A study of the reactivity of (methyl 2-acetamidoacrylate)-tricarbonyliron(0) leading to a novel synthesis of β,β,β-trialkyl α-amino acids

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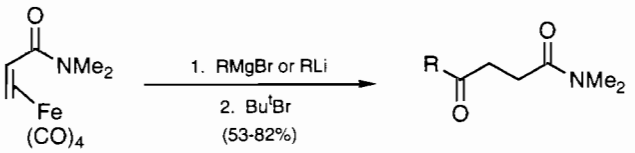
Abstract

(Methyl 2-acetamidoacrylate)tricarbonyliron(0) (**3**) reacts with 2 equivalents of methyllithium to give methyl *N*-acetylalaninate (**4**) and 2-acetamido-4-oxopentanoate (**5**) when the reaction is quenched with trifluoroacetic acid. Production of methyl *N*-acetylalaninate is dependent only on the presence of trifluoroacetic acid, and the ratio of **4** to **5** generated in these reactions is related to the quantity of trifluoroacetic acid used to quench them. Addition of two equivalents of methyllithium followed by tertiary haloalkanes gives protected β,β,β-trialkyl α-amino acids which may be hydrolysed to give tert-leucine (**13**) and the new α-amino acids 2-amino-3,3-dimethylpentanoic acid (**14**) and 2-amino-3,3-dimethylhexanoic acid (**15**).

Key words: Iron complexes; Carbonyl complexes; Amino acid complexes

Introduction

We have been interested for some time now in the reactions of hard nucleophiles with iron carbonyl complexes of unsaturated organic molecules. We have studied the addition of Grignard and organolithium reagents to tricarbonyliron(0) complexes of α,β-unsaturated ketones [1], tetracarbonyliron(0) complexes of α,β-unsaturated esters [2] and tetracarbonyliron(0) complexes of α,β-unsaturated amides [3]. All of these reactions led to the acylation of the unsaturated organic molecule. For example, addition of a range of Grignard and organolithium reagents to the readily formed tetracarbonyliron(0) complex of *N,N*-dimethylacrylamide (**1**) gave γ-ketoamides (**2**) in good yield (53–82%) via selective nucleophilic attack on a metal carbonyl and transfer of the resulting acyl group from the metal to the β carbon of the α,β-unsaturated amide.



1 **2**

In view of current interest in the chemistry of α-amino acids, we recently wondered whether or not it would be possible to extend this acylation chemistry to complexes of α,β-unsaturated α-amino acids. A literature search for appropriate iron carbonyl complexes revealed (methyl 2-acetamidoacrylate)tricarbonyliron(0) (**3**) [4]. The reactions of complex **3** with triphenylphosphine and trimethylphosphite had been examined [4], but otherwise the reactivity of this interesting complex had not been probed. The results of our initial studies into the reactivity of complex **3**, some of which have been briefly published previously [5], are described below.

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Experimental

Reactions under nitrogen were performed using standard vacuum line and Schlenk tube techniques [6]. Tetrahydrofuran (FHF) was distilled from sodium benzophenone ketyl. Diethyl ether was dried over sodium wire. Petroleum ether, which refers to the fraction boiling in the range 40–60 °C, was distilled. $[Fe_2(CO)_9]$ [7], methyl 2-acetamidoacrylate [8], 2-iodo-2-methylbutane [9] and 2-iodo-2-methylpentane [9] were prepared using literature procedures. The concentration of MeLi was determined by titration against diphenylacetic acid [10]. All alkyl halides were distilled. All other reagents were used as obtained from commercial sources. M.ps were obtained on a Reichert 7905 hot-stage microscope and a Gallenkamp capillary m.p. apparatus and are uncorrected. The m.p. of the organoiron complex was measured in a sealed capillary under nitrogen. Elemental analyses were performed by Imperial College microanalytical service. IR spectra were obtained on a Perkin-Elmer 1710 FTIR instrument. NMR spectra were recorded in $CDCl_3$ (unless stated otherwise) at room temperature on Jeol GSX 270 (270 MHz ^1H, 67.9 MHz ^{13}C) and Bruker AM 500 (500 MHz ^1H, 125.8 MHz ^{13}C) spectrometers. Mass spectra were recorded on a VG Mass Lab 12/250 instrument at the SERC Mass Spectrometry Service Centre, Swansea, and on a VG Micromass 7070E instrument at Imperial College using EI, CI and FAB techniques.

