A New Synthesis of α-Amino-acids by the Reaction of Grignard Reagents with Ethyl *N*-Trichloroethylidenecarbamate

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The reactions of methyl-, ethyl-, n-propyl-, n-butyl-, allyl-, and benzyl-magnesium halides with ethyl *N*-trichloroethylidenecarbamate (1) gave 1-substituted ethyl 2,2,2-trichloroethylcarbamates, which afforded α-amino-acids on hydrolysis and decarboxylation. By this method DL-alanine and DL-norleucine were obtained in 53 and 60% overall yields, respectively. When branched alkyl Grignard reagents such as isopropyl-, isobutyl- and s-butylmagnesium bromide were used, attack on the imino-group was hindered by the trichloromethyl group and only reduction occurred to give ethyl 3,3-dichloro-1-ethoxycarbonyl-4-trichloromethylazetidin-2-ylcarbamate (4) and ethyl [2,2,2-trichloro-1-(*N*-ethoxycarbonyl-2,2,2-trichloroethylamino)ethyl]carbamate (5).

TREATMENT of benzyl benzyliminoacetate, which contains the N=C–C=O system, with Grignard reagents is reported [1,2] to give both *C*- and *N*-alkylation products. This result is as expected since alkylation of the C=N system by Grignard reagents generally occurs on the carbon atom (owing to the difference in the electronegativities of C and N), but αβ-unsaturated carbonyl compounds usually give Michael addition products (by attack on N in this case). The C=N–C=O system would therefore be expected to give only Michael addition products. Indeed, the alkylidenecarbamate (1) is known to undergo Michael addition with water, alcohols, and amines to give α-amino-alchohols, α-amino-ethers, and *gem*-diamines.[3] We report here the reaction of the

[1] J-C. Fiaud and H. B. Kagan, *Tetrahedron Letters*, 1970, 1813.

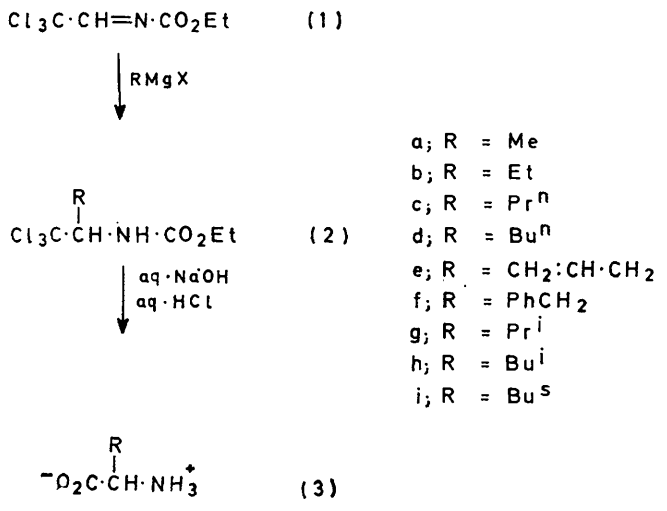
[2] J-C. Fiaud and H. B. Kagan, *Tetrahedron Letters*, 1971, 1019.

[3] H. Ulrich, B. Tucker, and A.-R. Sayigh, *J. Org. Chem.*, 1968, **33**, 2887.

carbamate (1) with Grignard reagents to give *C*-alkylation products (2), hydrolysis and decarboxylation of which gives α-amino-acids.

RESULTS AND DISCUSSION

This method for synthesis of α-amino-acids is summarised in Scheme 1. The reactions of methyl-, ethyl-,



SCHEME 1

n-propyl-, n-butyl-, allyl-, and benzyl-magnesium halides with the carbamate (1) proceeded readily to afford the Michael adducts (2) in 43—77% yields (see Table); no

Reactions of the carbamate (1) with Grignard reagents RMgX

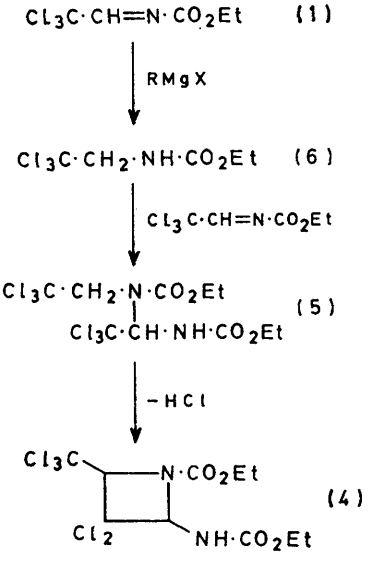
R	Yield (%) (2)	(4)	(5)
Me	56		0
Et	43		0
Pr^n	67	15	0
Bu^n	77	4.8	0
CH_2:CH·CH_2	37	41	0
$PhCH_2$	15	13	13
Pr^i	0	30	45
Bu^i	0	20	66
Bu^s	0		

products of attack on the carbonyl group were observed. The products (2) were identified by elemental analysis and i.r. and n.m.r. spectra. The azetidine (4) was obtained as a by-product.

