Surprising Reactivity of (Methyl 2-Acetamidoacrylate)tricarbonyliron(0) leading to the Synthesis of β,β,β-Trialkyl α-Amino Acids

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Addition of methyllithium followed by tertiary haloalkanes to readily available and air-stable (methyl 2-acetamidoacrylate)tricarbonyliron(0) **1**, gives protected β,β,β-trialkyl α-amino acids which are hydrolysed to give *tert*-leucine **10** and the new α-amino acids 2-amino-3,3-dimethylpentanoic acid **11** and 2-amino-3,3-dimethylhexanoic acid **12**.

Although the synthesis of (methyl 2-acetamidoacrylate)tricarbonyliron(0) **1** was reported over ten years ago,[1] the reactivity of this transition metal complex, which may be regarded as a potential precursor to a wide range of α-amino acids, has been left unexplored to date. We recently initiated a research programme designed to investigate the chemistry of complex **1**, and we report herein the results of some of our first experiments. These have revealed, to our surprise, that carbon atom C-3 in complex **1** may be *replaced* by alkyl groups derived from haloalkanes. As will be illustrated below, the reaction is most efficient when *tertiary* haloalkanes are used. These haloalkanes generate highly hindered products which after deprotection yield exhaustively β-branched α-amino acids such as *tert*-leucine **10**, 2-amino-3,3-dimethylpentanoic acid **11** and 2-amino-3.3-dimethylhexanoic acid **12**. It is of note that the resulting two-step modification of dehydroalanine leading to β,β,β-trialkyl substituted α-amino acids is complementary to most existing modification and *de novo* approaches to α-amino acids.[2]

(Methyl 2-acetamidoacrylate)tricarbonyliron(0) **1** was readily prepared from commercially available 2-acetamidoacrylic acid **2** and diiron nonacarbonyl. Thus, the acid **2** was converted into its methyl ester **3** in 89% yield by treatment with K_2CO_3–MeI,[3] and the ester **3** was subsequently reacted with $Fe_2(CO)_9$ to give **1** as an air-stable crystalline solid in 88–98% yield.†

During initial studies on complex **1**, we found that addition of alkyllithium reagents to complex **1** followed by treatment with a proton source gave protected γ-keto-α-amino acids such as **4**, presumably *via* alkyllithium attack on a metal–carbonyl ligand and acyl group transfer to C-3 of the organic ligand.‡ As part of a series of experiments designed to probe and optimise this reaction, the effects of several different proton quenches were examined. Thus, the following experiment was carried out in order to test the efficiency of

† Conversion of methyl 2-acetamidoacrylate **3** into its tricarbonyliron(0) complex **1** was carried out using a modification of the literature method.[1] In a typical reaction, $Fe_2(CO)_9$ (15.2 g, 41.8 mmol) was treated with methyl 2-acetamidoacrylate **3** (2.70 g, 18.88 mmol) in Et_2O (150 cm^3) for 14 h at 30 °C. The resulting brown mixture was filtered through a short plug of alumina and the yellow ethereal solution produced was concentrated to dryness to give (methyl 2-acetamidoacrylate)tricarbonyliron(0) **1** as a yellow air-stable microcrystalline solid (4.70 g, 88%).

‡ Acylation of complex **1** and the production of γ-keto-α-amino acids will be reported elsewhere. For related reactions see ref. 4.

