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Friedel−Crafts Type Reaction of Ferrocene with β-Ketoesters

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Abstract: The reaction of ferrocene with β-ketoesters in the presence of $BF_3{\cdot}Et_2O$ or CF_3SO_3H affords β-ferrocenyl-α,β-unsaturated esters in 56−83% yield. In the case of α-unsubstituted-β-ketoesters the reaction is totally *E*-stereoselective.

Numerous applications of functionalized ferrocenes in modern chemical, biological, and material sciences[1] (asymmetric catalysis,[2] red-ox active polymers and dendrimers,[3] nonlinear optical materials,[4] molecular electronic devices,[5] biosensors,[6] components of complex photochemical systems,[7] drugs,[8] etc.) have created a need for efficient and selective methods by which carbon chains bearing various functional groups can be attached to this metallocene. High reactivity of ferrocene toward electrophiles[9] makes electrophilic substitution a particularly attractive path to functionalized ferrocenes. The Friedel−Crafts acylation followed by a transformation of the acyl function has found a plethora of applications in the synthesis of substituted ferrocenes.[10] Furthermore, ferrocene reacts in the presence of strong acids with aldehydes and ketones to afford ferrocenyl alcohols, which can be transformed into other products.[11]

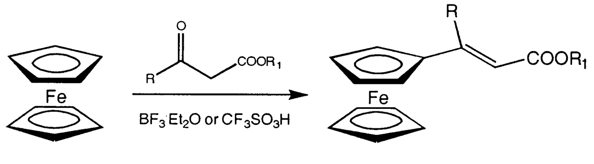

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FIGURE 1. Reaction of ferrocene with β-ketoesters in the presence of an acid.

TABLE 1. The Yields of 1 Obtained in the Reaction of Ferrocene with β-Ketoesters

product	R	R_1	acid	yield of **1**,[a] %
1a	Me	Et	$BF_3{\cdot}Et_2O$	33
1a	Me	Et	CF_3SO_3H	83
1a	Me	Et	CF_3SO_3H	43[b]
1b	Et	Me	$BF_3{\cdot}Et_2O$	30
1b	Et	Me	CF_3SO_3H	70
1c	n-Pr	Et	$BF_3{\cdot}Et_2O$	0
1c	n-Pr	Et	CF_3SO_3H	49
1d	Ph	Et	$BF_3{\cdot}Et_2O$	trace
1d	Ph	Et	CF_3SO_3H	56

[a] Yields obtained using FcH: β-ketoester:acid 1:2:4 molar ratio at room temperature for 5 h. [b] Reaction time 2 h.

We have recently become interested in the development of simple and efficient procedures enabling introduction of more complex functionality to the ferrocene moiety. We have found that ferrocene can be directly acetoacetylated by diketene in the presence of a Lewis acid.[12] Here we report that ferrocene reacts in the presence of $BF_3{\cdot}Et_2O$ or CF_3SO_3H with readily accessible β-ketoesters to afford β-ferrocenyl-α,β-unsaturated esters **1** in good yield and with high stereoselectivity (Figure 1). The reaction was carried out in dichloromethane at room temperature. The highest yields were obtained using the molar ratio ferrocene:β-ketoester:acid 1:2:4 (Table 1). In all cases CF_3SO_3H-promoted reactions afforded the highest yields of **1**. ^1H NMR spectra of the crude reaction mixture showed that in all cases only one stereoisomer was formed (under conditions such that 1% of the other stereoisomer would have been easily detected). Diastereoselectivity is therefore estimated as >99:1.

Nuclear Overhauser Effect (NOE) data revealed that **1a**−**d** have the (*E*)-configuration. The NOE enhancement of the ferrocenyl protons (α and those in the unsubstituted ring) signals was observed upon saturation of the vinylic proton signal. There was no NOE between the vinylic proton and the protons of the R group. The NOE data for **1a** are shown in Figure 2.

A tentative explanation of the observed high stereoselectivity is based on the assumption that stable α-ferrocenyl carbenium ions[13] are formed in strongly acidic reaction medium from ferrocene and β-ketoesters, which exist in two conformations: more stable **I** and less stable **II** (Figure 3). The *exo*-deprotonation, expected for such

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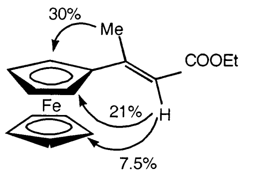
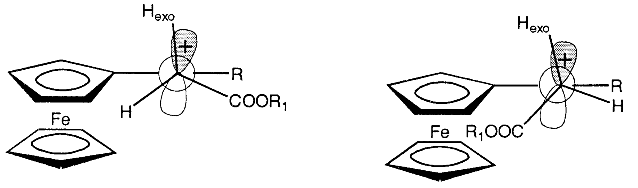


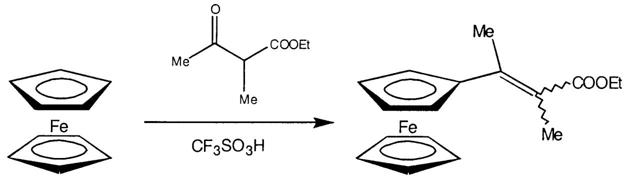
1a

FIGURE 2. NOE data for **1a**.



