed to the radical-stabilizing ability of the ferrocenyl group.

1. Introduction

The great interest in ferrocenyl-substituted organic compounds is associated both with the peculiar chemical behavior of the ferrocene systems and with the unusual properties it imparts on the organic moiety.[1] Due to its unique structure, different membrane-permeation properties, and anomalous metabolism, ferrocene is often incorporated into a compound in order to obtain unexpected or enhanced biological activities.[2,3] A successful example is hydroxyferrocifen, which was obtained by replacing the phenyl ring of hydroxytamoxifen by a ferrocenyl group (Fig. 1).[3] Hydroxyferrocifen is the first molecule shown to be active against both hormone-dependent and hormone-independent breast cancer cells.[3] In contrast, hydroxytamoxifen, the active metabolite of tamoxifen, is active only against hormone-dependent cancer cells.[4] Notably, the integration of a ferrocenyl group into the structure generates surprising antiproliferative effects on both type of cancer cells. It appears so far that ferrocene derivatives act via mechanisms different from those of cisplatin and thus may lend themselves to treatment of a wider range of cancers. In general, the antitumor effect of ferrocene compounds is attributed to the redox properties of the central iron atom, in that only the oxidation state +3 (as in ferrocenium cations), which is readily produced by biological oxidation, exhibits inhibitory effects.[5] Therefore, in recent years, considerable interest has been devoted to the synthesis of new ferrocene derivatives, which could be potential antitumor substances.[6,7]



Tamoxifen (R = H)
Hydroxytamoxifen (R = OH)

Ferrocifen (R = H)
Hydroxyferrocifen (R = OH)

Figure 1. Structures of tamoxifens and ferrocifens.

The rapid spread of cancer has sparked an intense chemical search for new structure leads, which may be of use in designing novel antitumor drugs. In this regard, the 2-methylene-4-cyclopentene-1,3-dione pharmacophore (**1**) has occupied a unique position in the design and synthesis of novel biologically active agents that exert remarkable anticancer activities (Fig. 2). Inayama and co-workers synthesized a series of 2-arylidene-4-cyclopentene-1,3-diones (**2**) and examined their antitumor activity.[8] All compounds exhibited a high degree of activity, but the 3-methoxy-4-hydroxybenzylidene derivatives possessed the greatest potency.[8] Recently, using this innovative pharmacophore, Hori and co-workers have prepared new derivatives of 2-hydroxyarylidene-4-cyclopentene-1,3-diones as new candidates for antitumor agents.[9] Their comprehensive evaluation of these agents with respect to protein tyrosine kinase (PTK) inhibition, mitochondrial inhibition, antitumor activity, and hepatotoxicity demonstrates that PTK inhibitors TX-1123 and TX-1925 (Fig. 2) are more promising

Keywords: Ferrocenylidenecyclopentenediones; Ferrocenyl quinones; Alkynylcyclobutenones; Cyclobutenediones; Cyclobutenols; Rearrangement; Radicals.
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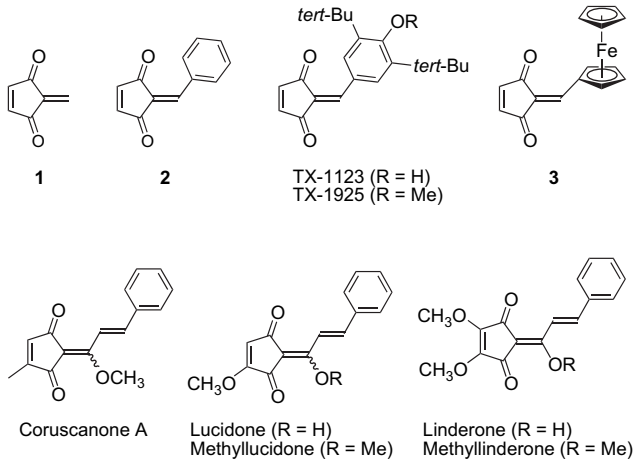


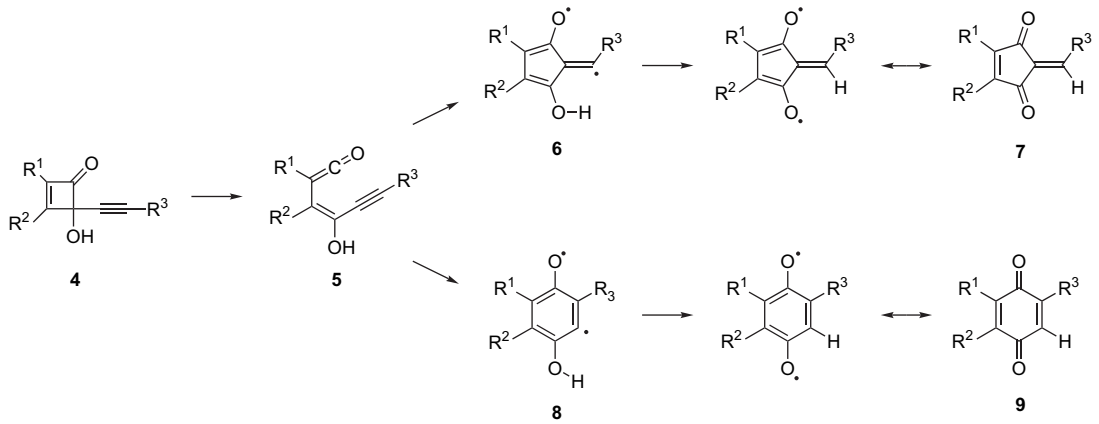
Figure 2. Structures of 2-methylene-4-cyclopentene-1,3-dione (**1**) and related pharmacophores and molecules.

candidates for antitumor agents than well known compound tyrphostin AG17.[9] Naturally occurring lucidone, linderone, and their methyl derivatives methyllucidone and methyllinderone,[10,11] and coruscanone A[12] also contain a 2-methylene-4-cyclopentene-1,3-dione (**1**) pharmacophore in their structures and show farnesyl protein transferase inhibition, antitumor, and/or antifungal activities.

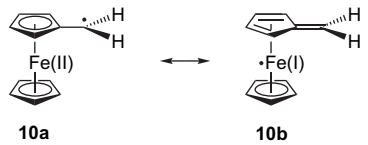
Our attention was then directed toward the synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-dione derivatives, such as **3**, since the incorporation of the essential structural features of 2-methylene-4-cyclopentene-1,3-dione (**1**) pharmacophore with a ferrocenyl moiety could provide compounds with enhanced antitumor activities. Surprisingly, 2-ferrocenylidene-4-cyclopentene-1,3-diones (**3**) are not known. The development of a general synthetic entry to such compounds is therefore of considerable interest since it could lead to a new source of biologically active compounds.

Recently, as shown by Moore and co-workers,[13] 4-alkynyl-4-hydroxycyclobutenones (**4**) have emerged as valuable reagents in organic synthesis since such cyclobutenones undergo a remarkably selective electrocyclic ring opening to give the corresponding conjugated ketenes **5** (Scheme 1). Ketenes **5** then experience five- and/or six-membered ring closure to afford diradicals **6** and/or **8**, which finally lead to 2-alkylidene-4-cyclopentene-1,3-diones (**7**) and/or benzoquinones (**9**) after an intramolecular transfer of the H atom. The selectivity of the rearrangement to give either cyclopentenediones **7** or benzoquinones **9** is significantly influenced by the R^3 substituent in that radical-stabilizing groups, such as alkoxy, phenyl, and trimethylsilyl, favor exclusively, or in part, the cyclopentenedione formation.[14,15] As suggested by Moore,[13b,c] the aromatic stabilization associated with six-membered ring formation is apparently outweighed by direct stabilization of the vinyl radical by the adjacent R^3 substituent when five-membered ring formation takes place. Recently, Engels and co-workers have theoretically studied the substituent effects on the cyclization of 1,3-hexadiene-5-ynone derivatives to the corresponding five- and six-membered diradicals at the density functional theory (DFT) level (B3LYP/6-31G*).[16] They have found that, in addition to a radical-stabilizing group such as Ph as the alkyne substituent (R^3), electron donor groups such as OH and OMe at the other positions are required to make five-membered ring formation as the major pathway. The nature of certain electronic effects of a ferrocenyl substituent was studied by Nesmeyanov et al.[17] It was found that the ferrocenyl substituent exhibits a strong positive inductive effect and a weak positive conjugation effect. Recently, Creary et al. examined the quantitative ability of the ferrocenyl group to stabilize free radicals by employing the experimental methylenecyclopropane rearrangement probe.[18] They found that a ferrocenyl group is 1.6 times better at stabilizing an α radical than a phenyl group. Computational studies have also been carried out in order to gain further insight into the radical-stabilizing ability of ferrocenyl group.[19] DFT (B3LYP/LANL2DZ) calculations on ferrocenyl-substituted methyl radical **10** showed that the radical-stabilizing ability of the ferrocenyl group can be explained by a spin delocalization mechanism involving the Fe atom and a major contribution from an η^4-form, as represented by **10b** (Scheme 2), where the iron is formally a 17-electron system in the +1 oxidation state. Moreover, calculations at the same level indicated that ferrocenylmethyl radical **10** is more stable than the benzyl radical by 1.5 kcal mol^{-1}, in agreement with the experimental results.[19]

In light of these results, it is expected that the thermal rearrangement of alkynylcyclobutenones **4** bearing a ferrocenyl



Scheme 1. Mechanism for the formation of 2-alkylidenecyclopentenediones **7** and benzoquinones **9** from 4-alkynylcyclobutenones **4**.



Scheme 2. Stabilization of ferrocenylmethyl radical.

group as the R^3 substituent should produce 2-ferrocenylidene-4-cyclopentene-1,3-dione derivatives as the major product of the reaction. This methodology, however, has not been utilized for the synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-diones, presumably due to the scarce availability of the starting ferrocenylcyclobutenones. As part of our general involvement in ferrocene-containing potential pharmaceuticals, we have investigated the synthesis of ferrocenylcyclobutenones and their rearrangements to 2-ferrocenylidene-4-cyclopentene-1,3-diones.[20] We herein report the results of this study.

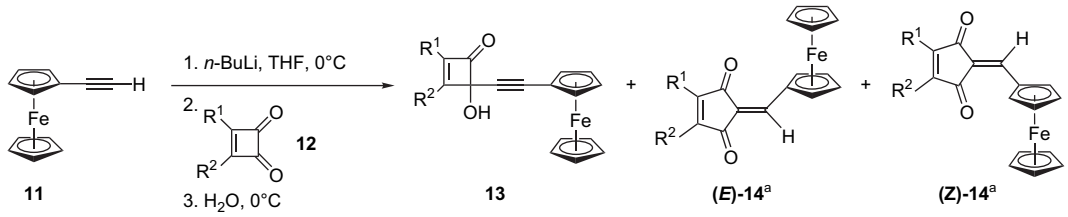
2. Results and discussion

Initially, starting materials were prepared. The synthesis of ethynylferrocene **11** was accomplished from acetylferrocene in two steps according to a well known literature procedure[21] (acetylferrocene is readily available in large quantities from ferrocene according to a standard protocol).[22] Treatment of acetylferrocene with phosphorus oxychloride in DMF led to (2-formyl-1-chlorovinyl)ferrocene, which upon base-induced elimination using aqueous sodium hydroxide in dioxane provided ethynylferrocene **11** in good yield.[21] Cyclobutenediones **12A–D** were prepared from squaric acid according to Liebeskind's procedure.[23] For the synthesis of diphenylcyclobutenedione **12E**, squaric acid was first reacted with thionyl chloride to afford semisquaric chloride.[24] Friedel–Crafts reaction of semisquaric chloride with ferrocene in the presence of $AlCl_3$ produced cyclobutenedione **12E**.[25]

We next synthesized 4-ferrocenylethynylcyclobutenones **13** as shown in Table 1. Treatment of ethynylferrocene **11** with *n*-butyllithium produced in situ lithioethynylferrocene that was further reacted with cyclobutenediones **12** to yield the corresponding cyclobutenones **13**. It should be noted that 4-ferrocenylethynyl-substituted cyclobutenones **13**, especially 2-phenyl-substituted cyclobutenones **13C** and **13E**, were found to be quite reactive and, during the isolation, they partly decomposed and/or rearranged to the corresponding 2-ferrocenylidenecyclopentenediones **14** in varying amounts. Interestingly, 2-methyl-substituted cyclobutenones **13B** and **13D** were insoluble in hexane and it was possible to obtain these compounds in pure form by filtrating their hexane solution. The easy isolation of these derivatives prevented in part their rearrangement to the corresponding cyclopentenediones, and allowed us to have their pure samples for spectroscopic identification. Notably, 2-phenyl-substituted cyclobutenones **13C** and **13E** were highly reactive since they started more rapidly to decompose and/or undergo rearrangement, and it was not possible to obtain pure samples for characterization. That is why, after synthesis, 2-phenyl-substituted cyclobutenones **13C** and **13E** were isolated as crude products and immediately subjected to rearrangement. Moreover, it was observed that, during the chromatographic purification, silica gel accelerated the conversion of cyclobutenones **13** to cyclopentenediones **14** to some extent.

Subsequently, we investigated the rearrangements of 4-ferrocenylethynylcyclobutenones **13** to 2-ferrocenylidenecyclopentenediones **14**. The results are summarized in Table 2. In fact, for these conversions, we employed three different procedures. Firstly, we used a typical thermolysis procedure, which, in general, is the most commonly used protocol for such rearrangements. For this purpose, cyclobutenones **13** were heated in refluxing dioxane at 100 °C for 4 h (Method A). Recently, to run reactions on the surface of solids has attracted considerable interest since, in this way, reactions can be accelerated or new chemistry may occur.[26] We found that when heated with silica gel as a solvent free grinded solid mixture in an oven at 125 °C for a short reaction time, such as 15 min (Method B), cyclobutenones **13** were quickly rearranged to cyclopentenediones **14**. More importantly, stirring a mixture of cyclobutenones **13** and silica gel in ethyl

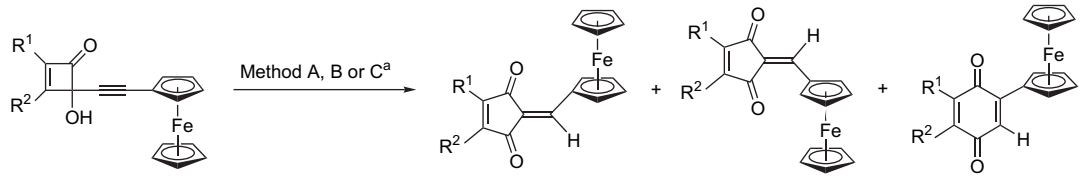
Table 1. Synthesis of 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenones (**13**)



Entry	Starting compound	R^1	R^2	Products (Yields, %)[b]
1	**11A+12A**	*i*-PrO	*i*-PrO	**13A** (65)+**14A** (5)
2	**11A+12B**	Me	*i*-PrO	**13B** (34)+(*E*)-**14B** (19)+(*Z*)-**14B** (9)
3	**11A+12C**	Ph	*i*-PrO	**13C**[c]+(*E*)-**14C** (35)
4	**11A+12D**	Me	Me	**13D** (38)+**14D** (22)
5	**11A+12E**	Ph	Ph	**13E**[c]+**14E** (37)

[a] When R^1 and R^2 are the same, this structure presents compound **14**.
[b] Isolated yields.
[c] For this compound, yield calculation could not be made since, during isolation, it was continuously decomposed and/or rearranged to the corresponding cyclopentenedione. That is why this compound was isolated as a crude product and immediately subjected to rearrangement.

Table 2. Synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-diones (**14**)



Entry	Starting compound	R^1	R^2	Method[a]	Products (Yields, %)[c]
1	**13A**	*i*-PrO	*i*-PrO	A	**14A** (70)+**15A** (2)
2	**13A**	*i*-PrO	*i*-PrO	B	**14A** (67)
3[d]	**13A**	*i*-PrO	*i*-PrO	C	**14A** (34)
4	**13B**	Me	*i*-PrO	A	(*E*)-**14B** (61)+(*Z*)-**14B** (3)+**15B** (4)
5	**13B**	Me	*i*-PrO	B	(*E*)-**14B** (45)+(*Z*)-**14B** (32)
6	**13B**	Me	*i*-PrO	C	(*E*)-**14B** (51)+(*Z*)-**14B** (6)
7	**13C**	Ph	*i*-PrO	A	(*E*)-**14C** (53)[e]
8	**13C**	Ph	*i*-PrO	C	(*E*)-**14C** (56)[e]
9	**13D**	Me	Me	A	**14D** (55)+**15D** (8)
10	**13D**	Me	Me	B	**14D** (71)+**15D** (5)
11	**13D**	Me	Me	C	**14D** (74)+**15D** (8)
12	**13E**	Ph	Ph	A	**14E** (58)[f]
13	**13E**	Ph	Ph	C	**14E** (45)[f]

[a] Method A: dioxane, 100 °C, 4 h; Method B: SiO_2, 125 °C, 15 min; Method C: SiO_2, ethyl acetate, 25 °C, 24 h.
[b] When R^1 and R^2 are the same, this structure presents compound **14**.
[c] Isolated yields.
[d] For this reaction, reaction time was 48 h.
[e] For this compound, yield was calculated from ethynylferrocene (**11**) since, in this reaction, crude cyclobutenone **13C**, obtained from **11**, was used.
[f] For this compound, yield was calculated from ethynylferrocene (**11**) since, in this reaction, crude cyclobutenone **13E**, obtained from **11**, was used.

acetate at room temperature for overnight (Method C) also afforded cyclopentenediones **14**, which is a clear indicative of the high reactivity of 4-ferrocenylethynyl-substituted cyclobutenones **13**. To the best of our knowledge, these last two procedures (Methods B and C) have not been used previously for effecting such rearrangements. In terms of chemical yields, all methods we used appear to be comparable with each other.

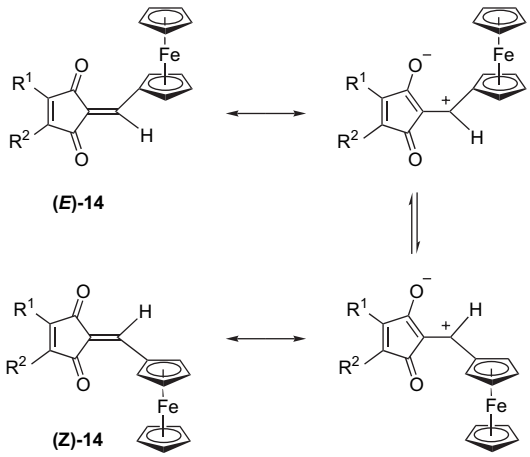
As can be seen in Table 2, all protocols produced the expected cyclopentenediones **14** as the major or single product of the reaction. From unsymmetrically substituted cyclobutenones **13B** and **13C** (Table 2, entries 4–8), mostly or exclusively *E* isomers of cyclopentenediones ((*E*)-**14**) were obtained. In reactions with **13B**, *Z* isomer ((*Z*)-**14**) was also observed but in minor amounts except the one case (Table 2, entry 5), in which *Z* isomer was the significant proportion of the product. In some cases, ferrocenyl quinones were also resulted from these reactions as the minor products.[27] On the basis of the mechanism in Scheme 1 as suggested by Moore,[13] the most or exclusive formation of 2-ferrocenylidenecyclopentenediones **14**, as compared to quinones, clearly shows the radical-stabilizing ability of the ferrocenyl group, a result consistent with the findings of Creary as well.[18,19]

As mentioned before, the reactions of Methods B and C were performed in the presence of silica gel. To verify the silica gel effect, the reactions of **13A** in entries 2 and 3 of Table 2 were repeated in the absence of silica gel. First reaction gave a very low yield of cyclopentenedione **14A**. In the second reaction, conversion to **14A** was almost insignificant. Both results clearly demonstrate that the use of silica gel in these reactions, i.e., in Methods B and C, is vital. The effect of silica gel should be similar to that of a weak Lewis and/or Brønsted acid.

It is interesting to note that 2-ferrocenylidenecyclopentenediones **14** and ferrocenyl quinones **15** can be easily differentiated from each other via their respective ^{1}H NMR spectra. The vinyl proton in quinones **15** appears at 6.67–6.80 ppm while that in cyclopentenediones **14** resonates at 7.22–7.69 ppm since the latter is conjugated to the two carbonyl groups and, as expected, it is more deshielded. In addition, during mass analysis under FAB conditions, ferrocenyl quinones **15** were reduced to the corresponding hydroquinones, as indicated by the MS and HRMS results, but such reductions were not observed for cyclopentenediones **14**. We also realized that ferrocenyl-substituted cyclopentenediones **14** and quinones **15** can be recognized by their colors since cyclopentenediones **14** are in claret red or purple color while quinones **15** are in green color.

The major or exclusive isomer of differently substituted cyclopentenediones **14B** and **14C** was assigned as the *E* isomer. As shown by Moore,[13] in the conversion of diradical intermediate **6** to alkylidenecyclopentenedione **7** (Scheme 1), the H atom migration occurs intramolecularly, which translates to the indicated *E* stereochemistry of the major or exclusive isomer of **14B** and **14C**. The formation of the minor *Z* isomer in some cases may not actually represent a new reaction pathway since it is a secondary product of the reaction and results from the initially formed *E* isomer through partial isomerization or equilibration. It was already shown that the treatment of *E* isomer of a 2-benzylidene-4-cyclopentene-1,3-dione derivative with silica gel resulted in its facile equilibration with the *Z* isomer.[13b] Similarly, when heated with silica gel as a grinded solid mixture at

125 °C for 1 h, pure (*E*)-**14B** equilibrated with its *Z* isomer. A possible mechanism for this isomerization is given in Scheme 3. During the *E*–*Z* isomerization, a positive charge develops at the exo β-carbon atom adjacent to ferrocenyl group (Scheme 3), but it is well stabilized since the ferrocenyl group is much more effective at carbocation stabilization than it is at radical stabilization.[18] In addition, the ferrocenyl group is a better carbocation stabilizing group than the phenyl group.[28]



Scheme 3. A possible mechanism for the *E*–*Z* isomerization of 2-ferrocenylidenecyclopentenediones **14**.

3. Conclusion

In summary, we have described a squarate-based synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-diones (**14**), which are the first examples of these kind, containing a ferrocene moiety. When refluxed in dioxane at 100 °C, heated with silica gel as a solvent free grinded solid mixture at 125 °C or stirred with silica gel in ethyl acetate at room temperature, 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenones (**13**) afford 2-ferrocenylidenecyclopentenediones **14** as the major or single product of the reaction, accompanied by minor amounts of ferrocenyl quinones in some cases. The formation of 2-ferrocenylidene-4-cyclopentene-1,3-diones is attributed to the radical-stabilizing ability of the ferrocenyl group, which has not been utilized before in such reactions.

4. Experimental

4.1. General consideration

Nuclear magnetic resonance (^{1}H and ^{13}C) spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (*J* values) are reported in hertz (Hz) and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). DEPT ^{13}C NMR information is given in parenthesis as C, CH, CH_2, and CH_3. Infrared spectra were recorded on a Perkin–Elmer 1600 Series FT-IR spectrometer. Band positions are reported in reciprocal centimeters (cm^{-1}). Band intensities are reported relative to the most intense band and are listed as: br (broad), vs (very strong), s (strong), m (medium), w (weak), and vw (very weak). Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained on a VG-7070E magnetic sector instrument using fast atom bombardment (FAB); *m*/*z* values are reported, followed by the relative intensity in parentheses. The matrix used for FAB was ethylene glycol or a mixture of dithiothritol and dithioerithitol. Flash chromatography was performed using thick-walled glass columns and 'flash grade' silica (Merck 230–400 mesh). Routine thin layer chromatography (TLC) was effected by using precoated 0.25 mm silica gel plates purchased from Merck. The relative proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio. Ethynylferrocene (**11**)[21] and cyclobutenediones **12A**–**E** were synthesized according to the well known literature procedures.[23–25] All other commercially available reagents and reactants were obtained in reagent grade and used without purification. All reaction solvents were distilled for purity. Diethyl ether, THF, and dioxane were distilled from sodium/benzophenone ketyl. The inert atmosphere was created by slight positive pressure (ca. 0.1 psi) of argon.

4.2. General procedure for synthesis of 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenones (13) (Table 1)

To a solution of ethynylferrocene (**11**)[21] (252 mg, 1.2 mmol) in THF (15 mL) at 0 °C under argon was added via syringe *n*-butyllithium (0.65 mL of a 1.7 M hexane solution, 1.1 mmol) over a period of 15 min. The mixture was stirred for 45 min at the same temperature, and then transferred via cannula to a solution of the corresponding cyclobutenedione **12**[23–25] (1.0 mmol) in THF (15 mL) at −78 °C under argon. The reaction mixture was stirred at −78 °C for 3 h and then quenched with water (10 mL) at −78 °C. The mixture was allowed to warm to room temperature and diluted with diethyl ether (50 mL). The layers were separated and the aqueous layer was extracted with ether (2×50 mL). After drying over $MgSO_4$, the combined organic layers were removed on a rotary evaporator. Final purification was achieved by flash chromatography on silica gel using 9:1 hexane/ethyl acetate followed by 4:1 hexane/ethyl acetate as the eluent. The products given in Table 1 were isolated with the indicated yields.

4.3. Spectral data for cyclobutenones 13

4.3.1. 4-Ferrocenylethynyl-4-hydroxy-2,3-diisopropoxy-2-cyclobutenone (13A). R_f=0.30 in 4:1 C_6H_{14}/EtOAc; off yellow solid; 265.3 mg (65%); ^{1}H NMR ($CDCl_3$): δ 5.01 (septet, 1H, *J*=6.1 Hz), 4.87 (septet, 1H, *J*=6.1 Hz), 4.41 (s, 2H), 4.17 (s, 7H), 3.10 (br s, 1H), 1.45 (d, 3H, *J*=6.1 Hz), 1.43 (d, 3H, *J*=6.1 Hz), 1.29 (d, 3H, *J*=6.1 Hz), 1.28 (d, 3H, *J*=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 181.0 (C), 164.8 (C), 134.3 (C), 88.3 (C), 80.0 (C), 79.7 (C), 78.2 (CH), 74.5 (CH), 72.0 (CH), 70.4 (CH), 69.3 (CH), 63.9 (C), 23.1 (CH_3, two methyl carbons overlap), 22.9 (CH_3, two methyl carbons overlap); IR (CH_2Cl_2): 3358 (w), 3323 (br), 2975 (m), 2928 (m), 2223 (w), 1773 (s), 1627 (vs), 1458 (w), 1388 (s), 1322 (s), 1261 (s), 1096 (s) cm^{-1}; MS (FAB): 409 ($[M+H]^+$, 55), 408 ($[M]^+$, 100), 395 (11), 324 (19), 311 (6), 213 (18), 199 (7), 137 (17), 136 (16), 43 (11), 41 (9); HRMS (FAB) calcd for $C_{22}H_{24}FeO_4$: 408.1034. Found: 408.1024.

4.3.2. 4-Ferrocenylethynyl-4-hydroxy-3-isopropoxy-2-methyl-2-cyclobutenone (13B). R_f=0.25 in 4:1 C_6H_{14}/EtOAc; brownish yellow solid; 123.8 mg (34%); ^{1}H NMR ($CDCl_3$): δ 5.08 (septet, 1H, J=6.1 Hz), 4.40 (s, 2H), 4.17 (s, 7H), 3.34 (s, 1H), 1.68 (s, 3H), 1.50 (d, 3H, J=6.1 Hz), 1.46 (d, 3H, J=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 187.6 (C), 180.3 (C), 124.9 (C), 89.4 (C), 84.2 (C), 79.9 (C), 78.5 (CH), 72.0 (CH), 70.4 (CH), 69.4 (CH), 63.8 (C), 23.4 (CH_3), 23.1 (CH_3), 7.0 (CH_3); IR (CH_2Cl_2): 3559 (w), 3308 (br), 2976 (w), 2926 (vw), 2223 (w), 1764 (s), 1623 (vs), 1463 (vw), 1397 (s), 1312 (s), 1097 (s) cm^{-1}; MS (FAB): 365 ([M+H]$^+$, 81), 364 ([M]$^+$, 87), 347 (82), 322 (100), 305 (25), 295 (16), 257 (96), 255 (13), 210 (11), 183 (6), 157 (8), 121 (20), 85 (9); HRMS (FAB) calcd for $C_{20}H_{20}FeO_3$: 364.0762. Found: 364.0775.

4.3.3. 4-Ferrocenylethynyl-4-hydroxy-2,3-dimethyl-2-cyclobutenone (13D). R_f=0.17 in 4:1 C_6H_{14}/EtOAc; brown solid; 121.6 mg (38%); ^{1}H NMR ($CDCl_3$): δ 4.39 (s, 2H), 4.18 (s, 2H), 4.16 (s, 5H), 2.58 (s, 1H), 2.20 (s, 3H), 1.75 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 189.8 (C), 177.2 (C), 151.1 (C), 89.2 (C), 87.1 (C), 80.4 (C), 72.0 (CH), 70.6 (CH), 69.4 (CH), 63.9 (C), 10.9 (CH_3), 8.4 (CH_3); IR (CH_2Cl_2): 3568 (w), 3392 (br), 3099 (vw), 2960 (vw), 2219 (m), 1765 (vs), 1637 (s), 1432 (w), 1380 (w), 1303 (w), 1259 (w), 1176 (w), 1099 (m) cm^{-1}; MS (FAB): 321 ([M+H]$^+$, 68), 320 ([M]$^+$, 100), 303 (76), 275 (50), 255 (90), 253 (11), 183 (10), 155 (14), 121 (13), 115 (4), 85 (5); HRMS (FAB) calcd for $C_{18}H_{16}FeO_2$: 320.0500. Found: 320.0489.

4.4. General procedures for the synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-diones (14) (Table 2)

4.4.1. Method A. A dioxane (15 mL) solution of the corresponding cyclobutenone **13** (0.50 mmol) was heated to reflux at 100 °C under argon for a period of 4 h. The mixture was then allowed to cool to room temperature and the solvent was removed on a rotary evaporator. Final purification was achieved by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent. The products given in Table 2 according to Method A were isolated with the indicated yields.

4.4.2. Method B. A ground mixture of the corresponding cyclobutenone **13** (0.10 mmol) and silica gel (0.5 g) were heated on a watch glass in an oven at 125 °C for 15 min. After cooling to room temperature, the residue was loaded onto a silica gel flash column and purified by using 9:1 hexane/ethyl acetate as the eluent. The products given in Table 2 according to Method B were isolated with the indicated yields.

4.4.3. Method C. A mixture of the corresponding cyclobutenone **13** (0.10 mmol) and silica gel (0.5 g) in ethyl acetate (10 mL) was stirred at room temperature under argon for 24 h (note that for the reaction in Table 2, entry 3, reaction time was 48 h). After the solvent was removed on a rotary evaporator, the residue was loaded onto a silica gel flash column and purified by using 9:1 hexane/ethyl acetate as the eluent. The products given in Table 2 according to Method C were isolated with the indicated yields.

4.5. Spectral data for cyclopentenediones 14 and ferrocenyl quinones 15

4.5.1. 2-Ferrocenylidene-4,5-diisopropoxy-4-cyclopentene-1,3-dione (14A). R_f=0.40 in 9:1 C_6H_{14}/EtOAc; claret red oily solid; 142.8 mg (70%, Method A), 27.3 mg (67%, Method B), 13.9 mg (34%, Method C); ^{1}H NMR ($CDCl_3$): δ 7.22 (s, 1H), 5.50 (septet, 1H, J=6.2 Hz), 5.44 (septet, 1H, J=6.2 Hz), 5.14 (pseudo t, 2H, J=1.7 Hz), 4.56 (pseudo t, 2H, J=1.7 Hz), 4.13 (s, 5H), 1.36 (d, 6H, J=6.2 Hz), 1.34 (d, 6H, J=6.2 Hz); ^{13}C NMR ($CDCl_3$): δ 187.7 (C), 186.1 (C), 150.9 (C), 147.1 (C), 139.0 (CH), 121.6 (C), 76.2 (C), 74.9 (CH), 74.7 (CH), 74.2 (CH), 73.4 (CH), 70.4 (CH), 23.5 (CH_3), 23.4 (CH_3); IR (CH_2Cl_2): 2982 (w), 2933 (vw), 1668 (vs), 1620 (vs), 1461 (vw), 1377 (m), 1305 (s), 1102 (s), 1029 (s) cm^{-1}; MS (FAB): 409 ([M+H]$^+$, 36), 408 ([M]$^+$, 75), 367 (12), 366 (9), 324 (41), 301 (27), 259 (100), 186 (9), 135 (10), 121 (8), 103 (18), 85 (18), 45 (34); HRMS (FAB) calcd for $C_{22}H_{24}FeO_4$: 408.1024. Found: 408.1035.

