Tetrahedron Letters, Vol.26, No.26, pp 3075-3078, 1985 0040-4039/85 \$3.00 + .00
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A PRACTICAL SYNTHESIS OF α,β-UNSATURATED IRON ACYLS. CHIRAL ENOATE SYNTHONS.

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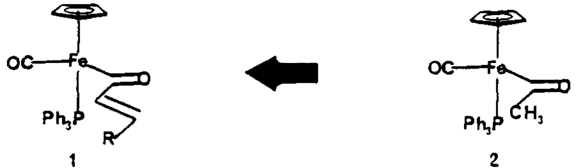
Abstract: A simple preparation of α,β-unsaturated iron acyls is described. The title compounds are very useful as chiral enoate synthons.

Recent examples of very diastereoselective reactions of chiral η^5-CpFe(CO)(PPh$_3$)COR complexes (alkylations,[3] aldol reactions,[4,5] imine condensations[6]) encouraged us to look for similar selectivities in the reactions of α,β-unsaturated iron acyls 1. In order to extend any encouraging diastereoselectivities to the corresponding optically active systems, we required a synthesis of unsaturated iron acyls 1 from the parent acetyl compound 2 which is available as either optical antipode.[7] This communication details our practical synthesis of α,β-unsaturated iron acyls and the following Letter presents, in preliminary form, our observations of exceptionally stereoselective conjugate addition - alkylation reactions of 1.



1 2

The enolate formed from treatment of η^5-CpFe(CO)(PPh$_3$)COCH$_3$ with lithium diisopropylamide in THF at -42°C is known to condense with aldehydes and ketones to provide high yields of the corresponding aldol products 3.[3-5,8] Attempted dehydration of these compounds under a variety of acidic or basic conditions was not successful; however, acetylation of the hydroxyl group of 3 followed by acetate elimination with potassium t-butoxide provided a practical method for preparing quantities of the desired α,β-unsaturated iron acyls 1 (Table 1).

While the aldol reaction and acetylation were straightforward, the potassium t-butoxide induced elimination of HOAc had to be kept at low temperature and monitored closely for completion of the reaction. If the reaction was allowed to warm, or if it proceeded too long, varying degrees of isomerization to the β,γ-unsaturated enone isomer resulted. For example, treatment of enone 1 (R = Me, R' = H) with excess potassium t-butoxide in THF at 0°C for 3 hr gave a 52:48 mixture of recovered 1 and the β,γ-isomer 4 in high yield (Eq. 1).[9] Following this lead, treatment of 1 with LDA/HMPA in THF at -78°C formed the extended enolate under kinetic conditions, and reaction with MeI occurred with good stereoselectivity to form the α-methylated products 5 and 6 in a 7:1 ratio in 44% yield (Eq. 2).[9,10]

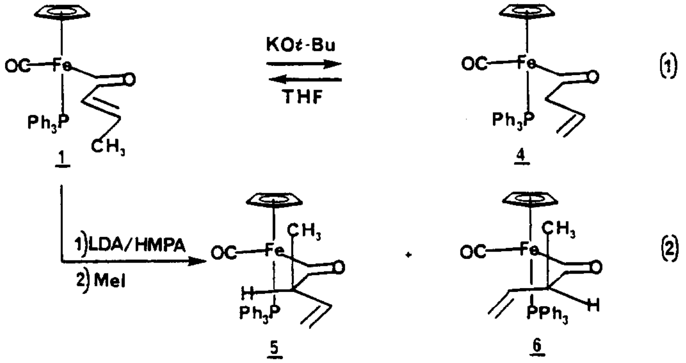
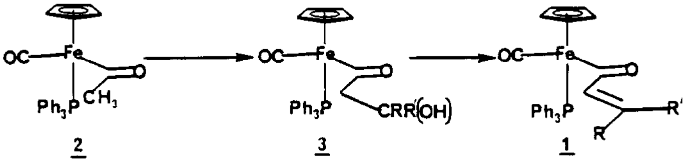


Table 1. Preparation of α,β-Unsaturated Iron Acyls.[9]



R	R'	%3	%1	m. p. 1
Me	H	93	82	137-138.5
Ph	H	87	93	122.5-124.5
i-Pr	H	86	78[11]	-
Me	Me	81	65	130-131.5
	H	83	80	-