(Methyl 2-acetamidoacrylate)tricarbonyliron(0) (3)

Methyl 2-acetamidoacrylate (0.600 g, 4.2 mmol) and $[Fe_2(CO)_9]$ (3.36 g, 9.24 mmol) were heated together in diethyl ether (20 cm^3) at 30 °C for 14 h under nitrogen. The resulting mixture was filtered through a plug of alumina and the solvent removed under reduced pressure to give pure title compound **3** as an orange microcrystalline solid (1.16 g, 98%). An analytical sample was obtained by recrystallisation from pentane, m.p. 103–105 °C (decomp.) *Anal.* Found: C, 38.14; H, 2.99; N, 4.96. Calc. for $C_9H_9NO_6Fe$: C, 38.19; H, 3.20; N, 4.94%. ν_{max}(hexane) (cm^{-1}): 2057vs, 1985vs, 1974vs (C≡O), 1671m (C=O/ester). δ_H (270 MHz): 1.85 (3H, s, CH_3CO), 1.99 (1H, d, *J* 4.3, CH_2=C), 2.85 (1H, d, *J* 4.3, CH_2=C), 3.73 (3H, s, CH_3O), 8.24 (1H, br, NH). δ_C {^1H} (125.8 MHz): 19.2 (CH_3CO), 34.6 (CH_2=C), 51.7 (CH_3O), 70.7 (C=CH_2), 176.3, 176.9 (CO_2CH_3 and CONH), 207.9, 211.5 and 214.0 (C≡O). *m/z* (EI, 70 eV, 150 °C): 283 (M^+, 0.3%), 255 (M−CO, 5), 227 (M−2CO, 8), 199 (M−3CO, 9), 171 [M−Fe(CO)$_2$, 12], 143 [M−Fe(CO)$_3$, 85], 101 [M−Fe(CO)$_3$−CH_2CO, 100].

Reaction of (methyl 2-acetamidoacrylate)tricarbonyliron(0) (3) with MeLi and excess TFA

(Methyl 2-acetamidoacrylate)tricarbonyliron(0) (**3**) (0.219 g, 0.77 mmol) was dissolved in THF (15 cm^3) under a nitrogen atmosphere and the solution cooled to −78 °C. Methyllithium (1.3 cm^3, 1.54 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 40 min. The reaction was quenched by the addition of trifluoroacetic acid (0.3 cm^3, 3.9 mmol), maintained at −78 °C for 5 min and then stirred at room temperature for a further 2 h. The THF was removed under reduced pressure, diethyl ether (20 cm^3) was added to the orange residue and the mixture was stirred under air for 20 h. The resulting brown mixture was filtered through deactivated alumina eluting with ethyl acetate (150 cm^3). The solvent was evaporated to yield a yellow oil (0.077 g) containing a 3:1 mixture of methyl *N*-acetylalaninate (**4**) and methyl 2-acetamido-4-oxopentanoate (**5**). Chromatography (Al_2O_3; ethyl acetate: petroleum ether, 1:1) afforded a white solid identified as methyl *N*-acetylalaninate (**4**) (0.021 g, 20%) by comparison of its m.p. and ^1H NMR spectrum with literature values [11] and examination of its IR, ^{13}C NMR and mass spectra (see below for data), and a yellow oil identified as methyl 2-acetamido-4-oxopentanoate (**5**) (0.014 g, 10%) contaminated with **4** (**5**:**4** = 3:1) by its ^1H NMR spectrum: δ_H 2.02 (3H, s, CH_3CONH), 2.18 (3H, s, CH_3COCH), 3.01 (1H, dd, *J* 19.5, CH_2), 3.23 (1H, dd, *J* 19, 5, CH_2), 3.74 (3H, s, CH_3O), 4.77 (1H, dt, *J* 9, 5, CH), 6.49 (1H, d, *J* 9, NH).

Methyl N-acetylalaninate (4)

A degassed solution of (methyl 2-acetamidoacrylate)tricarbonyliron(0) (**3**) (0.170 g, 0.6 mmol) in dry THF (10 cm^3) was stirred under nitrogen and cooled to −78 °C. Trifluoroacetic acid (0.23 cm^3, 3 mmol) was added and the mixture was stirred at −78 °C for 5 min and allowed to warm to room temperature. The THF was evaporated under reduced pressure and diethyl ether (20 cm^3) was added to the solid residue. The brown mixture was stirred under air for 16 h and after filtration through a plug of alumina using ethyl acetate as eluent (150 cm^3) the solvent was evaporated to afford methyl *N*-acetylalaninate (**4**) as white crystals (0.078 g, 90%); m.p. 44–45 °C (lit. [11] 45–47 °C). δ_H (270 MHz): 1.38 (3H, d, *J* 7.08, CH_3CH), 1.99 (3H, s, CH_3CO), 3.73 (3H, s, CH_3O), 4.57 (1H, m, CH_3CH), 6.17 (1H, br, NH). δ_C {^1H} (69.7 MHz): 18.3 (CH_3CH), 22.9 (CH_3CO), 47.9 (CH), 52.3 (OCH_3), 169.6 (CONH), 173.6 ($COOCH_3$). *m/z* (EI): 145 (M^+, 2%), 102 (M−CH_3CO, 1.2), 86 (M−CO_2CH_3, 48%), 44 (CO_2, 100).