4.5.2. (*E*)-2-Ferrocenylidene-4-isopropoxy-5-methyl-4-cyclopentene-1,3-dione ((*E*)-14B). R_f=0.58 in 9:1 C_6H_{14}/EtOAc; claret red solid; mp 99.5–100.3 °C; 111.0 mg (61%, Method A), 16.4 mg (45%, Method B), 18.6 mg (51%, Method C); ^{1}H NMR ($CDCl_3$): δ 7.25 (s, 1H), 5.61 (septet, 1H, J=6.1 Hz), 5.21 (s, 2H), 4.60 (s, 2H), 4.15 (s, 5H), 1.93 (s, 3H), 1.36 (d, 6H, J=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 191.0 (C), 189.5 (C), 163.8 (C), 140.7 (CH), 134.7 (C), 122.6 (C), 76.1 (C), 74.5 (CH) (ferrocenyl CH and isopropoxy CH overlap), 73.8 (CH), 70.5 (CH), 23.7 (CH_3), 7.6 (CH_3); IR (CH_2Cl_2): 2980 (vw), 1712 (w), 1668 (vs), 1605 (vs), 1492 (w), 1376 (vs), 1319 (m), 1247 (w), 1127 (m), 1088 (s), 1024 (s) cm^{-1}; MS (FAB): 365 ([M+H]$^+$, 73), 364 ([M]$^+$, 100), 322 (35), 299 (16), 257 (100), 155 (12), 119 (26), 85 (30); HRMS (FAB) calcd for $C_{20}H_{20}FeO_3$: 364.0762. Found: 364.0775.

4.5.3. (*Z*)-2-Ferrocenylidene-4-isopropoxy-5-methyl-4-cyclopentene-1,3-dione ((*Z*)-14B). R_f=0.45 in 9:1 C_6H_{14}/EtOAc; claret red solid; 5.5 mg (3%, Method A), 11.7 mg (32%, Method B), 2.2 mg (6%, Method C); ^{1}H NMR ($CDCl_3$): δ 7.39 (s, 1H), 5.58 (septet, 1H, J=6.1 Hz), 5.20 (s, 2H), 4.64 (s, 2H), 4.18 (s, 5H), 1.97 (s, 3H), 1.40 (d, 6H, J=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 192.3 (C), 188.0 (C), 166.3 (C), 141.0 (CH), 130.0 (C), 122.2 (C), 76.2 (C), 74.6 (CH), 74.4 (CH), 73.8 (CH), 70.5 (CH), 23.6 (CH_3), 7.5 (CH_3).

4.5.4. (*E*)-2-Ferrocenylidene-4-isopropoxy-5-phenyl-4-cyclopentene-1,3-dione ((*E*)-14C). R_f=0.48 in 4:1 C_6H_{14}/EtOAc; purple solid; mp 130.5–131.4 °C; 112.9 mg (53%, Method A), 23.9 mg (56%, Method C); ^{1}H NMR ($CDCl_3$): δ 7.97 (d, 2H, J=7.2 Hz), 7.45–7.35 (m, 4H), 5.91 (septet, 1H, J=6.1 Hz), 5.27 (pseudo t, 2H, J=1.7 Hz), 4.65 (pseudo t, 2H, J=1.7 Hz), 4.15 (s, 5H), 1.41 (d, 6H, J=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 189.6 (C), 189.4 (C), 162.7 (C), 142.3 (CH), 132.1 (C), 130.0 (CH), 129.4 (CH), 128.5 (CH), 122.7 (C), 76.1 (C), 75.7 (CH), 74.9 (CH), 74.1 (CH), 70.6 (CH), 23.8 (CH_3); IR (CH_2Cl_2): 2982 (vw), 1712 (w), 1668 (vs), 1617 (s), 1593 (m), 1491 (vw), 1376 (m), 1322 (w), 1268 (m), 1126 (w), 1088 (w), 1023 (m) cm^{-1}; MS (FAB): 427 ([M+H]$^+$, 87), 426 ([M]$^+$, 100), 384 (47), 361

(12), 320 (30), 319 (91), 245 (4), 189 (4), 149 (4), 121 (5), 85 (4); HRMS (FAB) calcd for $C_{25}H_{22}FeO_3$: 426.0918. Found: 426.0908.

4.5.5. 2-Ferrocenylidene-4,5-dimethyl-4-cyclopentene-1,3-dione (14D). R_f=0.49 in 4:1 C_6H_{14}/EtOAc; purple solid; mp 170.5–171.6 °C; 88.0 mg (55%, Method A), 22.7 mg (71%, Method B), 23.7 mg (74%, Method C); ^{1}H NMR ($CDCl_3$): δ 7.40 (s, 1H), 5.24 (pseudo t, 2H, J=1.7 Hz), 4.64 (pseudo t, 2H, J=1.7 Hz), 4.13 (s, 5H), 2.02 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 194.7 (C), 193.5 (C), 154.0 (C), 150.2 (C), 142.8 (CH), 121.1 (C), 76.0 (C), 74.6 (CH), 74.1 (CH), 70.6 (CH), 9.6 (CH_3), 9.5 (CH_3); IR (CH_2Cl_2): 2982 (w), 2933 (vw), 1712 (w), 1668 (vs), 1604 (vs), 1492 (w), 1376 (vs), 1326 (s), 1248 (m), 1126 (s), 1088 (s), 1023 (s) cm^{-1}; MS (FAB): 321 ([M+H]$^+$, 51), 320 ([M]$^+$, 100), 256 (23), 255 (84), 149 (14), 121 (9), 85 (9), 69 (6); HRMS (FAB) calcd for $C_{18}H_{16}FeO_2$: 320.0500. Found: 320.0514.

4.5.6. 2-Ferrocenylidene-4,5-diphenyl-4-cyclopentene-1,3-dione (14E). R_f=0.42 in 4:1 C_6H_{14}/EtOAc; purple solid; mp 198.3–199.2 °C; 129.1 mg (58%, Method A), 20.0 mg (45%, Method C); ^{1}H NMR ($CDCl_3$): δ 7.69 (s, 1H), 7.46–7.40 (m, 4H), 7.38–7.31 (m, 6H), 5.34 (s, 2H), 4.72 (s, 2H), 4.21 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 193.2 (C), 192.0 (C), 151.0 (C), 147.5 (C), 146.2 (CH), 130.6 (CH), 130.5 (CH), 130.3 (C), 130.1 (C), 130.0 (CH), 129.5 (C), 128.8 (CH), 76.2 (C), 75.1 (CH), 74.8 (CH), 70.8 (CH), note that CH peaks of phenyl groups overlap; IR (CH_2Cl_2): 2982 (w), 2933 (vw), 1712 (w), 1668 (vs), 1616 (vs), 1606 (vs), 1492 (w), 1376 (vs), 1326 (m), 1248 (w), 1127 (m), 1088 (s), 1024 (s) cm^{-1}; MS (FAB): 446 ([M+2H]$^+$, 39), 445 ([M+H]$^+$, 100), 444 ([M]$^+$, 81), 379 (67), 377 (9), 323 (6), 279 (5), 202 (5), 135 (8), 119 (15), 85 (13); HRMS (FAB, [M]$^+$) calcd for $C_{28}H_{20}FeO_2$: 444.0813. Found: 444.0825; HRMS (FAB, [M+H]$^+$) calcd for $C_{28}H_{21}FeO_2$: 445.0891. Found: 445.0914.

4.5.7. 5-Ferrocenyl-2,3-diisopropoxy-1,4-benzoquinone (15A). R_f=0.41 in 9:1 C_6H_{14}/EtOAc; green solid; 4.1 mg (2%, Method A); ^{1}H NMR ($CDCl_3$): δ 6.67 (s, 1H), 4.91 (s, 2H), 4.89 (septet, 1H, J=6.2 Hz), 4.74 (septet, 1H, J=6.2 Hz), 4.57 (s, 2H), 4.13 (s, 5H), 1.33 (d, 6H, J=6.2 Hz), 1.31 (d, 6H, J=6.2 Hz); ^{13}C NMR ($CDCl_3$): δ 184.8 (C), 184.0 (C), 147.2 (C), 145.8 (C, two quaternary carbons overlap), 125.5 (CH), 76.3 (C), 76.2 (CH, two isopropoxy CH overlap), 72.5 (CH), 70.9 (CH), 70.1 (CH), 23.1 (CH_3), 23.0 (CH_3); IR (CH_2Cl_2): 2975 (w), 2928 (vw), 1637 (s), 1567 (s), 1453 (w), 1378 (w), 1261 (vs), 1181 (m), 1101 (s), 1049 (w) cm^{-1}; MS (FAB): 410 ([M+2H]$^+$, 100), 409 ([M+H]$^+$, 14), 408 ([M]$^+$, 16), 368 (18), 325 (23), 291 (29), 259 (24), 213 (17), 186 (8), 121 (8); HRMS (FAB) calcd for $C_{22}H_{24}FeO_4$: 408.1024. Found: 408.1015.

For *5-ferrocenyl-2-isopropoxy-3-methyl-1,4-hydroquinone* (formed by reduction of **15A** during mass analysis), HRMS (FAB) calcd for $C_{22}H_{26}FeO_4$: 410.1180. Found: 410.1199.

4.5.8. 5-Ferrocenyl-2-isopropoxy-3-methyl-1,4-benzoquinone (15B). R_f=0.59 in 9:1 C_6H_{14}/EtOAc; green solid; 7.3 mg (4%, Method A); ^{1}H NMR ($CDCl_3$): δ 6.67 (s, 1H), 4.92 (s, 2H), 4.91 (septet, 1H, J=6.1 Hz), 4.58 (s, 2H), 4.12 (s, 5H), 1.96 (s, 3H), 1.31 (d, 6H, J=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 187.7 (C), 183.5 (C), 154.8 (C), 148.8 (C), 131.0 (C), 126.0 (CH), 76.6 (C), 76.3 (CH), 72.5 (CH), 70.9 (CH), 70.3 (CH), 23.4 (CH_3), 9.9 (CH_3); IR (CH_2Cl_2): 2975 (vw), 2928 (vw), 1646 (vs), 1580 (vs), 1453 (vw), 1378 (w), 1317 (vw), 1256 (s), 1181 (vs), 1096 (s), 1016 (m) cm^{-1}; MS (FAB): 366 ([M+2H]$^+$, 75), 365 ([M+H]$^+$, 68), 364 ([M]$^+$, 100), 323 (27), 322 (19), 257 (45), 229 (9), 186 (3), 149 (6), 121 (6), 85 (4); HRMS (FAB) calcd for $C_{20}H_{20}FeO_3$: 364.0762. Found: 364.0775.

For *5-ferrocenyl-2-isopropoxy-3-methyl-1,4-hydroquinone* (formed by reduction of **15B** during mass analysis), HRMS (FAB) calcd for $C_{20}H_{22}FeO_3$: 366.0918. Found: 366.0912.

4.5.9. 5-Ferrocenyl-2,3-dimethyl-1,4-benzoquinone (15D). R_f=0.53 in 9:1 C_6H_{14}/EtOAc; green solid; 12.8 mg (8% yield, Method A), 1.6 mg (5%, Method B), 2.6 mg (8%, Method C); ^{1}H NMR ($CDCl_3$): δ 6.80 (s, 1H), 4.91 (s, 2H), 4.55 (s, 2H), 4.11 (s, 5H), 1.94 (s, 3H), 1.93 (s, 3H); IR (CH_2Cl_2): 3680 (w), 3586 (vw), 2919 (w), 1641 (vs), 1623 (s), 1585 (s), 1453 (w), 1378 (w), 1317 (m), 1247 (s), 1030 (m) cm^{-1}; MS (FAB): 322 ([M+2H]$^+$, 72), 321 ([M+H]$^+$, 88), 320 ([M]$^+$, 100), 287 (5), 255 (42), 253 (4), 209 (4), 177 (4), 155 (14), 119 (24), 85 (23); HRMS (FAB, [M]$^+$) calcd for $C_{18}H_{16}FeO_2$: 320.0500. Found: 320.0489.

For *5-ferrocenyl-2,3-dimethyl-1,4-hydroquinone* (formed by reduction of **15D** during mass analysis), HRMS (FAB) calcd for $C_{18}H_{18}FeO_2$: 322.0656. Found: 322.0667.

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Propynylferrocene and (phenylethynyl)ferrocene

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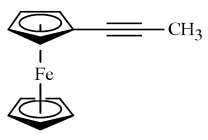
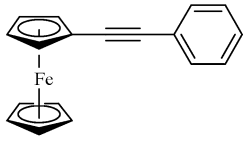
The title compounds, propynylferrocene, $[Fe(C_5H_5)(C_8H_7)]$, (I), and (phenylethynyl)ferrocene, $[Fe(C_5H_5)(C_{13}H_9)]$, (II), are stabilized by weak C—H···π interactions. The C≡C bond distances in these molecules are in the range 1.182 (3)–1.192 (3) Å. In (II), the ferrocenyl and phenyl groups are perpendicular, making an angle of 89.06 (13)°, which is a rare occurrence.

Comment

Recently, alkyne chemistry has experienced a major renaissance due to the involvement of molecules with C≡C bonds in the frontiers of modern organic chemistry, namely biochemistry, materials science and organometallic chemistry (Stang & Diederich, 1995; Diederich *et al.*, 2005). In this regard, ferrocenylalkynes occupy an important position since they can be converted to a structurally diverse set of ferrocenyl (Fc) compounds that are attractive synthetic targets owing to their physical, chemical and biological properties (Togni & Hayashi, 1995). The Fc group is often incorporated into a bioactive compound to obtain enhanced biological activities (Zora *et al.*, 2002, 2003; Jaouen *et al.*, 2004). In addition, the Fc group is ideal for use in drug design owing to its low toxicity, stability and lipophilicity (Biot *et al.*, 2000).



(I)



(II)

There is considerable interest in the synthesis of new materials with large second-order optical non-linearities because of their potential use in device applications related to telecommunications, optical computing, optical storage and optical information processing (Williams, 1984; Chemla & Zyss, 1987). In this regard, ferrocene-based donor–acceptor chromophores have been investigated widely for their linear and non-linear optical properties (Barlow & Marder, 2000; Stankovic *et al.*, 2001). In particular, ethynylferrocene (Wurst *et al.*, 1995; Polin & Schottenberger, 1996) and its derivatives (Nock & Schottenberger, 1993; Ingham *et al.*, 1994) have attracted substantial interest owing to the potential for electronic communication through the unsaturated alkyne linkage to the Fe center. There are also examples of ethynylferrocene linked through the alkyne spacer group to other metal centers (Berry *et al.*, 2004; Laus *et al.*, 2005). In this respect, the crystal structures of ethynylferrocene (Wurst *et al.*, 1995; Steiner *et al.*, 1996) and its derivatives (Ingham *et al.*, 1994; Dufkova *et al.*, 2003; Hocek *et al.*, 2004) have gained importance. We report here the crystal structures of propynylferrocene, (I), and (phenylethynyl)ferrocene, (II).

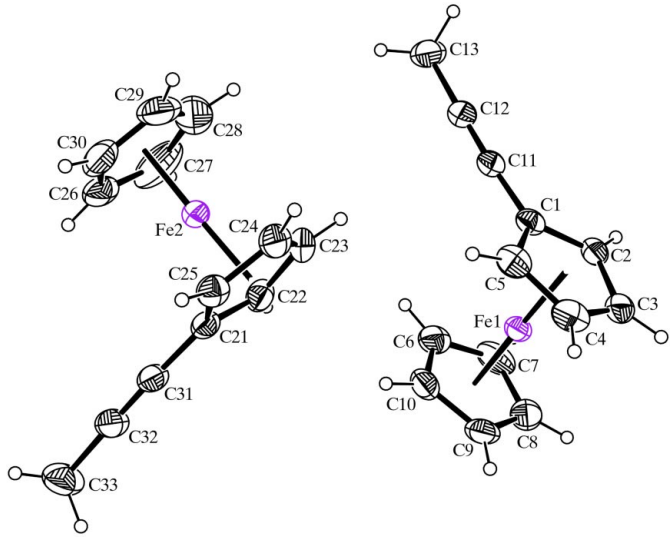


Figure 1
A view of the two molecules of (I), showing the atom-numbering scheme and 30% probability displacement ellipsoids.

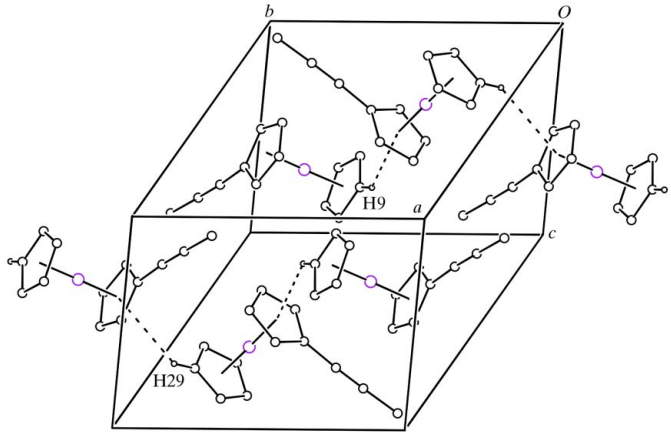


Figure 2
A packing diagram of (I), showing the C—H···π interactions as dashed lines. H atoms not involved in C—H···π interactions have been omitted for clarity.

The molecular structure of (I) is shown in Fig. 1. Selected bond distances and angles are given in Table 1. There are two molecules present in the asymmetric unit of (I). The C≡C bond distances in these molecules are 1.182 (3) and 1.184 (3) Å, which are in accord with those in similar complexes, *e.g.* 1,1,3-triferrocenylprop-2-yn-1-ol [1.180 (13) Å; Lucasser *et al.*, 1995] and 1-trimethylsilylethynylferrocene [1.188 (7) Å; Schottenberger *et al.*, 1999]. The Fe—Cg_s and Fe—Cg_{as} distances are in the range 1.6388 (11)–1.6467 (11) Å, and the Cg_s—Fe—Cg_{as} angles are 178.64 (8) and 178.77 (5)°, where Cg_s and Cg_{as} are the substituted and unsubstituted Cp ring centroids. The Cp rings in each molecule are almost parallel since the angles between the Cp ring planes are 1.43 (10) and 1.71 (19)°. The Cp rings of the Fc groups deviate slightly from an eclipsed conformation, as evidenced by the average C—Cg_s—Cg_{as}—C torsion angles of 7.41 (3) and −4.71 (3)°. The C—C bond distances in the Cp rings range from 1.342 (5) to 1.427 (3)°, while the Fe—C bond lengths range between 2.006 (3) and 2.0510 (17)°, all of which are as expected.

As in ethynylferrocene (Wurst *et al.*, 1995; Steiner *et al.*, 1996), there are no direction-specific aromatic π–π interactions between adjacent rings in (I), but there are two C—H···π interactions (Table 2 and Fig. 2).

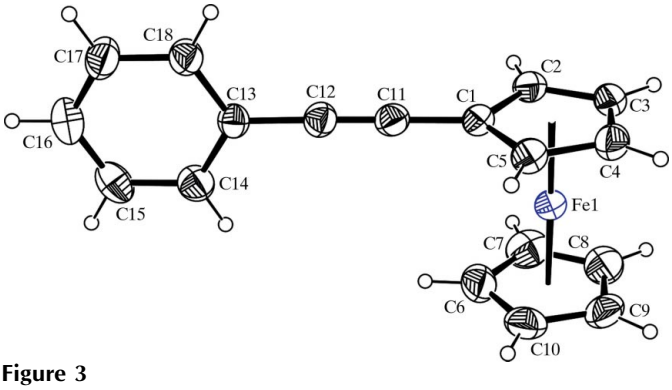


Figure 3
A view of (II), showing the atom-numbering scheme and 50% probability displacement ellipsoids.

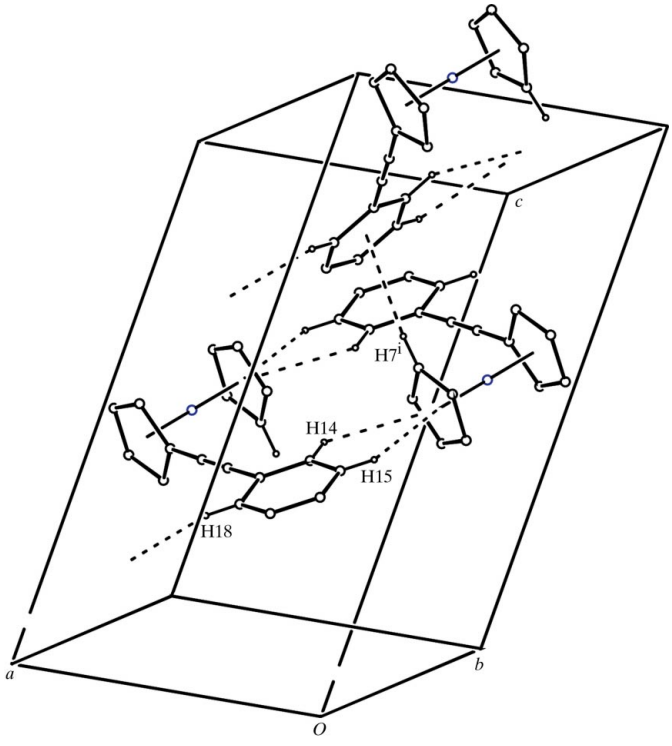


Figure 4
A packing diagram of (II), showing the C—H···π interactions as dashed lines. H atoms not involved in C—H···π interactions have been omitted for clarity. [Symmetry code: (i) $-x+1, -y+1, -z+1$.]

The molecular structure of (II) is shown in Fig. 3. Selected bond distances and angles are given in Table 3. Compound (II) comprises Fc and phenyl rings linked by an acetylene residue. The unusual feature of (II) is that the substituted Cp and phenyl rings are almost perpendicular, with an angle of 89.06 (13)°, which is a rare occurrence. This is clearly an indication of the interrupted conjugation between the Fc and Ph groups. However, in 1,1′-bis(phenylethynyl)ferrocene (Ingham *et al.*, 1994), a closely related compound, there is not a large tilting of the phenyl groups from the planes of the cyclopentadienyl rings since the angles between the phenyl rings and the cyclopentadienyl rings are 11.2 (2) and 26.6 (2)°. Moreover, a literature search for crystal structures incorporating the diphenylacetylene group has revealed some derivatives, *viz.* tolane (Mavridis & Moustakali-Mavridis, 1977), perfluorodiphenylacetylene (Goodhand & Hamor, 1979), octafluoronaphthalene–diphenylacetylene (1/1) (Collings *et al.*, 2001) and *N*-[4-(phenylethynyl)phenyl]benzamide (Yin *et al.*, 2005). In all, ethynyl-bridged phenyl rings are found to be almost coplanar, which is in contrast to the situation in (II).

The C≡C bond length in (II) is 1.192 (3) Å, which is in agreement with those in 1,1′-bis(phenylethynyl)ferrocene (Ingham *et al.*, 1994) and (*Z*)-1,4-diferrocenylbut-1-en-3-yne [1.199 (4) Å; Wurst *et al.*, 1995]. The Fc group is almost in an eclipsed conformation since the average C11—Cg_s—Cg_{as}—C6 pseudo-torsion angle is 0.60 (4)°. The centroids of the Cp rings are almost equidistant from Fe atoms, as indicated by the Fe—Cg_s and Fe—Cg_{as} distances of 1.641 (12) and 1.642 (12) Å, respectively. The Cg_s—Fe—Cg_{as} angle is 179.16 (6)°. The Cp rings are almost parallel since the angle between the Cp ring planes is 1.62 (16)°. The C—C bond distances in the Cp rings range from 1.390 (4) to 1.428 (3) Å. The Fe—C bond lengths are in the range 2.021 (3)–2.039 (2) Å.

As in compound (I) and ethynylferrocene (Wurst *et al.*, 1995; Steiner *et al.*, 1996), compound (II) is also stabilized by four C—H···π interactions, two of them, C14—H14···π and C15—H15···π, in the chelate ring form (Table 4 and Fig. 4).

Experimental

Compound (I) was prepared from ethynylferrocene by the Vilsmeier–Haack formylation (Doisneau *et al.*, 1992). Suitable crystals of (I) were obtained by slow evaporation of a 19:1 hexane–ethyl acetate solution at room temperature. Compound (II) was synthesized by a modified literature procedure (Okuro *et al.*, 1993). Iodobenzene

(0.3 ml, 2.38 mmol) and ethynylferrocene (500 mg, 2.38 mmol) were added to a mixture of CuI (23 mg, 0.12 mmol), PPh_3 (62 mg, 0.24 mmol), K_2CO_3 (493 mg, 3.57 mmol) and dimethylformamide (4.8 ml) under argon. The resulting mixture was refluxed at 393 K for 16 h. The solution was then extracted with ether, washed with water and dried over $MgSO_4$. Final purification was achieved by flash column chromatography on silica gel using hexane as the eluant. The product was obtained in 47% yield. The spectroscopic data for (II) were in agreement with those reported previously for this compound (Stepnicka *et al.*, 1999). Single crystals of (II) were obtained by slow evaporation of a 19:1 hexane–ethyl acetate solution at room temperature.

Compound (I)

Crystal data

$[Fe(C_5H_5)(C_8H_7)]$
M_r = 224.08
Triclinic, $P\overline{1}$
a = 9.8232 (7) Å
b = 10.3192 (7) Å
c = 11.1465 (8) Å
α = 76.431 (5)°
β = 86.740 (6)°
γ = 70.527 (5)°
V = 1035.25 (13) Å^3
Z = 4
D_x = 1.437 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 1.41 mm^{-1}
T = 296 (2) K
Prism, red
0.60 × 0.49 × 0.40 mm

Data collection

Stoe IPDS-II diffractometer
ω scan
Absorption correction: integration (*X-RED32*; Stoe & Cie, 2002)
T_{min} = 0.558, T_{max} = 0.670
15013 measured reflections
4072 independent reflections
3613 reflections with $I > 2\sigma(I)$
R_{int} = 0.046
θ_{max} = 26.0°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.027
$wR(F^2)$ = 0.074
S = 1.01
4072 reflections
255 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0394P)^2 + 0.2017P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for (I).

C1—C11	1.429 (3)	C21—C31	1.427 (3)
C11—C12	1.184 (3)	C31—C32	1.182 (3)
C12—C13	1.464 (3)	C32—C33	1.461 (3)
C5—C1—C2	107.29 (17)	C22—C21—C31	125.93 (18)
C2—C1—C11	126.30 (17)	C25—C21—C31	126.5 (2)
C12—C11—C1	176.28 (19)	C32—C31—C21	177.5 (2)
C11—C12—C13	178.9 (2)	C31—C32—C33	178.9 (2)
C11—C1—C2—C3	177.69 (17)	C31—C21—C22—C23	−178.92 (18)

Table 2
Hydrogen-bond geometry (Å, °) for (I).

*Cg*1 and *Cg*2 are the centroids of the C1–C5 and C21–C25 rings, respectively.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C9—H9···*Cg*2^{i}	0.93	3.10	3.874 (2)	142
C29—H29···*Cg*1^{ii}	0.93	3.12	3.889 (3)	141

Symmetry codes: (i) $-x+1, -y+1, -z+1$; (ii) $-x+1, -y, -z+1$.

Compound (II)

Crystal data

$[Fe(C_5H_5)(C_{13}H_9)]$
M_r = 286.14
Monoclinic, $P2_1/c$
a = 8.7368 (9) Å
b = 10.6296 (15) Å
c = 15.1113 (16) Å
β = 105.327 (8)°
V = 1353.5 (3) Å^3
Z = 4
D_x = 1.404 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 1.10 mm^{-1}
T = 296 (2) K
Plate, red
0.62 × 0.51 × 0.14 mm

Data collection

Stoe IPDS-II diffractometer
ω scan
Absorption correction: integration (*X-RED32*; Stoe & Cie, 2002)
T_{min} = 0.583, T_{max} = 0.848
7479 measured reflections
2650 independent reflections
1865 reflections with $I > 2\sigma(I)$
R_{int} = 0.045
θ_{max} = 26.0°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.029
$wR(F^2)$ = 0.069
S = 0.91
2650 reflections
172 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.036P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

Table 3
Selected geometric parameters (Å, °) for (II).

C1—C11	1.429 (3)	C12—C13	1.440 (3)
C11—C12	1.192 (3)		
C5—C1—C2	107.25 (18)	C12—C11—C1	178.5 (3)
C5—C1—C11	126.0 (2)	C11—C12—C13	179.0 (2)
C11—C1—C2—C3	179.9 (2)	C12—C13—C14—C15	−179.1 (2)

Table 4
Hydrogen-bond geometry (Å, °) for (II).

*Cg*1, *Cg*2 and *Cg*3 are the centroids of the C1–C5, C6–C10 and C13–C18 rings, respectively.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C7—H7···*Cg*3^{ii}	0.93	3.13	3.927 (3)	145
C14—H14···*Cg*2^{i}	0.93	3.14	3.817 (3)	131
C15—H15···*Cg*2^{i}	0.93	3.25	3.870 (3)	126
C18—H18···*Cg*1^{iii}	0.93	2.72	3.535 (3)	147

Symmetry codes: (i) $-x+1, -y+1, -z+1$; (ii) $-x+1, y-\frac{1}{2}, -z+\frac{1}{2}$; (iii) $-x+2, y+\frac{1}{2}, -z+\frac{1}{2}$.

All H atoms were refined using the riding-model approximation, with C—H = 0.93 Å for aromatic H atoms [$U_{iso}(H) = 1.2U_{eq}(C)$] and C—H = 0.96 Å for methyl H atoms [$U_{iso}(H) = 1.5U_{eq}(C)$].

For both compounds, data collection: *X-AREA* (Stoe & Cie, 2002); cell refinement: *X-AREA*; data reduction: *X-RED32* (Stoe & Cie, 2002); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: HJ3011). Services for accessing these data are described at the back of the journal.

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2-Pyridiniohydrazinium dichloride

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The crystal structure of the title compound, $C_5H_9N_3^{2+}\cdot 2Cl^-$, is stabilized by N—H···Cl hydrogen bonds, forming a three-dimensional network. Each chloride anion forms three hydrogen bonds with N atoms, and the hydrazine unit forms $R_2^1(5)$ motifs with one of the Cl^- anions. The aromatic ring is almost coplanar with both the N atoms of the hydrazine substituent and with one of the Cl^- anions.

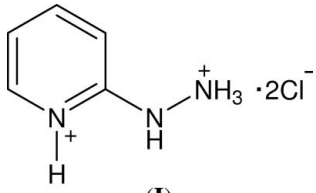
Key indicators

Single-crystal X-ray study
T = 296 K
Mean σ(C–C) = 0.002 Å
R factor = 0.026
wR factor = 0.068
Data-to-parameter ratio = 16.5

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Comment

Hydrogen bonding plays a key role in molecular recognization and the engineering of organic solids (Desiraju, 1989; Melendez & Hamilton, 1998). The design of highly specific solid-state compounds is of considerable significance in organic chemistry, due to the important applications of these compounds in the development of new optical, magnetic and electronic systems (Lehn, 1992). We present here the crystal structure of the title compound, (I).



(**I**)

The asymmetric unit of (I) (Fig. 1 and Table 1) contains a hydrazinopyridine ring, protonated at the pyridine N1 and hydrazine N3 atoms, and two Cl^- anions multiply hydrogen-bonded to the N—H groups.

In the crystal structure of (I), there are six types of hydrogen bonds between the N and Cl^- anions, forming a three-dimensional network (Fig. 2 and Table 2). Each Cl^- anion forms three hydrogen bonds with N atoms, and the hydrazine unit forms $R_2^1(5)$ motifs (Etter, 1990) with the Cl2 anions (Fig. 2). The aromatic ring plane is inclined at 5.66 (9)° to the C1—N2—N3—H3*A* plane, and the Cl1 anion is coplanar with the pyridinium cation [deviation 0.0060 (6) Å; Fig. 1].

Experimental

2-Hydrazinopyridine (100 mg) was dissolved in diethyl ether (5 ml) and concentrated HCl was added until a precipitate was obtained. The precipitate was filtered off, dissolved in water and filtered again. Slow evaporation of the solvent afforded single crystals of (I) [m.p. 485–486 K (decomposition)].

