Tetrahedron Letters,Vol.26,No.26,pp 3079-3082,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

STEREOSELECTIVE CONJUGATE ADDITION - ALKYLATIONS OF α,β-UNSATURATED IRON ACYLS

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Abstract: Conjugate additions and conjugate addition-alkylations proceed with very high stereoselectivity to α,β-unsaturated acyls of η^5-CpFe(CO)(PPh_3). Oxidative cleavage of the products provides high yields of organic acid derivatives (esters, β-lactams) with almost complete control of relative stereochemistry.

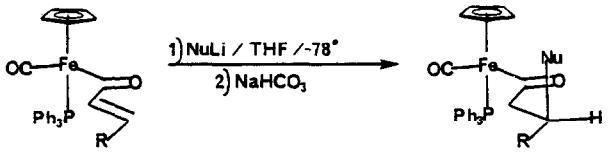
In the preceding Letter a practical synthesis of α,β-unsaturated iron acyls was presented. These compounds were prepared in order to probe the possibility of chiral iron controlled diastereoselectivity in conjugate addition reactions. The incredible influence of the η^5-CpFe(CO)(PPh_3) group on this chemistry is described herein. Davies has recently communicated a small number of results similar to our own.[3]

Treatment of E-unsaturated acyls 1 or 2 with lithium nucleophiles NuLi (Nu = Ph, Bu, $PhCH_2NH$, PrNH, PhNH, allylNH, $MeOCH_2CH_2NH$) resulted in an extremely selective conjugate addition reaction to provide practically only one product diastereomer 3 after low temperature protonation of the intermediate enolate (Table 1). Assignment of relative stereochemistry to the product of conjugate addition of amine nucleophiles was accomplished by comparison of the 360MHz ^{1}H NMR spectra of products 3 with spectra previously obtained from the rigorously identified β-aminoiron acyl products produced by condensation of imines with the enolate of η^5-CpFe(CO)(PPh_3)$COCH_3$.[4] Stereochemistry of the products formed from conjugate addition of the carbon nucleophiles was assumed to follow analogously.

In an extention of this chemistry, we trapped the intermediate enolate formed from conjugate addition of the nucleophile to enone 1 with a variety of electrophiles (Table 2). Again, an incredibly selective series of reactions ensued that provided very high yields of essentially only one product diastereomer, 4, in most cases. Confirmation of relative stereochemistry for these reactions was based upon 1) the results shown in Table 1, 2) the pronounced tendency of alkylations of the enolate of η^5-CpFe(CO)(PPh_3)$COCH_2R$ to occur away from

the PPh_3 ligand[7] and 3) analysis of the organic product formed after high-yield oxidative cleavage of the iron acyl 4.

Table 1. Stereoselective Conjugate Addition Reactions[5,6]

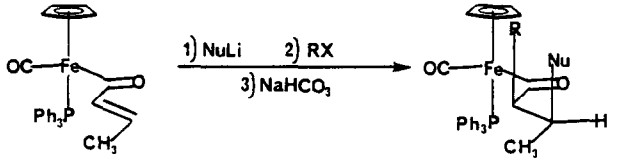


1 R=CH_3
2 R=Ph

3

R	Nu	Diastereomer Ratio	Isolated Yield, %
Me	Bu	30:1	97
Me	Ph	30:1	98
Me	PrNH	31:1	97
Me	$PhCH_2NH$	30:1	99
Me	allylNH	22:1	99
Me	$MeOCH_2CH_2NH$	30:1	69
Me	PhNH (-42°)	10:1	69
Ph	allylNH	31:1	79
Ph	$MeOCH_2CH_2NH$	18:1	63

Table 2. Stereoselective Conjugate Addition - Alkylation Reactions[6,8]