Reaction of (methyl 2-acetamidoacrylate)tricarbonyliron(0) (3) with MeLi and 'BuBr

(Methyl 2-acetamidoacrylate)tricarbonyliron(0) (**3**) (0.177 g, 0.62 mmol) was dissolved in THF (10 cm^3) under a nitrogen atmosphere and the solution cooled to −78 °C. Methyllithium (0.87 cm^3, 1.25 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 40 min and then treated with 'BuBr (0.3 cm^3, 2.6 mmol). After 5 min at −78 °C the reaction mixture was allowed to warm to room temperature and then stirred for a further 2 h at room temperature. The THF was removed from the brown mixture and diethyl ether (20 cm^3) was added to the dark residue. The mixture was stirred under air for 20 h and the resulting mixture was filtered through a plug of alumina using ethyl acetate as eluent. Subsequent solvent removal under reduced pressure left a yellow oil (0.045 g) which contained approximately equal amounts of methyl *N*-acetyl-tert-leucinate (**7**) and methyl 2-acetamido-4-oxopent-2-enoate (**6**). Column chromatography (SiO_2; dichloromethane:ethyl acetate:petroleum ether, 1:1:3) gave methyl *N*-acetyl-tert-leucinate (**7**) (see below for data) and methyl 2-acetamido-4-oxopent-2-enoate (**6**) (0.025 g, 22%) as a white solid which was recrystallised from a diethyl ether:pentane solvent mixture, m.p. 52 °C (found 186.0770; calc. for $C_8H_{11}NO_4$ 186.0766). $\nu_{max}(CHCl_3)$ (cm^{-1}): 3414w (NH), 1741s (C=O/ester), 1718s (C=O/ketone), 1665s (C=O/amide), 1600s (C=C). δ_H (270 MHz): 2.18 (3H, s, CH_3CONH or $CH_3COCH{=}C$), 2.26 (3H, s, CH_3CONH or $CH_3COCH{=}C$), 3.86 (3H, s, CO_2CH_3), 5.76 (1H, s, $CH_3COCH{=}C$), 11.15 (1H, br, NH). δ_C {^{1}H} (125.8 MHz): 23.5 (CH_3CONH), 31.1 ($CH_3COCH{=}C$), 53.0 (CO_2CH_3), 106.5 ($CH_3COCH{=}C$), 142.3 ($CH_3CO{-}CH{=}C$), 164.5 (CO_2CH_3), 168.6 (CH_3CONH), 200.7 ($CH_3COCH{=}C$). *m/z* (CI, NH_3): 186 (MH^+, 100%), 144 ($MH-CH_2CO$, 100).

Methyl N-acetyl-tert-leucinate (7)

Methyllithium (1.43 cm^3, 2 mmol) was added dropwise to a solution of (methyl 2-acetamidoacrylate)-tricarbonyliron(0) (**3**) (0.238 g, 1 mmol) in THF (25 cm^3) at −78 °C. The mixture was stirred for 40 min at −78 °C and then treated with 'BuI (1.2 cm^3, 10 mmol) and stirred for a further 5 min at −78 °C. The reaction mixture was then allowed to warm to room temperature, during which time it became very dark, and then stirred for a further 2 h at room temperature. The solvent was removed under reduced pressure and diethyl ether (25 cm^3) was added to the dark residue. The resulting suspension was irradiated with a 100 W household light bulb under air for 19 h. Filtration of the product mixture through a short plug of alumina, eluting with ethyl acetate (300 cm^3), and subsequent solvent removal gave a pale yellow oil which contained a 3:1 mixture of the title compound **7** and methyl 2-acetamido-4-oxopent-2-enoate (**6**). Column chromatography (SiO_2; dichloromethane:ethyl acetate:petroleum ether, 4:7:9) gave the title compound **7** as a white crystalline solid (0.074 g, 40%). An analytical sample was obtained by recrystallisation from petroleum ether, m.p. 106–08 °C (found 188.1287; calc. for $C_9H_{18}NO_3$ 188.1287). $\nu_{max}(CHCl_3)$ (cm^{-1}): 3437m (NH), 1733s (C=O/ester), 1676s (C=O/amide). δ_H (270 MHz): 0.97 (9H, s, $(CH_3)_3C$), 2.04 (3H, s, CH_3CONH), 3.73 (3H, s, CO_2CH_3), 4.49 (1H, d, *J* 9.5, $CHC(CH_3)_3$), 5.97 (1H, br, NH). δ_C {^{1}H} (125.8 MHz): 23.4 (CH_3CONH), 26.5 {26.6} [$(CH_3)_3C$], 34.7 {34.9} [$(CH_3)_3C$], 51.8 {51.8} (CO_2CH_3), 59.9 {60.4} ($NHCHCO_2CH_3$), 169.7 (CH_3CONH), 172.3 {171.4} (CO_2CH_3) (figures in parentheses {} were obtained from the spectrum of Mosher's amide of the methyl ester of tert-leucine [12]). *m/z* (CI, NH_3): 188 (MH^+, 100%), 131 ($MH-C(CH_3)_3$, 56), 99 ($MH-C(CH_3)_3-CH_3OH$, 59), 43 (CH_3CO, 100).