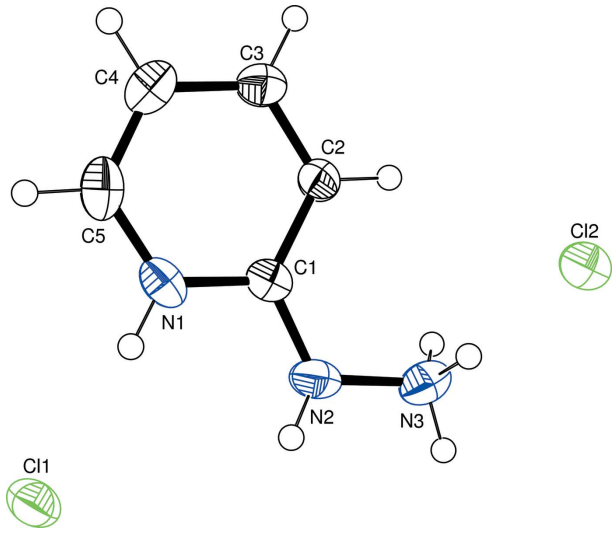


Figure 1
A view of the asymmetric unit of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

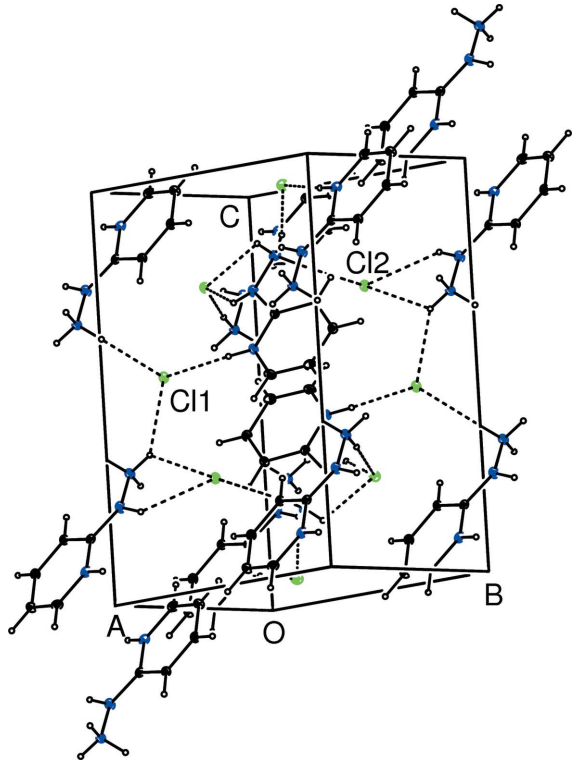


Figure 2
A packing diagram for (I), with hydrogen bonds drawn as dashed lines.

Crystal data

$C_5H_9N_3^{2+}\cdot 2Cl^-$
M_r = 182.05
Monoclinic, $P2_1/n$
a = 7.3787 (11) Å
b = 8.5682 (9) Å
c = 12.637 (2) Å
β = 93.179 (12)°
V = 797.70 (19) Å^3
Z = 4
D_x = 1.516 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.74 mm^{-1}
T = 296 (2) K
Block, brown
0.58 × 0.47 × 0.31 mm

Data collection

Stoe IPDS II diffractometer
ω scans
Absorption correction: integration (*X-RED32*; Stoe & Cie, 2002)
T_{min} = 0.684, T_{max} = 0.826
4066 measured reflections
1564 independent reflections
1388 reflections with $I > 2\sigma(I)$
R_{int} = 0.024
θ_{max} = 26.0°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.026
$wR(F^2)$ = 0.068
S = 1.05
1564 reflections
95 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0349P)^2 + 0.2627P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ < 0.001
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

C1—N1	1.338 (2)	C5—N1	1.345 (2)
C1—N2	1.356 (2)	N2—N3	1.410 (2)
N1—C1—N2	115.51 (14)	N2—C1—C2	125.76 (14)
N1—C1—C2	118.71 (14)	C1—N2—N3	118.95 (14)
N1—C1—N2—N3	−174.86 (13)		

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···Cl1	0.86	2.17	3.0259 (14)	175
N3—H3A···Cl2^{i}	0.89	2.55	3.1441 (15)	125
N3—H3A···Cl1^{ii}	0.89	2.61	3.1674 (15)	121
N3—H3B···Cl2	0.89	2.19	3.0730 (16)	173
N3—H3C···Cl1^{iii}	0.89	2.21	3.0800 (15)	167
N2—H2A···Cl2^{i}	0.83 (3)	2.49 (3)	3.1092 (15)	132.6 (19)

Symmetry codes: (i) $-x+\frac{1}{2}, y-\frac{1}{2}, -z+\frac{3}{2}$; (ii) $x-\frac{1}{2}, -y+\frac{1}{2}, z+\frac{1}{2}$; (iii) $-x+\frac{3}{2}, y+\frac{1}{2}, -z+\frac{3}{2}$.

Atom H2A was located in a difference map and refined isotropically [N—H = 0.83 (3) Å]. All other H atoms were refined using the riding-model approximation, with C—H = 0.93 Å and N—H = 0.86 Å, and with U_{iso}(H) = 1.2U_{eq}(C,N).

Data collection: *X-AREA* (Stoe & Cie, 2002); cell refinement: *X-AREA*; data reduction: *X-RED32* (Stoe & Cie, 2002); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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Coupling of cyclopropylcarbene–chromium complex with ferrocenyl alkynes: synthesis of 5-ferrocenyl-5-hydroxy-2-cyclopentenones and 4-ferrocenyl-4-cyclopentene-1,3-diones

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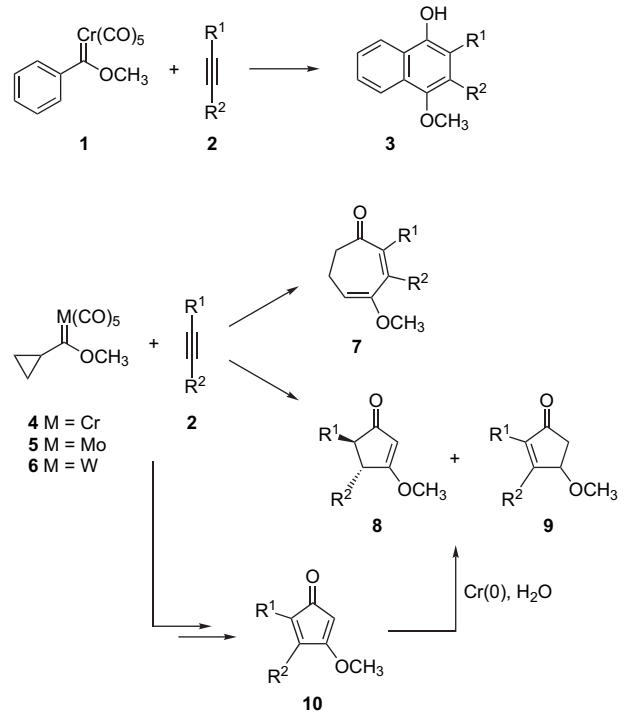
Abstract—The coupling of ferrocenyl alkynes with cyclopropylcarbene–chromium complex leads to ferrocenyl-substituted 2-cyclopentenones with or without a hydroxy substituent, namely 4-cyclopentene-1,3-diones, 2-cyclobutenones, and α,β-unsaturated aldehydes in varying amounts. The reaction initially produces a cyclopentadienone intermediate, then to the double bond of which, bearing a ferrocenyl group, addition of water occurs to afford hydroxy-substituted 2-cyclopentenones. In all the products, the hydroxy group ends up α to the ferrocenyl moiety. In contrast, where no addition of water occurs, the alkenic bond is reduced to give 2-cyclopentenones. A secondary reaction product, namely 4-cyclopentene-1,3-dione, is formed by hydrolysis of the cyclopentadienone intermediates.

1. Introduction

Fischer type metal carbene complexes have emerged as valuable reagents for organic synthesis in recent years.[1] One of the most intensely studied reactions of metal carbene complexes is the coupling of α,β-unsaturated Fischer carbene complexes, such as **1**, with alkynes **2**, known as the Dötz reaction (Scheme 1).[2,3] The first product ever isolated from this type of reaction has been a phenol derivative, such as **3**, which is normally the predominant product of the reaction. Under appropriate conditions, cyclobutenones, cyclopentenones, furans, cyclohexadienones, indenes, and vinylketenes have also resulted from these reactions.[2,3] An ever-continuing aspect of these studies has been the use of a structurally diverse set of Fischer carbene complexes to afford a diverse array of organic compounds. Interestingly, as shown by Herndon and co-workers,[4] the analogous reaction, which employs cyclopropyl-substituted carbene–chromium complex **4** and alkynes **2**, did not produce the expected cycloheptadienones **7**, rather it gave exclusively the cyclopentenone derivatives **8** and **9** (Scheme 1). The scope, limitations, and mechanism of this five-membered ring-forming reaction were studied in detail.[4] It was shown that the reaction initially produces



Scheme 1.

Keywords: Fischer metal carbene; Chromium–carbene complex; Ferrocene; Ferrocenyl alkynes; Carbocyclic five-membered rings; Cyclopentenones; Cyclopentenediones; Cyclobutenones; α,β-Unsaturated aldehydes; Coupling.
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a cyclopentadienone derivative, such as **10**, which is then reduced to cyclopentenones **8** and **9** by the low-valent chromium by-products and water. Notably, the conversion of complex **4** and alkynes **2** to cyclopentenones allows the construction of highly functionalized five-membered ring systems from readily available reagents. The analogous molybdenum and tungsten carbene complexes **5** and **6**, however, produced the seven-membered ring derivatives **7** upon reaction with alkynes.[5]

Cyclopentenones are present in a variety of biologically important molecules such as jasmonoids and prostaglandins (PGs).[6,7] For some time, PGs have attracted considerable attention since they play an important role in the human body, controlling a wide variety of physiological responses.[8] More recently, studies on the biological activities of the so-called 'cyclopentenone PGs' have shown that these compounds have the potential to become very important in a therapeutic context. Some cyclopentenone PGs, such as Δ^7-PG-A_1 and its methyl derivative, display significant anti-tumor activity as well.[9] It should be noted that the α,β-unsaturated carbonyl functionality is essential for many of the biological actions of such compounds, as confirmed in model studies, where 2-cyclopentenone has exhibited significant biological activity, while related compounds, cyclopentanone and cyclopentene, were found to be unreactive.[10] Furthermore, due to the versatility of α,β-unsaturated carbonyl functionality, cyclopentenones are very useful building blocks for the synthesis of other biologically active compounds, such as cyclopentanoid antibiotics.[7] Although numerous methods are known for the synthesis of cyclopentenones and related pharmacophores,[7,11] new variants continue to appear stimulated by the broad spectrum of biological activity of these type of compounds.

Recent studies have shown that the integration of a ferrocenyl group into such structures may enhance their biological activities or generate new medicinal properties.[12,13] Surprisingly, cyclopentenones bearing a ferrocenyl moiety are rare.[14] The development of a general synthetic entry to ferrocenyl-substituted cyclopentenones is therefore of interest since it could lead to a new source of biologically active compounds. We anticipated that the reaction between ferrocenyl alkynes and cyclopropylcarbene–chromium complex **2** would produce 2-ferrocenyl-2-cyclopentenone derivatives. This methodology, however, has not been utilized for the synthesis of ferrocenyl-substituted cyclopentenones, presumably due to the scarce availability of starting ferrocenyl alkynes. As part of our general involvement in ferrocene[15,16] and metal carbene chemistry,[17] as well as small and medium-size ring systems,[18] we have investigated the reaction between ferrocenyl alkynes and the cyclopropylcarbene–chromium complex **4**, which affords ferrocenyl-substituted cyclopentenones.[19] We herein report the results of this study.

2. Results and discussion

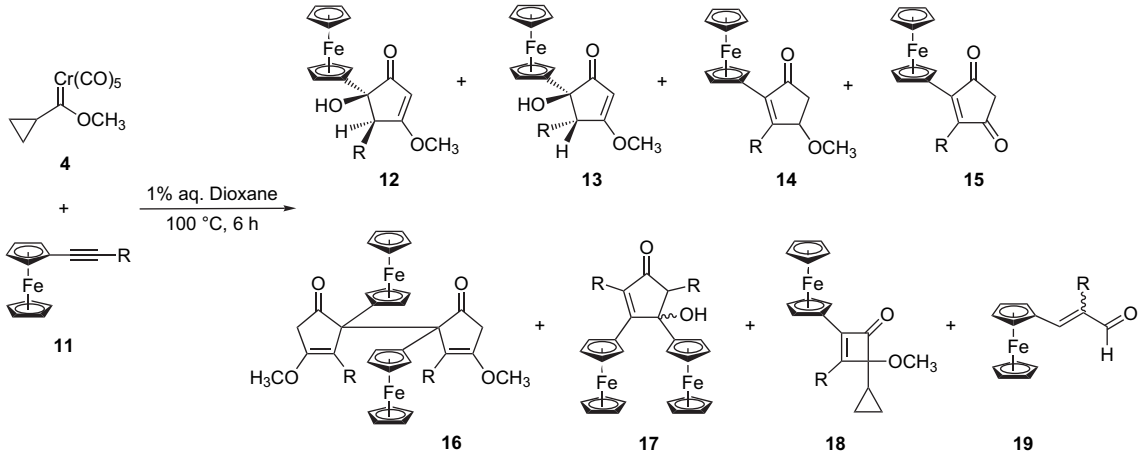
The synthesis of ferrocenyl alkynes was accomplished from ethynylferrocene (**11a**)[20] according to known or modified literature procedures. Treatment of ethynylferrocene (**11a**) with *n*-butyllithium produced in situ lithioethynylferrocene that was further reacted with methyl iodide, benzyl bromide or trimethylsilyl chloride to yield propynylferrocene (**11b**), (3-phenylpropynyl)ferrocene (**11c**), and (trimethylsilylethynyl)ferrocene (**11d**), respectively.[21] On the other hand, the reaction of ethynylferrocene (**11a**) and iodobenzene in the presence of copper iodide, triphenylphosphine, and potassium carbonate in refluxing DMF produced (phenylethynyl)ferrocene (**11e**).[22] Diferrocenylethyne (**11f**) was synthesized by the metathesis of propynylferrocene (**11b**) in the presence of molybdenum hexacarbonyl and 2-fluorophenol in refluxing chlorobenzene.[23] Cyclopropylcarbene–chromium complex **4** was prepared from cyclopropyl bromide and chromium hexacarbonyl according to a standard procedure.[4d]

Subsequently, we investigated the reactions of ferrocenyl alkynes **11** with carbene complex **4**. The results of this study are summarized in Table 1. The reactions were carried out under optimal conditions, in which a 1:1.5 mole ratio of carbene complex **4** and alkyne **11**, respectively, was added to a refluxing 1% aq dioxane solution over a period of 2 h, and then the resulting reaction mixture was further refluxed for 6 h. As indicated in Table 1, the coupling of a variety of ferrocenyl alkynes **11** with carbene complex **4** led to varying amounts of 2-cyclopentenones with or without a hydroxy substituent, giving 4-cyclopentene-1,3-diones, 2-cyclobutenones, and/or α,β-unsaturated aldehydes.

The most interesting aspect in these reactions was the formation of 5-hydroxy-2-cyclopentenone derivatives **12** and/or **13** (Table 1). To the best of our knowledge, such hydroxy-substituted cyclopentenones have not been observed previously from similar reactions. The structure of compound **12b** was unambiguously determined by X-ray crystal analysis, as shown in Figure 1.[24] Although two molecules are present in the asymmetric unit of **12b**, only one molecule is shown in Figure 1 for clarity. In the solid state, the five-membered ring is very close to planarity and ferrocenyl group is almost in an eclipsed conformation. As concluded from X-ray structure, in the major diastereomers **12a–f**, ferrocenyl and the R groups are trans while they are cis in the minor diastereomer **13b**. For a particular case, cyclopentenone **12** could be expected to be more stable than its diastereomer **13** on the basis of steric considerations. From these reactions, cyclopentenones **14**, which do not contain a hydroxy group, were also isolated (Table 1).

The proposed mechanism for the formation of cyclopentenones **12–14** is outlined in Scheme 2. The loss of a cis carbon monoxide ligand from complex **4** and coordination of alkyne **11** produces alkyne–carbene complex **20**, which undergoes a [2+2] cycloaddition reaction to afford metallacyclobutene **21**. Electrocyclic ring opening then occurs to yield internally coordinated vinyl carbene complex **22**. The involvement of metallacyclobutenes in these processes has recently been questioned by Hofmann, and found to be unfavorable on the basis of theoretical calculations.[25] Thus complex **22** could be directly formed from **20** via alkyne insertion without formation of metallacyclobutene **21**. It should be noted that the mechanism up to vinyl carbene complex **22** is identical to that proposed for the Dötz reaction.[3] Afterward, cyclopropane ring of **22** opens by a 1,5-alkyl shift to give metallacycloheptadiene **23**. CO insertion affords metallacyclooctadienone **24**, which then converts to complex **26** with and/or without formation of complex **25**. The fragmentation

Table 1. Reaction of cyclopropylcarbene–chromium complex **4** with ferrocenyl alkynes **11**



Entry[a]	Starting alkyne	R	Products (isolated yield, %)
A	**11a**	H	**12a** (45)+**17a** (6)
B	**11b**	CH_3	**12b** (36)+**13b** (16)+**14b** (17)+**15b** (17)+**16b** (4)+**19b**[b] (6)
C	**11c**	CH_2–Ph	**12c** (16)+**15c** (57)
D	**11d**	$Si(CH_3)_3$	**12a** (26)
E	**11e**	Ph	**12e** (31)+**14e** (5)+**15e** (55)
F	**11f**	Fc (ferrocenyl)	**12f** (18)+**14f** (9)+**15f** (32)+**18f** (7)

[a] Entry letters define R group for compounds **11**–**19**.
[b] Configuration of double bond was not determined.

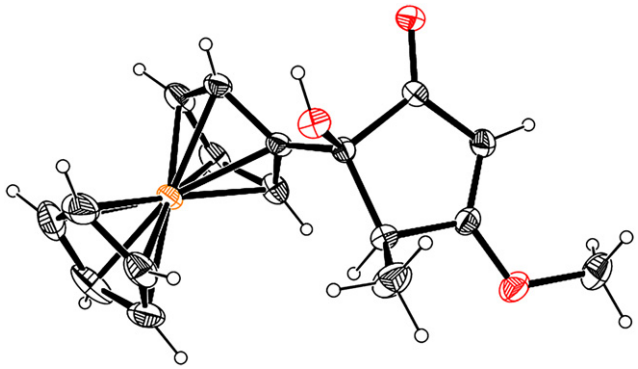
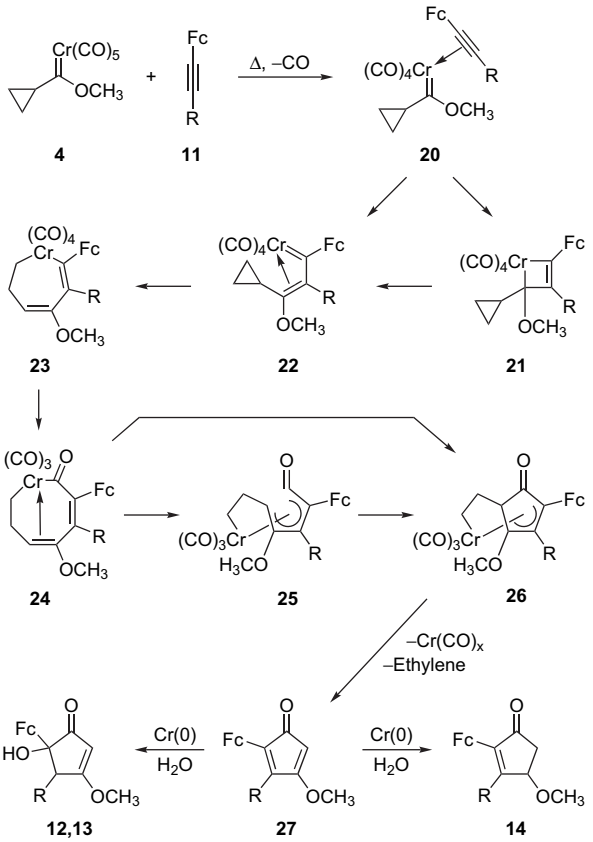


Figure 1. ORTEP diagram of (4*R*(*S*),5*R*(*S*))-5-ferrocenyl-5-hydroxy-3-methoxy-4-methyl-2-cyclopentenone (**12b**): ellipsoids are drawn at 20% probability.

of complex **26** with ethylene loss yields cyclopentadienone **27**. It should be noted that the formation of cyclopentadienone intermediates in these processes was already verified by the Herndon group using similar reactions.[4b]

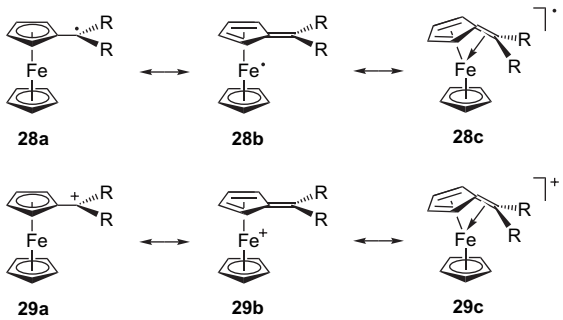
Eventually, in **27**, water addition occurs to the double bond adjacent to ferrocenyl group, which provides 5-hydroxy-2-cyclopentenones **12** and/or **13** (Scheme 2), in contrast to earlier studies.[4] Although, the mechanism of this addition is unclear at present, it might be a transition metal catalyzed or mediated process in our reaction conditions, which may proceed through a radical or ionic mechanism. It is interesting to note that the hydroxy substituent in cyclopentenones **12** and **13** ends up α to the ferrocenyl group. This might be attributed to the developing radical or positive charge at that carbon during the course of the reaction, which is well stabilized, although it is also α to the carbonyl, since the ferrocenyl group is very effective at stabilizing an α radical[26] or



Scheme 2.

carbocation,[27] especially the latter. In general, as depicted in Scheme 3, the radical and carbocation stabilizing ability of the ferrocenyl group can be explained by a delocalization

mechanism involving the Fe atom and a major contribution from an η^4-form, as represented by structures **28b** and **29b**, respectively.[26,27] More recently, regarding the ferrocenyl-stabilized carbocations, the combination of physical methods and calculations has affirmed a fulvenoid structure, such as **29c**, in which, depending upon the steric and electronic nature of the substituents R, the exocyclic double bond leans toward the metal to maximize the metal–ligand interaction, which increases the stability of the complex.[27c] Similarly, in the light of these studies, a fulvenoid type structure, such as **28c**, can be proposed for the ferrocenyl-stabilized radicals.



Scheme 3.

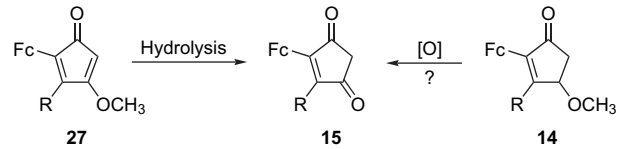
It is tempting to simply argue that the exceptional radical or carbocation stabilizing aptitude of the ferrocenyl group in the α position could facilitate the water addition to cyclopentadienone **27** to afford cyclopentenones **12** and/or **13**. This is also indirectly supported by the previous studies of Herndon that the reaction of carbene complex **4** with phenylacetylene, 1-phenylpropyne or diphenylacetylene did not produce any hydroxy-substituted cyclopentenones, rather it gave exclusively cyclopentenones **8** and/or **9**, where R^1=Ph, R^2=H, Me or Ph (Scheme 1).[4] Therefore, the formation of 5-hydroxy-2-cyclopentenones **12** and/or **13** in these reactions is attributed to the ferrocenyl group since it is a much better radical and carbocation stabilizing group than the phenyl group.

To deduce whether the effect of the ferrocenyl group in these processes is internal or external, the reaction between carbene complex **4** and diphenylacetylene was carried out in the presence of ferrocene under the same conditions. However, this reaction afforded only cyclopentenones **8** and/or **9**, where R^1=R^2=Ph, no hydroxy-included cyclopentenones were formed. This is clearly indicative of the internal effect of the ferrocenyl group, which could relate to its radical and/or carbocation stabilizing ability as mentioned above.

In contrast, no water addition occurs in the formation of cyclopentenones **14**; instead, the other double bond of cyclopentadienone **27**, adjacent to methoxy group, is reduced by the combination of Cr(0) species and water (Scheme 2), as manifested in previous studies.[4] Notably, for this reduction, a hydrogen source is needed. As suggested,[4a] water and low oxidation state chromium may interact to form metal hydrides, which could furnish the source of hydrogen. Alternatively, Cr(0) may reduce H_2O to H_2, which could also supply the source of hydrogen. The detailed studies of Herndon have shown that water, not the hydrogen gas, provides the source of hydrogen for these reductions.[4a] It was also proposed that reduction mechanism involves a net two-electron transfer-double protonation process.[4e]

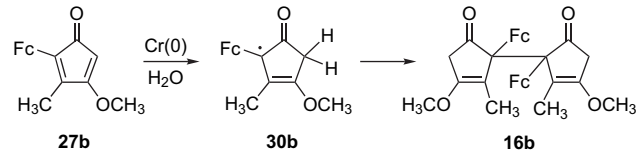
As can be seen in Scheme 2, the overall regiochemistry of the reaction is set in the metallacyclobutene forming step (**20**→**21**) or in the vinyl carbene forming step (**20**→**22**), where the larger group of alkyne (i.e., ferrocenyl group) ends up α to the chromium in order to minimize steric interactions. Following this substituent through the mechanism, it is predicted that the larger group will be α to the carbonyl in the final products **12**–**14**. The observed regiochemistry is consistent with those found in the similar reactions.[4,5]

In some reactions, ferrocenyl-substituted cyclopentenediones **15** were also observed (entries B, C, E, and F). Notably, in most cases, they were the major product of the reaction. In fact, cyclopentenediones **15** are the secondary products of the reaction, resulting from the hydrolysis of initially formed cyclopentadienones **27** (Scheme 4), which is presumably catalyzed by low-valent chromium and water. The hydrolysis of 3-alkoxy-2,4-cyclopentadienones to 4-cyclopentene-1,3-diones is a well-known process.[28] Alternatively, the oxidation of 4-methoxy-2-cyclopentenones **14** by metal species could also be expected to produce cyclopentenediones **15** to some extent, but these types of oxidations do not have ample precedent.



Scheme 4.

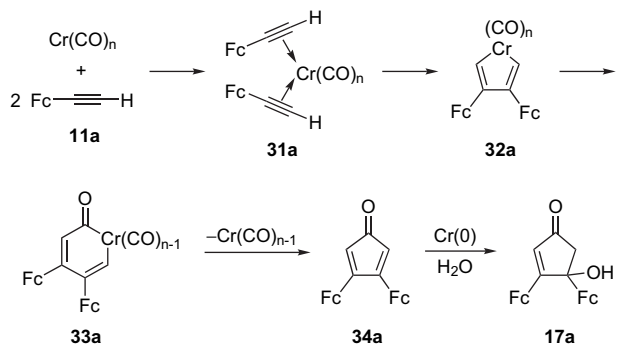
Surprisingly, from the reaction between carbene complex **4** and propynylferrocene (**11b**), a dimeric cyclopentenone derivative was also isolated and assigned as compound **16b** (entry B). The proposed mechanism for its formation is illustrated in Scheme 5. Under the reaction conditions, cyclopentadienone **27b** first produces radical **30b**, which is then dimerized to compound **16b**. This clearly provides an indirect evidence for the reduction of cyclopentadienones **27** through the radical type mechanism.



Scheme 5.

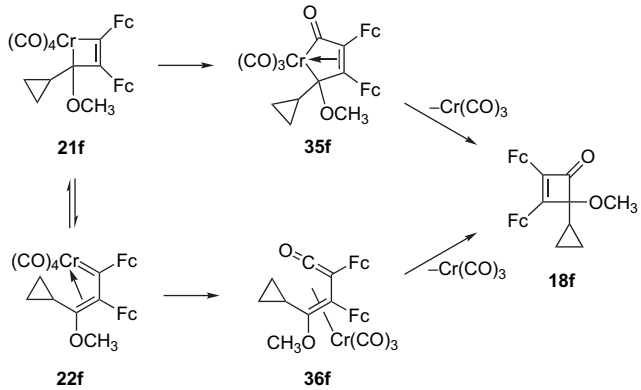
Interestingly, the reaction of carbene complex **4** with ethynylferrocene (**11a**) produced a side product, identified as 4-hydroxy-2-cyclopentenone **17a** (entry A), in addition to 5-hydroxy-2-cyclopentenone **12a**. The proposed mechanism for the formation of **17a** is outlined in Scheme 6. Coordination of two ethynylferrocene molecules (**11a**) to an in situ formed unsaturated $Cr(CO)_n$ species gives alkyne complex **31a**, which converts to metallacyclopentadiene **32a** through

a Reppe-type coupling.[29] CO insertion then affords metallacyclohexadienone **33a**, which generates cyclopentadienone **34a** upon reductive elimination. Finally, water addition to one of the double bonds yields hydroxy-substituted cyclopentenone **17a**. As expected, the hydroxy substituent ends up α to the ferrocenyl group for the reasons mentioned above. It should be noted that the coupling of terminal alkynes with metal carbenes often produce cyclopentadienones, similar to **34a**, and their reduction products as the side products.[4d]



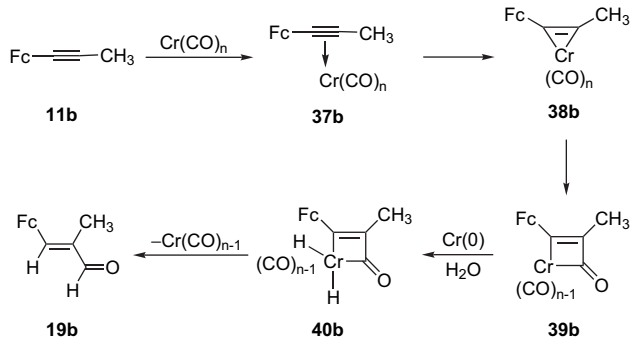
Scheme 6.

From the reaction with diferrocenylacetylene (**11f**) (entry F), a cyclobutenone derivative, **18f**, was also obtained. Cyclobutenones are frequently observed as the minor by-products in the coupling of alkynes with metal carbene complexes. Their formation is mechanistically important since they support the intermediacy of metallacyclobutenes, vinyl carbenes, and/or vinylketenes.[2b,4d] Cyclobutenone **18f** could arise via two possible pathways as depicted in Scheme 7. Metallacyclobutene **21f** first gives CO insertion to afford internally coordinated metallacyclopentenone **35f**, which produces cyclobutenone **18f** upon reductive elimination Alternatively, vinyl carbene complex **22f** experiences CO insertion and yields vinylketene complex **36f**, which furnishes cyclobutenone **18f** after electrocyclic ring closure followed by decomplexation. Note that metallacyclobutene **21f** and vinyl carbene complex **22f** are interconvertible and their formation has been shown in Scheme 2. It should be noted that cyclobutenone **18f** was also observed in the reaction between pentacarbonyl[(cyclopropyl)methoxymethylene]molybdenum complex and diferrocenylacetylene (**11f**), the formation of which presumably involves similar intermediates.[30]



Scheme 7.

Surprisingly, an α,β-unsaturated aldehyde derivative, **19b**,[31] was also formed in these reactions (entry B), most likely arising via a hydroformylation reaction,[31] as proposed in Scheme 8. Coordination of alkyne **11b** to an in situ formed unsaturated $Cr(CO)_n$ species produces alkyne complex **37b**, which converts to metallacyclopropene **38b**. CO insertion then provides metallacyclobutene **39b**. Oxidative addition of hydrogen into chromium yields hydrido complex **40b**, which, upon tandem reductive eliminations, affords aldehyde **19b**.[32] Importantly, for the oxidative addition step (**39b**→**40b**), hydrogen is needed. Presumably, as noted before, water could furnish the source of hydrogen upon interaction with Cr(0).



Scheme 8.

It should be noted that the reaction between (trimethylsilylethynyl)ferrocene (**11d**) and carbene complex **4** revealed a complex reaction mixture; only cyclopentenone **12a** could be isolated (entry D), in which desilylation occurred.

In general, as can be seen in Table 1, a variety of ferrocenyl alkynes **11** participated smoothly in the coupling with chromium complex **4**, producing 5-hydroxy-2-cyclopentenones **12** and/or 4-cyclopentene-1,3-diones **15** as the major products of these reactions. It is particularly noteworthy that α-hydroxy cyclic ketones, such as 5-hydroxy-2-cyclopentenone derivatives, occupy a central position in the synthesis of complex natural products, which stimulated an intense search for oxidants capable of effecting the direct α-hydroxylation of cyclic ketones.[33] Along this line, 4-cyclopentene-1,3-diones have also proven as useful precursors, particularly for the synthesis of 2-alkylidene/arylidene-4-cyclopentene-1,3-diones,[34] which show a high degree of anti-tumor activity.[15d,35]

3. Conclusions

In summary, we have shown that cyclopropylcarbene–chromium complex **4** can couple with ferrocenyl alkynes **11** to afford ferrocenyl-substituted 2-cyclopentenones, 4-cyclopentene-1,3-diones, 2-cyclobutenones, and/or α,β-unsaturated aldehydes in varying amounts. For the first time, 5-hydroxy-2-cyclopentenones resulted from these reactions. Formation of these new products was attributed to the radical or carbocation stabilizing ability of the ferrocenyl group, which has not been utilized before in such reactions. Interestingly, an α,β-unsaturated aldehyde derivative was also isolated from these reactions, which most likely happens via a hydroformylation reaction, a rare occurrence for metal

carbene complexes. In conclusion, we anticipate that these new insights will be of value in the continued development of the synthetic applications of Fischer carbene complexes in synthesis.