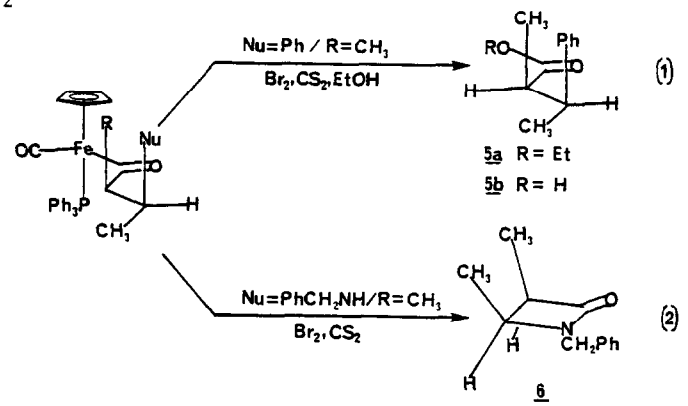
1

4

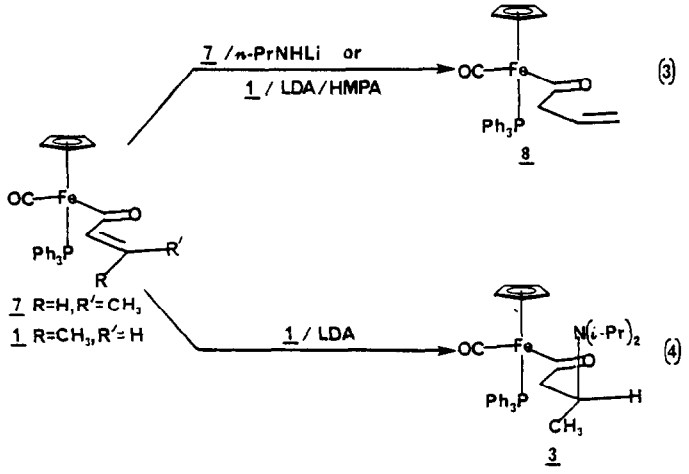
Nu	RX	Diastereomer Ratio	Isolated Yield, %
Ph	MeI	30:1	93
$PhCH_2NH$	MeI	24:1	95
$PhCH_2NH$	EtI	20:1	99
$PhCH_2NH$	$PhCH_2Br$	15:1	99
$PhCH_2NH$	allylBr	30:1	92

Confirmation of the relative stereochemistry of the organic fragments of the iron complexes shown in Table 2 was achieved by the following reactions. Treatment of 4 (Nu = Ph, R = Me) with 1.1 eq of Br_2 at -78°C in EtOH/CS_2 (with just enough CH_2Cl_2 to maintain solubility of 4) instantaneously gave the ethyl ester 5a in 83% yield after workup and chromatography (Eq. 1). Hydrolysis of ester 5a provided the known carboxylic acid 5b with melting point (132-134°C) and 360 MHz ^1H NMR data identical with those values in the literature.[9] The relative stereochemistry for the conjugate addition-alkylation sequence using the amine nucleophiles was confirmed by

oxidative decomposition of 4 (Nu = $PhCH_2NH$, R = Me) to the known β-lactam 6[10] in 78% yield using 1.1eq of Br_2 in CS_2 at -78°C (Eq. 2).



Independent from the report of Davies,[3] we had also attempted conjugate addition to the Z-unsaturated iron acyl 7[11] (using PrNHLi instead of BuLi) and similarly observed deprotonation to the extended enolate instead, which gave the pure β,γ-isomer 8 in 98% yield after quenching with aqueous $NaHCO_3$, workup, and chromatography (Eq. 3). On the assumption that both this deprotonation and the conjugate additions to the E-unsaturated iron acyls were proceeding via directed attack by coordination of the iron acyl oxygen to the lithium counterion of RLi and RNHLi, addition of HMPA should interfere with this process and allow a standard deprotonation of the E-isomer to occur. As predicted, reaction of 1 with lithium diisopropylamide in the presence of HMPA (THF, -78°C) gave, after workup and chromatography, a 66% yield of the β,γ isomer 8 along with 17% recovered 1 (Eq. 3) while the same reaction in the absence of HMPA led to the conjugate addition product 3 (R = Me, Nu = $N(iPr)_2$) in 47% yield (Eq. 4).



In summary, α,β-unsaturated iron acyls appear to be excellent chiral enoate synthons with demonstrated potential for control over relative stereochemistry in acyclic systems and with anticipated potential for absolute stereochemistry control. The cleavages of the iron acyl bond described herein and in our earlier papers[4,12,13] are performed under exceptionally mild conditions and have, thus far, provided uniformly high yields of the organic derivatives. Complete details of this chemistry will be described in a full paper.

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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5. Typical reaction conditions: amine (distilled off KOH) was deprotonated with 1 eq of BuLi (1.6M in hexane) in THF (ca. 0.1M in each reactant) at 0°C. After 30 min the reaction was cooled to -78°C and the α,β-unsaturated iron acyl (ca. 0.1M in THF) was added slowly dropwise. The deep red color of the enolate formed. After 1 hr at -78°C the reaction was quenched with excess aqueous $NaHCO_3$, extracted into CH_2Cl_2, dried (Na_2SO_4), condensed on a rotary evaporator and chromatographed on SiO_2 using CH_2Cl_2 to remove excess amine and 1% Et_3N in EtOH to remove the product.

6. All new compounds gave satisfactory IR, 360 MHz ^1H NMR and combustion analyses.

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8. Typical reaction conditions: the enolate formed by conjugate addition of nucleophiles to the α,β-unsaturated iron acyl was prepared as described in Reference 5. Rather than quenching with $NaHCO_3$, the enolate was alkylated by addition of RX (1M in THF) to the reaction mixture at -78°C (MeI reacted instantaneously, benzyl bromide required 1 hr at -78°C, ethyl iodide and allyl bromide were warmed to 0°C to complete the alkylation). Then the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and subjected to the same workup described in Reference 5.

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(Received in USA 18 March 1985)