Methyl 2-acetamido-3,3-dimethylpentanoate (9)

Methyllithium (1.43 cm^3, 2 mmol) was added dropwise to a solution of (methyl 2-acetamidoacrylate)-tricarbonyliron(0) (**3**) (0.238 g, 1 mmol) in THF (25 cm^3) at −78 °C. The mixture was stirred for 40 min at −78 °C and then treated with 2-iodo-2-methylbutane (1.98 g, 10 mmol) and stirred for a further 5 min at −78 °C. The reaction mixture was then allowed to warm to room temperature, stirred for a further 2 h, irradiated with a 100 W household light bulb and filtered exactly as described above in the preparation of methyl *N*-acetyl-tert-leucinate (**7**). Subsequent solvent removal gave a pale yellow oil which contained a 3:1 mixture of the title compound **9** and methyl 2-acetamido-4-oxopent-2-enoate (**6**). Column chromatography (SiO_2; diethyl ether) afforded the title compound **9** as a white crystalline solid (0.060 g, 30%). An analytical sample was obtained by recrystallisation from a diethyl ether:pentane solvent mixture, m.p. 62–63 °C (found 202.1440; calc. for $C_{10}H_{20}NO_3$ 202.1443). $\nu_{max}(CHCl_3)$ (cm^{-1}): 3438m (NH), 1733s (C=O/ester), 1675s (C=O/amide). δ_H (270 MHz): 0.87 (3H, t, *J* 7, CH_3CH_2), 0.90 (3H, s, $(CH_3)_2CCH_2CH_3$), 0.91 (3H, s, $(CH_3)_2CCH_2CH_3$), 1.31 (2H, q, *J* 7, CH_3CH_2), 2.02 (3H, s, CH_3CONH), 3.71 (3H, s, CO_2CH_3), 4.54 (1H, d, *J* 9.5, $NHCHCO_2CH_3$), 5.96 (1H, br d, *J* 9.5, NH). δ_C {^{1}H} (125.8 MHz): 8.1 (CH_3CH_2), 23.0 and 23.1 ($(CH_3)_2CCH_2CH_3$), 23.3 (CH_3CONH), 31.7 (CH_3CH_2), 37.2 ($(CH_3)_2CCH_2CH_3$), 51.8 (CO_2CH_3), 58.5 ($NHCHCO_2CH_3$), 169.7 (CH_3CONH), 172.5 (CO_2CH_3). *m/z* (CI, NH_3): 202 (MH^+, 100%), 170 ($MH-CH_3OH$, 10), 142 ($MH-CH_3OH-CO$, 9).

Methyl 2-acetamido-3,3-dimethylhexanoate (10)

Methyllithium (1.43 cm^3, 2 mmol) was added dropwise to a solution of (methyl 2-acetamidoacrylate)-tricarbonyliron(0) (3) (0.238 g, 1 mmol) in THF (25 cm") at -78 "C. The mixture was stirred for 40 min at − 78 °C and then treated with 2-iodo-2-methylpentane (2.12 g, 10 mmol) and stirred for a further 5 min at -78 "C. The reaction mixture was then allowed to warm to room temperature, stirred for a further 2 h, irradiated with a 100 W household light bulb, and filtered exactly as described above in the preparation of methyl *N*-acetyl-tert-leucinate (7). Subsequent solvent removal gave a pale yellow oil which contained a 5:2 mixture of the title compound 10 and methyl 2-acetamido-4-oxopent-2-enoate (6). Column chromatography (SiO_2; diethyl ether: petroleum ether, 17:3) afforded the title compound 10 as a white crystalline solid (0.041 g, 20%). An analytical sample was obtained by recrystallisation from a diethyl ether:pentane solvent mixture, m.p. 50–51 °C (found 216.1600; calc. for $C_{11}H_{22}NO_3$ 216.1600). $\nu_{max}(CHCl_3)$ (cm-'): 3438m (NH), 1734s (C=O/ester), 1675s (C=O/amide). δ_H (270 MHz): 0.88 (3H, t, *J* 7, CH_3CH_2), 0.91 (3H, s, $(CH_3)_2CCH_2CH_2$), 0.92 (3H, s, $(CH_3)_2CCH_2CH_2$), 1.17-1.35 (4H, m , $CH_3CH_2CH_2$), 2.03 (3H, s, CH_3CONH), 3.71 (3H, s, CO_2CH_3), 4.54 (1H, d, *J* 9.5, $NHCHCO_2CH_3$), 5.92 (1H, br d, *J* 9.5, NH). δ_C {' H} (125.8 MHz): 14.8 (CH_3CH_2), 16.9 (CH_3CH_2), 23.4 and 23.6 ($(CH_3)_2CCH_2CH_2CH_3$), 37.2 ($(CH_3)_2CCH_2$-CH_2CH_3), 41.7 ($CH_3CH_2CH_2$), 51.8 (CO_2CH_3), 58.8 ($NHCHCO_2CH_3$), 169.7 (CH_3CONH), 172.4 (CO_2CH_3). *m/z* (CI, NH,): 216 (MH^+, 37%), 156 ($MH-CH_3$-OH-CO, 52), 131 ($MH-C_6H_{13}$, 100), 99 ($MH-C_6H_{13}-CH_3OH$, 75), 43 (CH_3CO, 73).

