Preparation of Azetidines from 1,3-Aminopropanols

Peter G. Sammes * and Steven Smith
Department of Organic Chemistry, The University, Leeds LS2 9JT

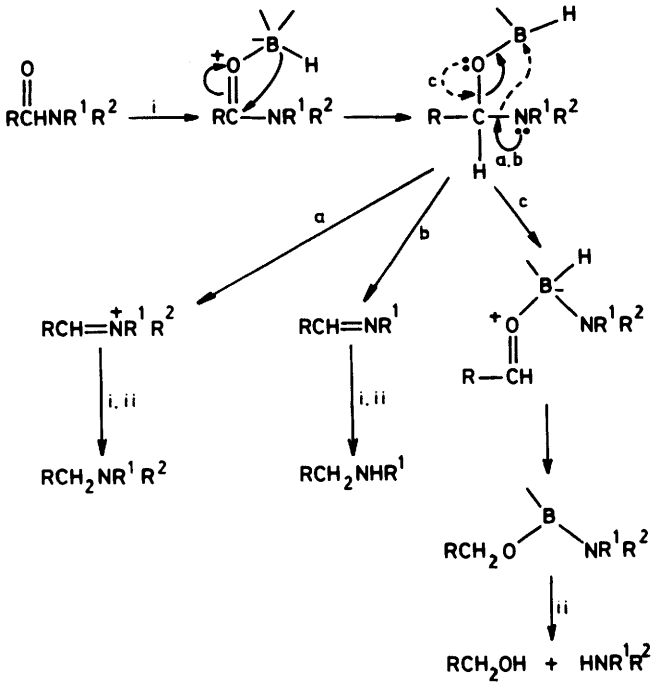
The preparation of 1,3-amino alcohols by the reduction of azetidin-2-ones with diborane is described. New methods for the cyclisation of the aminopropanols to the corresponding azetidines are reported; these methods centre on the use of a modified Mitsunobu reaction.

Relative to the aziridines, few studies on azetidines have been reported.[1] A possible reason for this difference is the difficulties associated with their preparation. Two main methods have been investigated, reduction of azetidin-2-ones and the cyclisation of 1,3-halogenopropylamines. Direct formation of azetidines by reduction of the more accessible azetidin-2-ones (β-lactams) is sometimes possible, for example, by using modified aluminium hydrides,[2] but such reagents tend to be indiscriminate, reducing other functional groups, such as esters.[3] For other reducing agents the product depends on whether the azetidinone is *N*-substituted or not. For example, lithium aluminium hydride, which reduces tertiary amides to amines,[4] gives amino propanols with *N*-substituted azetidinones[5] and azetidines with *N*-unsubstituted azetidinones.[6] Before our study the situation with the more selective reducing agent, diborane, was not so clear. There were reports that the diborane reduction of both *N*-unsubstituted azetidinones[7] and *N*-substituted azetidinones produces azetidines.[8] Subsequently we have shown the latter report to be incorrect, diborane giving only the amino alcohol on reduction of penicillins.[9]

Monocyclic azetidinones bearing an *N*-alkyl group also produce the amino propanol on diborane reduction.[7] In agreement with these results, the lactam (**1**), formed from the readily available lactam (**2**), afforded only the amino alcohol (**3**) on reduction with diborane. Similarly, the desthiopenicillin (**4**) gave only the amino alcohol (**5**). These results may be accommodated as shown in Scheme 1, the critical stage being the relative ease of cleavage of the C–O or C–N bond at the intermediate stage; C–O cleavage resulted in the formation of amine whilst C–N bond cleavage leads to the formation of the amino alcohols. The latter course is favoured for *N*-substituted azetidines.