4. Experimental

4.1. General consideration

Nuclear magnetic resonance (^{1}H and ^{13}C) spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). DEPT ^{13}C NMR information is given in parenthesis as C, CH, CH_2 and CH_3. Infrared spectra were recorded on a Perkin–Elmer 1600 FTIR or Bruker Vertex 70 FTIR spectrometer. Band positions are reported in reciprocal centimeters (cm^{-1}). Band intensities are reported relative to the most intense band and are listed as: br (broad), vs (very strong), s (strong), m (medium), w (weak), and vw (very weak). Mass spectra (MS) were obtained on a Finnigan MAT 95 spectrometer, using EI at 70 eV, or on a Bruker Daltonics spectrometer using MALDI-TOF, in which matrix was DCTP; m/z values are reported. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 95 spectrometer by preselected-ion peak matching at $R\approx 10{,}000$ to be within ± 3 ppm of the exact masses. Elemental analyses were carried out on a LECO CHNS-932 instrument. Flash chromatography was performed using thick-walled glass columns and 'flash grade' silica (Merck 230–400 mesh). Routine thin layer chromatography (TLC) was effected by using precoated 0.25 mm silica gel plates purchased from Merck. The relative proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio. Ferrocenyl alkynes (**11a–f**)[3–6] and cyclopropylcarbene–chromium complex **4**[4d] were synthesized according to a well-known literature procedures. All other commercially available reagents and reactants were obtained in reagent grade and used without purification. All reaction solvents were distilled for purity. Diethyl ether, THF, and dioxane were distilled from sodium/benzophenone ketyl. The inert atmosphere was created by slight positive pressure (ca. 0.1 psi) of argon.

4.2. General procedure for the reaction of cyclopropylcarbene–chromium complex 4 with ferrocenyl alkynes 11 (Table 1)

To a three-neck round-bottom flask equipped with reflux condenser, stopper, and septum, under argon, was added 20 mL of 1% aqueous dioxane solution. The dioxane solution was heated to reflux. To this refluxing solution was added a solution of carbene complex **4** (0.5 mmol) and ferrocenyl alkyne **11** (0.75 mmol) in dioxane (10 mL) by syringe pump over a period of 2 h. After the addition was complete, the mixture was allowed to reflux for a period of 6 h. The mixture was then allowed to cool to room temperature, and the solvent was removed on a rotary evaporator. Ethyl acetate (50 mL) was added, and the solution was filtered through Celite. The solvent was removed in vacuo, and the residue purified by flash chromatography on silica gel (eluant: hexane/EtOAc from 19:1 to 1:1). The products given in Table 1 were isolated with the indicated yields.

4.2.1. Spectral data for products given in Table 1.

4.2.1.1. 5-Ferrocenyl-5-hydroxy-3-methoxy-2-cyclopentenone (12a). Yellow solid; mp 190.5–190.7 °C; 70.2 mg (45% yield from **4** and **11a**), 40.6 mg (26% yield from **4** and **11d**); ^{1}H NMR ($CDCl_3$): δ 5.29 (s, 1H), 4.28 (s, 1H), 4.19 (br s, 8H), 3.89 (s, 3H), 3.08 (d, 1H, J=17.4 Hz), 2.97 (d, 1H, J=17.4 Hz), 2.82 (s, 1H); IR (CH_2Cl_2): 3053 (s), 2982 (m), 2682 (vw), 2302 (w), 1692 (w), 1599 (w), 1402 (s), 1270 (vs), 896 (s), 733 (vs) cm^{-1}; MS (EI): 312 (M^+, 100), 294, 247, 229, 213, 185, 169, 145, 129, 121, 56; HRMS calcd for $C_{16}H_{16}FeO_3$: 312.0449. Found: 312.0452. Anal. Calcd for $C_{16}H_{16}FeO_3$: C, 61.57; H, 5.17. Found: C, 61.21; H, 5.42.

4.2.1.2. (4*R*(*S*),5*R*(*S*))-5-Ferrocenyl-5-hydroxy-3-methoxy-4-methyl-2-cyclopentenone (12b). Brownish yellow solid; mp 127.5–127.8 °C; 58.7 mg (36% yield); ^{1}H NMR ($CDCl_3$): δ 5.21 (s, 1H), 4.20 (s, 1H), 4.18 (s, 5H), 4.14 (br s, 3H), 3.87 (s, 3H), 3.13 (q, 1H, J=7.3 Hz), 2.76 (s, 1H), 1.27 (d, 3H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$): δ 203.7 (C), 192.4 (C), 99.1 (CH), 92.7 (C), 77.2 (C), 68.9 (CH), 68.4 (CH), 68.3 (CH), 66.2 (CH), 65.9 (CH), 58.7 (CH_3), 48.0 (CH), 13.7 (CH_3); IR (CH_2Cl_2): 3056 (s), 2983 (w), 2298 (vw), 1691 (w), 1582 (s), 1418 (w), 1270 (vs), 892 (w), 744 (vs) cm^{-1}; MS (EI): 326 (M^+, 100), 308, 261, 243, 213, 186, 185, 149, 129, 84; HRMS calcd for $C_{17}H_{18}FeO_3$: 326.0605. Found: 326.0602.

4.2.1.3. (4*R*(*S*),5*R*(*S*))-4-Benzyl-5-ferrocenyl-5-hydroxy-3-methoxy-2-cyclopentenone (12c). Off yellow solid; mp 63.6–63.9 °C; 32.2 mg (16% yield); ^{1}H NMR ($CDCl_3$): δ 7.36–7.26 (m, 3H), 7.22–7.10 (m, 2H), 5.20 (s, 1H), 4.13 (s, 3H), 4.10 (s, 5H), 4.01 (s, 1H), 3.82 (s, 3H), 3.36 (dd, 1H, J=7.8, 4.4 Hz), 3.12 (dd, 1H, J=13.8, 7.8 Hz), 2.97 (dd, 1H, J=13.8, 4.4 Hz), 2.76 (s, 1H); IR (CH_2Cl_2): 3050 (s), 2977 (m), 2685 (vw), 2303 (w), 1699 (w), 1591 (m), 1420 (s), 1267 (vs), 898 (s), 746 (vs) cm^{-1}; MS (EI): 402 (M^+, 100), 384, 337, 319, 311, 246, 228, 213, 189, 170, 121, 91; HRMS calcd for $C_{23}H_{22}FeO_3$: 402.0918. Found: 402.0916.

4.2.1.4. (4*R*(*S*),5*R*(*S*))-5-Ferrocenyl-5-hydroxy-3-methoxy-4-phenyl-2-cyclopentenone (12e). Dark yellow solid; mp 183.3–183.6 °C; 60.2 mg (31% yield); ^{1}H NMR ($CDCl_3$): δ 7.11–6.99 (m, 3H), 6.71 (d, 2H, J=6.7 Hz), 5.55 (s, 1H), 4.30 (s, 1H), 4.24 (s, 5H), 3.96 (s, 1H), 3.83 (s, 3H), 3.76 (s, 1H), 3.73 (s, 1H), 3.50 (s, 1H), 3.12 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 203.0 (C), 186.8 (C), 135.3 (C), 129.4 (CH), 127.6 (CH), 126.9 (CH), 102.8 (CH), 91.1 (C), 81.9 (C), 68.8 (CH), 68.4 (CH), 67.6 (CH), 67.3 (CH), 66.3 (CH), 58.9 (CH), 58.6 (CH_3); IR (CH_2Cl_2): 3056 (s), 2987 (m), 2681 (w), 2303 (w), 1704 (s), 1597 (vs), 1421 (m), 1354 (m), 1267 (vs), 1171 (m), 1020 (m), 902 (m), 825 (m), 748 (vs) cm^{-1}; MS (EI): 388 (M^+, 100), 372, 323, 305, 234, 213, 178, 175, 165, 121, 93; HRMS calcd for $C_{22}H_{20}FeO_3$: 388.0762. Found: 388.0761. Anal. Calcd for $C_{22}H_{20}FeO_3$: C, 67.82; H, 5.19. Found: C, 68.06; H, 5.43.

4.2.1.5. (4*R*(*S*),5*R*(*S*))-4,5-Diferrocenyl-5-hydroxy-3-methoxy-2-cyclopentenone (12f). Brownish yellow solid;

mp 199.5–199.7 °C; 44.7 mg (18% yield); ^{1}H NMR ($CDCl_3$): δ 5.37 (s, 1H), 4.30 (s, 1H), 4.25 (s, 7H), 4.20 (s, 7H), 4.14 (s, 1H), 3.99 (s, 1H), 3.98 (s, 3H), 3.88 (s, 1H), 2.74 (s, 1H), 2.13 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 202.6 (C), 187.8 (C), 101.2 (CH), 93.4 (C), 84.5 (C), 78.9 (C), 69.5 (CH), 69.4 (CH), 69.2 (CH), 68.6 (CH), 68.5 (CH), 68.4 (CH), 68.0 (CH), 66.9 (CH), 66.7 (CH), 66.1 (CH), 58.6 (CH_3), 54.6 (CH); IR (CH_2Cl_2): 3055 (s), 2983 (m), 2682 (vw), 2301 (w), 1698 (w), 1596 (w), 1423 (m), 1270 (vs), 898 (m), 762 (vs) cm^{-1}; MS (EI): 496 (M$^+$, 100), 478, 358, 293, 283, 248, 213, 199, 129, 121; HRMS calcd for $C_{26}H_{24}Fe_2O_3$: 496.0424. Found: 496.0426.

4.2.1.6. (4*S*(*R*),5*R*(*S*))-5-Ferrocenyl-5-hydroxy-3-methoxy-4-methyl-2-cyclopentenone (13b). Off yellow solid; mp 81.5–81.8 °C; 26.1 mg (16% yield); ^{1}H NMR ($CDCl_3$): δ 5.30 (s, 1H), 4.33 (s, 5H), 4.30 (s, 1H), 4.18 (s, 1H), 4.16 (s, 1H), 3.81 (s, 3H), 3.75 (s, 1H), 3.06 (q, 1H, J=7.3 Hz), 2.98 (s, 1H), 0.74 (d, 3H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$): δ 203.5 (C), 189.3 (C), 100.5 (CH), 80.4 (C), 77.2 (C), 69.6 (CH), 69.4 (CH), 67.9 (CH), 67.8 (CH), 66.4 (CH), 58.5 (CH_3), 46.8 (CH), 12.0 (CH_3); IR (CH_2Cl_2): 3052 (m), 2981 (w), 1700 (m), 1591 (s), 1463 (vw), 1354 (w), 1268 (vs), 1104 (vw), 896 (vw), 819 (vw), 746 (vs) cm^{-1}; MS (EI): 326 (M$^+$, 100), 308, 262, 261, 243, 213, 185, 131, 113, 78; HRMS calcd for $C_{17}H_{18}FeO_3$: 326.0605. Found: 326.0607.

4.2.1.7. 2-Ferrocenyl-4-methoxy-3-methyl-2-cyclopentenone (14b). Brown solid; mp 96.3–97.1 °C; 26.4 mg (17% yield); ^{1}H NMR ($CDCl_3$): δ 4.79 (s, 1H), 4.69 (s, 1H), 4.30 (s, 2H), 4.27 (dd, 1H, J=6.0, 2.1 Hz), 4.08 (s, 5H), 3.40 (s, 3H), 2.69 (dd, 1H, J=18.0, 6.0 Hz), 2.39 (dd, 1H, J=18.0, 2.1 Hz), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 202.9 (C), 164.3 (C), 139.0 (C), 79.9 (CH), 74.8 (C), 69.4 (CH), 68.9 (CH), 68.8 (CH), 68.6 (CH), 56.9 (CH_3), 41.1 (CH_2), 15.6 (CH_3); IR (CH_2Cl_2): 3053 (s), 2981 (m), 2683 (vw), 2300 (w), 1703 (w), 1414 (m), 1267 (vs), 1097 (vw), 896 (m), 755 (vs) cm^{-1}; MS (EI): 310 (M$^+$, 100), 279, 258, 227, 212, 186, 163, 129, 121, 91, 55; HRMS calcd for $C_{17}H_{18}FeO_2$: 310.0656. Found: 310.0659.

4.2.1.8. 2-Ferrocenyl-4-methoxy-3-phenyl-2-cyclopentenone (14e). Reddish orange solid; 9.3 mg (5% yield); ^{1}H NMR ($CDCl_3$): δ 7.45–7.35 (m, 5H), 4.89 (dd, 1H, J=5.9, 1.5 Hz), 4.58 (s, 1H), 4.39 (s, 1H), 4.34 (s, 1H), 4.26 (s, 1H), 4.09 (s, 5H), 3.47 (s, 3H), 2.80 (dd, 1H, J=18.2, 5.9 Hz), 2.57 (dd, 1H, J=18.2, 1.5 Hz); IR (CH_2Cl_2): 3050 (s), 2982 (m), 2679 (vw), 2307 (w), 1701 (w), 1420 (m), 1273 (vs), 901 (m), 751 (vs); MS (EI): 372 (M$^+$, 100), 356, 342, 291, 277, 249, 191, 165, 149, 121; HRMS calcd for $C_{22}H_{20}FeO_2$: 372.0813. Found: 372.0816.

4.2.1.9. 2,3-Diferrocenyl-4-methoxy-2-cyclopentenone (14f). Reddish orange solid; mp 188.5–188.7 °C; 21.6 mg (9% yield); ^{1}H NMR ($CDCl_3$): δ 4.90 (s, 2H), 4.85 (d, 1H, J=5.5 Hz), 4.55 (s, 1H), 4.46 (s, 2H), 4.43 (s, 1H), 4.37 (s, 1H), 4.25 (s, 1H), 4.14 (s, 5H), 4.08 (s, 5H), 3.45 (s, 3H), 2.69 (dd, 1H, J=18.2, 5.5 Hz), 2.51 (d, 1H, J=18.2 Hz); IR (CH_2Cl_2): 3051 (s), 2983 (m), 2683 (vw), 2306 (w), 1702 (w), 1420 (m), 1270 (vs), 899 (m), 748 (vs) cm^{-1}; MS (EI): 480 (M$^+$, 100), 478, 415, 355, 328, 300, 263, 240, 235, 178, 121; HRMS calcd for $C_{26}H_{24}Fe_2O_2$: 480.0475. Found: 480.0474.

4.2.1.10. 4-Ferrocenyl-5-methyl-4-cyclopentene-1,3-dione (15b). Claret red solid; mp 130.1–130.7 °C; 25.0 mg (17% yield); ^{1}H NMR ($CDCl_3$): δ 5.03 (s, 2H), 4.57 (s, 2H), 4.12 (s, 5H), 2.93 (s, 2H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 199.5 (C), 199.1 (C), 156.2 (C), 150.3 (C), 72.1 (C), 71.7 (CH), 70.5 (CH), 70.0 (CH), 41.8 (CH_2), 10.5 (CH_3); IR (KBr): 3131 (vw), 3096 (w), 2919 (w), 1732 (s), 1687 (vs), 1596 (vs), 1457 (s), 1332 (s), 1271 (vs), 1189 (s); MS (MALDI-TOF): 294 (M$^+$, 100), 292, 264, 242, 220, 219; HRMS calcd for $C_{16}H_{14}FeO_2$: 294.0343. Found: 294.0341.

4.2.1.11. 4-Benzyl-5-ferrocenyl-4-cyclopentene-1,3-dione (15c). Claret red solid; mp 153.4–153.8 °C; 105.5 mg (57% yield); ^{1}H NMR ($CDCl_3$): δ 7.33–7.27 (m, 2H), 7.25–7.10 (m, 3H), 4.98 (s, 2H), 4.56 (s, 2H), 4.03 (s, 5H), 3.97 (s, 2H), 3.02 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 199.4 (C), 199.2 (C), 157.7 (C), 151.2 (C), 136.8 (C), 128.8 (CH), 128.2 (CH), 126.7 (CH), 72.2 (CH), 71.7 (C), 70.8 (CH), 70.2 (CH), 42.1 (CH_2), 29.9 (CH_2); IR (KBr): 3134 (vw), 3096 (w), 2958 (vw), 1736 (m), 1694 (vs), 1594 (s), 1496 (m), 1455 (m), 1349 (m), 1352 (s), 1267 (s); MS (MALDI-TOF): 370 (M$^+$, 100), 368, 316, 301, 251, 250, 235, 195; HRMS calcd for $C_{22}H_{18}FeO_2$: 370.0656. Found: 370.0659.

4.2.1.12. 4-Ferrocenyl-5-phenyl-4-cyclopentene-1,3-dione (15e). Purple solid; mp 171.2–171.4 °C; 98.0 mg (55% yield); ^{1}H NMR ($CDCl_3$): δ 7.45–7.33 (m, 3H), 7.31–7.22 (m, 2H), 4.66 (s, 2H), 4.48 (s, 2H), 4.08 (s, 5H), 3.11 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 199.1 (C), 197.8 (C), 156.5 (C), 150.2 (C), 130.7 (C), 129.3 (CH), 128.9 (CH), 128.6 (CH), 72.1 (CH), 71.5 (C), 71.2 (CH), 70.5 (CH), 42.6 (CH_2); IR (KBr): 3139 (vw), 3094 (w), 3078 (w), 2956 (vw), 1731 (s), 1696 (vs), 1582 (s), 1489 (m), 1440 (m), 1382 (m), 1352 (s), 1257 (s), 1186 (m); MS (MALDI-TOF): 356 (M$^+$, 100), 354, 294, 250, 242; HRMS calcd for $C_{21}H_{16}FeO_2$: 356.0500. Found: 356.0503.

4.2.1.13. 4,5-Diferrocenyl-4-cyclopentene-1,3-dione (15f). Purple solid; 74.2 mg (32% yield); ^{1}H NMR ($CDCl_3$): δ 4.79 (s, 4H), 4.47 (s, 4H), 4.06 (s, 10H), 3.03 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 197.6 (C), 152.2 (C), 73.5 (C), 71.1 (CH), 70.5 (CH), 70.3 (CH), 43.2 (CH_2); IR (CH_2Cl_2): 3050 (s), 2985 (m), 2301 (w), 1725 (m), 1690 (vs), 1574 (w), 1475 (m), 1417 (m), 1381 (w), 1311 (w), 1275 (vs), 1211 (w), 1156 (vw), 1108 (w), 902 (m), 825 (w), 748 (vs) cm^{-1}; MS (EI): 464 (M$^+$, 100), 399, 396, 341, 277, 232, 186, 165, 152, 121; HRMS calcd for $C_{25}H_{20}Fe_2O_2$: 464.0162. Found: 464.0159.

4.2.1.14. 1,1′-Diferrocenyl-4,4′-dimethoxy-5,5′-dimethylbicyclopentyl-3,3′-diene-2,2′-dione (16b). Dark yellow solid; mp 156.8–157.2 °C; 12.4 mg (4% yield); ^{1}H NMR ($CDCl_3$): δ 4.78 (s, 1H), 4.75 (s, 1H), 4.35 (s, 1H), 4.34 (s, 1H), 4.11 (s, 5H), 3.16 (s, 3H), 2.62 (d, 1H, J=18.9 Hz), 2.40 (d, 1H, J=18.9 Hz), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 202.0 (C), 163.9 (C), 142.2 (C), 87.6 (C), 74.1 (C), 69.8 (CH), 69.4 (CH), 69.3 (CH), 69.2 (CH), 68.4 (CH), 50.9 (CH_3), 40.8 (CH_2), 15.6 (CH_3); IR (CH_2Cl_2): 3054 (m), 2989 (vw), 2365 (vw), 1704 (w), 1423 (vw), 1273 (vs), 1105 (vw), 896 (vw), 749 (vs) cm^{-1}; MS (EI): 618 (M$^+$, 100), 556, 492, 310, 309, 294, 229, 199, 159, 121, 77; HRMS calcd for $C_{34}H_{34}Fe_2O_4$: 618.1156. Found: 618.1153.

4.2.1.15. 3,4-Diferrocenyl-4-hydroxy-2-cyclopentenone (17a). Dark red solid; mp 154.8–155.2 °C; 14.0 mg (6% yield); ^{1}H NMR ($CDCl_3$): δ 6.07 (s, 1H), 4.70 (s, 1H), 4.69 (s, 1H), 4.61 (s, 1H), 4.46 (s, 1H), 4.43 (s, 1H), 4.25 (s, 7H), 4.00 (s, 1H), 3.96 (s, 5H), 3.37 (d, 1H, J=17.7 Hz), 2.99 (d, 1H, J=17.7 Hz), 2.67 (s, 1H); IR (CH_2Cl_2): 3052 (s), 2981 (m), 2685 (vw), 2306 (w), 1686 (w), 1583 (w), 1426 (m), 1268 (vs), 899 (m), 741 (vs) cm^{-1}; MS (EI): 466 (M^+, 100), 450, 383, 328, 300, 233, 186, 178, 152, 121; HRMS calcd for $C_{25}H_{22}Fe_2O_2$: 466.0319. Found: 466.0320.

4.2.1.16. 4-Cyclopropyl-2,3-diferrocenyl-4-methoxy-2-cyclobutenone (18f). Dark purple solid; mp 160.5–160.8 °C; 17.7 mg (7% yield); ^{1}H NMR ($CDCl_3$): δ 5.02 (s, 1H), 4.92 (s, 1H), 4.89 (s, 1H), 4.64 (s, 1H), 4.62 (s, 1H), 4.40 (s, 1H), 4.39 (s, 1H), 4.30 (s, 5H), 4.18 (s, 5H), 4.06 (s, 1H), 3.28 (s, 3H), 1.44 (m, 1H), 0.85 (m, 1H), 0.71 (m, 1H), 0.63 (m, 1H), 0.39 (m, 1H); MS (EI): 506 (M^+, 100). The spectral data are in agreement with those reported previously for this compound.[30]

4.2.1.17. 3-Ferrocenyl-2-methylpropenal (19b). Reddish orange solid; mp 67.9–68.1 °C; 7.6 mg (6% yield); ^{1}H NMR ($CDCl_3$): δ 9.44 (s, 1H), 7.07 (s, 1H), 4.59 (t, 2H, J=1.8 Hz), 4.48 (t, 2H, J=1.8 Hz), 4.14 (s, 5H), 1.91 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 194.5 (C), 151.4 (CH), 134.8 (C), 72.0 (C), 71.4 (CH), 71.1 (CH), 69.7 (CH), 10.6 (CH_3); IR (CH_2Cl_2): 3052 (s), 2976 (m), 2682 (vw), 2411 (vw), 2307 (w), 1669 (vs), 1616 (vs), 1420 (m), 1259 (vs), 896 (m), 751 (vs) cm^{-1}; MS (EI): 254 (M^+, 100), 242, 226, 213, 189, 185, 160, 134, 121, 81; HRMS calcd for $C_{14}H_{14}FeO$: 254.0394. Found: 254.0392.

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Coupling of pentacarbonyl[(cyclopropyl)methoxymethylene]-molybdenum complex with ferrocenylalkynes: Synthesis of ferrocenyl-substituted cycloheptadienones and cycloheptenediones

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Abstract

Pentacarbonyl[(cyclopropyl)methoxymethylene]molybdenum complex reacts with ferrocenyl alkynes to afford ferrocenyl-substituted 2,4-cycloheptadienones as major products, accompanied by varying amounts of 2-cycloheptene-1,4-diones and/or 2-cyclobutenones. 2-Cycloheptene-1,4-diones are secondary reaction products and result from initially formed 2,4-cycloheptadienones via hydrolysis. In one reaction, a hydroxy-substituted 2,4-cycloheptadienone derivative was isolated, which was not observed previously from similar reactions.

Keywords: Fischer metal carbene; Molybdenum carbene complex; Ferrocene; Ferrocenyl alkynes; Carbocyclic seven-membered rings; Cycloheptadienones; Cycloheptenediones; Cyclobutenones; Coupling

1. Introduction

Carbocyclic seven-membered rings are present in a variety of biologically-important molecules, including phorbol esters [1], colchicine derivatives [2], guaiazulenes [3], guaianolides [3] and pseudoguiainolides [3,4], the latest having more than 1000 varieties [4]. Some of them exhibit high biological activities such as antitumor, antiulcer, antisistosomal, anthelmintic, cardiotonic, contraceptive, immunomodulation, root-growth stimulatory, root-growth and germination inhibitory activities, as well as preventive or curative activities for crop diseases [5]. Recent studies have suggested that the integration of a ferrocenyl group into such structures may enhance their biological activities or generate new medicinal properties [6,7]. A typical example is hydroxyferrocifen [7], (*Z*)-[(Et)(Fc)C=C(*p*-C_6H_4-OH)*p*-C_6H_4-O-CH_2-CH_2-NMe_2], a ferrocenyl analog of hydroxytamoxifen which is a drug currently used in the treatment of hormone-dependent breast cancer lines [8]. The replacement of the phenyl ring by a ferrocenyl (Fc) moiety has brought about novel pharmacological properties for hydroxyferrocifen since it is active against both hormone-dependent and hormone-independent breast cancer cells whereas its phenyl counterpart, hydroxytamoxifen, is active only against hormone-dependent cancer cells [7,8]. Due to its unique structure, different membrane-permeation properties and anomalous metabolism, ferrocene is often incorporated into a compound in order to get unexpected or enhanced biological activities [9]. Surprisingly, seven-membered ring carbocycles bearing a ferrocenyl moiety are very rare. The development of a general synthetic entry to such compounds is therefore of considerable interest since it could lead to a new source of biologically active compounds.

These ring systems are typically constructed by ring expansion reactions, cyclization reactions, cycloaddition reactions and synthetic modifications of other seven-membered rings [10]. Recently, Fischer type metal carbene

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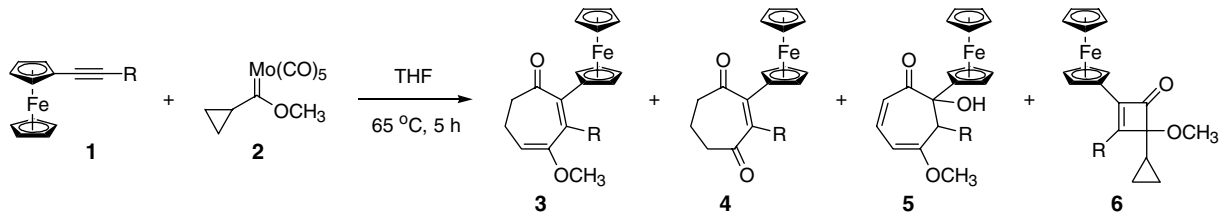


Scheme 1. Reaction of carbene complex **2** with ferrocenyl alkynes **1**. For definition of R group for compounds **1** and **3**–**6**, see Table 1.

complexes have emerged as valuable reagents for organic synthesis [11]. An ever continuing aspect of these studies has been the use of a structurally diverse set of Fischer carbene complexes to afford a diverse array of compounds. In this regard, as shown by the Herndon research group [12,13], the reaction between alkynes and pentacarbonyl-[(cyclopropyl)methoxymethylene]metal complexes represent a very rapid entry to the corresponding 2,4-cycloheptadienones. This methodology, however, has not been utilized for the synthesis of 2-ferrocenyl-2,4-cycloheptadienones, presumably due to the scarce availability of the starting ferrocenyl alkynes. As part of our general interest in ferrocene [14,15] and metal carbene chemistry [13,16], as well as small and medium-size ring systems [17], we have investigated the reaction between ferrocenyl alkynes **1** and pentacarbonyl[(cyclopropyl)methoxymethylene]molybdenum complex **2** to afford ferrocenyl-substituted cycloheptadienones **3** (Scheme 1) [18]. We herein report the results of this study.

2. Results and discussion

2.1. Synthesis of starting materials

The synthesis of ferrocenyl alkynes were achieved from ethynylferrocene [19] according to known or modified literature procedures [20–22]. Treatment of ethynylferrocene with *n*-butyllithium produced in situ lithioethynylferrocene that was further reacted with methyl iodide and benzyl bromide to yield propynylferrocene (**1A**) and (3-phenylpropynyl)ferrocene (**1B**), respectively [20]. On the other hand, the reaction of ethynylferrocene and iodobenzene in the presence of copper iodide, triphenylphosphine and potassium carbonate in refluxing DMF produced (phenylethynyl)ferrocene (**1C**) [21]. Diferrocenylethyne (**1D**) was synthesized by the metathesis of propynylferrocene in the presence of molybdenum hexacarbonyl and 2-fluorophenol in refluxing chlorobenzene [22]. Pentacarbonyl[(cyclopropyl)methoxymethylene]molybdenum complex **2** was prepared from cyclopropyl bromide and molybdenum hexacarbonyl according to a standard protocol [13b].

2.2. Coupling of pentacarbonyl [(cyclopropyl)methoxymethylene]molybdenum complex 2 with ferrocenyl alkynes 1

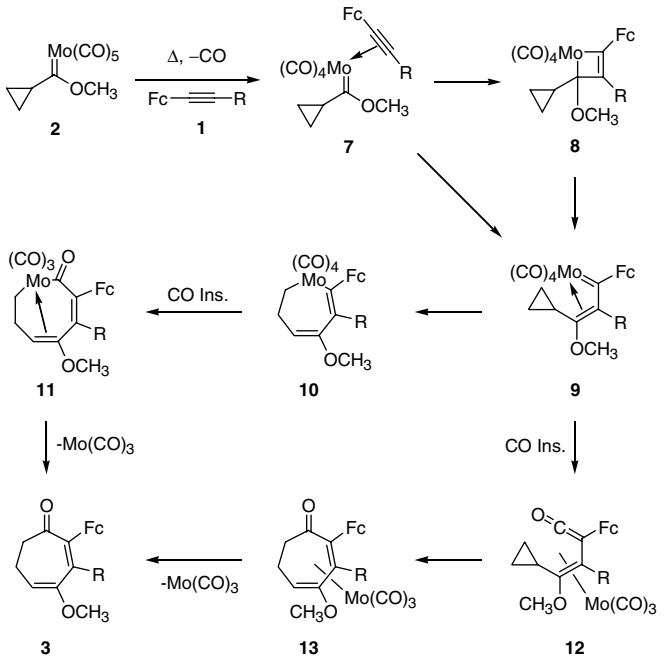
We next investigated the reaction of carbene complex **2** with ferrocenyl alkynes **1**. The results are summarized in Scheme 1 and Table 1. The reactions were carried out under optimal conditions, which involve heating a 1:1.5 mole ratio of carbene complex **2** and alkyne **1**, respectively, in THF at 65 °C. Initially, the reaction between propynylferrocene (**1A**) and carbene complex **2** was examined, which afforded the expected cycloheptadienone (**3A**) as the major product of the reaction, along with the varying amounts of cycloheptenedione (**4A**) and hydroxy-substituted cycloheptadienone (**5A**) (entry A). The coupling of carbene complex **2** with benzylferrocenylacetylene (**1B**) produced two products, cycloheptadienone (**3B**) and cycloheptenedione (**4B**), with **3B** the major product of the reaction (entry B). A similar trend was observed in the reaction of **2** with (phenylethynyl)ferrocene (**1C**), where cycloheptadienone (**3C**) and cycloheptenedione (**4C**) were obtained, the former being the major product (entry C). On the other hand, the reaction between diferrocenylacetylene (**1D**) and carbene complex **2** revealed a complex reaction mixture; only cycloheptadienone (**3D**) and cyclobutenone (**6D**) could be isolated (entry D). Triphenylphosphine is often used to improve the yields of products in metal carbene reactions [13]. Triphenylphosphine could displace carbon monoxide at early stage of the reaction, which could then be replaced by the alkyne. When the same reactions, however, were carried out in the presence of triphenylphosphine, low yields of products were obtained in contrast to previous studies [13a], which may be attributed to the probable steric effect caused by triphenylphosphine and ferrocene moieties. That is why; all reactions in this study were performed without using triphenylphosphine.

Table 1
Reaction of carbene complex **2** with ferrocenyl alkynes **1**

Entry[a]	Alkyne	R	Products (isolated yield, %)
A	**1A**	CH_3	**3A** (47) + **4A** (12) + **5A**[b] (12)
B	**1B**	CH_2Ph	**3B** (70) + **4B** (13)
C	**1C**	Ph	**3C** (72) + **4C** (10)
D	**1D**	Fc (ferrocenyl)	**3D** (15) + **6D** (8)

[a] Entry letters define R group for compounds **1** and **3**–**6**.
[b] Relative stereochemistry of substituents at carbons 6 and 7 was not determined.

As noted in Table 1, cycloheptadienones (**3**) have been obtained as the major products from the reactions between molybdenum carbene complex **2** and ferrocenyl alkynes (**1**). In the light of previous studies [13,23], the proposed mechanism for their formation is outlined in Scheme 2. The loss of a carbon monoxide ligand from complex **2** and coordination



Scheme 2. Proposed mechanism for the formation of cycloheptadienones (**3**).