tert-Leucine hydrochloride salt (13)

A mixture of methyl *N*-acetyl-tert-leucinate (7) (0.027 g, 0.152 mmol) and 6 N HCl (1.5 cm^3) was heated to reflux for 3 h and then allowed to cool to room temperature. The reaction mixture was washed with $CHCl_3$ (2 X 1 cm') and the aqueous layer was separated. Removal of the water under reduced pressure gave a pale yellow crystalline solid that was washed with ethyl acetate and filtered to give white crystals of the title compound 13 (0.0165 g, 65%). An analytical sample was obtained by recrystallisation from a water:ethanol solvent mixture, m.p. 212 °C (subl.) (found 132.1025; calc. for $C_6H_{14}NO_2$ 132.1025). ν_{max}(nujol) (cm-'): 1729m (C=O). δ_H (500 MHz, D_2O): 1.08 (9H, s, $(CH_3)_3C$), 3.65 (1H, s, NHCHCOOH). δ_C {' H} (125.8 MHz, D_2O): 28.5 ($(CH_3)_3C$), 35.2 ($(CH_3)_3C$), 65.3 (NH_3CHCO_2H), 174.7 (CO_2H). *m/z* (EI): 132 [(M-Cl)+, 30%], 86 (M- Cl $-H_2O-$ CO, 67), 75 [M-Cl $-(CH_3)_3C$, 100].

2-Amino-3,3-dimethylpentanoic acid hydrochloride salt (14)

A mixture of methyl 2-acetamido-3,3-dimethylpentanoate (9) (0.022 g, 0.109 mmol) and 6 N HCl (1.5 cm^3) was heated to reflux for 4 h and then allowed to cool to room temperature. The reaction mixture was washed with $CHCl_3$ (2 X 1 cm") and the aqueous layer was separated. Removal of the water under reduced pressure gave a pale white solid that was washed with ethyl acetate and filtered to give white crystals of the title compound 14 (0.017 g, 86%). An analytical sample was obtained by recrystallisation from a water:ethanol solvent mixture, m.p. 209 °C (subl.) (found 146.1180; calc. for $C_7H_{16}NO_2$ 146.1181). ν_{max}(nujol) (cm^{-1}): 1730m (C=O). δ_H (500 MHz, D_2O): 0.88 (3H, t, *J* 7.3, CH_3CH_2), 1.02 (6H, s, $(CH_3)_3CCH_2CH_3$), 1.44 (2H, q, *J* 7.3, CH_3CH_2), 3.70 (1H, s, NH_3CHCO_2H). δ_C {' H} (125.8 MHz, D_2O): 10.0 (CH_3CH_2), 25.0 and 25.4 ($(CH_3)_2CCH_2CH_3$), 33.8 (CH_3CH_2), 38.0 ($(CH_3)_2$-CCH_2CH_3), 63.6 (NH_3CHCO_2H), 174.7 (CO_2H). *m/z* (CI, NH,): 146 [(M-Cl)", 100%] and 100 (M-Cl $-H_2O$ -CO, 20).

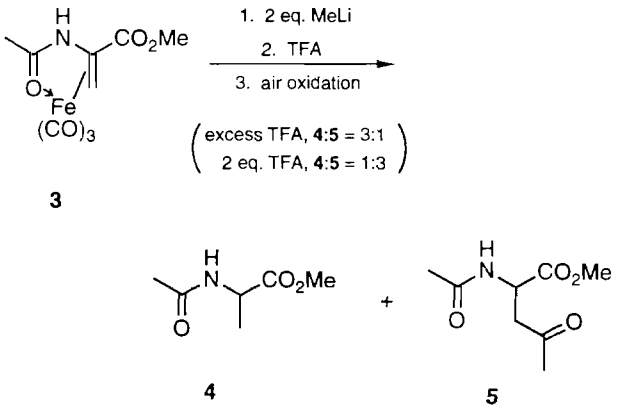
2-Amino-3,3-dimethylhexanoic acid hydrochloride salt (15)