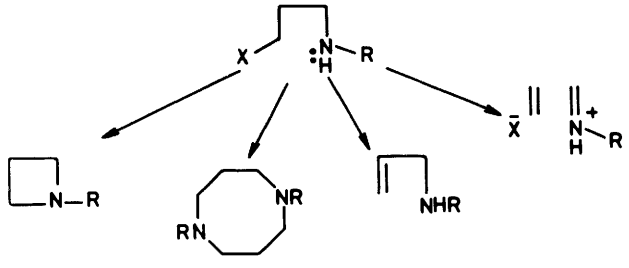
The alternative route to azetidines involves cyclisation of γ-substituted aminopropanes bearing a good leaving group such as halide, although in many cases poor yields are observed owing to competing reactions, such as elimination, dimerisation, and Grob fragmentation (Scheme 2).[1,10] The factors which affect the relative rates of these processes have been studied by Vaughan *et al.*[11] Since no reports have appeared on the use of the triphenylphosphine–diethyl azodicarboxylate system[13] for dehydration of 1,3-amino alcohols to azetidines, application of this method was examined.

Reaction of 3-*N*-benzylaminopropan-1-ol (**6**) with a small excess of triphenylphosphine and diethyl azodicarboxylate in benzene rapidily produced a less polar compound, identified as the substituted hydrazine derivative (**7**), characterised as its hydrogen oxalate salt. Presumably compound (**7**) is formed by attack of the hydrazide anion produced in the course of the reaction. The anion must be able to compete as a nucleophile against intramolecular amine group attack, especially since the latter involves formation of the strained four-membered ring (Scheme 3). The amino group is insufficiently acidic to transfer a proton to the hydrazide anion. It was argued that if the



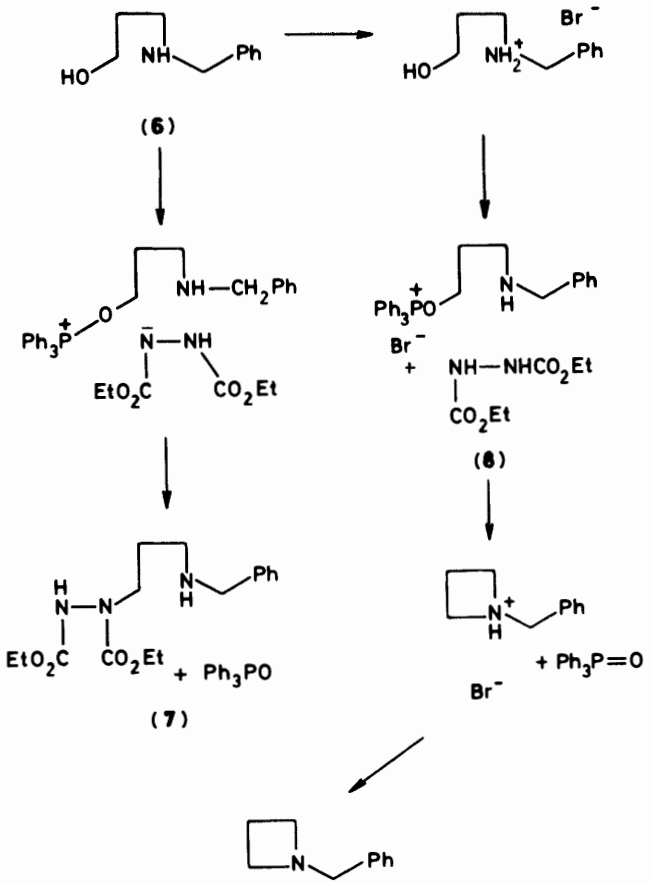
Reagents: i, B_2H_6; ii, H_3O^+

Scheme 1. Path a: tertiary amides; path b: secondary amides (R^2 = H); path c: tertiary amides with weak C–N bond or strained rings



Scheme 2.

hydrazide ion could be removed by protonation, to give the much less nucleophilic, neutral hydrazide species (**8**), intramolecular amine attack might be observed. Initially the reaction was repeated using the hydrobromide salt of the amino alcohol (**1**). Treatment with the triphenylphosphine–diethyl azodicarboxylate reagent in benzene, containing a little dimethylformamide to give a homogeneous solution, afforded a new product identified as the required *N*-benzylazetidine (**9**), with no formation of the hydrazide (**7**). In order to avoid problems with