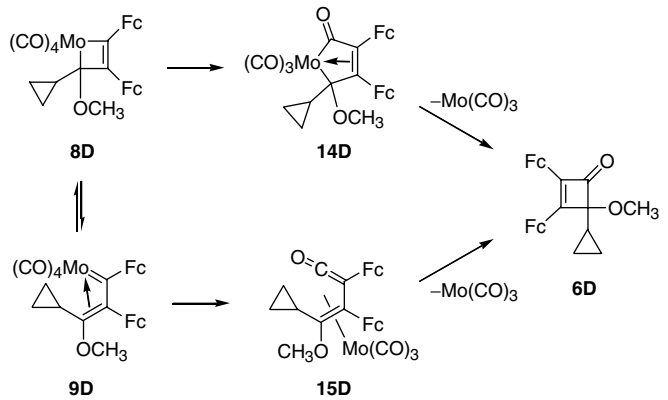
of alkyne **1** produces alkyne-carbene complex **7**, which undergoes a [2+2] cycloaddition reaction to afford metallacyclobutene (**8**). Electrocyclic ring opening then occurs to yield internally-coordinated vinyl carbene complex **9**. The involvement of metallacyclobutenes in these processes has recently been questioned by Hofmann and found to be unfavorable on the basis of theoretical calculations [24]. Thus, complex **9** could be directly formed from **7** via alkyne insertion without formation of metallacyclobutene (**8**). Afterwards, complex **9** undergoes a 1,5-alkyl shift to give metallacycloheptadiene (**10**). CO insertion then occurs to afford metallacyclooctadienone (**11**), which upon reductive elimination yields cycloheptadienones (**3**). Alternatively, CO insertion in **9** produces vinylketene complex **12**. Cyclopropane ring of **12** then opens by a 1,5-alkyl shift to generate metallacycloheptadienone (**13**), which upon decomplexation affords cycloheptadienones (**3**). As noted by Herndon [13b] using similar reactions, two variations (**9** → **10** → **11** → **3** vs. **9** → **12** → **13** → **3**) in this mechanism can be envisaged, which differ in their timing of CO insertion versus cyclopropane ring opening step (Scheme 2). The former pathway is the currently-favored mechanism since there is evidence that cyclopropane ring opening reactions can arise from (2-cyclopropylvinyl)carbene complexes [25]. Conversely, (2-cyclopropylvinyl)ketenes obtained from thermolysis of 4-cyclopropyl-2-cyclobutenones do not produce cycloheptadienones [13b,26]. Thus the later mechanism can only be operative if vinylketene-metal complexes are very different in their reactivity.

In all products, the larger group of the alkyne (i.e. Fc group) has ended up α to the carbonyl, which is the regiochemistry observed in such reactions [12,13,23]. In fact, the regiochemistry of the reaction is set up in the formation of metallacyclobutene (**8**) and/or vinyl carbene complex **9** (Scheme 2), where the larger Fc group ends up α to the molybdenum in order to minimize steric interactions. Following this substituent through the mechanism in Scheme 2, it is predicted that Fc group will be α to the carbonyl group in the final products.

Cycloheptenediones (**4**) were also resulted from these reactions (Table 1) but in low yields. In fact, cycloheptenediones (**4**) are secondary product of the reactions and result from the initially formed cycloheptadienones (**3**) via hydrolysis of enol ether functionality. Note that when subjected to acidic hydrolysis, cycloheptadienones (**3**) provides cycloheptenediones (**4**) in very high yields. That is why; if the crude reaction mixture is hydrolyzed under acidic conditions before chromatography, 2- or 3-ferrocenyl-substituted 2-cycloheptene-1,4-diones (**4**) can be obtained as the major products of the reactions.

Interestingly, from the reaction with propynylferrocene (**1A**) (Table 1, entry A), a new product was isolated and assigned as a 7-hydroxy-2,4-cycloheptadienone derivative, **5A**. To the best of our knowledge, such product was not observed previously from similar reactions. It should be noted that, at relatively higher temperatures, 4-methoxy-2,4-cycloheptadienone derivatives are well known to convert to thermodynamically more stable 5-methoxy-2,4-cycloheptadienones by two consecutive 1,5-H shifts [12,13]. Although, at present, we do not speculate the mechanism for the formation of this product, which requires further study, it is apparent that, during the rearrangement of the initially formed cycloheptadienone **3A** to **5A**, water addition occurs somehow. Interestingly, in **5A**, hydroxy substituent ends up α to the ferrocenyl group. This might be attributed to the developing radical or positive charge at that carbon during the course of the reaction, which is well stabilized, although it is also α to the carbonyl, since the ferrocenyl group is very effective at stabilizing an α radical or carbocation [14d,27]. In addition, the ferrocenyl group is a much better radical and carbocation stabilizing group than the phenyl group.

The reaction with diferrocenylacetylene (**1D**) afforded the products in relatively low yields (Table 1, entry D), as compared to that with diphenylacetylene [13]. Low yields of these products might be due to the steric effect caused by two ferrocenyl groups of **1D** during the course of the reaction. In this reaction, cyclobutenone derivative **6D** was also formed. Cyclobutenones are often observed in the reaction of metal carbenes with alkynes [28]. Cyclobutenone (**6D**) could arise via two possible pathways as depicted in Scheme 3. Metallacyclobutene (**8D**) first gives CO insertion to afford internally-coordinated metallacyclopentenone (**14D**), which produces cyclobutenone (**6D**) upon reductive elimination Alternatively, vinylcarbene complex **9D** experiences CO insertion and yields vinylketene complex **15D**, which furnishes cyclobutenone (**6D**) after electrocyclic ring closure followed by decomplexation. Note that metallacyclobutene (**8D**) and vinyl carbene complex **9D**



Scheme 3. Proposed mechanism for the formation of cyclobutenone (**6D**).

are interconvertible and their formation has been shown in Scheme 2.

On the other hand, the reaction of metal carbene complex **2** with ethynylferrocene (a terminal alkyne) or 3-ferrocenylpropynal (an electron-deficient alkyne) failed, presumably due to the polymerization or electron-deficiency of the alkyne system, a result consistent with the findings of previous investigators using similar systems [13].

In the reactions between molybdenum complex **2** and conventional alkynes, furanone formation was reported to be a major competing pathway [13]. Furanone formation, however, was not a problem when diphenylacetylene is the alkyne or when phosphine ligands such as triphenylphosphine are used as an additive. On the other hand, in our reaction conditions, even in the absence of triphenylphosphine, furanones were not observed. Apparently, the presence of ferrocenyl moiety electronically and/or sterically prevents the formation furanone type products.

*2.3. Crystal structure of 3-benzyl-2-ferrocenyl-4-methoxy-2,4-cycloheptadienone (**3B**)*

The structure of cycloheptadienone (**3B**) was determined by X-ray crystal analysis. ORTEP diagram of **3B** is shown in Fig. 1. Details of cell data, X-ray data collection, structure solution and refinement are given in Table 2. Selected bond distances and angles are denoted in Table 3. A complete list of atomic coordinates, bond distances and angles, anisotropic thermal parameters, hydrogen atom coordinates have been deposited and are available upon request, Supplementary data.

In the solid state, seven-membered ring adopts a boat-like conformation and, as a result, conjugation between double bonds is largely interrupted as shown by the C12–C11–C17–O1 and C11–C12–C13–C14 torsion angles of 107.41(18)° and 42.2(2)°, respectively. C15 and C16 methylene carbons in the ring exist in a staggered gauche conformation and the related torsion angle (C14–C15–C16–C17) is 50.7(2)°. O1–C17, C11–C12 and C13–C14 bond distances are 1.211(2), 1.344(2) and 1.327(2) Å, respectively, and all are as expected. Ferrocenyl group is in a slightly distorted eclipsed conformation as concluded from

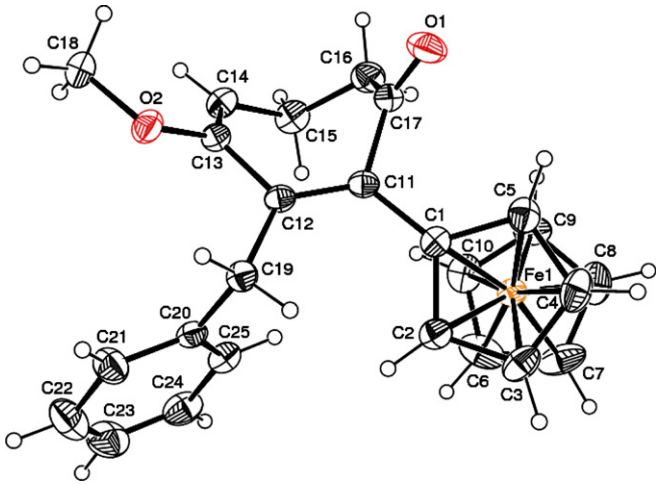


Fig. 1. ORTEP diagram of 3-benzyl-2-ferrocenyl-4-methoxy-2,4-cycloheptadienone (**3B**). Ellipsoids are drawn at 30% probability.

Table 2
Crystallographic data and structure refinement parameters for **3B**

Empirical formula	$C_{25}H_{24}FeO_2$
Formula weight	412.29
Crystal size (mm)	0.390 × 0.300 × 0.180
Crystal shape	Prism
Temperature (K)	296(2)
Crystal system	Triclinic
Space group	$P\bar{1}$
a (Å)	7.7443(5)
b (Å)	11.3769(7)
c (Å)	11.5864(7)
α (°)	76.372(5)
β (°)	80.118(5)
γ (°)	89.386(5)
V (Å^3)	976.90(11)
Z	2
D_x (g cm^{-3})	1.402
μ (Mo Kα) (mm^{-1})	0.790
Radiation/wavelength (Å)	Mo Kα/0.71073
Transmission factors (T_{min}, T_{max})	0.7651, 0.8892
θ_{max} (°)	26
Index range (hkl)	−9/8, −14/14, −14/14
Reflections measured	21 080
Independent reflections (R_{int})	3839 (0.0387)
Reflections with $I > 2\sigma(I)$	3249
Number of parameters	254
Number of restraints	0
$R[F^2 > 2\sigma(F^2)]$	0.0257
$wR(F^2)$	0.0648
Goodness-of-fit (F^2)	1.030
Maximum, minimum $\Delta\rho$ (e/Å^3)	0.198, −0.286

the average C–Cg$_s$–Cg$_{as}$–C torsion angle of −14.11(9)°, where Cg$_s$ and Cg$_{as}$ are the substituted and unsubstituted Cp ring centroids, respectively. The centroids of Cp rings are almost equidistant from Fe atom as indicated by the Fe–Cg$_s$ and Fe–Cg$_{as}$ distances of 1.648(17) and 1.657(17) Å, respectively, and the Cg$_s$–Fe–Cg$_{as}$ angle is 177.48(11)°. Cp rings of ferrocenyl group are almost parallel since the angle between Cp ring planes is 3.67(12)°. The C–C bond distances in Cp rings alter from 1.382(3) to 1.435(2) Å,

Table 3
Selected bond distances (Å), bond angles (°) and torsion angles (°) for **3B**

C1–C2	1.435(2)	C12–C13	1.486(2)
C1–C11	1.469(2)	C12–C19	1.512(2)
C1–Fe1	2.0697(15)	C13–C14	1.327(2)
C2–C3	1.407(2)	C13–O2	1.3736(19)
C3–C4	1.402(3)	C14–C15	1.499(2)
C4–Fe1	2.0361(18)	C15–C16	1.513(3)
C6–C7	1.382(3)	C16–C17	1.493(2)
C6–C10	1.387(3)	C17–O1	1.211(2)
C7–C8	1.414(3)	C18–O2	1.4260(19)
C8–Fe1	2.0342(19)	C19–C20	1.511(2)
C10–Fe1	2.0460(19)	C20–C21	1.381(2)
C11–C12	1.344(2)	C21–C22	1.387(3)
C11–C17	1.516(2)	C22–C23	1.369(4)
C5–C1–C2	106.21(14)	O2–C13–C12	110.33(13)
C11–C1–Fe1	126.93(10)	O1–C17–C16	121.82(15)
C12–C11–C17	117.80(13)	O1–C17–C11	118.59(15)
C11–C12–C13	120.66(13)	C20–C19–C12	114.45(13)
C11–C12–C19	124.87(14)	C21–C20–C19	119.92(15)
C14–C13–C12	124.10(14)	C10–Fe1–C1	111.47(7)
C5–C1–C11–C12	−154.60(16)	C15–C16–C17–C11	31.5(2)
C5–C1–C11–C17	18.2(2)	C12–C11–C17–O1	107.41(18)
C17–C11–C12–C13	11.9(2)	C11–C12–C19–C20	−114.66(16)
C11–C12–C13–O2	−140.06(14)	C12–C19–C20–C21	−133.55(16)
C12–C13–C14–C15	−3.6(3)	C12–C13–O2–C18	−179.21(13)

while Fe–C bond lengths vary between 2.029(19) and 2.070(15) Å, all of which are as expected [21a].

Crystals of cycloheptadienone (**3B**) are stabilized by C–H…O intermolecular hydrogen bond and C–H…π interactions (Fig. 2). There is a single type of intermolecular hydrogen bond, [C9–H9…O1^{i}: H…O = 2.59 Å, C…O = 3.511(2) Å, C–H…O = 171°, (i) $-x$, $1-y$, $1-z$], linking the molecules and generate cyclic centrosymmetric $R_2^2(14)$ dimers which ring centroid at (1, 1/2, 1/2) [29]. Centrosymmetric dimers are linked through C15–H15a…Cg$_{as}^{ii}$ [Cg$_{as}$ is the centroid of the C6…C10 ring; H15a…Cg = 2.975 Å, C15…Cg = 3.736(2) Å, C15–H15a…Cg = 136.20°, (ii) $1-x$, $1-y$, $1-z$] and C14–H14…Cg$_{p}^{iii}$ [Cg$_{p}$ is the centroid of the C20…C25 ring; H14…Cg = 2.903 Å, C4…Cg = 3.783(2) Å, C14–H14…Cg = 158.35° (iii) $1-x$, $1-y$, $-z$] interactions.

3. Conclusion

In summary, we have investigated the reaction between pentacarbonyl[(cyclopropyl)methoxymethylene]molybdenum complex **2** and ferrocenyl alkynes **1**, affording ferrocenyl-substituted 2,4-cycloheptadienones (**3**) as the major products, along with the minor amounts of 2-cycloheptene-1,4-diones (**4**) and/or 2-cyclobutenones (**6**). The reaction is regioselective and general for internal alkynes unless the alkyne is electron-deficient. The hydrolysis of 2,4-cycloheptadienones (**3**) under acidic conditions provides 2-cycloheptene-1,4-diones (**4**) in very high yields. In the case of diferrocenylacetylene (**1D**), steric effects are more pronounced, lowering the yields of products. In conclusion, our study has shown that, under appropriate conditions,

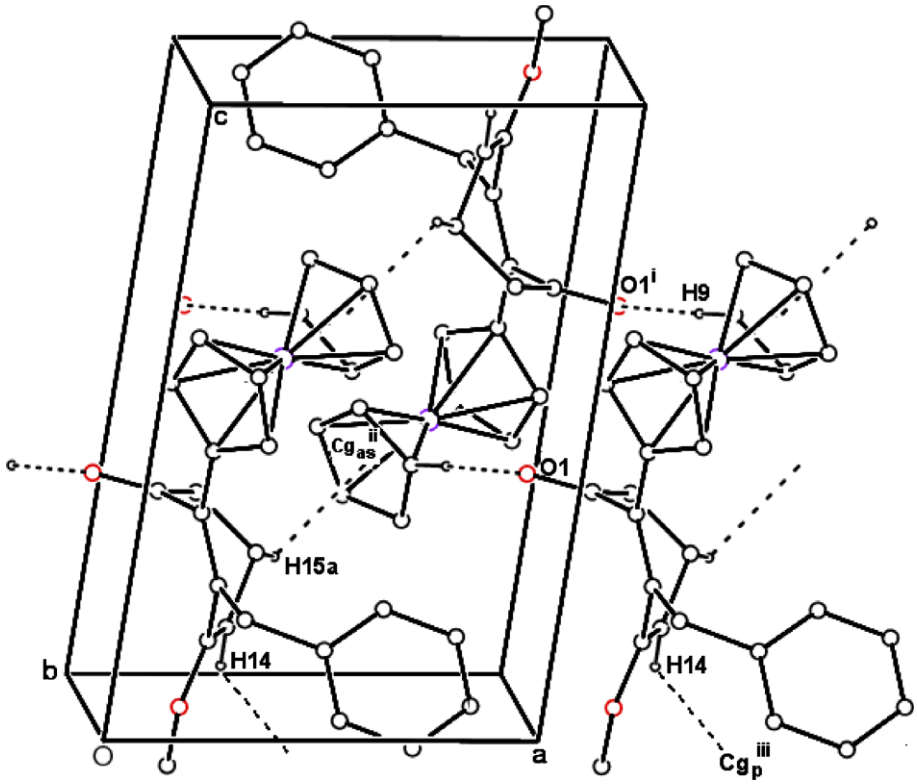


Fig. 2. A packing diagram for **3B**, showing the C–H…O, C–H…\π interactions represented as dashed lines. H atoms not involved in hydrogen bonds have been omitted for clarity. [Symmetry codes: (i) $-x$, $1-y$, $1-z$; (ii) $1-x$, $1-y$, $1-z$; (iii) $1-x$, $1-y$, $-z$].

ferrocenyl alkynes follow the reactivity patterns of conventional alkynes upon reaction with metal carbene complexes.

4. Experimental

4.1. General consideration

Nuclear Magnetic Resonance (^{1}H and ^{13}C) spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). DEPT ^{13}C NMR information is given in parenthesis as C, CH, CH_2 and CH_3. Infrared spectra were recorded on a Perkin Elmer 1600 Series FT-IR spectrometer. Band positions are reported in reciprocal centimeters (cm^{-1}). Band intensities are reported relative to the most intense band and are listed as: br (broad), vs (very strong), s (strong), m (medium), w (weak), vw (very weak). Mass spectra (MS) were obtained on a Finnigan MAT 95 spectrometer, using electron impact (EI) at 70 eV; m/z values are reported. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 95 spectrometer by preselected-ion peak matching at $R \approx 10000$ to be within ± 3 ppm of the exact masses. Flash chromatography was performed using thick-walled glass columns and 'flash grade' silica (Merck 230-400 mesh). Routine thin layer chromatography (TLC) was effected by using precoated 0.25 mm silica gel plates purchased from Merck. The relative proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio. Ferrocenyl alkynes **1A**–**D** [19–22] and pentacarbonyl[(cyclopropyl)methoxymethylene]molybdenum complex **2** [13b] were synthesized according to the well known literature procedures. All other commercially available reagents and reactants were obtained in reagent grade and used without purification. All reaction solvents were distilled for purity. Diethyl ether, THF and dioxane were distilled from sodium/benzophenone ketyl. The inert atmosphere was created by slight positive pressure (ca. 0.1 psi) of argon.

4.2. General procedure for the reaction of pentacarbonyl-[(cyclopropyl)methoxymethylene]molybdenum complex **2** with ferrocenyl alkynes **1** (Table 1)

A solution of molybdenum carbene complex **2** (0.50 mmol) and ferrocenyl alkyne **1** (0.75 mmol) in THF (30 mL) was refluxed under argon until all carbene complex was consumed. The progress of the reaction was monitored by routine TLC for the disappearance of carbene complex. The mixture was then cooled to 25 °C, and the solvent was removed on a rotary evaporator. Final purification was achieved by flash chromatography on silica gel. Eluting with 19:1 hexane–ethyl acetate followed by 9:1 hexane–ethyl acetate afforded the products given in Table 1 with the indicated yields.

4.3. Spectral data for products

4.3.1. 2-Ferrocenyl-4-methoxy-3-methyl-2,4-cycloheptadienone (**3A**)

^{1}H NMR ($CDCl_3$): δ 5.13 (t, 1H, $J = 7.3$ Hz), 4.41 (s, 2H), 4.28 (s, 2H), 4.08 (s, 5H), 3.49 (s, 3H), 2.86 (pseudo t, 2H, $J = 6.4$ Hz), 2.36 (pseudo q, 2H, $J = 6.8$), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 206.1 (C), 158.1 (C), 137.7 (C), 132.2 (C), 98.5 (CH), 79.3 (C), 69.9 (CH), 69.6 (CH), 68.9 (CH), 54.6 (CH_3), 51.6 (CH_2), 20.1 (CH_2), 16.5 (CH_3); IR (CH_2Cl_2): 3052 (s) 1683 (s), 1629 (m), 1422 (m), 1362 (m), 1272 (vs), 1258 (vs), 1203 (m), 1130 (m), 1105 (m) cm^{-1}; MS (EI): 336.2 (M^+), 334.2, 308.2, 293.1, 255.0, 227.0, 199.1, 186.0, 153.1, 129.1, 121.0, 115.1; HRMS (EI): calcd. for $C_{19}H_{20}FeO_2$: 336.0813. Found: 336.0816.

4.3.2. 3-Benzyl-2-ferrocenyl-4-methoxy-2,4-cycloheptadienone (**3B**)

^{1}H NMR ($CDCl_3$): δ 7.34–7.28 (m, 3H), 7.19 (m, 2H), 5.13 (t, 1H, $J = 7.3$ Hz), 4.41 (t, 2H, $J = 1.8$ Hz), 4.25 (t, 2H, $J = 1.8$ Hz), 4.08 (s, 5H), 3.80 (s, 2H), 3.36 (s, 3H), 2.98 (pseudo t, 2H, $J = 6.7$ Hz), 2.45 (pseudo q, 2H, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$): δ 205.7 (C), 157.1 (C), 139.8 (C), 139.5 (C), 133.5 (C), 128.4 (CH), 128.1 (CH), 125.9 (CH), 99.8 (CH), 78.3 (C), 69.6 (CH), 69.3 (CH), 69.1 (CH), 54.6 (CH_3), 51.7 (CH_2), 35.2 (CH_2), 20.3 (CH_2); IR (CH_2Cl_2): 3056 (vs), 2981 (m), 2682 (w), 2301 (m), 1688 (s), 1627 (m), 1424 (vs), 1260 (vs), 1049 (m), 902 (s) cm^{-1}; MS (EI): 412.2 (M^+), 398.2, 384.2, 370.2, 331.1, 318.1, 303.1, 275.1, 253.1, 217.1, 213.0, 186.1, 151.2, 137.1, 121.0; HRMS (EI): calcd. for $C_{25}H_{24}FeO_2$: 412.1126. Found: 412.1130.

4.3.3. 2-Ferrocenyl-4-methoxy-3-phenyl-2,4-cycloheptadienone (**3C**)

^{1}H NMR (acetone-d_6): δ 7.25 (m, 3H), 7.05 (m, 2H), 5.46 (t, 3H, $J = 7.3$ Hz), 4.16 (t, 2H, $J = 1.8$ Hz), 4.09 (s, 5H), 3.87 (t, 2H, $J = 1.8$ Hz), 3.38 (s, 3H), 3.03 (pseudo t, 2H, $J = 6.5$ Hz), 2.64 (pseudo q, 2H, $J = 6.5$ Hz); ^{13}C NMR (acetone-d_6): δ 204.6 (C), 157.6 (C), 139.1 (C), 138.7 (C), 133.7 (C), 129.5 (CH), 127.9 (CH), 127.1 (CH), 100.4 (CH), 77.5 (C), 69.3 (CH), 69.2 (CH), 69.0 (CH), 54.1 (CH_3), 51.5 (CH_2), 20.4 (CH_2); IR (CH_2Cl_2): 3049 (vs), 2988 (s), 2680 (m), 2521 (w), 2407 (w), 2298 (s), 1682 (s), 1418 (m), 1259 (vs), 1158 (w), 900 (vs) cm^{-1}; MS (EI): 398.2 (M^+), 370.2, 339.2, 317.1, 303.1, 261.1, 226.1, 202.1, 186.1, 165.1, 127.2, 119.1; HRMS (EI): calcd. for $C_{24}H_{22}FeO_2$: 398.0969. Found: 398.0972.

4.3.4. 2,3-Diferrocenyl-4-methoxy-2,4-cycloheptadienone (**3D**)

^{1}H NMR ($CDCl_3$): δ 5.09 (t, 1H, $J = 7.4$ Hz), 4.21 (s, 2H), 4.17 (s, 2H), 4.12 (s, 2H), 4.11 (s, 5H), 4.08 (s, 5H),

3.98 (s, 2H), 3.64 (s, 3H), 2.91 (pseudo t, 2H, $J = 6.4$ Hz), 2.44 (q, 2H, $J = 6.9$ Hz); IR (CH_2Cl_2): 3054 (vs), 2989 (s), 2682 (m), 2406 (w), 2304 (m), 1700 (s), 1418 (s), 1266 (vs), 1102 (w), 897 (s) cm^{-1}; MS (EI): 506.2 (M^+), 438.1, 394.1, 362.2, 308.1, 242.1, 186.0, 113.1; HRMS (EI): calcd. for $C_{28}H_{26}Fe_2O_2$: 506.0632. Found: 506.0635.

*4.3.5. 2-Ferrocenyl-3-methyl-2-cycloheptene-1,4-dione (**4A**)*

^{1}H NMR ($CDCl_3$): δ 4.49 (s, 2H), 4.43 (s, 2H), 4.16 (s, 5H), 2.83 (t, 2H, $J = 6.8$ Hz), 2.61 (pseudo t, 2H, $J = 6.0$ Hz), 2.04 (pseudo p, 2H, $J = 6.3$ Hz), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 204.2 (C), 203.4 (C), 148.6 (C), 134.8 (C), 77.3 (C), 70.7 (CH), 70.4 (CH), 69.7 (CH), 43.3 (CH_2), 41.7 (CH_2), 17.2 (CH_2), 16.4 (CH_3); IR (CH_2Cl_2): 3052 (s), 2985 (m), 1696 (s), 1663 (s), 1420 (m), 1272 (vs), 1260 (vs) 1108 (w), 895 (m) cm^{-1}; MS (EI): 322.1 (M^+), 320.1, 294.1, 277.1, 258.0, 257.0, 229.0, 199.0, 167.1, 149.1, 121.0; HRMS (EI): calcd. for $C_{18}H_{18}FeO_2$: 322.0656. Found: 322.0659.

*4.3.6. 2-Benzyl-3-ferrocenyl-2-cycloheptene-1,4-dione (**4B**)*

^{1}H NMR ($CDCl_3$): δ 7.25 (t, $J = 7.2$ Hz, 2H), 7.19–7.10 (m, 3H), 4.47 (s, 2H), 4.38 (s, 2H), 4.17 (s, 5H), 3.94 (s, 2H), 2.81 (t, 2H, $J = 5.8$ Hz), 2.49 (pseudo t, 2H, $J = 5.3$ Hz), 2.06 (pseudo p, 2H, $J = 5.3$ Hz); IR (neat): 3104 (w), 2937 (w), 1696 (vs), 1664 (vs), 1578 (m), 1497 (w), 1259 (m), 1213 (s), 1107 (m), 1053 (m), 1004 (m) cm^{-1}; MS (EI): 398.2 (M+), 370.2, 333.1, 305.1, 275.1, 248.1, 234.1, 191.1, 178.1, 165.1, 121.0; HRMS (EI): calcd. for $C_{24}H_{22}FeO_2$: 398.0969. Found: 398.0966.

*4.3.7. 2-Ferrocenyl-3-phenyl-2-cycloheptene-1,4-dione (**4C**)*

^{1}H NMR ($CDCl_3$): δ 7.36–7.29 (m, 3H), 7.02 (dd, 2H, $J = 7.8$, 1.3 Hz), 4.19 (t, 2H, $J = 1.8$ Hz), 4.08 (s, 5H), 3.80 (t, 3H, $J = 1.8$ Hz), 2.90 (t, 2H, $J = 6.0$ Hz), 2.58 (pseudo t, 2H, $J = 6.6$ Hz), 2.15 (pseudo p, 2H, $J = 6.4$ Hz); ^{13}C NMR ($CDCl_3$): δ 197.6 (C), 156.3 (C), 137.8 (C), 135.3 (C), 130.2 (CH), 128.3 (CH), 127.1 (CH), 81.7 (C), 70.5 (CH), 70.2 (CH), 69.6 (CH), 38.2 (CH_2), 30.7 (CH_2), 22.7 (CH_2); IR (CH_2Cl_2): 3048 (vs), 2985 (s), 2680 (w), 2305 (m), 1650 (s), 1578 (m), 1422 (s), 1358 (m), 1265 (vs), 1175 (m), 891 (s) cm^{-1}; MS (EI): 384.2 (M^+), 357.2, 356.2, 300.2, 291.1, 263.1, 235.1, 202.1, 178.1, 165.1, 152.1, 112.0; HRMS (EI): calcd. for $C_{23}H_{20}FeO_2$: 384.0813. Found: 384.0816.

*4.3.8. 7-Ferrocenyl-7-hydroxy-5-methoxy-6-methyl-2,4-cycloheptadienone (**5A**)*

^{1}H NMR ($CDCl_3$): δ 6.58 (dd, 1H, $J = 12.4$, 8.7 Hz), 5.99 (d, 1H, $J = 12.4$ Hz), 4.94 (d, 1H, $J = 8.7$ Hz), 4.39 (s, 1H), 4.23 (s, 1H), 4.13 (s, 1H), 4.07 (s, 6H), 3.92 (s, 1H), 3.42 (s, 3H), 2.53 (q, 1H, $J = 7.3$ Hz), 1.12 (d, 3H, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$): δ 198.2 (C), 174.2 (C), 140.4 (CH), 120.9 (CH), 95.4 (CH), 89.9 (C), 69.4 (C), 68.7 (CH), 67.6 (CH), 67.1 (CH), 66.9 (CH), 66.3 (CH), 55.6 (CH_3), 48.5 (CH), 11.1 (CH_3); MS (EI): 352.2 (M^+), 336.2, 322.1, 287.1, 269.1, 243.1, 242.1, 214.1, 213.0, 186.1, 139.1, 121.0, 115.1; HRMS (EI): calcd. for $C_{19}H_{20}FeO_3$: 352.0762. Found: 352.0759.

*4.3.9. 2,3-Diferrocenyl-4-cyclopropyl-4-methoxy-2-cyclobutenone (**6D**)*

^{1}H NMR ($CDCl_3$): δ 5.02 (s, 1H), 4.92 (s, 1H), 4.89 (s, 1H), 4.64 (s, 1H), 4.62 (s, 1H), 4.40 (s, 1H), 4.39 (s, 1H), 4.30 (s, 5H), 4.18 (s, 5H), 4.06 (s, 1H), 3.28 (s, 3H), 1.44 (m, 1H), 0.85 (m, 1H), 0.71 (m, 1H), 0.63 (m, 1H), 0.39 (m, 1H); IR (CH_2Cl_2): 3054 (m), 1743 (s), 1695 (m), 1606 (m), 1483 (m), 1261 (vs), 1103 (m), 916 (m), 821 (m), 755 (vs) cm^{-1}; MS (EI): 506.1 (M^+), 478.2, 464.1, 394.1, 328.0, 273.1, 215.1, 197.0, 186.0, 149.0; HRMS (EI): calcd for $C_{28}H_{26}Fe_2O_2$: 506.0632. Found 506.0634.

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Appendix A. Supplementary material

CCDC 621658 contains the supplementary crystallographic data for **3B**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j. jorganchem. 2006.12.008.

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Note

Efficient one-pot synthesis of cyanoferrocene from ferrocenecarboxaldehyde using $NH_2OH \cdot HCl/KI/ZnO/CH_3CN$ system

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Abstract

A new and efficient one-pot synthesis of cyanoferrocene from ferrocenecarboxaldehyde is described by employing the $NH_2OH \cdot HCl/KI/ZnO/CH_3CN$ system.

Keywords: Nitriles; Ferrocene; Ferrocenyl; Oximes; KI/ZnO; Ferrocenecarboxaldehyde; Ferrocenylcyanide; Ferrocenylnitrile; Ferrocenylcarbonitrile; Cyanoferrocene

1. Introduction

Recently, nitrile chemistry has experienced a major change by involvement of molecules with C≡N bonds in organic synthesis since nitriles serve as useful synthetic intermediates for pharmaceuticals, agricultural chemicals, dyes and material chemistry [1–8]. In particular, nitriles can be transformed to a variety of heterocyclic compounds including imidazoles [2], oxazoles [3], 2-oxazolines [4], thiazoles [5], triazoles [6] and tetrazoles [7], which possess a broad spectrum of biological activity. In addition, they can be converted to amines, ketones, carboxylic acids, esters and amides [8]. It should be noted that for the synthesis of nitriles, numerous methods are available [9,10], and new variants continue to appear. The most widely used general method is based on the dehydration of the corresponding aldoximes [10]. It is also well known that the cyano group itself is present in biologically important molecules including HIV protease inhibitors and 5-lipoxygerase inhibitors [11].

In this regard, cyanoferrocene [12,13] has occupied an important position since it can be converted to a structurally diverse set of ferrocenyl compounds that are attractive synthetic targets due to their chemical and biological properties [14]. Ferrocenyl group is often incorporated into a bioactive compound to obtain unexpected or enhanced biological activities [15]. In addition, ferrocenyl group is ideal for use in drug design due to its low toxicity, stability and lipophilicity [16]. Therefore, the development of a general synthetic entry to cyanoferrocene would be great interest. Although numerous methods are known for preparation of nitriles [9,10], SciFinder search has revealed only few reports for the synthesis of cyanoferrocene [17–19]. Pauson research group tried several procedures to synthesize cyanoferrocene but the highest yield (78%) was obtained by the dehydration of the corresponding oximes with dicyclohexylcarbodiimide [17]. Zhang and co-workers prepared cyanoferrocene in 60% yield by refluxing ferrocenecarboxaldehyde with *N*-methylpyrrolidone, Et_3N and $NH_2OH \cdot HCl$ [18]. Nekrasov and Yur'eva synthesized cyanoferrocene in 86% yield by cyanation of ferricenium salts with hydrocyanic acid through an electrochemical process [19]. Although, since its discovery, ferrocene and its derivatives are among the most thoroughly studied compounds, we were surprised that there has been limited study of ferrocenylnitriles. In continuation of our interest in ferrocene chemistry [20,21], we now wish to describe a new and efficient one-pot method for synthesis of cyanoferrocene from ferrocenecarboxaldehyde [22].