A mixture of methyl 2-acetamido-3,3-dimethylhexanoate (10) (0.029 g, 0.109 mmol) and 6 N HCl (1.5 cm^3) was heated to reflux for 4 h and then allowed to cool to room temperature. The reaction mixture was washed with $CHCl_3$ (2X 1 cm') and the aqueous layer was separated. Removal of the water under reduced pressure gave a pale yellow solid from which white crystals (0.019 g, 73%) of the title compound 15 were separated by addition of ethyl acetate, m.p. 202 °C (decomp.) (found 160.1340; calc. for $C_8H_{18}NO_2$ 160.1338). ν_{max}(nujol) (cm-'): 1730. δ_H (270 MHz, D_2O): 0.87 (3H, t, *J* 6, CH_3CH_2), 1.03 (3H, s, $(CH_3)_2CCH_2$-CH_2CH_3), 1.04 (3H, s, $(CH_3)_2CCH_2CH_2CH_3$), 1.34 (4H, m, $(CH_3)_2CCH_2CH_2CH_3$), 3.80 (1H, s, NH_3CHCO_2H). δ_C (125.8 mHz, D_2O): 16.7 ($CH_3CH_2CH_2$), 19.1 ($CH_3CH_2CH_2$), 25.6 and 25.9 ($(CH_3)_2CCH_2CH_2CH_3$), 38.0 ($(CH_3)_2CCH_2CH_2CH_3$), 43.5 ($CH_3CH_2CH_2$), 63.9 (NH_3CHCO_2H), 174.5 (CO_2H). *m/z* (CI, NH,): 160 [(M-Cl)' , 100%], 114 ($M-Cl-H_2O-CO$, 22).

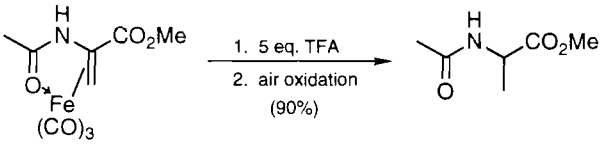
Results and discussion

(Methyl 2-acetamidoacrylate)tricarbonyliron(0) (3) was prepared in two steps from commercially available 2-acetamidoacrylic acid and diiron nonacarbonyl as follows. First the acid was converted into its methyl ester by treatment with K_2CO_3–MeI [8] (89% yield), and then the ester was reacted with $Fe_2(CO)_9$ to give 3 as an air-stable crystalline solid (98% yield).

The first reaction of complex **3** that we examined was its reaction with methyllithium. Thus complex **3** was stirred with 2 equiv. of methyllithium in THF at −78 °C for 40 min and then an excess of trifluoroacetic acid was added. Air oxidation and work-up gave a yellow oil which, from its ^{1}H NMR spectrum, contained essentially two products in a 3:1 ratio. Isolation of the major product by chromatography gave a pure white solid which was identified as methyl *N*-acetylalaninate (**4**) by comparison of its m.p. and ^{1}H NMR spectrum with literature values [11] and examination of its IR, ^{13}C NMR and mass spectra. The minor product was a light yellow oil and was contaminated with **4**. Nevertheless the compound could be identified as methyl 2-acetamido-4-oxopentanoate (**5**) from its ^{1}H NMR spectrum.



Whilst we were pleased to observe the formation of the acylated product **5**, the predominance of methyl *N*-acetylalaninate (**4**) in the product mixture was clearly a problem. It was postulated that the *N*-acetylalaninate **4** was formed from the reaction between complex **3** and the trifluoroacetic acid used to quench the reaction mixture. This hypothesis was tested by stirring complex **3** with 5 equiv. of trifluoroacetic acid in THF at −78 °C for 5 min and then at room temperature for 2 h. Air oxidation and work-up led to the isolation of a 90% yield of the *N*-acetylalaninate **4**. When the reaction was carried out in the same way but using trifluoracetic acid-d in place of trifluoroacetic acid, the reduced product was obtained in 81% isolated yield. Examination of the ^{1}H NMR and ^{2}H NMR spectra of the product revealed that deuterium had been incorporated at its α and β positions. The deuterium incorporation, calculated from the ^{1}H NMR spectrum, was 75% at the α position and 40% at the β position. Thus the methyl 2-acetamidoacrylate ligand is hydrogenated by protons and electrons derived from the trifluoroacetic acid and the iron(0), respectively. This is consistent with the observation that complexes of the type (alkene)-tetracarbonyliron(0) are readily decomposed by HCl or HBr to the corresponding alkane and Fe^{2+}; there is some evidence that this process proceeds via an iron alkyl intermediate [13].