I **II**

FIGURE 3. Conformations of carbenium ions formed from ferrocene and β-ketoesters in a strongly acidic medium.



1e (*E*):(*Z*) ~1:1

FIGURE 4. Nonstereoselective reaction of ferrocene with ethyl α-methylacetoacetate.

ions,[13] explains preferential formation of the (*E*)-stereoisomer of **1** from more stable **I**.

If the stereoselectivity of the investigated reaction originates from different steric interactions between the ferrocene moiety and H_β or the $COOR_1$ group one can expect that replacement of this hydrogen by bulkier alkyl groups will decrease diastereoselection. In fact, we have found that reaction of ferrocene with ethyl α-methylacetoacetate is totally nonstereoselective giving **1e** as an unseparable 1:1 1:1 mixture of (*E*)- and (*Z*)-isomers (Figure 4).

Under the conditions used for the abovementioned reactions ferrocene does not react with ethyl pivaloylacetate, *t*-$BuCOCH_2COOEt$, and ethyl trifluoroacetoacetate, CF_3COCH_2COOEt. In our opinion the lack of reactivity of the former may be due to a steric hindrance, while the low basicity of the carbonyl oxygen in the latter may hamper protonation (or complex formation with a Lewis acid)[14] required for activation of the carbonyl carbon atom.

Some additional features of the investigated reaction are worthy noting. First, in no case was formation of the 1,1′-disubstituted product noted. Second, there is no formation of β-hydroxyesters via reaction of the α-ferrocenyl carbenium ions with water during the workup as is observed in the case of the reaction of ferrocene with simple carbonyl compounds.[11] Third, the reaction takes place chemoselectively at the keto group in the β-ketoester (it has recently been demonstrated that esters in the presence of CF_3SO_3H can acylate arenes[15]).

Reaction of activated arenes (phenols or phenol ethers) with β-ketoesters in the presence of acids is a well-known method of synthesis of coumarines (Pechmann reaction).[16] It presumably proceeds via a Friedel-Crafts-type reaction forming initially β-arylacrylic acid esters, undergoing subsequent cyclization via reaction with the OR group present in the arene. In one case the β-arylacrylic acid ester was isolated (in low yield).[17] In the case of the reaction of ferrocene with β-ketoesters the high intrinsic reactivity of the metallocene makes possible electrophilic attack of the activated ester but there is no possibility of subsequent cyclization forming the oxygen heterocycle.

In conclusion, an easy, one-step method of synthesis of β-ferrocenyl-α,β-unsaturated esters from ferrocene has been developed, displaying in the case of formation of trisubstituted carbon−carbon double bond practically total (*E*)-diastereoselectivity.

Experimental Section

General Methods. All reactions were carried out under an argon atmosphere. Dichloromethane and chloroform were dried over calcium hydride and distilled before use. The term “petrol” refers to the fraction of petroleum ether boiling in the range of 40−60 °C. All reagents were purchased commercially. Flash column chromatography was performed using Kieselgel 60 (230−400 mesh ASTM) and chloroform as eluent. The NMR spectra were recorded with deuterated chloroform as solvent, and chemical shifts are quoted in parts per million downfield of tetramethylsilane. ^{13}C NMR spectra were recorded with broad band proton decoupling. Infrared spectra were recorded with chloroform as solvent.

General Procedure. At room temperature $BF_3 \cdot Et_2O$ or CF_3SO_3H, (4 mmol) was added .to an argon-saturated, stirred solution of ferrocene (1 mmol) in dichloromethane (15 mL). After the mixture was stirred for 5 min, a solution of β-ketoester (2 mmol) in the same solvent (5 mL) was added dropwise, and the stirring was continued for 5 h. The reaction mixture was then quenched with water (15 mL), the organic layer was separated, and the aqueous layer was extracted with dichloromethane (5 × 20 mL). The solvent was removed from combined and dried organic extracts and the residue was extracted with petrol (5 × 20 mL). Evaporation to dryness and flash column chromatography afforded β-ferrocenyl-α,β-unsaturated esters as orange, air-stable solids or oils. The yields are given in Table 1.