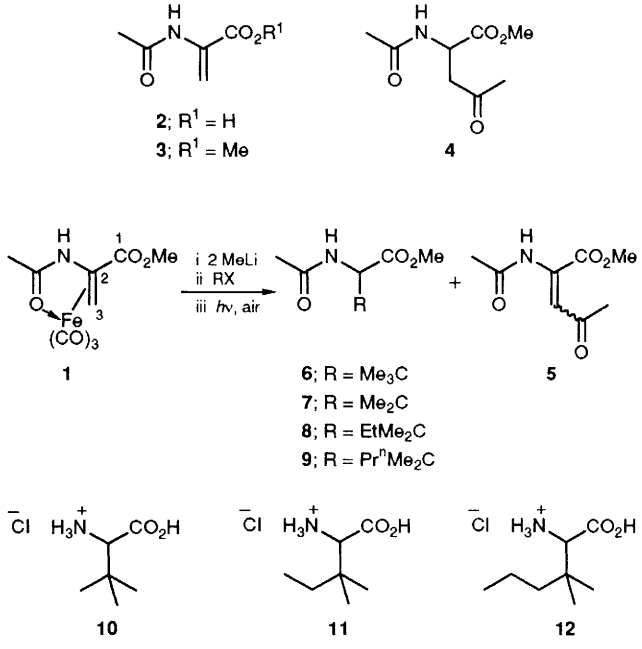
Table 1 Formation of protected α-amino acids **6–9** from complex **1** and haloalkanes[a]

Entry	Haloalkane (RX)	Complex **1**/mmol	Yield of crude product/mg	Components of crude product and ratio	Isolated product (% yield based on **1**)
1	Me_3CI	0.4	44–55	**6**:**5**, 75:25	
2	Me_3CBr	0.4	48	**6**:**5**, 60:40	
3	Me_3CCl	0.4	8	[b]	
4	Me_3CI	1.0	99	**6**:**5**, 72:25	**6** (40)
5	Me_2HCI	0.4	31	**7**:**5**, 40:60	
6	Me_2HCBr	0.4	18	**7**:**5**, 40:60	
7	MeH_2CI	0.4	25	**5**[c]	
8	MeH_2CBr	0.4	7	**5**[c]	
9	$EtMe_2CI$	0.4	40	**8**:**5**, 80:20	
10	$EtMe_2CI$	1.0	92	**8**:**5**, 75:25	**8** (30)
11	Pr^nMe_2CI	0.4	45	**9**:**5**, 65:35	
12	Pr^nMe_2CI	1.0	70	**9**:**5**, 75:25	**9** (20)

[a] Typical reaction conditions are illustrated by the experimental procedure used for entry 4; methyllithium (1.43 cm^3, 1.4 mol dm^{-3}, 2.00 mmol) was added to an orange–yellow solution of complex **1** (0.283 g, 1.00 mmol) in dry THF (25 cm^3) at −78 °C under a nitrogen atmosphere. The mixture was stirred for 40 min at −78 °C and then treated with Me_3CI (1.2 cm^3, 1.85 g, 10 mmol) and stirred for a further 5 min at −78 °C. The reaction mixture was then allowed to warm to room temp., 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 resulting 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 (*ca.* 300 cm^3)] and subsequent solvent removal gave a pale-yellow oil which was examined by ^1H NMR spectroscopy (see Table 1). The crude product mixture was chromatographed [SiO_2; dichloromethane–ethyl acetate–light petroleum (40–60 °C), 4:7:9] and compound **6** isolated (0.074 g, 40%) as a white crystalline solid. [b] Complex mixture obtained containing compounds **6** and **5** and other unidentified products. [c] Complex mixture obtained containing compound **5** and other unidentified products.

2-bromo-2-methylpropane (*tert*-butyl bromide) as a proton quench. An orange–yellow solution of complex **1** in tetrahydrofuran (THF) was treated with two equivalents of methyllithium at −78 °C under a nitrogen atmosphere and stirred for 40 minutes. After quenching with Me_3CBr at −78 °C, the reaction mixture was stirred for a further 2 hours during which time it was allowed to warm to room temperature. Removal of the THF gave a dark residue which was suspended in diethyl ether and stirred under air overnight. Subsequent filtration through alumina and solvent evaporation gave a pale-yellow oil which was examined by ^1H NMR spectroscopy. The spectrum revealed that the crude product contained approximately equal amounts of two compounds, neither of which was the expected γ-keto-α-amino acid **4**. Column chromatography led to the isolation of pure samples of the two compounds and these were identified as the protected α-amino acids **5** and **6** on the basis of their IR, ^1H NMR, ^{13}C NMR spectra and their mass spectroscopic data.§