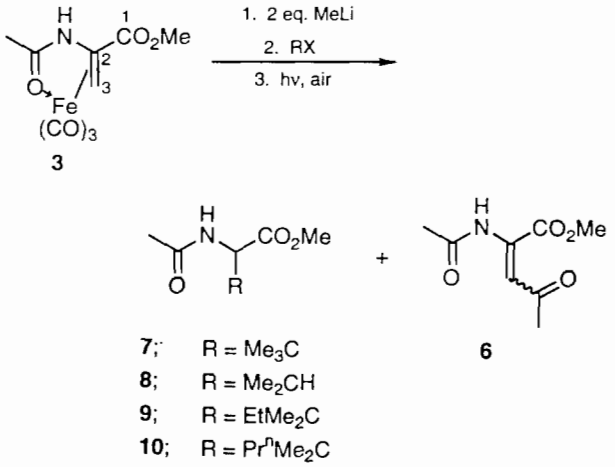


3 **4**

Once it had been established that the trifluoroacetic acid was producing the unwanted methyl *N*-acetylalaninate (**4**) in the acylation reaction, the addition of 2 equiv. of methyllithium to complex **3** was repeated but using only 2 equiv. of trifluoroacetic acid to quench the reaction. After air oxidation and work-up, a mixture of methyl 2-acetamido-4-oxopentanoate (**5**) and *N*-acetylalaninate (**4**) was obtained in a much improved ratio of 3:1 (measured from the ^{1}H NMR spectrum of the crude product).

Whilst quenching the methyllithium addition with only 2 equiv. of trifluoroacetic acid had led to a reversal of the product ratio in favour of the required acylated compound **5**, the presence of methyl *N*-acetylalaninate (**4**) continued to hamper purification of **5**. Thus several other quenches were investigated including 2-bromo-2-methylpropane. In this case air oxidation and work-up gave a yellow oil, the ^{1}H NMR of which revealed that it contained approximately equal amounts of two compounds, neither of which was the acylated derivative **5** or the reduced product **4**. Both new products were isolated by column chromatography. The first to be identified had a ^{1}H NMR spectrum similar to that obtained for methyl 2-acetamidoacrylate. The spectrum of the new compound contained only one olefinic proton, however, and an extra three-proton singlet in the region typical of acetyl groups. The compound was identified as the unsaturated acylated compound methyl 2-acetamido-4-oxopent-2-enoate (**6**) and characterised by recording its m.p., IR, ^{13}C NMR and mass spectra. The accurate mass determination was also in agreement with the proposed structure. (It should be noted that only one geometric isomer of compound **6** was formed in the reaction, but n.O.e. experiments designed to determine its structure were inconclusive.) The second compound produced spectroscopic data which were initially very confusing. The IR spectrum contained an NH absorption at 3437 cm^{-1} and two absorptions at 1733 and 1676 cm^{-1} corresponding to the ester and the acetamido carbonyls, respectively. The ^{1}H NMR spectrum contained, in addition to the easily identifiable resonances associated with the ester and acetamido groups, a nine-proton singlet at δ 0.97 ppm which seemed to be due to a tert-butyl group and a one-proton doublet at δ 4.49 ppm which is in the region

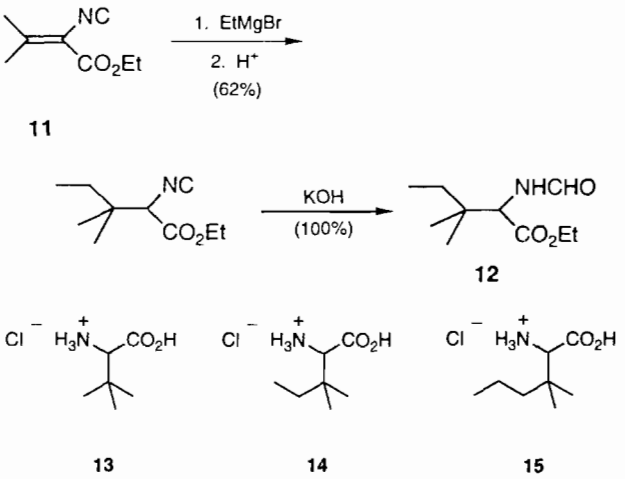
characteristic of the CH of α-substituted α-amino acids. The ^{13}C NMR spectrum contained a very intense resonance at δ 26.5 ppm and a very small signal at δ 34.7 ppm which supported the hypothesis that a tert-butyl group was present in the product, and a signal at δ 59.9 ppm that could be attributed to a methine carbon α to the ester and to the amide. The base peak of the CI mass spectrum of the product occurred at *m/z* 188. From these data, an accurate mass determination, and correlation of the ^{13}C NMR data with those obtained from Mosher's amide of the methyl ester of tert-leucine [12], it was concluded that the second product was the entirely unexpected compound methyl *N*-acetyl-tert-leucinate (**7**).



Whilst the formation of the unsaturated acylated compound **6** was relatively consistent with the pattern of reactivity observed between complex **3** and methyllithium using TFA as the quenching reagent, the formation of compound **7** in which C-3 of the complex appeared to have been replaced by the tert-butyl group of the bromoalkane, was surprising and unprecedented. It was thus decided to investigate the reaction which led to the formation of compound **7** in more detail.