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2. Results and discussion

Firstly, as will be discussed later, we tried several protocols available for aromatic nitriles but all afforded cyanoferrocene in relatively low yields. Sometimes, as compared to the corresponding aromatic molecules, ferrocenyl compounds can behave somewhat differently. That's why; we undertook a detailed study to optimize reaction conditions for higher yield of cyanoferrocene. The results from a systematic study are summarized in Table 1.

Initially, ferrocenecarboxaldehyde was refluxed with a slight excess of hydroxylamine hydrochloride in acetonitrile for 2 h (entry 1). From this reaction, mostly corresponding oxime isomers were isolated and cyanoferrocene was obtained in very low yield. When the same reaction was performed in the presence of varying amounts of sodium iodide as used previously in similar reactions [10u,10aa], cyanoferrocene formed in 49–60% yields (entries 2–4). It is noteworthy that the use of excess NaI did not improve the yield (entry 3). The reactions carried out with KCl, KBr and KI gave relatively lower yields of cyanoferrocene (15–32%, entries 5–7).

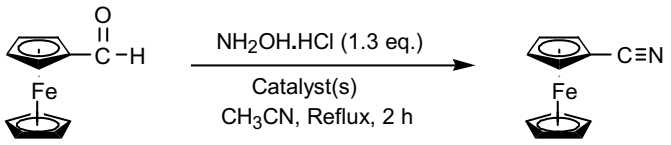
In the light of recent studies [10w,23], we thought that surface properties of ZnO might accelerate the dehydration of in situ formed ferrocenecarboxaldehyde oximes to cyanoferrocene. When the reactions were carried out in the presence of ZnO and metal halide, they afforded cyanoferrocene in higher yields (entries 8–11), as compared to those performed without ZnO (entries 4–7). The highest yield (85%) was obtained with a 1/1 KI/ZnO combination (entry 11). To the best of our knowledge, KI/ZnO system was used for the first time for synthesis of a nitrile compound [24]. We repeated this reaction for varying reaction times as well and found that the reaction was almost complete in 2.0–2.5 h. Longer reaction times did not improve the yield. It should be noted that CH_3CN appeared to be the most effective and appropriate solvent to convert ferrocenecarboxaldehyde to cyanoferrocene since it is polar enough and easily removed at the end of reaction. The reactions performed under refluxing conditions in CH_3OH and THF yielded mostly ferrocenecarboxaldehyde oximes. When carried out in refluxing DMF or benzonitrile, the reaction mostly produced decomposition products.

It should be noted that other combinations of KI/ZnO gave slightly lower yields (entries 12 and 13) or seriously lowered the yield (entry 14). The reaction with I_2/ZnO also yielded cyanoferrocene in low yield (40%, entry 15). Interestingly, the use of ZnO without metal halide was not so effective that moderate yields of cyanoferrocene were observed (entries 16 and 17).

As shown in Table 2, we also tried several other methods including NH_2OSO_3H/KI/ZnO, $NH_2OCH_3 \cdot HCl$/KI/ZnO, I_2/NH_3 [10j], cyanuric chloride/DMF [10l], and CH_3COCl/ZnO [10w] (entries 18–22), but all produced cyanoferrocene in lower yields (20–50%).

We reasoned that reaction conditions present in entry 11 provided the highest yield of cyanoferrocene. We repeated this reaction many times, even with varying amount of ferrocenecarboxaldehyde (100 mg, 500 mg, 1 g, 2 g and 3 g), and in each case we obtained similar and reproducible results. We also observed that oil bath temperature during the reflux should not exceed 100 °C since over this temperature some decomposition occurred and slightly lowered the yield of cyanoferrocene.

Table 1
Synthesis of cyanoferrocene from ferrocenecarboxaldehyde

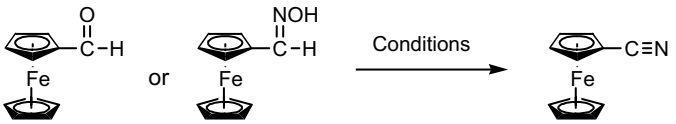


(1.0 eq.)

Entry	Catalyst(s)	Equivalent(s)	Isolated yield (%)
1	–	–	5
2	NaI	0.5	56
3	NaI	1.0	60
4	NaI	1.5	49
5	KCl	1.0	15
6	KBr	1.0	18
7	KI	1.0	32
8	NaI/ZnO	1.0/1.0	79
9	KCl/ZnO	1.0/1.0	50
10	KBr/ZnO	1.0/1.0	55
11[a]	**KI/ZnO**	**1.0/1.0**	**85**
12	KI/ZnO	1.5/1.0	81
13	KI/ZnO	1.0/1.5	82
14	KI/ZnO	1.5/1.5	40
15	I_2/ZnO	1.0/1.0	40
16	ZnO	1.0	53
17	ZnO	1.5	63

[a] When the reaction was carried out for 0.5 and 1 h, instead of 2 h, cyanoferrocene was obtained in 18% and 64% yields, respectively.

Table 2
Synthesis of cyanoferrocene by other methods



(1.0 eq.) (1.0 eq.)

Entry	Starting compound	Conditions (equivalents)	Isolated yield (%)
18	Aldehyde	NH_2OSO_3H (1.3), KI/ZnO (1.0/1.0), CH_3CN, reflux, 2 h	27
19	Aldehyde	$NH_2OCH_3 \cdot HCl$ (1.3), KI/ZnO (1.0/1.0), CH_3CN, reflux, 2 h	29
20	Aldehyde	I_2 (1.1), NH_3, THF, rt	37
21[a]	Oxime	Cyanuric chloride (1.3), DMF, rt	50
22[a]	Oxime	CH_3COCl/ZnO (3.0/3.0), 80 °C	20

[a] In this reaction, a mixture of oxime isomers was used.

3. Conclusion

In summary, we disclosed a new and efficient one-pot reaction for synthesis of cyanoferrocene from ferrocenecarboxaldehyde through dehydration of in situ formed the corresponding oximes using the $NH_2OH \cdot HCl/KI/ZnO/CH_3CN$ system, which offers a useful method for the preparation of cyanoferrocene due to its simplicity and high yield. We anticipate that this new method will be of value in the continued development of the synthetic applications of cyanoferrocene in organic and organometallic chemistry.

4. Experimental

Procedure for synthesis of cyanoferrocene. To a homogeneous mixture of ferrocenecarboxaldehyde (107.0 mg, 0.5 mmol), $NH_2OH \cdot HCl$ (45.2 mg, 0.65 mmol), KI (83.0 mg, 0.5 mmol) and ZnO (40.7 mg, 0.5 mmol) in a round-bottom flask at room temperature under argon was added acetonitrile (5.5 ml). The resulting mixture was then refluxed for 2 h with efficient stirring and heating (note that oil bath temperature during the reflux should not exceed 100 °C). Subsequently, aqueous $Na_2S_2O_3$ (5%, 1 mL) was added to the cooled mixture and the stirring was continued for additional 15 min. After the mixture was filtrated to remove solid particles, it was diluted with water (10 mL) and extracted with ethyl acetate (2×25 mL). Collected organic layers were dried on $MgSO_4$ and concentrated in a rotary evaporator. The crude cyanoferrocene was purified by flash chromatography on silica gel using 19:1 hexane/ethyl acetate followed by 9:1 and 4:1 hexane/ethyl acetate, respectively, as the eluent. The orange fraction with $R_f = 0.7$ (2:1 hexane/ethyl acetate) was collected to give cyanoferrocene (89.7 mg, 85% yield; mp 106.4–106.7 °C, lit. 17 mp 107–108 °C). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 4.59 (pseudo t, 2H, $J = 1.75$ Hz), 4.32 (pseudo t, 2H, $J = 1.75$ Hz), 4.27 (s, 5H); ^{13}C NMR ($CDCl_3$; 100 MHz): δ 120.1 (*C*N), 71.7 (C_5H_4), 70.6 (C_5H_4), 70.5 (C_5H_5), 51.8 (*ipso*-C_5H_4); IR (CH_2Cl_2): 2225.8 (CN) cm^{-1}.

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Synthesis of ferrocenyl pyrazoles by the reaction of (2-formyl-1-chlorovinyl)ferrocene with hydrazines

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Abstract

Synthesis of ferrocenyl-substituted pyrazoles via the reaction between (2-formyl-1-chlorovinyl)ferrocene and hydrazine derivatives is described. Depending upon the substitution pattern of hydrazine, the reaction affords 1-alkyl/aryl-5-ferrocenylpyrazoles and/or 1-alkyl/aryl-3-ferrocenylpyrazoles. The reaction appears to be general for a variety of hydrazine derivatives.

Keywords: Ferrocene; Ferrocenyl; Pyrazole; Hydrazine; Hydrazinium salt; Hydrazide; Propenal; Density functional theory; B3LYP

1. Introduction

Pyrazoles have occupied a unique position in the design and synthesis of novel biologically active agents that exert remarkable anticancer activities [1]. In fact, pyrazoles have been studied for over a century as an important class of heterocyclic compounds and still continue to attract considerable attention due to the broad range of biological activities they possess, including analgesic, antimicrobial, antiviral, anti-inflammatory, hypoglycemix, anti-hypertensive and antitumor properties [1,2]. Recent studies have shown that the integration of a ferrocenyl group into such structures may enhance their biological activities or generate new medicinal properties [3,4]. Due to its unique structure, different membrane-permeation properties and anomalous metabolism, ferrocene is often incorporated into a compound in order to obtain unexpected or enhanced biological activities [3,4]. Thus, in recent years, considerable effort has been devoted to the synthesis of new ferrocene derivatives since the properly functionalized derivatives could be potential antitumor substances [5,6]. Although pyrazoles are among the most thoroughly studied compounds [7], we were surprised that there has been very limited study of the ferrocenyl-substituted pyrazoles [8]. In this regard, as shown by Terent'ev and co-workers [9], the reaction between (2-formyl-1-chlorovinyl)ferrocene (**1**) and hydrazines (**2**) represents a rapid entry into ferrocenyl pyrazoles (**3**) (Scheme 1), but this reaction was not studied in much detail and the low yields of ferrocenyl pyrazoles **3** were obtained. As part of a program to synthesize new ferrocenyl-substituted heterocyclic compounds as potential pharmaceuticals, we have reinvestigated this reaction and improved the yields [10]. We herein report the results of this study.

2. Results and discussion

2.1. Synthesis of starting materials

(2-Formyl-1-chlorovinyl)ferrocene (3-chloro-3-ferrocenylpropenal) (**1**) was synthesized from acetylferrocene according to the well-known literature procedure [11], in which treatment of acetylferrocene with phosphorous oxychloride in DMF led to formation of (2-formyl-1-chlorovinyl)ferrocene (**1**). Acetylferrocene is readily available in large quantities from ferrocene according to a standard

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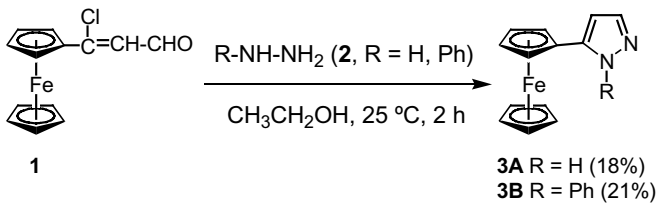


Scheme 1.

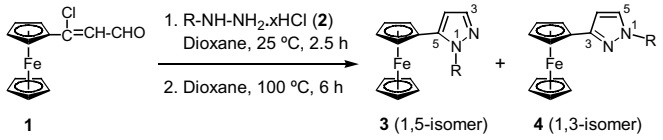
protocol [12]. Hydrazine derivatives **2** used in this study were all commercially available.

2.2. Synthesis of ferrocenyl pyrazoles 3 and 4

The reaction was initially examined under a variety of conditions, and the best results were obtained as follows: 3-chloro-3-ferrocenylpropenal (**1**) was first reacted with the excess amounts (3 equivalents) of hydrazine derivative (**2**) at 25 °C in dioxane under argon for 2.5 h. The resulting mixture was then refluxed at 100 °C for 6 h, and the products were isolated by flash chromatography. The results are summarized in Table 1. If available, hydrazinium salts, instead of hydrazines, were used in these reactions since they gave relatively higher yields of pyrazoles.

As can be seen from Table 1, 1-alkyl/aryl-5-ferrocenylpyrazoles (**3**) and/or 1-alkyl/aryl-3-ferrocenylpyrazoles (**4**) were resulted from these reactions, which are commonly called 1,5- and 1,3-isomers, respectively. It should be noted that 1,5- and 1,3-isomers of pyrazoles can be differentiated on the basis of their ^{13}C NMR spectra, as concluded from the spectral data of similar pyrazole derivatives [13]. In general, C5 peak in 1,5-isomer is relatively upfield and appears around 140 ppm while corresponding C3 peak in 1,3-isomer is relatively downfield and resonates around 150 ppm (see Table 1 for atom numbering). Moreover, in 1,5-isomer, the absolute value of chemical shift difference between C5 and C3 carbons is mostly smaller than that between respective C3 and C5 carbons in 1,3-isomer, i.e. $|\Delta\delta(C5–C3)_{1,5\text{-isomer}}| < |\Delta\delta(C3–C5)_{1,3\text{-isomer}}|$.

Table 1
Reaction of (2-formyl-1-chlorovinyl)ferrocene (**1**) with hydrazines **2**



Entry[a]	R	x	Products (isolated yield, %)
A	H	2	**3A** (51)
B	Ph	1	**3B** (67) + **4B** (4)
C	CH_2-CH_2-OH	2	**3C** (3) + **4C** (34)
D	CH_2-Ph	2	**3D** (55)
E	p-C_6H_4-CO_2H	1	**3E** (47)
F	o-C_5H_4N	0	**3F** (60)
G	CO-p-C_6H_4-OH	0	**4G** (43) + **3A** (50)

[a] Entry letters define R group for compounds **2**, **3** and **4**, and x for compound **2**.

The reaction between ferrocenylpropenal **1** and hydrazine dihydrochloride (**2A**) led to formation of a pyrazole derivative, which was tentatively assigned as 5-ferrocenylpyrazole (**3A**) (entry A). It should be noted that owing to annular tautomerism, pyrazoles can exist in two tautomeric forms such as **3A** and **4A**. In fact, proton transfer in pyrazoles is a formally 1,5-hydrogen shift and the barriers for such processes in both solution and solid state are in the range of 10–14 kcal/mol [14]. As anticipated, tautomers **3A** and **4A** can be in equilibrium or interconvert in part. Unfortunately, we were unsuccessful to obtain a well-resolved ^{13}C NMR spectrum from this compound at 25 °C and even −15 °C to identify the corresponding tautomer(s). In fact, pyrazole **3A** is a known compound [9], but there is a lack of specific spectroscopic data (such as ^{13}C NMR data) in the literature to differentiate it from its tautomer **4A**. Our efforts to spectroscopically distinguish between pyrazoles **3A** and **4A** are going on.

We also calculated the relative energies of pyrazoles **3A** and **4A** at the density functional theory (DFT) level (B3LYP/6-31G*) [15,16] by using the GAUSSIAN-98 program package [17], and found that **4A** is more stable than **3A** by 0.3 kcal/mol. Note that, in gas phase (DFT calculations), **4A** is the more stable while, in solution and solid state, it might correspond to a metastable structure, which requires further study. As shown by Elguero and co-workers [13d], pyrazoles can exist in different tautomeric forms depending upon their physical phase or state. For instance, in gas phase and solution, 3-phenylpyrazole is more stable than its tautomer, 5-phenylpyrazole. However, in solid state, crystals of 3-phenylpyrazole evolved to be 5-phenylpyrazole [13d].

The reaction of ferrocenylpropenal **1** with phenylhydrazine dihydrochloride (**2B**) afforded 5-ferrocenyl-1-phenylpyrazole (**3B**) along with a very small amount of 3-ferrocenyl-1-phenylpyrazole (**4B**) (entry B). Interestingly, the reaction between ferrocenylpropenal **1** and (2-hydroxyethyl)hydrazinium dichloride (**2C**) [18] produced 2-(3-ferrocenylpyrazol-1-yl)ethanol (**4C**) as the major product, accompanied by the very small amount of 2-(5-ferrocenylpyrazol-1-yl)ethanol (**3C**) (entry C). On the other hand, the reaction of ferrocenylpropenal **1** with benzylhydrazine dihydrochloride (**2D**) led to a single pyrazole derivative, 1-benzyl-5-ferrocenylpyrazole (**3D**) (entry D). It should be noted that tautomeric assignments of pyrazoles **3B–D** and **4B–C** were based on both chemical shifts and absolute values of chemical shift differences of corresponding C3 and C5 carbons, as mentioned before. Note that the structures of ferrocenyl pyrazoles **3B**, **3D** and **4C** were unambiguously identified by X-ray analysis as well, but the results of this study will be reported separately as a part of another study.

The reaction of ferrocenylpropenal **1** with 4-hydrazinobenzoic acid (**2E**) yielded 4-(5-ferrocenylpyrazol-1-yl)benzoic acid (**3E**) (entry E). Similarly, the reaction between

ferrocenylpropenal **1** and 2-pyridiniohydrazinium dichloride (**2F**) [19] led to 2-(5-ferrocenylpyrazol-1-yl)pyridine (**3F**) (entry F). On the other hand, the reaction of ferrocenylpropenal **1** with 4-hydroxybenzhydrazide (**2G**) afforded two products, namely (3-ferrocenylpyrazol-1-yl)(4-hydroxyphenyl)methanone (**4G**) and 5-ferrocenylpyrazole (**3A**) (entry G).

For the formation of pyrazoles **3** (1,5-isomer) and **4** (1,3-isomer), three mechanistic pathways are available as depicted in Scheme 2. The reaction proceeds via tandem conjugate addition–elimination of hydrazine **2** with ferrocenylpropenal **1** followed by cyclization and/or condensation of the resulting β-hydrazinoenones **5** and **6** (pathways A and B), or via condensation of hydrazine **2** with ferrocenylpropenal **1** followed by cyclization through tandem conjugate addition–elimination of the resulting α,β-unsaturated hydrazone **7** (pathway C). It should be noted that pathway A leads to 1,3-pyrazole isomer **4** while pathways B and C go to 1,5-pyrazole isomer **3**. Apparently, depending upon the substitution pattern of hydrazine derivative **2**, one pathway or more than one pathway can be operative during the course of the reaction.

Interestingly, the reaction of ferrocenylpropenal **1** with 4-hydroxybenzhydrazide (**2G**) produced 5-ferrocenylpyrazole (**3A**) in addition to pyrazole **4G** (entry G). For the formation of pyrazole **3A**, we have proposed two mechanistic pathways as illustrated in Scheme 3. According to pathway A, formation of pyrazole **3A** may not actually represent a different reactivity pattern since it is a secondary product of the reaction and results from the initially formed pyrazole **4G** by hydrolysis. Nucleophilic addition of benzhydrazide **2G** to carbonyl function of pyrazole **4G** provides a hydrazide derivative, **8**, which is not normally stable and eliminates benzoic acid hydrazide **9** to give pyrazole **4A**. As mentioned before, pyrazole **4A** can be in equilibrium with and/or interconvert to its tautomer **3A**. Alternatively, as outlined in pathway B, benzhydrazide **2G** may react with itself via nucleophilic addition, yielding hydrazide derivative **10**. Elimination of benzoic acid hydrazide **9** from **10** then affords in situ hydrazine, the reaction of which with ferrocenylpropenal **1** yields pyrazole **3A** as well (Scheme 3). At present, it is not clear which mechanism is operating but there are precedents for both pathways [20,21].

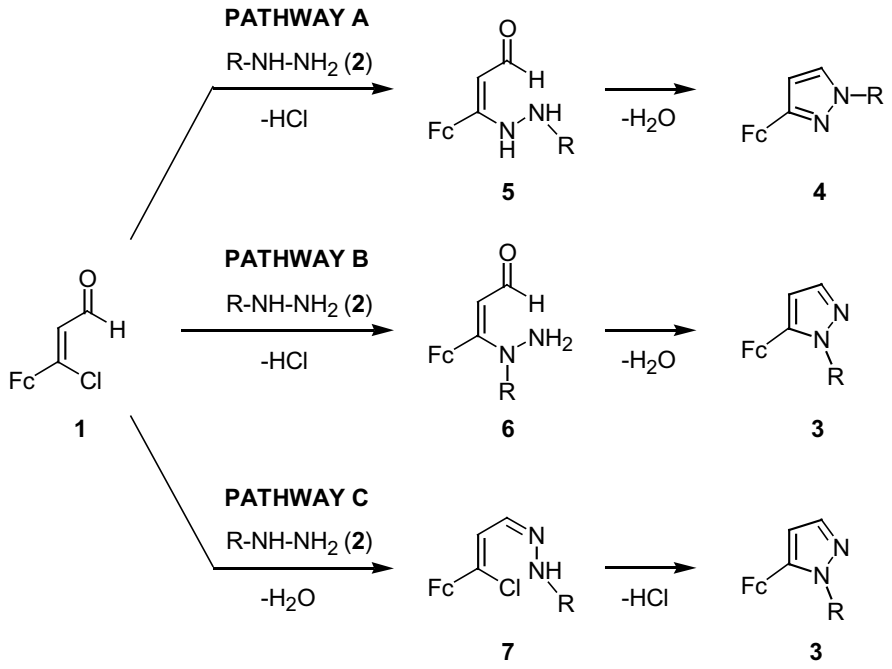
3. Conclusion

In summary, we have reinvestigated in detail the reaction between (2-formyl-1-chlorovinyl)ferrocene (**1**) and hydrazines **2** and improved the yields of pyrazoles **3** and/or **4**. In most cases, 1,5-pyrazole isomers **3** has resulted from these reactions as the single or the major products. The regioselectivity of the reactions is mainly governed by the nature of the substituents in hydrazines **2**. Due to the ready availability of ferrocenylpropenal **1** and hydrazines **2**, this method represents a versatile synthesis of ferrocenyl-substituted pyrazoles **3** and/or **4**.

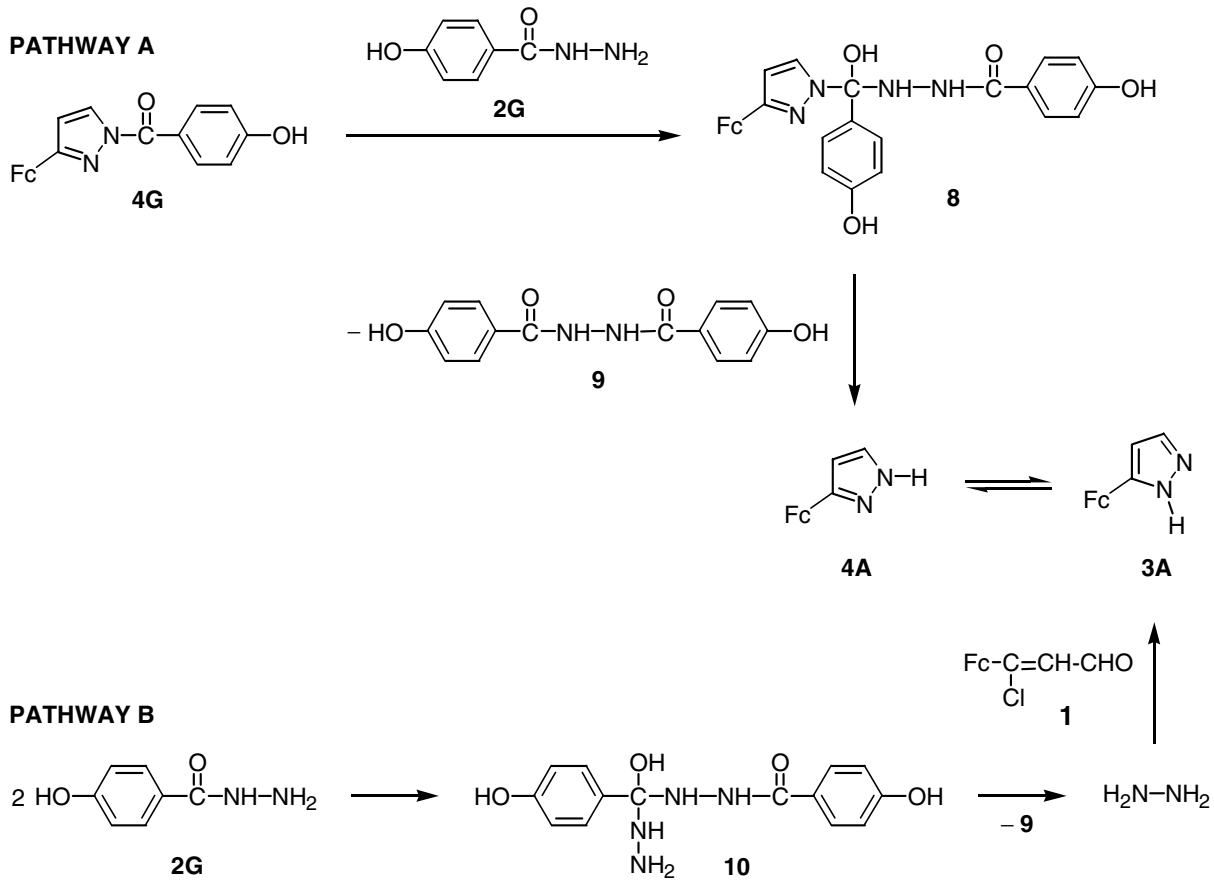
4. Experimental

4.1. General consideration

Nuclear magnetic resonance (^{1}H and ^{13}C) spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultra-



Scheme 2.



Scheme 3.

shield (400 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). DEPT ^{13}C NMR information is given in parenthesis as C, CH, CH_2 and CH_3. Infrared spectra were recorded on a Perkin–Elmer 1600 Series FT-IR spectrometer or on a Bruker Vertex 70 Spectrometer using attenuated total reflection (ATR). Band positions are reported in reciprocal centimeters (cm^{-1}). Mass spectra (MS) were obtained on a Finnigan MAT 95 spectrometer, using electron impact (EI) at 70 eV; m/z values are reported. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 95 spectrometer by preselected-ion peak matching at $R \approx 10{,}000$ to be within ± 3 ppm of the exact masses. Flash chromatography was performed using thick-walled glass columns and 'flash grade' silica (Merck 230–400 mesh). Routine thin layer chromatography (TLC) was effected by using precoated 0.25 mm silica gel plates purchased from Merck. The relative proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio. (2-Formyl-1-chlorovinyl)ferrocene (**1**) [14] and acetylferrocene [15] were synthesized according to the well-known literature procedures. All other commercially available reagents and reactants were obtained in reagent grade and used without purification. All reaction solvents were distilled for purity. Diethyl ether, THF and dioxane were distilled from sodium/benzophenone ketyl. The inert atmosphere was created by slight positive pressure (ca. 0.1 psi) of argon.

*4.2. General procedure for the synthesis of ferrocenyl pyrazoles **3** and **4** (Table 1)*

To the solution of (2-formyl-1-chlorovinyl)ferrocene (**1**) (100 mg, 0.364 mmol) in dioxane (25 mL) under argon was added hydrazine derivative or salt (**2**) (1.092 mmol). The resulting mixture was stirred for 2.5 h at room temperature and then heated at reflux for 6 h. After the reaction was complete, the mixture was cooled to 25 °C, and the solvent was removed on a rotary evaporator. The residue was dissolved in water (20 mL) and extracted with chloroform (3 × 30 mL). The combined chloroform layers were dried over magnesium sulfate and removed in a rotary evaporator. Final purification was achieved through flash chromatography on silica gel (eluent: hexane/EtOAc from 19:1 to 1:1). The products given in Table 1 were isolated with the indicated yields.

4.3. Spectral data for products

4.3.1. 5-Ferrocenyl-1H-pyrazole (**3A**)

^{1}H NMR ($CDCl_3$): δ 7.52 (s, 1H), 6.33 (s, 1H), 4.58 (s, 2H), 4.28 (s, 2H), 4.04 (s, 5H), NH peak was not observed due to H/D exchange and/or tautomerism; IR (neat): 3115, 3026, 2875, 2840, 2816, 1598, 1565, 1463, 1415, 1289, 1102, 1053, 999, 937, 810, 764 cm^{-1}; MS (EI): 252 (M^+), 250, 224, 187, 166, 158, 133, 121, 103, 77; HRMS (EI): calcd. for $C_{13}H_{12}FeN_2$: 252.0350. Found: 252.0352.

4.3.2. 5-Ferrocenyl-1-phenyl-1H-pyrazole (**3B**)

^{1}H NMR ($CDCl_3$): δ 7.62 (s, 1H), 7.40 (m, 5H), 6.50 (s, 1H), 4.17 (s, 2H), 4.14 (s, 2H), 4.05 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 141.5 (C), 140.4 (C), 140.0 (CH), 128.8 (CH), 128.0 (CH), 126.1 (CH), 106.8 (CH), 75.1 (C), 69.9 (CH), 68.8 (CH), 68.6 (CH); IR (CH_2Cl_2): 3089, 3036, 1665, 1597, 1557, 1498, 1402, 1259, 1145, 971, 923, 870 cm^{-1}; MS (EI): 328 (M^+), 326, 263, 235, 207, 170, 153, 121, 77, 56; HRMS (EI): calcd. for $C_{19}H_{16}FeN_2$: 328.0663. Found: 328.0661.

4.3.3. 3-Ferrocenyl-1-phenyl-1H-pyrazole (**4B**)

^{1}H NMR ($CDCl_3$): δ 7.84 (d, 1H, $J = 2.4$ Hz), 7.71 (d, 2H, $J = 7.8$ Hz), 7.44 (t, 2H, $J = 7.8$ Hz), 7.25 (t, 1H, $J = 7.8$ Hz), 6.48 (d, 1H, $J = 2.4$ Hz), 4.76 (s, 2H), 4.29 (s, 2H), 4.07 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 152.5 (C), 140.3 (C), 129.4 (CH), 127.4 (CH), 126.0 (CH), 119.0 (CH), 105.6 (CH), 78.4 (C), 69.6 (CH), 68.7 (CH), 66.9 (CH); IR (CH_2Cl_2): 3090, 3030, 2959, 2865, 1681, 1649, 1598, 1557, 1506, 1458, 1257, 1129, 1043, 868, 820 cm^{-1}; MS (EI): 328 (M^+), 326, 263, 246, 206, 178, 149, 121, 91, 77, 56; HRMS (EI): calcd. for $C_{19}H_{16}FeN_2$: 328.0663. Found: 328.0665.

4.3.4. 2-(5-Ferrocenylpyrazol-1-yl)ethanol (**3C**)

^{1}H NMR ($CDCl_3$): δ 7.46 (d, 1H, $J = 1.8$ Hz), 6.30 (d, 1H, $J = 1.8$ Hz), 4.49 (s, 2H), 4.36 (s, 2H), 4.33 (t, 2H, $J = 4.5$ Hz), 4.18 (s, 5H), 4.02 (t, 2H, $J = 4.5$ Hz), 3.09 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 141.4 (C), 138.7 (CH), 106.0 (CH), 74.9 (C), 69.6 (CH), 68.9 (CH), 68.8 (CH), 61.8 (CH_2), 51.0 (CH_2); IR (neat): 3331, 2965, 2937, 1562, 1460, 1331, 1070, 1043, 824, 800 cm^{-1}; MS (EI): 296 (M^+), 294, 265, 252, 231, 200, 187, 146, 121, 103; HRMS (EI): calcd. for $C_{15}H_{16}FeN_2O$: 296.0612. Found: 296.0610.

4.3.5. 2-(3-Ferrocenylpyrazol-1-yl)ethanol (**4C**)

^{1}H NMR ($CDCl_3$): δ 7.31 (s, 1H), 6.22 (s, 1H), 4.76 (s, 2H), 4.35 (s, 2H), 4.21 (t, 2H, $J = 4.3$ Hz), 4.12 (s, 5H), 3.97 (t, 2H, $J = 4.3$ Hz), 3.52 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 151.3 (C), 130.8 (CH), 103.0 (CH), 78.3 (C), 69.4 (CH), 68.3 (CH), 66.6 (CH), 62.1 (CH_2), 53.5 (CH_2); IR (neat): 3229, 3142, 2950, 2869, 1556, 1502, 1408, 1349, 1230, 1067, 824, 764 cm^{-1}; MS (EI): 296 (M^+), 294, 278, 264, 231, 213, 199, 173, 148, 121, 103, 81; HRMS (EI): calcd. for $C_{15}H_{16}FeN_2O$: 296.0612. Found: 296.0614.