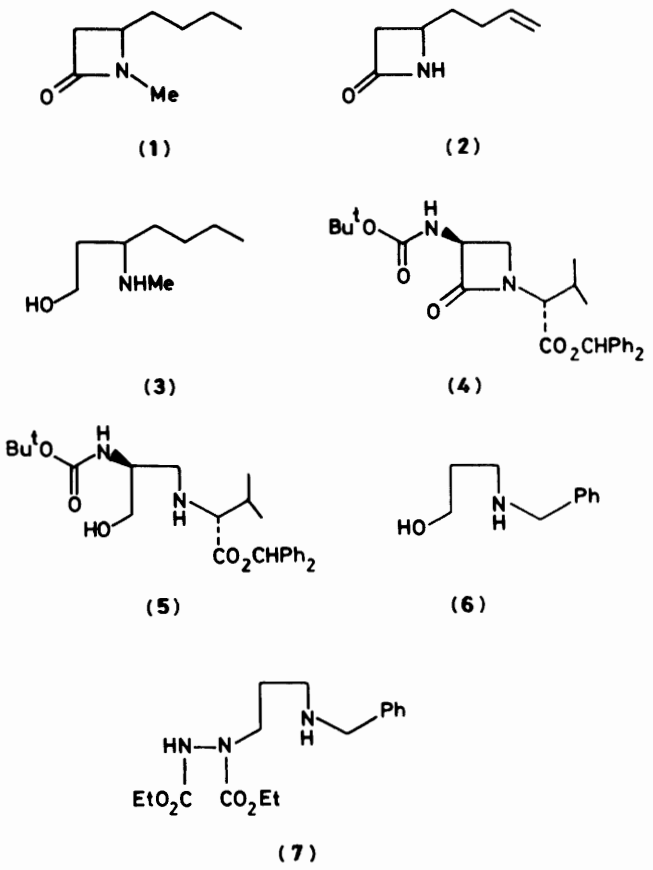


Scheme 3.

competitive displacement of the triphenylphosphine oxide by the counter anion, *e.g.* bromide anion, a non-nucleophilic acid salt was used. Thus with the fluoroborate salt of (**6**) again azetidine formation was observed. The salts of the amine (**6**) were very hygroscopic leading to contamination by water with the consequence that starting amino alcohol was recovered from the reaction mixture, even when using an excess of the dehydrating reagent. In order to avoid this problem certain Lewis acids could be employed, such as boron trifluoride–diethyl ether, added to the amino alcohol immediately prior to the addition of the triphenylphosphine and diethyl azodicarboxylate. However, in this case the rate of azetidine formation was considerably slower.[13]

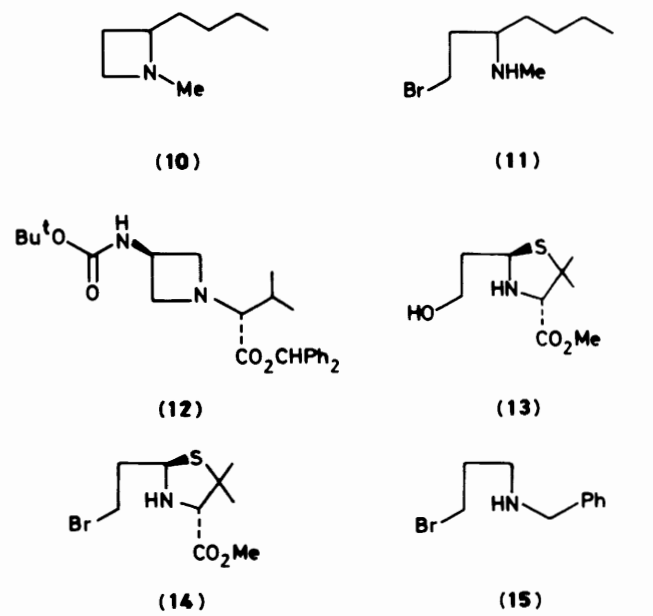
The success of these reactions prompted a further study of the alkylation of amines with alcohols using triphenylphosphine–diethyl azodicarboxylate. The results are summarised in the Table. All reactions were performed by adding diethyl azodicarboxylate to a solution of the amine (or its salt), alcohol and triphenylphosphine in dry solvents, usually at 0 °C using between 1 and 1.5 equiv. of the reagents. The yields reported are isolated yields and take no account of mechanical losses incurred in the isolation of the amine products, as a result, for example, of water solubility or volatility.