Preliminary investigations into the effect that reaction conditions had on the crude yield and the product ratio led to the irradiation of the reaction mixture during the air oxidation step with a 100 W household bulb, as this gave a better ratio of methyl *N*-acetyl-tert-leucinate (**7**) to methyl 2-acetamido-4-oxopent-2-enoate (**6**). Once this had been established, the effect of altering the halide of the haloalkane used to 'quench' the reaction mixture was investigated. These experiments showed that Me_3CI and Me_3CBr produced compound **7** much more effectively than Me_3CCl (Table 1, entries 1–3). Next the effect of the degree of substitution of the haloalkane was examined. These experiments revealed that 'alkylation' of complex **3** was dramatically reduced on moving to a secondary haloalkane (small amounts of protected valine were formed using Me_2HCI and Me_2HCBr, Table 1, entries 5 and 6), and that 'alkylation' did not occur at all when primary haloalkanes were used (Table 1, entries 7 and 8). Thus our attention refocussed on tertiary haloalkanes. Experiments using $EtMe_2CI$ and Pr^nMe_2CI (formed by addition of HI [9] to commercially available 2-methylbut-1-ene and 2-methylpent-1-ene in 68 and 81% yield, respectively) demonstrated that these iodoalkanes reacted in an analogous manner to Me_3CI (Table 1, entries 9 and 11, cf. entry 1).

It was noted at this point that standard general routes to α-amino acids are not easily applied to the synthesis of β,β,β-trialkyl α-amino acids and most known routes to tert-leucine [12, 14, 15] cannot or have not been extended to other β,β,β-trialkyl α-amino acids. (One significant exception involves the addition of Grignard reagents to β-substituted ethyl α-isocyanoacrylates [15] which has been used for example to convert the β,β-dimethylacrylate (**11**) to the *N*-formyl derivative **12** in 62% yield.) Therefore, the reactions between complex **3** and the tertiary iodoalkanes Me_3CI, $EtMe_2CI$ and Pr^nMe_2CI were repeated and pure samples of the protected α-amino acids **7**, **9** and **10** were isolated and fully characterised (Table 1, entries 4, 10 and 11). Subsequent hydrolysis of **7**, **9** and **10** (6 M HCl, reflux, 3–4 h) gave the hydrochloride salts of tert-leucine **13** and the new α-amino acids **14** and **15** all of which were purified and fully characterised. (The salts were obtained in yields of 65, 86 and 73%, respectively.)



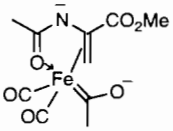
Any mechanistic interpretation of the results described above must necessarily be tentative at this stage. It is postulated, however, that addition of the two equivalents of methyllithium gives a dianion that may be represented by structure **16**. A '[2+2]' cycloaddition between the carbon–carbon and the iron–carbon double bonds of **16** would give ferracyclobutane **17**, a potential key intermediate in this chemistry. This may break down either by anion assisted cleavage of its two

TABLE 1. Formation of protected α-amino acids **7–10** from complex **3** and haloalkanes

Entry	Haloalkane (RX)	Complex **3** (mmol)	Yield of crude product (mg)	Components of crude product and ratio	Isolated product (% yield based on **3**)
1	Me_3CI	0.4	44–55	**7**:**6**, 75:25	
2	Me_3CBr	0.4	48	**7**:**6**, 60:40	
3	Me_3CCl	0.4	8	[a]	
4	Me_3CI	1.0	99	**7**:**6**, 75:25	**7** (40)
5	Me_2HCI	0.4	31	**8**:**6**, 40:60	
6	Me_2HCBr	0.4	18	**8**:**6**, 40:60	
7	MeH_2CI	0.4	25	**6**[b]	
8	MeH_2CBr	0.4	7	**6**[b]	
9	$EtMe_2CI$	0.4	40	**9**:**6**, 80:20	
10	$EtMe_2CI$	1.0	92	**9**:**6**, 75:25	**9** (30)
11	Pr^nMe_2CI	0.4	45	**10**:**6**, 65:35	
12	Pr^nMe_2CI	1.0	70	**10**:**6**, 75:25	**10** (20)

[a]Complex mixture obtained containing compounds **7** and **6** and unidentified products. [b]Complex mixture obtained containing compound **6** and unidentified products.

iron–carbon σ bonds to produce 2-acetamido-4-oxopent-2-enoate (**6**), or by collapse of the ferracyclobutane moiety to give the carbene **18**, a possible precursor of the 'alkylated' products **7–10**, and acetone. Experiments to probe this system further are underway.



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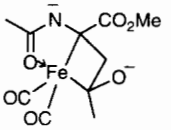

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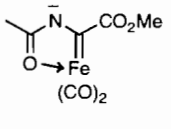

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