Whilst the formation of the unsaturated acylated compound **5** was relatively consistent with the anticipated reactivity between complex **1** and methyllithium, the formation of compound **6**, in which C-3 of the complex appears to have been replaced by the *tert*-butyl group of the bromoalkane, was highly surprising and unprecedented. We thus decided to investigate the formation of compound **6** and related compounds in more detail. Initially the effect of altering the halide was investigated. These experiments showed that Me_3CI and Me_3CBr produced compound **6** 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 **1** 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



§ *Spectroscopic data* for compounds **5** and **6**. Compound **5**: ν_{max} ($CHCl_3$)/cm^{-1} 3414w (NH), 1741s (C=O/ester), 1718s (C=O/ketone), 1665s (C=O/amide) and 1600s (C=C); δ_H (270 MHz, $CDCl_3$) 2.18 (3 H, s, CH_3CONH or CH_3COCH=C), 2.26 (3 H, s, CH_3CONH or CH_3COCH=C), 3.86 (3 H, s, CO_2CH_3) and 5.75 (1 H, s, CH_3COCH=C); δ_C (125.8 MHz, $CDCl_3$) 23.5 (CH_3CONH), 31.1 (CH_3COCH=C), 53.0 (CO_2CH_3), 106.5 (CH_3COCH=C), 142.3 (CH_3COCH=C), 164.5 (CO_2CH_3), 168.6 (CH_3CONH) and 200.7 (CH_3COCH=C); *m/z* (CI/NH_3) 186 (MH^+, 100%) and 144 (100, $MH^+ - CH_2CO$); (Found: 186.0770. $C_8H_{11}NO_4$ requires 186.0766). (The stereochemistry of the single isomer of **5** formed in all the reported reactions has yet to be determined.) Compound **6**: ν_{max} ($CHCl_3$)/cm^{-1} 3437m (NH), 1733s (C=O/ester) and 1676s (C=O/amide); δ_H (270 MHz, $CDCl_3$) 0.97 [9 H, s, $C(CH_3)_3$], 2.04 (3 H, s, CH_3CONH), 3.73 (3 H, s, CO_2CH_3), 4.49 (1 H, d, *J* 9.5 Hz, $CHBu^t$) and 5.97 (1 H, br s, NH); δ_C (125.8 MHz, $CDCl_3$) 23.4 (CH_3CONH), 26.5 {26.6} [$C(CH_3)_3$], 34.7 {34.9} [$C(CH_3)_3$], 51.8 {51.8} (CO_2CH_3), 59.9 {60.4} ($CHBu^t$), 169.7 (CH_3CONH) and 1762.3 {171.4} (CO_2CH_3) (figures in parentheses { } were obtained from the spectrum of the Mosher's amide of the methyl ester of *tert*-leucine[5]); *m/z* (CI/NH_3) 188 (MH^+, 100%); (Found: 188.1287. $C_9H_{18}NO_3$ requires 188.1287).

¶ All experiments reported in Table 1 were carried out as described in the text except that during the air oxidation step the reaction mixture was irradiated with a 100 W household light bulb in order to optimise iron–carbon bond cleavage. (See Table 1, footnote *a* for full experimental details of a typical procedure.)

'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[6] to commercially available 2-methylbut-1-ene and 2-methylpent-1-ene in 65 and 81% yield, respectively) demonstrated that these iodoalkanes reacted in an analogous manner to Me_3CI (Table 1, entries 9 and 11, compare with entry 1).

As standard general routes to α-amino acids are not easily applied to the synthesis of β,β,β-trialkyl α-amino acids, and as most known routes to *tert*-leucine[5,7,8] cannot be or have not been extended to other β,β,β-trialkyl α-amino acids,‖ the reactions between complex **1** and the tertiary iodoalkanes Me_3CI, $EtMe_2CI$ and Pr^nMe_2CI were repeated and pure samples of the protected α-amino acids **6**, **8**** and **9**** were isolated (Table 1, entries 4, 10 and 11). Subsequent hydrolysis of **6**, **8** and **9** (6 mol dm^{-3} HCl, reflux, 3–4 h) gave the hydrochloride salts of *tert*-leucine **10** and the new α-amino acids **11**** and **12**** in 65, 86 and 73% yield, respectively.