4.3.6. 1-Benzyl-5-ferrocenyl-1H-pyrazole (**3D**)

^{1}H NMR ($CDCl_3$): δ 7.44 (s, 1H), 7.23 (t, 2H, $J = 7.28$ Hz), 7.15 (t, 1H, $J = 7.28$ Hz), 6.96 (d, 2H, $J = 7.28$ Hz), 6.35 (s, 1H), 5.42 (s, 2H), 4.29 (s, 2H), 4.17 (s, 2H), 4.00 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 141.7 (C), 139.1 (C), 137.7 (CH), 128.6 (CH), 127.3 (CH), 126.2 (CH), 106.0 (CH), 74.9 (C), 70.5 (CH), 68.8 (CH), 68.4 (CH), 53.3 (CH_2); IR (neat): 3142, 3109, 2950, 2896, 1556, 1502, 1409, 1321, 1231, 1071, 873, 825, 765 cm^{-1}; MS (EI): 342 (M^+), 277, 252, 223, 185, 157, 121, 91, 65, 56; HRMS (EI): calcd. for $C_{20}H_{18}FeN_2$: 342.0819. Found: 342.0817.

4.3.7. 4-(5-Ferrocenylpyrazol-1-yl)benzoic acid (**3E**)

^{1}H NMR ($CDCl_3$): δ 8.00 (d, 2H, $J = 7.5$ Hz), 7.86 (d, 1H, $J = 8.5$ Hz), 7.05 (d, 2H, $J = 7.5$ Hz), 6.68 (d, 1H, $J = 8.5$ Hz), 4.63 (t, 2H, $J = 1.7$ Hz), 4.37 (t, 2H, $J = 1.7$ Hz), 4.19 (s, 5H), carboxylic acid peak was not observed due to H/D exchange; ^{13}C NMR ($CDCl_3$): δ 170.5 (C), 139.1 (CH), 137.8 (C), 137.0 (C), 132.3 (CH), 120.3 (C), 117.8 (CH), 111.9 (CH), 83.0 (C), 70.2 (CH), 70.1 (CH), 67.4 (CH); IR (CH_2Cl_2): 3057, 2928, 2851, 2671, 2542, 1727, 1694, 1603, 1451, 1417, 1316, 1286, 1262, 1171, 1127, 1070, 746, 733, 719 cm^{-1}; MS (EI): 372 (M^+), 370, 329, 307, 251, 234, 205, 178, 137, 120, 65, 56; HRMS (EI): calcd. for $C_{20}H_{16}FeN_2O_2$: 372.0561. Found: 372.0559.

4.3.8. 2-(5-Ferrocenylpyrazol-1-yl)pyridine (**3F**)

^{1}H NMR ($CDCl_3$): δ 8.11 (ddd, 1H, $J = 8.6$, 7.5, 1.8 Hz), 7.87 (d, 1H, $J = 9.0$ Hz), 7.58 (ddd, 1H, $J = 8.6$, 7.5, 1.8 Hz), 7.22 (d, 1H, $J = 8.5$ Hz), 6.77 (ddd, 1H, $J = 8.6$, 7.5, 1.8 Hz), 6.65 (d, 1H, $J = 9.0$ Hz), 4.58 (t, 2H, $J = 1.9$ Hz), 4.35 (t, 2H, $J = 1.9$ Hz), 4.18 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 155.9 (C), 146.9 (CH), 139.1 (CH), 138.5 (CH), 136.7 (C), 118.1 (CH), 115.8 (CH), 107.6 (CH), 83.4 (C), 70.1 (CH), 70.0 (CH), 67.3 (CH); IR (neat): 3178, 3142, 3048, 2951, 1561, 1535, 1435, 1301, 1141, 1088, 867, 805, 769 cm^{-1}; MS (EI): 329 (M^+), 302, 300, 271, 264, 237, 210, 184, 156, 149, 120, 89, 67; HRMS (EI): calcd. for $C_{18}H_{15}FeN_3$: 329.0615. Found: 329.0613.

4.3.9. (3-Ferrocenylpyrazol-1-yl)(4-hydroxyphenyl)-methanone (**4G**)

^{1}H NMR ($CDCl_3$): δ 8.33 (s, 1H), 8.21 (d, 2H, $J = 7.95$ Hz), 6.89 (d, 2H, $J = 7.95$ Hz), 6.51 (s, 1H), 5.87 (s, OH), 4.81 (s, 2H), 4.40 (s, 2H), 4.14 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 165.1 (C), 160.3 (C), 156.6 (C), 134.5 (CH), 131.5 (CH), 123.6 (C), 115.3 (CH), 107.9 (CH), 78.2 (C), 71.2 (CH), 71.1 (CH), 68.6 (CH); IR (neat): 3353, 3149, 1699, 1606, 1558, 1417, 1384, 1357, 1311, 1271, 1231, 1190, 1057, 895, 821, 756 cm^{-1}; MS (EI): 372 (M^+), 370, 307, 252, 224, 187, 158, 141, 121, 93, 84; HRMS (EI): calcd. for $C_{20}H_{16}FeN_2O_2$: 372.0561. Found: 372.0563.

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Synthesis of ferrocenyl pyrazoles by the reaction of 3-ferrocenylpropynal with hydrazinium salts

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Abstract

Synthesis of ferrocenyl-substituted pyrazoles via the reaction between 3-ferrocenylpropynal and hydrazinium salts is described. Depending upon the substitution pattern of hydrazine derivative, the reaction affords 1-alkyl/aryl-5-ferrocenylpyrazoles and/or 1-alkyl/aryl-3-ferrocenylpyrazoles. Structures of 5-ferrocenyl-1-phenyl-1*H*-pyrazole, 1-benzyl-5-ferrocenyl-1*H*-pyrazole and 2-(3-ferrocenylpyrazol-1-yl)ethanol were identified by X-ray crystallography.

Keywords: Ferrocene; Pyrazole; Hydrazine; Propynal; Cyclization; Condensation

1. Introduction

The rapid spread of cancer has sparked an intense chemical search for new structure leads which may be of use in designing novel antitumor drugs. In this regard, pyrazoles have been the focus of a large number of investigations in the design and synthesis of novel biologically active agents that show remarkable anticancer activities [1]. Pyrazoles have been studied for over a century as an important class of heterocyclic compounds and still continue to attract considerable attention due to the wide range of medicinal activities they possess, such as analgesic, antimicrobial, antiviral, anti-inflammatory, hypoglycemic, antihypertensive and antitumor properties [1,2]. Recent studies have shown that substitution of an aromatic nucleus of such structures with a ferrocene unit can lead to products with enhanced or unexpected biological activity which is absent or less manifest in the parent molecule [3,4]. Owing to its unique structure, different membrane-permeation behavior and anomalous metabolism, ferrocene is often integrated into a compound in order to obtain unexpected or enhanced biological activities [3,4]. Thus, in recent years, substantial effort has been devoted to the synthesis of new ferrocene derivatives since the properly functionalized derivatives could be potential antitumor substances [5,6]. Although pyrazoles are among the most intensely studied compounds [7–9], ferrocenyl-substituted derivatives are relatively less explored [10,11]. In this regard, the reactions of acetylenic ketones (alkynones) with hydrazines have been frequently used to synthesize pyrazole derivatives [8,9]. However, analogous reactions between acetylenic aldehydes (alkynals) and hydrazines are almost unknown since, to the best of our knowledge, there is only one example of such reaction [9]. It has been reported that the microwave-assisted reaction of 3-phenylpropynal with phenylhydrazine provided 1,3- and 1,5-diphenylpyrazoles in 58% and 28% yields, respectively [9]. As a part of our general

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involvement in ferrocene containing potential pharmaceuticals, we have investigated the reaction of 3-ferrocenylpropynal (**1**) with hydrazinium salts (**2**) since it provides an easy access to ferrocenyl pyrazoles **3** and/or **4** (Table 1) [12]. We herein report the results of this study.

2. Results and discussion

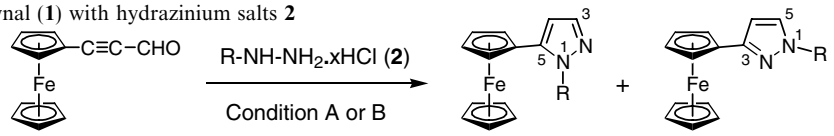
2.1. Synthesis of starting materials

3-Ferrocenylpropynal (**1**) was synthesized from ethynylferrocene by a Vilsmeier-Haack-type formylation [13]. Ethynylferrocene was prepared from acetylferrocene according to a well-known literature procedure [14]. Acetylferrocene is easily obtainable in large quantities from ferrocene according to a standard protocol [15]. Hydrazinium salts (**2**) were all commercially available, except (2-hydroxyethyl)hydrazinium dichloride (**2C**) which was prepared according to a standard procedure [16].

2.2. Synthesis of ferrocenyl pyrazoles 3 and 4

The reactions were carried out in refluxing dioxane (Condition A) or methanol (Condition B) with a mole

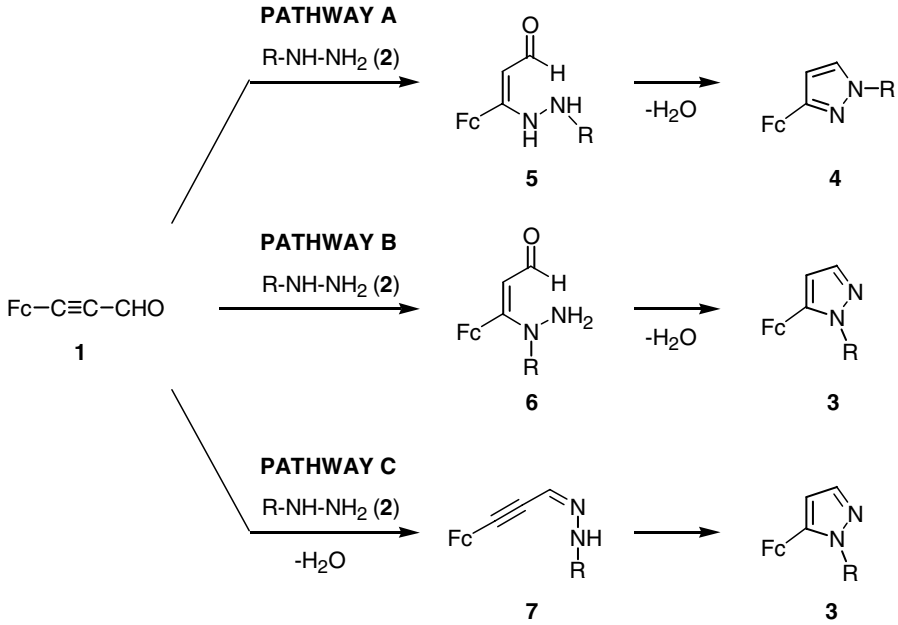
Table 1
Reaction of 3-ferrocenylpropynal (**1**) with hydrazinium salts **2**



1 **3** (1,5-isomer) **4** (1,3-isomer)

Entry[a]	R	x	Products (isolated yield, %)	
			Condition A[b]	Condition B[c]
A	H	2	**3A** (47)	**3A** (70)
B	Ph	1	**3B** (45) + **4B** (14)	**3B** (70) + **4B** (20)
C	CH_2–CH_2–OH	2	**3C** (6) + **4C** (19)	**3C** (31) + **4C** (25)
D	CH_2–Ph	2	**3D** (63)	**3D** (46) + **4D** (30)

[a] Entry letters define R group for compounds **2**, **3** and **4**, and x for compound **2**.
[b] Condition A: dioxane, 100 °C, 8 h.
[c] Condition B: CH_3OH, 65 °C, 5 h.



Scheme 1.

ratio of ferrocenylpropynal (**1**) to hydrazinium salt (**2**) of about 1:1.5, and the products were isolated by flash chromatography. The results are summarized in Table 1. Hydrazinium salts, instead of hydrazines, were employed in these reactions since they gave relatively higher yields of pyrazoles. According to our recent study, (2-formyl-1-chlorovinyl)ferrocene reacted with hydrazine derivatives to give pyrazoles, and we found the reactions in refluxing dioxane to give better results [11]. It is for the reason that the reactions between 3-ferrocenylpropynal (**1**) and hydrazinium salts (**2**) were initially carried out in refluxing dioxane (Condition A). However, in this condition,

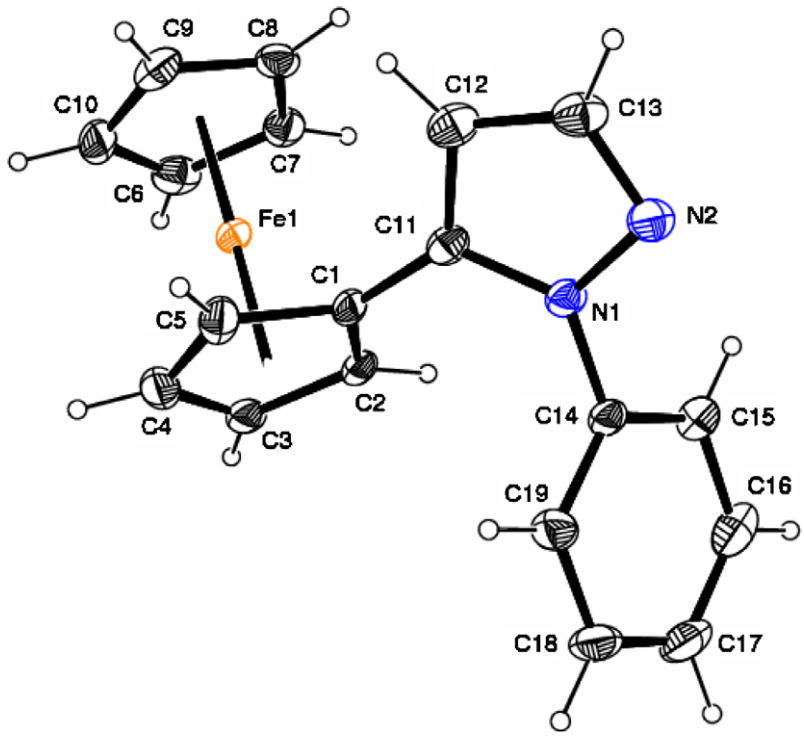


Fig. 1. ORTEP diagram of 5-ferrocenyl-1-phenyl-1*H*-pyrazole (**3B**). Ellipsoids are drawn at 20% probability.

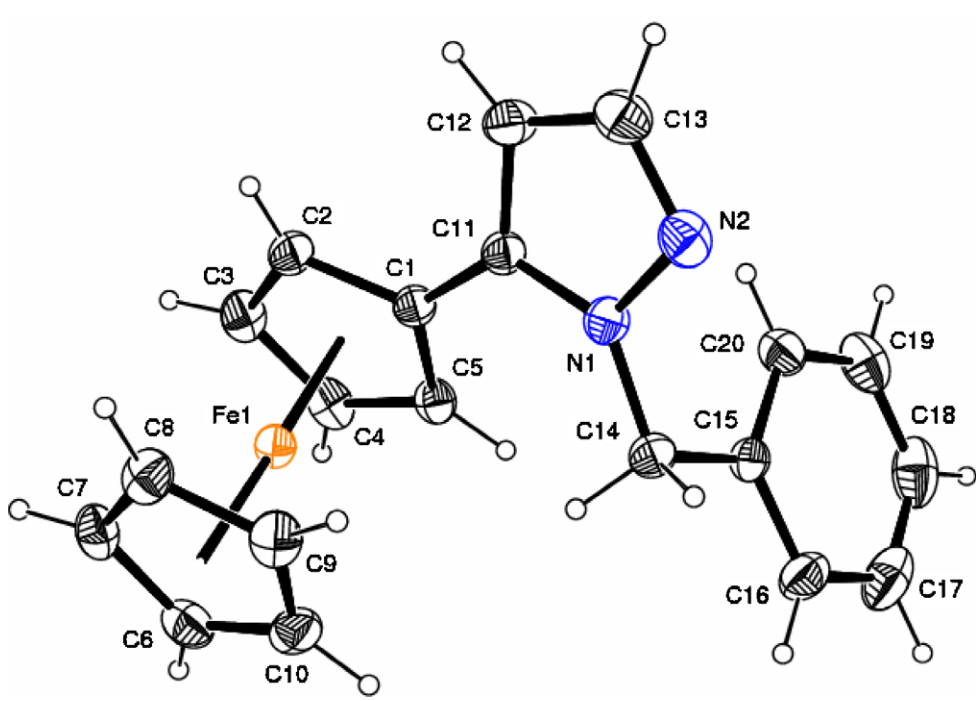


Fig. 2. ORTEP diagram of 1-benzyl-5-ferrocenyl-1*H*-pyrazole (**3D**). Ellipsoids are drawn at 20% probability.

pyrazole derivatives were obtained in relatively low yields. The same reactions were then performed in different solvents and refluxing methanol (Condition B) was found to shorten the reaction time with higher yields (Table 1).

As seen from Table 1, the reactions between 3-ferrocenylpropynal (**1**) and hydrazinium salts (**2**) yielded two kinds of pyrazoles, namely 1-alkyl/aryl-5-ferrocenylpyrazoles (**3**) and 1-alkyl/aryl-3-ferrocenylpyrazoles (**4**), which we will refer to as 1,5- and 1,3-isomers, respectively. 1,5- and 1,3-isomers of these types of pyrazoles can easily be identified on the basis of their ^{13}C NMR spectra [11]. In general, the C5 peak in 1,5-isomer is relatively upfield and resonates near 140 ppm while the corresponding C3 peak in 1,3-isomer is comparatively downfield and appears around 150 ppm (see Table 1 for atom numbering). Furthermore, in 1,5-isomer, the absolute value of chemical shift difference between C5 and C3 carbons is

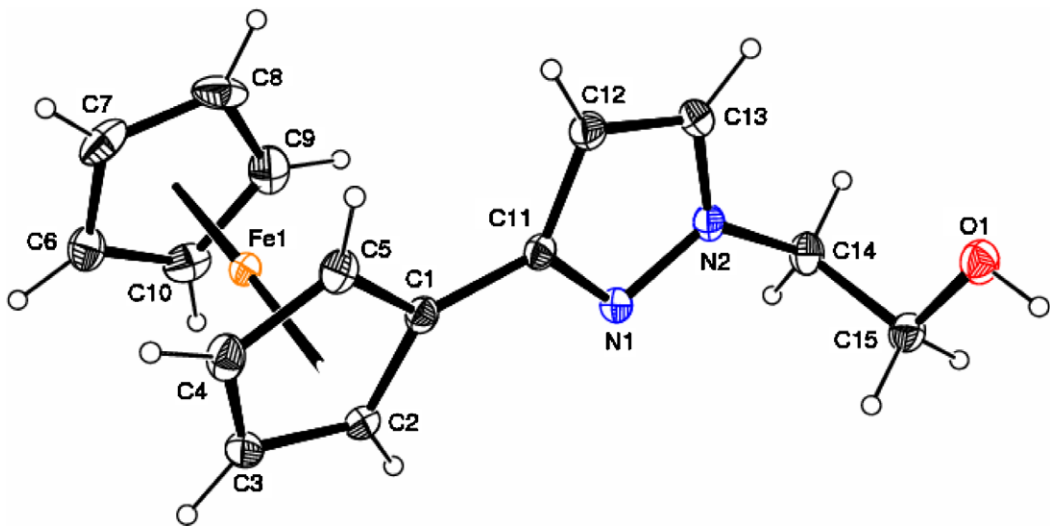


Fig. 3. ORTEP diagram of 2-(3-ferrocenylpyrazol-1-yl)ethanol (**4C**). Ellipsoids are drawn at 20% probability.

Table 2
Crystallographic data and structure refinement parameters for **3B**, **3D** and **4C**

	3B	**3D**	**4C**
Empirical formula	$C_{19}H_{16}FeN_2$	$C_{20}H_{18}FeN_2$	$C_{15}H_{16}FeN_2O$
Formula weight	328.19	342.21	296.15
Crystal size (mm)	0.470 × 0.380 × 0.260	0.640 × 0.570 × 0.440	0.780 × 0.423 × 0.210
Temperature (K)	293(2)	293(2)	296(2)
Crystal system	Orthorhombic	Triclinic	Monoclinic
Space group	$Pca2_1$	$P\bar{1}$	$P2_1/c$
a (Å)	21.999(2)	9.2923(5)	9.3038(17)
b (Å)	5.9827(6)	10.7911(6)	14.0340(3)
c (Å)	11.4051(9)	16.9299(9)	10.6563(16)
α (°)	90.000(0)	75.493(4)	90.000(0)
β (°)	90.000(0)	89.605(4)	110.482(13)
γ (°)	90.000(0)	75.870(4)	90.000(0)
V (Å^3)	1501.1(2)	1591.12(15)	1303.4(4)
Z	4	4	4
D_x (g cm^{-3})	1.452	1.429	1.509
μ (Mo Kα) (mm^{-1})	1.001	0.948	1.149
Radiation/wavelength (Å)	Mo Kα/0.71073	Mo Kα/0.71073	Mo Kα/0.71073
θ_{max} (°)	27.06	27.90	26.00
Index range (hkl)	−22/27, −7/7, −14/14	−12/12, −14/14, −22/22	−11/11, −17/17, −13/13
Reflections measured	7738	30561	15701
Independent reflections (R_{int})	3217	7544	2563
Reflections with $I > 2\sigma(I)$	2645	6232	2270
Number of parameters	199	415	172
Number of restraints	1	0	0
$R[F^2 > 2\sigma(F^2)]$	0.0399	0.028	0.0251
$wR(F^2)$	0.1236	0.0759	0.0660
Goodness-of-fit (F^2)	1.201	1.050	1.046
Maximum, minimum Δρ (e/Å^3)	0.882, −0.750	0.198, −0.351	0.217, −0.268

generally smaller than that between respective C3 and C5 carbons in 1,3-isomer [11], i.e. $|\Delta\delta(C5–C3)_{1,5\text{-isomer}}| < |\Delta\delta(C3–C5)_{1,3\text{-isomer}}|$.

The reaction between ferrocenylpropynal (**1**) and hydrazine dihydrochloride (**2A**) under both conditions led to formation of a pyrazole derivative, which was tentatively identified as 5-ferrocenylpyrazole (**3A**) (entry A). It is noteworthy to mention that owing to annular tautomerism, pyrazoles can exist in two tautomeric forms such as **3A** and **4A** [17]. Proton transfer in pyrazoles is a formal [1,5]-hydrogen shift and the barriers for such processes in both solid state and solution are about 10–14 kcal/mol [17c]. As we noted previously [11], we were unable to get a well-resolved ^{13}C NMR spectrum from this compound at both 25 and −15 °C to determine its tautomeric identity. In fact, pyrazole **3A** is a known compound [10c] but specific spectroscopic data (such as ^{13}C NMR data) to distinguish it from its tautomer **4A** has not been reported. Our efforts to differentiate these tautomers spectroscopically from each other are continuing.

The reaction of ferrocenylpropynal (**1**) with phenylhydrazine dihydrochloride (**2B**) afforded 5-ferrocenyl-1-phenylpyrazole (**3B**) and 3-ferrocenyl-1-phenylpyrazole (**4B**) (entry B). In both conditions, pyrazole **3B** was isolated as the major product. The reaction between ferrocenylpropynal **1** and (2-hydroxyethyl)hydrazinium dichloride (**2C**) [16] led to formation of 2-(5-ferrocenylpyrazol-1-yl)ethanol (**3C**) and 2-(3-ferrocenylpyrazol-1-yl)ethanol (**4C**) (entry C). Interestingly, in Condition A, pyrazole **4C** was obtained as the major product of the reaction while in Condition B, pyrazole **3C** was the major one. On the other hand, the reaction of ferrocenylpropynal (**1**) with benzylhydrazine dihydrochloride (**2D**) produced 1-benzyl-5-ferrocenylpyrazole (**3D**) and/or 1-benzyl-3-ferrocenylpyrazole (**4D**) depending upon the condition employed (entry D). In Condition B, pyrazole **3D** was isolated as the major product of the reaction. Note that the tautomeric assignments of these pyrazole isomers were based on both the chemical shifts and chemical shift differences of corresponding C3 and C5 carbons, as mentioned earlier [11]. The structures of ferrocenyl pyrazoles **3B**, **3D** and **4C** were also elucidated by X-ray analysis.

For the formation of pyrazoles **3** (1,5-isomer) and **4** (1,3-isomer), three mechanistic pathways are possible as illustrated in Scheme 1. In pathways A and B, the reaction occurs via a conjugate addition of hydrazine **2** to ferrocenylpropynal **1**, followed by cyclization and/or cyclocondensation of the resulting β-hydrazinoenones **5** and **6**. However, in pathway C, the reaction happens via condensation of hydrazine **2** with ferrocenylpropynal **1**, followed by cyclization through conjugate addition of the resulting α,β-unsaturated hydrazone **7**. It is noteworthy that pathway A leads to 1,3-pyrazole isomer **4** while pathways B and C go to 1,5-pyrazole isomer **3**. It seems that depending upon the substitution pattern of hydrazine derivative **2**, one pathway or more than one pathway can be functioning during the course of the reaction.

*2.3. Crystal structures of 5-ferrocenyl-1-phenyl-1H-pyrazole (**3B**), 1-benzyl-5-ferrocenyl-1H-pyrazole (**3D**) and 2-(3-ferrocenylpyrazol-1-yl)ethanol (**4C**)*

The structures of pyrazoles **3B**, **3D** and **4C** were determined by X-ray crystal analysis as well. ORTEP diagrams of **3B**, **3D** and **4C** are shown in Figs. 1–3, respectively. Note that although two molecules are present in the asymmetric unit of **3D**, only one molecule is shown in Fig. 2 for clarity. Details of cell data, X-ray data collection, structure solution and refinement are summarized in Table 2. Selected bond distances and angles are given in Table 3. A complete list of atomic coordinates, bond distances and angles, anisotropic thermal parameters, hydrogen atom coordinates for these structures have been deposited and are available upon request (see Section Appendix A).

The most striking feature for these structures is the deviation of the substituted cyclopentadienyl (Cp) and

Table 3
Selected bond distances (Å), bond angles (°) and torsion angles (°) for **3B**, **3D** and **4C**[a]

	3B	**3D**	**4C**
C1–Fe1	2.064(4)	2.0460(14)	2.0449(16)
C1–C2	1.413(6)	1.425(2)	1.427(2)
C1–C5	1.448(6)	1.425(2)	1.428(2)
C1–C11	1.444(6)	1.464(2)	1.462(2)
C2–C3	1.427(6)	1.415(2)	1.418(3)
C3–C4	1.405(7)	1.408(3)	1.416(3)
C4–C5	1.402(7)	1.421(2)	1.418(3)
C6–Fe1	2.028(4)	2.0484(17)	2.0393(19)
C11–N1	1.358(4)	1.3552(19)	1.337(2)
C11–C12	1.385(5)	1.375(2)	1.404(2)
C12–C13	1.385(6)	1.384(3)	1.364(3)
C13–N2	1.321(6)	1.313(2)	1.336(2)
C14–N1	1.422(4)	1.4414(19)	NA
C15–O1	NA	NA	1.410(2)
N1–N2	1.365(4)	1.3637(18)	1.3585(19)
C2–C1–C11	128.8(4)	122.48(14)	128.43(15)
C11–C1–Fe1	129.3(3)	130.41(10)	125.43(11)
C11–N1–N2	112.5(3)	112.26(13)	104.84(13)
C12–C11–C1	132.1(3)	128.49(14)	127.37(16)
C13–N2–N1	104.1(3)	104.21(14)	111.87(14)
C13–C12–C11	105.7(3)	105.76(15)	105.22(15)
C14–C15–O1	NA	NA	109.05(15)
C15–C14–N1	119.3(3)	113.90(12)	NA
N1–C11–C1	122.6(3)	126.00(13)	122.07(15)
C1–C11–N1–C14	−1.5(6)	3.7(2)	NA
C2–C1–C11–N1	−43.8(6)	156.31(15)	−12.9(3)
C5–C1–C11–C12	−46.9(7)	148.51(17)	−10.7(3)
C5–C1–C11–N1	133.1(4)	−29.5(2)	168.70(15)
C15–C14–N1–C11	117.3(4)	89.17(18)	NA
C15–C14–N2–C13	NA	NA	94.4(2)
C15–C14–N1–C11	117.3(4)	89.17(18)	NA
C15–C14–N1–N2	−64.7(5)	−84.20 (17)	NA
C15–C14–N2–N1	NA	NA	−81.4(2)
C2–C1–C11–N1	−43.8(6)	156.31(15)	−12.9(3)
C5–C1–C11–N1	133.1(4)	−29.5(2)	168.70(15)
N1–C14–C15–C16	179.9(4)	175.42(14)	NA
N2–C14–C15–O1	NA	NA	−69.0(2)

[a] NA, not applicable.

pyrazolyl (Py) rings from coplanarity depending upon steric effects, resulting interruption of the conjugation between these aromatic moieties. This deviation is 45.36(2)° in **3B**, 26.85(11)° and 33.52(6)° in **3D**, and 11.87(12)° in **4C**. The deviation angle increases in the order of **4C** < **3D** < **3B** depending upon the steric hindrance between Fc group and the substituent (2-hydroxyethyl, benzyl or phenyl) on N1 or N2 atom of pyrazolyl residue. The maximum steric interaction is observed between the Fc and Ph groups of **3B** (Fig. 1), and as a result, Ph ring in this compound is tilted from the pyrazolyl ring plane by an angle of 64.95(2)° as well, severely interrupting the conjugation. This is further supported by the dihedral angle of 57.6(2)° between the Ph and substituted Cp ring planes. It is noteworthy that the conjugation between aromatic moieties of **4C** is largely maintained as compared to those of **3B** and **3D**. Noticeably, pyrazolyl and phenyl rings in the molecules of **3D** are nearly perpendicular with an angle of 87.67(6)° and 83.90(6)° although these rings are separated by a methylene unit (Fig. 2). Another important structural characteristic is that, in **4C**, pyrazolyl and hydroxyl groups on C14 and C15 atoms, respectively, adopt a gauche conformation in the solid state, as indicated by the N2–C14–C15–O1 angle of −69.0(2)°, although C14 and C15 atoms exist in a staggered conformation (Fig. 3).

Bond distances in the pyrazolyl units of these structures are quite similar. N–N bond distances change from 1.359(19) to 1.365(17) Å, N–C bond lengths from 1.313(2) to 1.358(4) Å and C–C bond distances from 1.364(3) to 1.404(2) Å (Table 3), which are indicative of electron delocalization.

Fc group in**3B** and **3D** is almost in the eclipsed conformation since the average C–Cg_s–Cg_{as}–C torsion angle varies between −2.57(3)° and 3.58(3)°, where Cg_s and Cg_{as} are the substituted and unsubstituted Cp ring centroids, respectively. However, in **4C**, Fc group exists in a noticeably distorted eclipsed conformation as indicated by the average C–Cg_s–Cg_{as}–C torsion angle of 19.74(6)°. On the other hand, in all structures, the centroids of Cp rings are equidistant from Fe atom since the Fe–Cg_s and Fe–Cg_{as} distances are in the range of 1.641(9)–1.654(15) Å, and the Cg_s–Fe–Cg_{as} angles are between 177.65(7)° and 178.85(7)°. The C–C bond distances in Cp rings alter from 1.379(8) to 1.448(6) Å, while Fe–C bond lengths vary between 2.024(2) and 2.064(4) Å, all of which are as expected [6i,10m,10n,10o,10p].

In terms of crystal packing, each compound shows different molecular arrangement, which are stabilized by C–H…N or O–H…N intermolecular hydrogen bonds, and/or C–H…π interactions. The molecules of **3B** are stabilized by both C–H…N intermolecular hydrogen bonds and C–H…π interactions. In fact, there is a single type of intermolecular hydrogen bond, [C8–H8…N2:H…N = 2.694(4) Å, C…N = 3.407(5) Å, C–H…O = 137.03(3)°], which links the molecules and generate the C(9) chains along the [0 0 1] direction [18] (Fig. 4). In addition, C(9) chains are connected through C15–H15…$Cg1^{i}$ [Cg1 is the centroid of the C1–C6 ring; H15…Cg1 = 3.034 Å, C15…Cg1 = 3.884(5) Å, C15–H15…Cg1 = 152.77°, (i) x, $y+1$, z], C17–H17…$Cg2^{ii}$ [Cg2 is the centroid of the C6–C10 ring; H17…Cg2 = 3.083 Å, C17…Cg2 = 3.662(5) Å, C17–H17…Cg2 = 122.04° (ii) x, y, $z+1$] and C13–H13…$Cg3^{iii}$ [Cg1 is the centroid of the C14–C19 ring; H13…Cg3 = 2.867 Å, C13…Cg3 = 3.666(5) Å, C13–H13…Cg3 = 144.66°, (i) $1-x$, $2-y$, $z+1/2$] interactions.