1a: Mp 70−71 °C. ^1H NMR δ 6.02 (s, 1H, C=C*H*), 4.52 (t, 2H, $J = 1.9$ Hz, Cp), 4.37 (t, 2H, $J = 1.9$ Hz, Cp), 4.18 (q, 2H, $J = 7.1$ Hz, CH_2CH_3), 4.14 (s, 5H, Cp), 2.51 (s. 3H, CH_3), 1.31 (t, 3H, $J = 7.1$ Hz, CH_2CH_3). ^{13}C NMR δ 166.79 (C=O), 156.04 (C=*C*H−), 111.53 (−*C*=CH−), 85.15 (*Cp*−C=), 70.23 (*Cp*), 69.52 (Cp), 66.79 (*Cp*), 59.33 (CH_2-CH_3), 17.15(CH_3−C=), 14.28 (CH_2-CH_3). IR 1697, 1614 cm^{-1}. Anal. Calcd for $C_{16}H_{18}FeO_2$: C, 64.5; H, 6.5. Found: C, 64.7; H, 6.1.

1b: Mp 68−69 °C. ^1H NMR δ 6.00 (s, 1H, C=C*H*), 4.53 (t, 2H, $J = 1.8$ Hz, Cp), 4.38 (t, 2H, $J = 1.8$ Hz, Cp), 4.12 (s, 5H, Cp), 3.71 (s, 3H, O−CH_3), 2.95 (q, 2H, $J = 7.5$ Hz, CH_2CH_3), 1.22 (t, 3H, $J = 7.5$ Hz, CH_2CH_3). ^{13}C NMR δ 166.75 (C=O), 163.18 (C=*C*H), 110.28 (*C*=CH), 83.62 (Cp), 70.42 (Cp), 69.69 (Cp), 66.97 (Cp), 50.71 (CH_3), 24.46 (CH_2CH_3), 15.08 ($-CH_2CH_3$). IR ($CHCl_3$) 1706, 1614 cm^{-1}. Anal. Calcd for $C_{16}H_{18}FeO_2$: C, 64.5; H, 6.5. Found: C, 64.5; H, 6.2.

1c: Oil. ^1H NMR δ 6.01 (s, 1H, C=C*H*), 4.52 (t, 2H, $J = 1.9$ Hz, Cp), 4.38 (t, 2H, $J = 1.9$ Hz, Cp), 4.16 (q, 2H, $J = 7.1$ Hz,

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$-$O$-$CH_2CH$_3$), 4.12 (s, 5H, Cp), 2.89 (t, 2H, J = 7.9 Hz, $-$CH_2-CH$_2$CH$_3$), 1.71$-$1.52 (m, 2H, CH$_2$CH_2CH$_3$), 1.32 (t, 3H, J = 7.1 Hz, $-$O$-$CH$_2$CH_3), 1.04 (t, 3H, J = 7.3 Hz, $-$CH$_2$CH$_2$CH_3). ^{13}C NMR δ 166.51 (C=O), 161.18 (C=CH), 111.23 (C=CH), 84.06 (Cp), 70.32 (Cp), 69.68 (Cp), 67.01 (Cp), 59.35 (O$-$$CH_2CH_3$), 33.25 ($-$$CH_2CH_2CH_3$), 24.10 ($-CH_2$$CH_2CH_3$), 14.57 (O$-CH_2$$CH_3$), 14.31 ($-CH_2CH_2$$CH_3$). IR (CHCl$_3$) 1697, 1610 cm^{-1}. Anal. Calcd for $C_{18}H_{22}FeO_2$: C, 66.3; H, 6.8. Found: C, 65.9, H, 6.8.

1d: Mp 65$-$66 °C. ^{1}H NMR δ 7.33 (m, 5H, Ph), 6.25 (s, 1H, C=CH), 4.37 (t, 2H, J = 1.9 Hz, Cp), 4.30 (t, 2H, J = 1.9 Hz, Cp), 4.18 (s, 5H, Cp), 3.99 (q, 2H, J = 7,1 Hz, $-$CH_2CH$_3$), 1.08 (t, 3H, J = 7.1 Hz, $-$CH$_2$CH_3). ^{13}C NMR δ 165.92 (C=O), 158.55 (C=CH), 138.99 (*p*-Ph), 127.83 (*m*-Ph), 127.50 (*o*-Ph), 127.38 (Ph$-$), 112.74 (C=CH), 83.78 (Cp), 70.53 (Cp), 69.85 (Cp), 68.32 (Cp), 59.57 ($-$CH$_2$CH$_3$), 13.97 ($-$CH$_2$$CH_3$). IR (CHCl$_3$) 1706, 1610 cm^{-1}. Anal. Calcd for $C_{21}H_{20}FeO_2$: C, 70.0; H, 5.1. Found: C, 69.7; H, 5.5.

1e: Oil. ^{1}H NMR (CDCl$_3$, 200 MHz) δ 4.33 (m), 4.29 (m), 4.17 (s), 4.14 (s), 4.07 (q, J = 7.4 Hz), 2.34 (s), 2.14 (s), 1.96 (s), 1.91 (s), 1.33 (t, J = 7.4 Hz), 1.12 (t. J = 7.5 Hz). Anal. Calcd for $C_{17}H_{20}FeO_2$: C, 65.4; H, 6.5. Found: C, 65.4; H, 6.5.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **1a**$-$**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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