A typical, large-scale experimental procedure for the preparation of α,β-unsaturated iron acyls is described. Lithium diisopropylamide (LDA) was generated from 3.4mL of diisopropylamine and 15.2mL of n-BuLi (1.6M in hexanes, 22mmol) at 0°C in 80mL of THF. After 30 min the solution was cooled to -42°C and a solution of 10g iron acetyl 2 in 20mL of THF was added slowly dropwise to the LDA to generate a deep red-brown solution of the enolate. After stirring for 1.75 hr at -42°C, CH_3CHO (1.5mL, 27mmol) was added neat. The resulting dark solution was stirred an additional 40 min at -42°C and quenched by addition of 100mL of saturated aqueous $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2 (3 x 50mL) and the combined CH_2Cl_2 layers were dried (Na_2SO_4), filtered, and condensed on a rotary evaporator to leave the crude aldol product which was chromatographed on alumina (Alcoa F-20, 6 x 40cm). Elution with CH_2Cl_2 brought off unreacted iron acetyl 2 (680mg, 7%) and elution with EtOH yielded 9.73g of the desired aldol product 3 (R, R' = H, Me) as an orange solid (89%).[8] This material (9.73g, 19.5mmol) was dissolved in THF (80mL) and cooled to ca. -5°C. A solution of MeLi (15.7mL of 1.5M LiBr complex in ether, 23.4mmol) was then added and the solution slowly turned from orange to black with obvious methane evolution. After 70 min at -5°C, 2.4mL of Ac_2O (25.4mmol) was added with a concomitant color change from black to orange. After stirring for 30 min at 0°C, 100mL of saturated aqueous $NaHCO_3$ was added followed by the same workup as above. The crude orange product was divided into two portions, each of which was chromatographed on SiO_2 (Aldrich "Flash" grade, 6cm x 20cm) with 3:1 petroleum ether - EtOAc to yield 8.85g (84%) of the acetylated product and 770mg (8%) of recovered starting material. The acetylated product (mixture of diastereomers) showed: IR(CH_2Cl_2, cm^{-1}) 1910, 1725, 1603; 360MHz ^1H NMR ($CDCl_3$, δ) 7.48 (m, 6H), 7.39 (m, 9H), 4.99 and 4.89 (h each, J = 6Hz each, 1H total), 4.43 and 4.40 (d each, J = 1Hz, 5H total), 3.38 and 2.98 (dd each, J = 17Hz, 6Hz; J = 16Hz, 6Hz, 1H total), 2.77 and 2.61 (dd each, J = 16Hz, 6Hz; J = 17Hz, 6Hz), 1.96 and 1.89 (s each, 3H total), 1.07 and 0.73 (d each, J = 6Hz each, 3H total). Anal. Calcd for $C_{30}H_{29}FeO_4P$: C, 66.69; H, 5.41. Found: C, 66.47; H, 5.46. Finally, 8.85g (16.4mmol) of the acetylated product were dissolved in 80mL THF and cooled to -5°C. Potassium t-butoxide (2 equiv, 3.68g, 32.8mmol) was added in one portion with stirring. Analysis by tlc after 10 min showed no starting material present, so the reaction mixture was quenched with 100mL of saturated aqueous $NaHCO_3$ and the usual workup was applied. The resulting orange solid was divided into two portions each of which was chromatographed on SiO_2 (Aldrich "Flash" grade, 6cm x 20cm) eluting with 4:1 petroleum ether - EtOAc to yield a small foreband of mixed *E*- and *Z*-enone followed by a second band of pure *E*- α,β-unsaturated iron acyl 1 (R' = H, R = Me), 5.86g. Rechromatography of the foreband eluting with 20:1 CH_2Cl_2 - EtOAc gave first 276mg of pure *Z*-enone, then 152mg of a mixture of *E*- and *Z*-enone and finally 727mg of pure *E*-enone. The combined portions of pure *E*-**1** (R' = H, R = Me) totaled 6.59g (82%) and showed: mp 137-138.5°C (EtOAc/hexane) IR(CH_2Cl_2, cm^{-1}) 1920, 1633, 1570; 360MHz ^1H NMR ($CDCl_3$, δ) 7.42 (m, 6H), 7.28 (m, 9H), 6.49 (d, J = 15Hz, 1H), 5.50(dq, J = 15Hz, 1H), 4.41 (d, J = 1Hz, 5H), 1.56 (d, J = 7Hz, 3H); Anal. Calcd for $C_{28}H_{25}FeO_2P$: C, 70.09; H, 5.25. Found: C, 69.77; H, 5.60.

Acknowledgment. This project was supported by the National Science Foundation under grant CHE-8305055.

References and Notes

1. Fellow of the Alfred P. Sloan Foundation, 1983-1985.
2. Department of Chemistry, Florida State University, Tallahassee, Florida, 32306. M. E. W. thanks the Organic Division of the A. C. S. for a Proctor and Gamble sponsored Research Fellowship.
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9. All new compounds gave satisfactory IR, ^1H NMR and combustion analyses.
10. Assignment of the two diastereomers was achieved on the basis of the α-CH_3 ^1H NMR chemical shifts [in $CDCl_3$ **5**: 1.08 ppm (d, J = 7 Hz); **6**: 0.39 ppm (d, J = 7 Hz)] as described in S. G. Davies, I. M. Dordor, J. C. Walker, P. Warner, *Tetrahedron Lett.*, 1984, 2709.
11. The potassium t-butoxide elimination was performed at -42°C to minimize formation of the deconjugated isomer.

(Received in USA 18 March 1985)