On the other hand, the molecules of **3D** are stabilized only by C–H…π interactions. Interestingly, C39–H39…π interactions [C39–H39…$Cg1^{i}$; Cg1 is the centroid of the

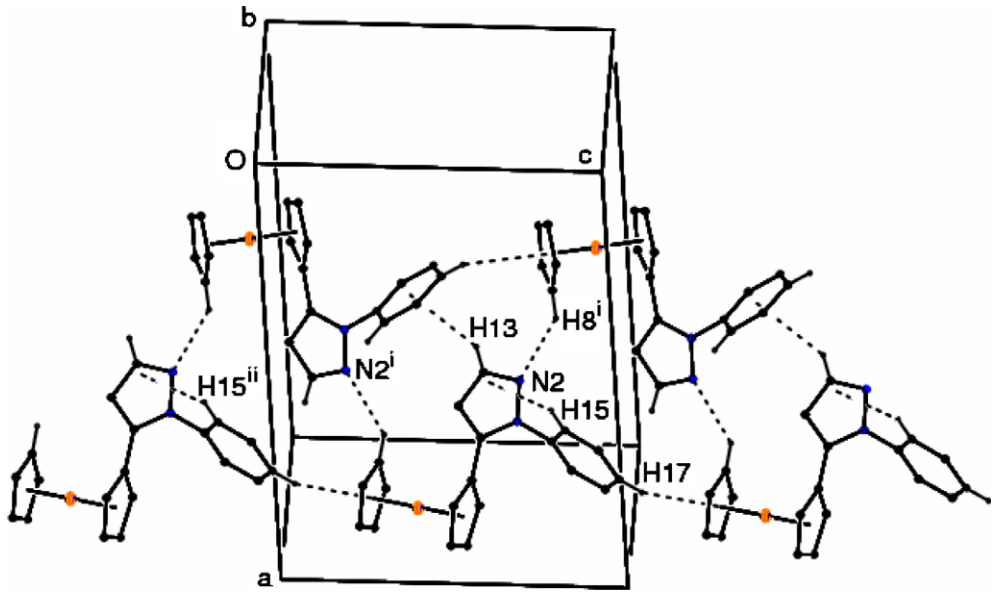


Fig. 4. Part of the crystal structure of **3B**, showing C–H…N intermolecular hydrogen bonds and C–H…π interactions as dashed lines. H atoms not involved in hydrogen bonds have been omitted for clarity [Symmetry code: (i) x, $1-y$, $1-z$, (ii) x, $1+y$, $1+z$].

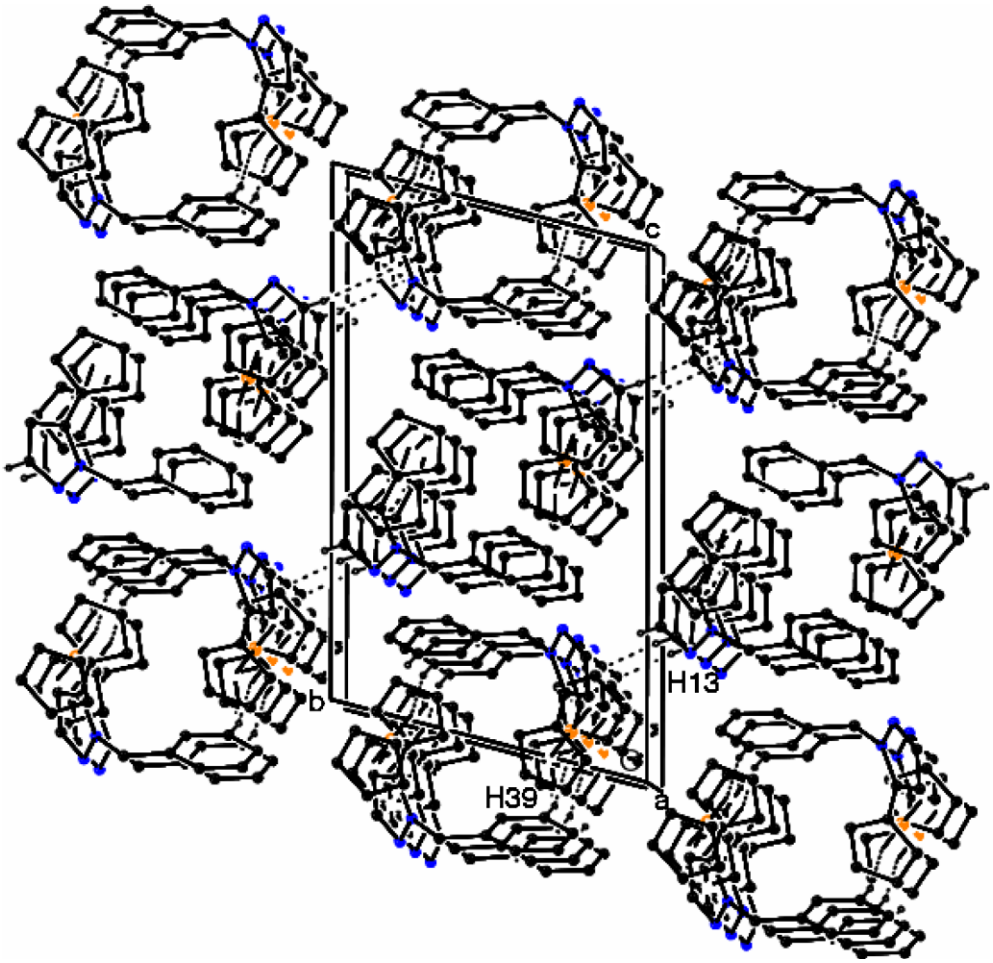


Fig. 5. A packing diagram of the crystal structure of **3D**, showing centrosymmetric $R_2^2(16)$ dimers and C–H. . .π interactions as dashed lines. H atoms not involved in hydrogen bonds have been omitted for clarity.

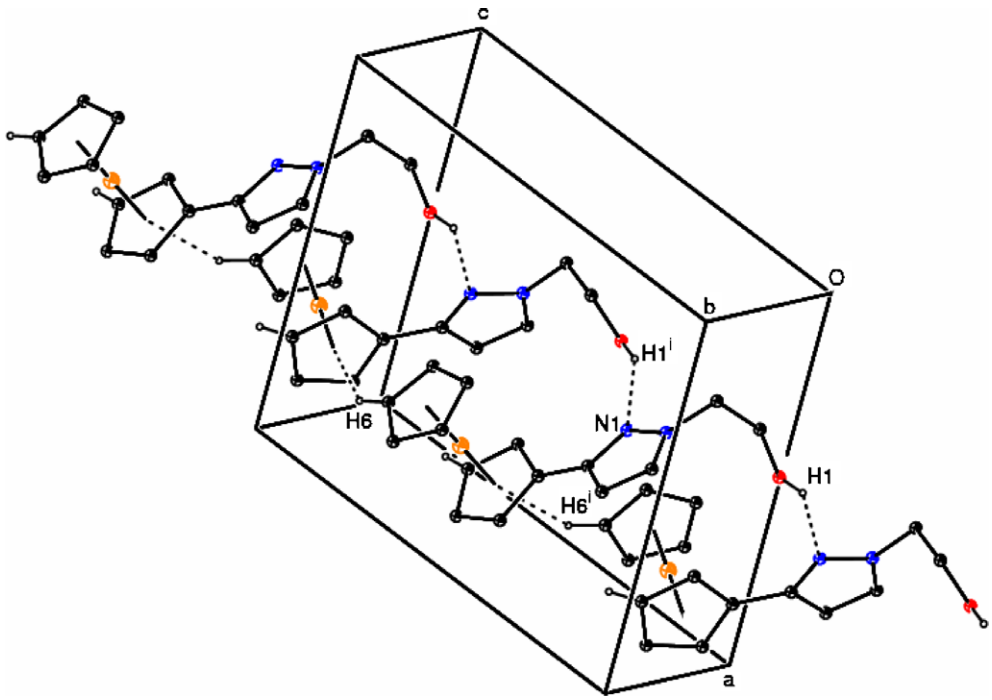


Fig. 6. Part of the crystal structure of **4C**, showing both O–H. . .N intermolecular hydrogen bonds and C–H. . .π interactions as dashed lines. H atoms not involved in hydrogen bonds have been omitted for clarity [Symmetry code: (i) x, $3/2 - y$, $z - 1/2$].

C21–C25 ring; H39...Cg1 = 2.853 Å, C39...Cg1 = 3.767(2) Å, C39–H39...Cg1 = 167.53°, (i) $x + 1$, $y - 1/2$, z] generate centrosymmetric $R_2^2(16)$ dimers [18] (Fig. 5), which are linked to each other through C13–H13...π interactions [C13–H13...Cg2^{ii}; Cg2 is the centroid of the N3/N4–C33 ring; H13...Cg2 = 2.676 Å, C13...Cg2 = 3.561(2) Å, C13–H13...Cg2 = 159.39°, (ii) $1/2 - x$, $2 - y$, $z - 1/2$]. Fascinatingly, as seen in Fig. 5, tunnels are formed inside these dimer heaps, a rare occurrence, which was not observed in the crystal structures of **3B** and **4C**.

The molecules of **4C** are stabilized by both O–H...N intermolecular hydrogen bonds and C–H...π interactions. Actually, there is a single type of intermolecular hydrogen bond, [O1–H1...N2: H...N1 = 2.16(2) Å, C...N = 2.881(2) Å, C–H...O = 177.00(3)°], which connects the molecules and yields the C(6) chains [18] (Fig. 6). It should be noted that C(6) chains are linked to each other through C6–H6...Cg1^{i} interactions [Cg1 is the centroid of the C1–C6 ring; H6...Cg1 = 3.094 Å, C6...Cg1 = 3.853(2) Å, C6–H6...Cg1 = 140.00°, (i) x, $1/2 - y$, $3/2 - z$].

3. Conclusion

The reaction between 3-ferrocenylpropynal (**1**) and hydrazines **2** is investigated in this work, yielding pyrazoles **3** (1,5-isomer) and/or **4** (1,3-isomer). In most cases, 1,5-pyrazole isomers **3** have resulted from these reactions as the single or the major products. The regioselectivity of the reactions is mainly governed by the nature of the substituents in hydrazines **2**. Owing to the ready availability of 3-ferrocenylpropynal (**1**) and hydrazines **2**, this method represents a versatile synthesis of ferrocenyl-substituted pyrazoles **3** and/or **4**.

The structures of compounds **3B**, **3D** and **4C** were identified by X-ray crystal analysis. Depending upon steric effects, ferrocenyl and pyrazolyl groups in these structures depart from coplanarity, and, as a result, conjugation between these aromatic moieties is interrupted to some extent. The maximum steric interaction is observed between Fc and Ph groups of **3B**, considerably tilting both from the pyrazolyl ring plane, severely interrupting conjugation.

We have demonstrated that, when treated with hydrazinium salts, acetylenic aldehydes, i.e. alkynals, afford pyrazoles, as in the case of acetylenic ketones or alkynones.

4. Experimental

4.1. General consideration

Nuclear magnetic resonance (^{1}H and ^{13}C) spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). DEPT ^{13}C NMR information is given in parenthesis as C, CH, CH_2 and CH_3. Infrared spectra were recorded on a Varian 5000 FT-IR spectrometer. Band positions are reported in reciprocal centimeters (cm^{-1}). Mass spectra (MS) were obtained on an Agilent 1100 Series LC MSD spectrometer, using electrospray ionization (ESI) (Fragmentor 100 eV, positive polarity). Elemental analyses were carried out on a LECO CHNS-932 instrument. Flash chromatography was performed using thick-walled glass columns and 'flash grade' silica (Merck 230–400 mesh). The relative proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio. 3-Ferrocenylpropynal (**1**) [13–15] and (2-hydroxyethyl)hydrazinium dichloride (**2C**) [16] were synthesized according to the known literature procedures. All other commercially available reagents and reactants were obtained in reagent grade and used without purification. All reaction solvents were distilled and/or dried for purity according to standard literature procedures. The inert atmosphere was created by slight positive pressure (ca. 0.1 psi) of argon.

4.2. General procedure for the synthesis of ferrocenyl pyrazoles 3 and 4 (Table 1)

To a solution of 3-ferrocenylpropynal (**1**) (100 mg, 0.420 mmol) in 10 mL of dioxane (Condition A) or methanol (Condition B) under argon was added hydrazine derivative (**2**) (1.260 mmol). The resulting mixture was then heated at reflux for 8 h (Condition A) or 5 h (Condition B). After the reaction was complete, the mixture was cooled to 25 °C, and the solvent was removed on a rotary evaporator. The residue was dissolved in water (20 mL) and extracted with chloroform (3 × 30 mL). The combined chloroform layers were dried over magnesium sulfate and removed in a rotary evaporator. Final purification was achieved through flash chromatography on silica gel (eluent: hexane/EtOAc from 19:1 to 1:1). The products given in Table 1 were isolated with the indicated yields.

4.3. Spectral data for products

We have recently reported the synthesis of ferrocenyl pyrazoles **3A–D** and **4B–C** by using a similar method [11]. Please refer to this study for the spectral data of these compounds.

4.3.1. 1-Benzyl-3-ferrocenyl-1H-pyrazole (4D)

^{1}H NMR ($CDCl_3$): δ 7.40–7.31 (m, 3H), 7.28 (s, 1H), 7.23 (d, 2H, $J = 7.2$ Hz), 6.32 (s, 1H), 5.34 (s, 2H), 4.77 (s, 2H), 4.34 (s, 2H), 4.14 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 150.8 (C), 137.0 (C), 130.1 (CH), 128.7 (CH), 127.9 (CH), 127.5 (CH), 103.7 (CH), 79.0 (C), 69.6 (CH), 68.5 (CH), 66.7 (CH), 55.8 (CH_2); IR (KBr): 3108, 3079, 3030, 2941, 1556, 1497, 1435, 1404, 1303, 1230, 1102, 1060, 1000, 874, 833, 813, 761, 716 cm^{-1}; MS (ESI, m/z): 343.1 $[M+H]^+$, 252.0; Anal. Calc. for $C_{20}H_{18}FeN_2$ with

0.263 mol $CHCl_3$ incorporation: C, 65.14; H, 4.93; N, 7.50. Found: C, 65.14; H, 5.62; N, 7.50% [19].

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Appendix A. Supplementary material

CCDC 653294, 653295 and 653296 contain the supplementary crystallographic data for **3B**, **3D** and **4C**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2007.10.035.

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[19] Note that solvent correction has been applied since compound **4D** incorporates 0.263 mol $CHCl_3$ solvent as indicated by Solvent Correction CHN Calculator, which is available at http://www.che.hw.ac.uk/research/services/solvent.html.

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Synthesis of ferrocenyl quinolines

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ABSTRACT

A convenient one-pot synthesis of ferrocenyl-substituted quinolines via a molecular iodine-catalyzed reaction of ferrocenylimines with enolizable aldehydes is reported. First, nucleophilic addition of the in situ generated enol to ferrocenylimine produces β-anilinopropionaldehyde, which then undergoes intramolecular Friedel–Crafts reaction to give dihydroquinoline derivative. Finally, subsequent dehydration and aerobic oxidation affords ferrocenyl quinolines.

1. Introduction

Quinolines are present in a wide range of natural and unnatural compounds with remarkable medicinal activities [1]. In this regard, quinolines have occupied a unique position in the design and synthesis of novel biologically active compounds since they are often used as antiinflammatory, antiasthmatic, antituberculosis, antibacterial, antihypertensive, antitumor and, most notably, antimalarial agents [2,3]. In the light of recent studies [4,5], it might be expected that combination of a ferrocenyl moiety with such structures may increase their biological activities or create new medicinal properties. It is noteworthy to mention that due to its unique structure, different membrane-permeation behavior and anomalous metabolism, ferrocene is frequently integrated into an organic compound in order to have enhanced or unexpected biological activities [4,5]. Although quinolines are among the most extensively studied heterocyclic compounds [3,6], ferrocenyl-substituted quinolines are not often found in the literature [7]. Therefore, the synthesis of quinoline derivatives directly linked to a ferrocene unit, such as 2-ferrocenylquinolines, is of considerable interest since their properly substituted 2-aryl analogues are biologically active and exist in the structures of various antitumor agents [8]. Quinolines are usually prepared by Skraup [9], Doebner–Miller [10], Riehm [11], Combes [12], Conrad–Limbach [13], Knorr [14], Friedländer [15], Povarov [16], Camps [17], Niementowski [18], Gould–Jacobs [19], and Pfitzinger [20] quinoline syntheses. Recently, as shown by the Shimizu [21], Baba [22] and Wang [23] research groups, the reactions of aromatic imines (in situ synthesized or isolated) with enolizable aliphatic aldehydes in the presence of metal, Brønsted or Lewis acid catalysts also led to formation of quinoline derivatives. In this respect, molecular iodine has gained considerable importance as a mild and nontoxic Lewis acid catalyst since it catalyzed various organic reactions with high efficiency and selectivity [24]. Owing to carbonyl activating property [25], molecular iodine was successfully used as a catalyst in the quinoline forming reactions of imines and aldehydes as well [23,26]. However, to the best of our knowledge, such reactions catalyzed by iodine were not used for the synthesis of ferrocenyl-substituted quinolines. As part of a program to synthesize new ferrocenyl-substituted heterocyclic compounds as potential pharmaceuticals [27], we have investigated molecular iodine-catalyzed reactions of ferrocenyl imines with enolizable aliphatic aldehydes to afford 2-ferrocenylquinolines. We herein report the results of this study.

2. Results and discussion

The reactions were initially examined under a variety of conditions, such as refluxing THF, benzene, dioxane and toluene with varying amounts of molecular iodine catalyst. The best results were obtained as follows: ferrocenylimine **1** (1.2 equiv.) was reacted with aldehyde **2** (1.0 equiv.) in the presence of molecular iodine (0.1 equiv.) at 100 °C in dioxane for 2 h, and the products were isolated by flash chromatography. The results are summarized in Table 1.

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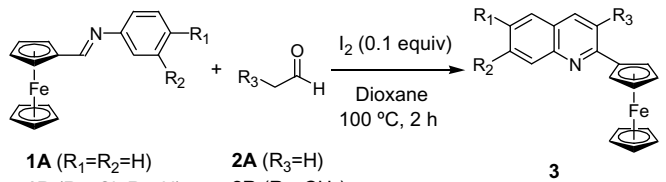
Table 1
Iodine-catalyzed reactions of ferrocenylimines **1** with enolizable aldehydes **2**



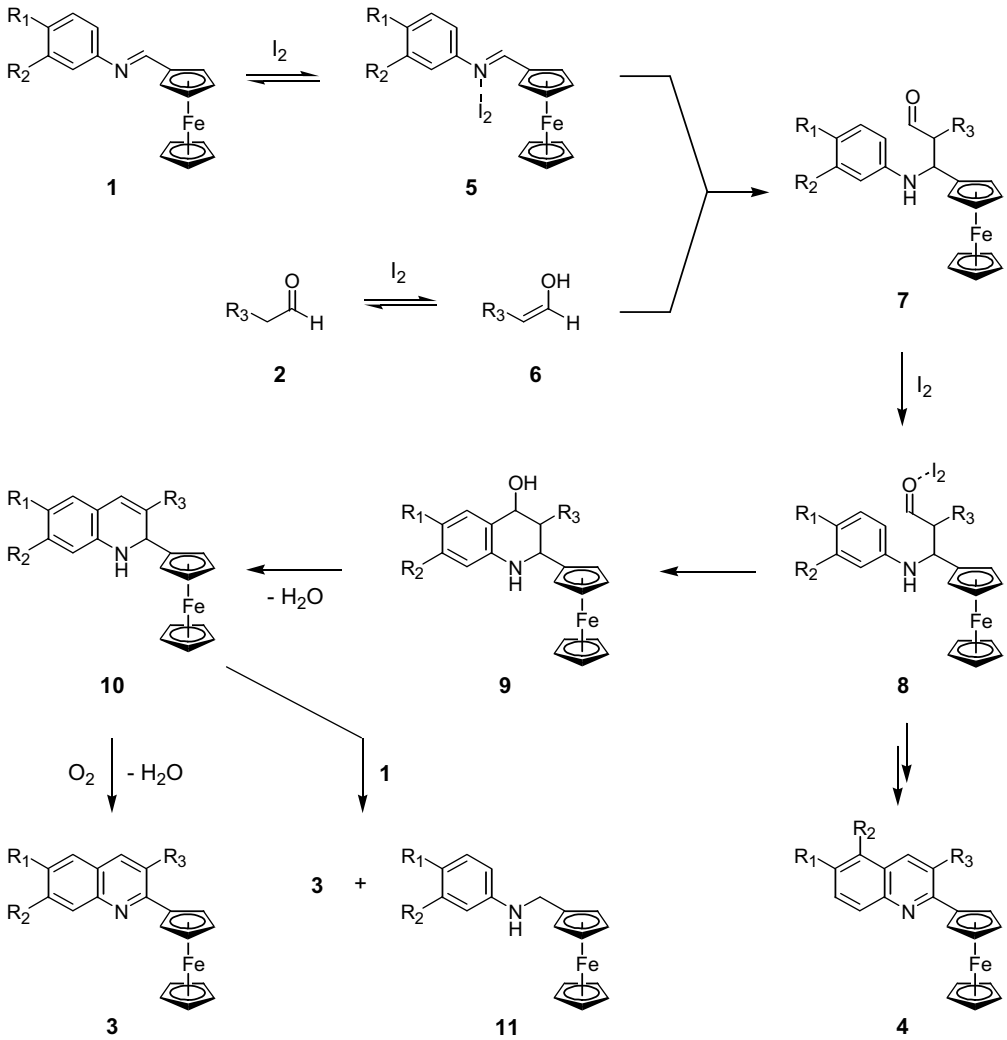
1A (R_1=R_2=H) **2A** (R_3=H)
1B (R_1=Cl, R_2=H) **2B** (R_3=CH_3)
1C (R_1=Br, R_2=H) **3**
1D (R_1=H, R_2=CH_3)

Entry[a]	Reacting Partners	R_1	R_2	R_3	Products (isolated yield, %)
A	**1A** + **2A**	H	H	H	**3A** (78)
B	**1B** + **2A**	Cl	H	H	**3B** (63)
C	**1C** + **2A**	Br	H	H	**3C** (65)
D	**1D** + **2A**	H	CH_3	H	**3D** (88)
E	**1D** + **2B**	H	CH_3	CH_3	**3E** (25)

[a] Entry letters define R_1, R_2 and R_3 groups for compound **3**.

As can be seen from Table 1, the reaction between *N*-(ferrocenylidene)aniline (**1A**) and acetaldehyde (**2A**) led to the formation of 2-ferrocenylquinoline (**3A**) in 78% yield (Entry A). Similarly, the reaction of acetaldehyde (**2A**) with 4-chloro-*N*-(ferrocenylidene)aniline (**1B**) and 4-bromo-*N*-(ferrocenylidene)aniline (**1C**) afforded 6-chloro-2-ferrocenylquinoline (**3B**) and 6-bromo-2-ferrocenylquinoline (**3C**) in 63% and 65% yields, respectively (Entries B and C). Interestingly, from the reaction between *N*-(ferrocenylidene)-3-methylaniline (**1D**) and acetaldehyde (**2A**), only one regioisomer, namely 2-ferrocenyl-7-methylquinoline (**3D**), was isolated in 88% yield (Entry D). The reaction of ferrocenylimine **1D** with propionaldehyde (**2B**) resulted in a complex mixture, from which only 2-ferrocenyl-3,7-dimethylquinoline (**3E**) was isolated even though in low yield (25%) (Entry E). Formation of polymeric by-products as well as the partial hydrolysis of starting imine **1D** lowered the yield of **3E**.

The mechanism proposed for the formation of quinolines **3** is depicted in Scheme 1. It is well known that in the presence of Lewis acids such as iodine, imines such as **1** can be activated. Similarly, in the presence of iodine, aldehydes such as **2** can be easily equilibrated with their enols. As anticipated, the reaction between in situ generated enol **6** and iodine-activated imine **5** affords β-anilinopropionaldehyde **7**. The intramolecular Friedel–Crafts reaction of iodine-activated β-anilinopropionaldehyde **8** produces tetrahydroquinolinol derivative **9**. The subsequent dehydration in **9** leads to formation of dihydroquinoline **10**. Finally, the aerobic oxidation of **10** yields the expected quinoline derivative **3**. Alternatively, dihydroquinoline **10** can be oxidized to quinoline **3** by the



Scheme 1.

starting imine **1** to some extent since it was reported that imines can behave as hydrogen acceptor in these types of reactions [21c]. In this case, reaction should also produce a secondary amine, i.e. (ferrocenylmethyl)aniline derivative **11** (Scheme 1). However, the formation of such amines in these reactions was not detected. It should be mentioned that iodine-activated β-propionaldehyde **8** can also produce ferrocenyl quinoline **4**, an isomer of **3**, via a similar mechanism (Scheme 1). However, the formation of such quinolines in these reactions was not observed.

3. Conclusion

We have investigated the iodine-catalyzed reaction between ferrocenylimines **1** and enolizable aldehydes **2** to afford 2-ferrocenylquinolines **3**. In all cases, the expected 2-ferroceylquinolines **3** were obtained from these reactions. Due to the ready availability of ferrocenylimines **1** and aldehydes **2**, this practical one-pot method represents a versatile synthesis of ferrocenyl-substituted quinolines **3**.

4. Experimental

4.1. General consideration

Nuclear Magnetic Resonance (^{1}H and ^{13}C) spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). DEPT ^{13}C NMR information is given in parenthesis as C, CH, CH_2 and CH_3. Infrared spectra were recorded on a Bruker Vertex 70 Spectrometer using attenuated total reflection (ATR). Band positions are reported in reciprocal centimeters (cm^{-1}). Mass spectra (MS) were obtained on a Bruker Daltonics spectrometer using Electrospray Ionization (ESI) with Micro-Tof; m/z values are reported (For each measurement, the mass scale was recalibrated with sodium formiate clusters, and samples were dissolved and measured in MeOH). High resolution mass spectra (HRMS) were also obtained on a Bruker Daltonics spectrometer. Flash chromatography was performed using thick-walled glass columns and 'flash grade' silica (Merck 230–400 mesh). The relative proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio. All other commercially available reagents and reactants were obtained in reagent grade and used without purification. All reaction solvents were distilled and/or dried for purity according to standard literature procedures. The inert atmosphere was created by slight positive pressure (ca. 0.1 psi) of argon.

4.2. Synthesis of starting materials

Ferrocenylimines, known also as ferrocenylaldimines or Schiff bases, were prepared by condensation of ferrocenecarboxaldehyde with corresponding aniline derivatives according to known literature procedures [28].

4.3. General procedure for the synthesis of ferrocenyl quinolines **3** (Table 1)

To a solution of ferrocenylimine **1** (0.72 mmol) and aldehyde **2** (0.60 mmol) in 3 mL of dioxane was added iodine (15.36 mg, 0.06 mmol). The resulting mixture was then heated at reflux for 2 h. After the reaction was complete, the mixture was cooled to 25 °C, and the solvent was removed on a rotary evaporator. Final purification of the obtained residue was achieved through flash chromatography on silica gel using hexane/EtOAc (24/1) as eluent. The products given in Table 1 were isolated with the indicated yields.

4.4. Spectral data for products

4.4.1. 2-Ferrocenylquinoline [(Quinolin-2-yl)ferrocene] (**3A**)

^{1}H NMR ($CDCl_3$): δ 8.06 (d, 1H, J = 8.5 Hz), 8.02 (d, 1H, J = 8.5 Hz), 7.74 (d, 1H, J = 8.0 Hz), 7.66 (pseudo t, 1H, J = 7.4 Hz), 7.56 (d, 1H, J = 8.5 Hz), 7.45 (pseudo t, 1H, J = 7.4 Hz), 5.08 (pseudo t, 2H, J = 1.6 Hz), 4.47 (pseudo t, 2H, J = 1.6 Hz), 4.05 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 159.5 (C), 148.3 (C), 135.4 (CH), 129.3 (CH), 129.0 (CH), 127.5 (CH), 126.7 (C), 125.4 (CH), 119.5 (CH), 84.0 (C), 70.4 (CH), 69.7 (CH), 68.0 (CH); IR (neat): 3092, 3061, 2922, 2851, 1614, 1599, 1556, 1510, 1424, 1280, 1129, 1104, 1092, 910, 907, 815, 756 cm^{-1}; MS (ESI, m/z): 314.06 $[M+H]^+$; HRMS (ESI): calc. for $C_{19}H_{16}FeN$: 314.0632 $[M+H]^+$. Found: 314.0627. The spectral data are in agreement with those previously reported [7a,7b,7d].

4.4.2. 6-Chloro-2-ferrocenylquinoline [(6-Chloroquinolin-2-yl)-ferrocene] (**3B**)

^{1}H NMR ($CDCl_3$): δ 7.94 (m, 2H), 7.70 (s, 1H), 7.56 (m, 2H), 5.05 (s, 2H), 4.47 (s, 2H), 4.04 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 160.0 (C), 146.6 (C), 134.5 (CH), 130.9 (CH), 130.5 (CH), 130.2 (C), 127.2 (C), 126.2 (CH), 120.3 (CH), 83.3 (C), 70.6 (CH), 69.7 (CH), 68.0 (CH); IR (neat): 3094, 2923, 2853, 1597, 1548, 1503, 1485, 1411, 1379, 1327, 1281, 1189, 1132, 1106, 1094, 1074, 1026, 999, 948, 873, 853, 811 cm^{-1}; MS (ESI, m/z): 370.00 $[M+Na]^+$, 348.02 $[M+H]^+$; HRMS (ESI): calc. for $C_{19}H_{14}ClFeNNa$: 370.0062 $[M+Na]^+$. Found: 370.0057; calc. for $C_{19}H_{15}ClFeN$: 348.0242 $[M+H]^+$. Found: 348.0237.

4.4.3. 6-Bromo-2-ferrocenylquinoline [(6-Bromoquinolin-2-yl)-ferrocene] (**3C**)

^{1}H NMR ($CDCl_3$): δ 7.91 (d, 1H, J = 8.5 Hz), 7.89 (d, 1H, J = 8.5 Hz), 7.88 (s, 1H), 7.70 (dd, 1H, J = 8.5, 2.0 Hz), 7.54 (d, 1H, J = 8.5 Hz), 5.04 (pseudo t, 2H, J = 1.6 Hz), 4.47 (pseudo t, 2H, J = 1.6 Hz), 4.04 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 160.1 (C), 146.9 (C), 134.4 (CH), 132.7 (CH), 130.7 (CH), 129.5 (CH), 127.8 (C), 120.2 (CH), 118.9 (C), 83.4 (C), 70.7 (CH), 69.7 (CH), 68.0 (CH); IR (neat): 3094, 3069, 2923, 1593, 1545, 1500, 1381, 1327, 1281, 1188, 1134, 1105, 1062, 1025, 944, 880, 844 cm^{-1}; MS (ESI, m/z): 413.95 $[M+Na]^+$, 391.97 $[M+H]^+$; HRMS (ESI): calc. for $C_{19}H_{15}BrFeN$: 391.9737 $[M+H]^+$. Found: 391.9733.

4.4.4. 2-Ferrocenyl-7-methylquinoline [(7-Methylquinolin-2-yl)-ferrocene] (**3D**)

^{1}H NMR ($CDCl_3$): δ 7.97 (d, 1H, J = 8.5 Hz), 7.84 (s, 1H), 7.62 (d, 1H, J = 8.2 Hz), 7.49 (d, 1H, J = 8.5 Hz), 7.29 (d, 1H, J = 8.2 Hz), 5.06 (s, 2H), 4.45 (s, 2H), 4.04 (s, 5H), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.4 (C), 148.5 (C), 139.6 (C), 135.1 (CH), 128.2 (CH), 127.6 (CH), 127.2 (CH), 124.7 (C), 118.7 (CH), 84.1 (C), 70.3 (CH), 69.6 (CH), 67.9 (CH), 21.8 (CH_3); IR (neat): 3094, 3037, 2914, 2854, 1625, 1595, 1558, 1517, 1435, 1277, 1104, 1091, 1027, 998, 874, 844, 811 cm^{-1}; MS (ESI, m/z): 350.06 $[M+Na]^+$, 328.08 $[M+H]^+$; HRMS (ESI): calc. for $C_{20}H_{18}FeN$: 328.0789 $[M+H]^+$. Found: 328.0783.

4.4.5. 2-Ferrocenyl-3,7-dimethylquinoline [(3,7-Dimethylquinolin-2-yl)ferrocene] (**3E**)

^{1}H NMR ($CDCl_3$): δ 7.83 (s, 1H), 7.79 (s, 1H), 7.58 (d, 1H, J = 8.2 Hz), 7.27 (d, 1H, J = 8.2 Hz), 5.09 (s, 2H), 4.44 (s, 2H), 4.10 (s, 5H), 2.74 (s, 3H), 2.54 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 158.3 (C), 146.9 (C), 138.5 (C), 136.4 (CH), 128.3 (C), 127.9 (CH), 127.8 (CH),

126.2 (CH), 124.9 (C), 85.5 (C), 70.0 (CH), 69.8 (CH), 69.5 (CH), 21.8 (CH_3), 21.4 (CH_3); IR (neat): 3092, 3071, 3051, 2969, 2920, 2854, 1625, 1599, 1502, 1453, 1410, 1383, 1323, 1268, 1140, 1105, 1074, 999, 896, 877, 823, 808, 779 cm^{-1}; MS (ESI, *m/z*): 342.09 $[M+H]^+$; HRMS (ESI): calc. for $C_{21}H_{20}FeN$: 342.0945 $[M+H]^+$. Found: 342.0940.

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