Finally, studies designed to determine the reaction pathway of the unprecedented organometallic transformation reported above, and to extend the α-amino acid synthesis to the production of optically pure β,β,β-trialkyl α-amino acids are currently in progress.

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‖ Although most reported routes to *tert*-leucine cannot be easily 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.[8] It is of note that this versatile route has been used to synthesise the *N*-formyl derivative of **11**.

** Compounds, which to the best of our knowledge have not been reported previously, gave IR, ^1H NMR, ^{13}C NMR and low resolution mass spectroscopic data consistent with their proposed structures. Satisfactory microanalytical data and/or high resolution MS data were also obtained for all new compounds.

References

1 A. de Cian, R. Weiss, J.-P. Haudegond, Y. Chauvin and D. Commereuc, *J. Organomet. Chem.*, 1980, **187**, 73.
2 G. C. Barrett, *Chemistry and Biochemistry of the Amino Acids*, Chapman and Hall, London, 1985; Tetrahedron Symposium-in-Print, No. 33, ed. Martin J. O'Donnell, *α-Amino Acid Synthesis*, *Tetrahedron*, 1988, **44**, 5253; R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, Pergamon Press, Oxford, 1989.
3 M. P. Bueno, C. Cativiela, C. Finol, J. A. Mayoral and C. Jaime, *Can. J. Chem.*, 1987, **65**, 2182.
4 D. Rakshit and S. E. Thomas, *J. Organomet. Chem.*, 1987, **333**, C3; T. N. Danks, D. Rakshit and S. E. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2091; A. Pouilhès and S. E. Thomas, *Tetrahedron Lett.*, 1989, **30**, 2285.
5 D. A. Evans, T. C. Britton, R. L. Dorow and J. F. Dellaria, *Tetrahedron*, 1988, **44**, 5525.
6 D. Landini and F. Rolla, *J. Org. Chem.*, 1980, **45**, 3527.
7 F. Knoop and G. Landmann, *Z. Physiol. Chem.*, 1914, **89**, 157; E. Abderhalden, W. Faust and E. Haase, *Z. Physiol. Chem.* 1934, **228**, 187; J. Pospisek and K. Blaha, *Collect. Czech. Chem. Commun.*, 1977, **42**, 1069; C. Hoffman, R. S. Tanke and M. J. Miller, *J. Org. Chem.*, 1989, **54**, 3750; T. Kolasa, S. K. Sharma and M. J. Miller, *Tetrahedron*, 1988, **44**, 5431; T. Bretschneider, W. Miltz, P. Münster and W. Steglich, *Tetrahedron*, 1988, **44**, 5403; P. Münster and W. Steglich, *Synthesis*, 1987, 223; T. Miyazawa, T. Nagai and T. Yamada, *Mem. Konan Univ., Sci. Ser.*, **23**, 51 (Chem. Abstr., 1980, **92**, 94681x); J. C. Speelman, A. G. Talma and R. M. Kellogg, *J. Org. Chem.*, 1989, **30**, 1055; J. L. Fauchere and C. Petermann, *Helv. Chim. Acta*, 1980, **63**, 824; H. Kunz, W. Pfrengle and W. Sager, *Tetrahedron Lett.*, 1989, **30**, 4109; H. Kunz and W. Pfrengle, *Tetrahedron*, 1988, **44**, 5487; G. C. Barrett and P. R. Cousins, *J. Chem. Soc., Perkin Trans. 1*, 1975, 2313; S. Takano, M. Akiyama and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1985, 770.
8 U. Schöllkopf and R. Meyer, *Angew. Chem.*, 1975, **87**, 624; *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 629.