However, reactions of the branched alkyl Grignard reagents isopropyl-, isobutyl-, and s-butyl-magnesium bromide with (1) did not give the corresponding adducts (2), but only the reduction products (4) and (5). Thus attack of bulky Grignard reagents on the C=N bond of (1) appears to be hindered by the trichloromethyl group. A suggested route to the products (4) and (5) is shown in Scheme 2.

The addition products (2) were hydrolysed and decarboxylated completely by stirring in aqueous 10% sodium hydroxide, and then refluxing in 2N-hydrochloric acid. The resulting crude α-amino-acids were purified in the usual manner, and identified by comparison (i.r. spectrum and paper and thin-layer chromatography) with authentic samples. DL-Alanine and DL-norleucine were obtained in 94 and 79% yields, respectively. Similar treatment of the adduct (2e) gave DL-threonine.

The hydrolysis and decarboxylation conditions are mild enough for retention of optical activity.[4] It should therefore be possible to introduce an optically active substituent at the α-position of an α-amino-acid by use of a reagent such as the imine formed from chloral and (−)-menthyl carbamate.



SCHEME 2

EXPERIMENTAL

Ethyl N-trichloroethylidenecarbamate (1), prepared from commercially available chloral and ethyl carbamate by the method of Ulrich,[3] had b.p. 74 °C at 1 mmHg.

Reactions of the Carbamate (1) *with Grignard Reagents.—General procedure.* To a stirred suspension of the Grignard reagent, freshly prepared from magnesium (0.01 g atom) and alkyl halide (0.01 mol) in dry ether (20 ml), was added dropwise the carbamate (1) (0.01 mol) in dry ether (10 ml) at 0 °C under nitrogen. The mixture was stirred at room temperature overnight. After hydrolysis with water, the organic layer was separated, dried ($MgSO_4$), and evaporated *in vacuo*. The yellow liquid products were purified by column chromatography on silica gel, and recrystallized from n-hexane.

Ethyl N-(2,2,2-*trichloro*-1-*methylethyl*)*carbamate* (2a), from (1) and methylmagnesium iodide, had m.p. 55—57 °C; $\nu_{max.}$ (KBr) 3 350, 1 690, 1 550, 1 260, and 800—770 cm^{-1}; δ ($CDCl_3$) 5.40—4.25 (2 H, m), 4.14 (2 H, q, *J* 7.2 Hz), 1.46 (3 H, d, *J* 6.6 Hz), and 1.27 (3H, t, *J* 7.2 Hz) (Found: C, 30.9; H 4.3; N, 5.9. $C_6H_{10}Cl_3NO_2$ requires C, 30.7; H, 4.25; N, 5.95%).

Ethyl N-(1-*trichloromethylpropyl*)*carbamate* (2b), from (1) and ethylmagnesium bromide, had m.p. 60—61 °C; $\nu_{max.}$ (KBr) 3 350, 1 695, 1 530, 1 270, and 820—780 cm^{-1}; δ ($CDCl_3$) 5.20—3.85 (2 H, m), 4.18 (2 H, q, *J* 7.2 Hz), 2.50—1.20 (5 H, m), and 1.26 (3 H, t, *J* 7.2 Hz) (Found: C, 33.6; H, 4.65; N, 5.5. $C_7H_{12}Cl_3NO_2$ requires C, 33.85; H, 4.85; N, 5.65%).

Ethyl N-(1-*trichloromethylbutyl*)*carbamate* (2c) from (1) and

[4] K. Matsumoto and K. Harada, *J. Org. Chem.*, 1966, **31**, 1956.

n-propylmagnesium bromide, had m.p. 63—64 °C; $\nu_{max.}$ (KBr) 3 350, 1 700, 1 550, 1 270, and 805—750 cm^{-1}; δ ($CDCl_3$) 5.30—3.93 (2 H, m), 4.18 (2 H, q, *J* 7.2 Hz), 2.50—1.20 (7 H, m), and 1.28 (3 H, t, *J* 7.2 Hz) (Found: C, 36.2; H, 5.45; N, 5.4 $C_8H_{14}Cl_3NO_2$ requires C, 36.6; H, 5.35; N, 5.35%).

Ethyl N-(1-*trichloromethylpentyl*)*carbamate* (2d), from (1) and n-butylmagnesium bromide, had m.p. 66—66.5 °C; $\nu_{max.}$ (KBr) 3 300, 1 700, 1 550, 1 265, and 810—780 cm^{-1}; δ ($CDCl_3$) 4.95br (1 H, d, *J* 9.6 Hz), 4.70—3.90 (1 H, m), 4.13 (2 H, q, *J* 7.2 Hz), 1.27 (3 H, t, *J* 7.2 Hz), and 2.60—0.70 (9 H, m) (Found: C, 38.9; H, 5.8; N, 5.15. $C_9H_{16}Cl_3NO_2$ requires C, 39.1; H, 5.8; N, 5.05%).

Ethyl N-(1-*trichloromethylbut*-2-*enyl*)*carbamate* (2e), from (1) and allylmagnesium chloride, had m.p. 74 °C; $\nu_{max.}$ (KBr) 3 350, 1 705, 1 645, 1 550, 1 270, and 800—780 cm^{-1}; δ ($CDCl_3$) 6.30—4.80 (4 H, m), 4.80—3.60 (1 H, m), 4.18 (2 H, q, *J* 7.2 Hz), 3.30—1.90 (2 H, m), and 1.28 (3 H, t, *J* 7.2 Hz) (Found: C, 36.8; H, 4.6; N, 5.4. $C_7H_{10}Cl_3NO_2$ requires C, 36.9; H, 4.65; N, 5.35%).

Ethyl N-(α-*trichloromethylphenethyl*)*carbamate* (2f), from (1) and benzylmagnesium bromide, had b.p. 164 °C at 1 mmHg; $\nu_{max.}$ (film) 3 450, 3 350, 1 705, 1 240, and 820 cm^{-1}; δ ($CDCl_3$) 7.35 (5 H, s), 5.43br (2 H, s), 4.75 (2 H, s), 4.18 (2 H, q, *J* 7.2 Hz), and 1.29 (3 H, t, *J* 7.2 Hz) (Found: C, 43.3; H, 4.35; N, 4.35. $C_{12}H_{14}Cl_3NO_2$ requires C, 46.4; H, 4.55; N, 4.5%).

Ethyl 3,3-*dichloro*-1-*ethoxycarbonyl*-4-*trichloromethylazetidin*-2-*ylcarbamate* (4) had m.p. 96—97.5 °C; $\nu_{max.}$ (KBr) 3 350, 1 570, 1 250, 810, and 730—690 cm^{-1}; δ ($CDCl_3$) δ 6.71 (1 H, d, *J* 9.6 Hz), 6.47 (1 H, s), 5.80 (1 H, d, *J* 9.6 Hz), 4.39 (2 H, q, *J* 7.2 Hz), 4.23 (2 H, g, *J* 7.2 Hz), and 1.31 (4 H, t, *J* 7.2 Hz) (Found: C, 30.3; H, 3.4; N, 7.0. $C_{10}H_{13}Cl_5N_2O_4$ requires C, 29.85; H, 3.25; N, 6.95%).

Ethyl [2,2,2-*trichloro*-1-(N-*ethoxycarbonyl*-2,2,2-*trichloroethylamino*)*ethyl*]*carbamate* (5) had m.p. 74—75 °C; $\nu_{max.}$ (KBr) 3 450, 1 740, 1 705, 1 500, 1 220, and 820—770 cm^{-1}; δ ($CDCl_3$) 7.70—7.00br (1 H, s), 6.23br (1 H, d, *J* 9.6 Hz), 5.14 (1 H, d, *J* 16 Hz), 4.65—3.95 (5 H, m), 1.35 (3 H, t, *J* 7.2 Hz), and 1.29 (3 H, t, *J* 7.2 Hz) (Found: C, 27.4; H, 3.3; N, 6.45. $C_{10}H_{14}Cl_6N_2O_4$ requires C, 27.35; H, 3.2; N, 6.4%).

Hydrolysis and Decarboxylation of the Adducts (2).—To the adduct (2) (1.3 mmol) was added 10% sodium hydroxide in ethanol–water (1:2; 20 ml). The suspension was stirred at room temperature for 3 days, the resulting clear solution was acidified with 6N-hydrochloric acid and evaporated to dryness under reduced pressure. The residue was dissolved in 2N-hydrochloric acid (20 ml) and refluxed for 24 h in an oil-bath. Extraction with ether removed the unchanged starting materials and the aqueous solution was evaporated. The dried residue was desalted by the usual method [5] and applied to a Dowex 50 W-X8 column. Amino-acids were eluted with aqueous 3% ammonia. The amino-acid fraction was concentrated *in vacuo*. Samples recrystallized from alcohol were identified by comparison (paper and thin-layer chromatography and i.r. spectrum) with authentic materials.

[5/943 *Received*, 19*th May*, 1975]

[5] E. J. Corey, R. J. McCauooy, and H. S. Sachdev, *J. Amer. Chem. Soc.*, 1970, **92**, 2476.