The results show that the reaction is not limited to intramolecular examples. However, in the case of benzylamine a mixture of products was obtained, perhaps indicating mono- and di-alkylation. Poor results were obtained with aniline hydrochloride, presumably owing to the reduced nucleophilicity



of aniline compared with aliphatic amines. Interestingly, the formation of *N*-benzylpiperidine was observed either with the hydrochloride or the free base. In the latter example the reaction must succeed owing to a faster rate of attack on the phosphonylated alcohol by the piperidine than by the hydrazide anion.

Some of the known methods[14] for cyclising amino alcohols were also tried. For example, 3-methylaminoheptan-1-ol (**3**) with triphenylphosphine and carbon tetrabromide in dry acetonitrile[14a] gave a good yield (78%) of the azetidine (**10**).



None of the amino alcohols (**3**) or the amino bromide (**11**) were detected in this reaction. Presumably, in this case, nitrogen participation, to form the azetidine, is efficient and excludes formation of the amino bromide. Control experiments with the amino bromide (**15**) showed that it does not cyclise to the azetidine (**9**) under these reaction conditions. This indicates that the formation of (**10**) from (**3**) does not proceed *via* intermediate formation of the amino bromide (**11**). A similar result was observed for the desthiopenicillin-derived alcohol (**5**), which gave, directly, the azetidine (**12**). These results contrast with that observed with the penicillin-derived alcohol (**13**).[13] In this case treatment with triphenylphosphine–carbon tetrabromide results in formation of the bromide (**14**) since the nitrogen of the thiazolidine group is a very weak nucleophile[13] and the reaction would involve formation of a strained, fused azetidine.

Experimental

M.p.s were recorded on a hot-stage apparatus and are uncorrected. I.r. spectra were obtained on various Perkin-Elmer spectrophotometers using chloroform as solvent unless otherwise stated. ^{1}H N.m.r. spectra were recorded on either a Perkin-Elmer R32 (90 MHz) or Jeol FX 90Q (90 MHz) instrument and are quoted in p.p.m. relative to tetramethylsilane as internal standard, using deuteriochloroform as solvent unless otherwise specified; highfield (400 MHz) spectra were obtained *via* the S.E.R.C. service run at the University of Sheffield.

Thin layer chromatography (t.l.c.) was performed on either aluminium plates pre-coated with Merck Kieselgel (0.2 mm) or on glass plates coated before use with Merck Kieselgel 60 GF_{254}. Acidic products were eluted with the solvent system ethyl acetate–methanol–acetic acid (50:10:1). Preparative layer chromatography (p.l.c.) was performed using 20 × 20 cm plates coated with 1 mm of Kieselgel 60 GF_{265} and, for column chromatography, Lichroprep Si60 was employed. Solvents were generally of S.L.R. grade and were purified and dried as necessary by standard methods. Solvents for chromatography were distilled before use. Light petroleum refers to the fraction of boiling range 60—80 °C; DMF denotes dimethylformamide, THF tetrahydrofuran, and EtOAc ethyl acetate. Reactions were generally carried out under oxygen-free nitrogen. Extracts were dried over anhydrous sodium sulphate and acidifications were performed using 10% orthophosphoric acid solution.

(±)-4-*Butyl*-1-*methylazetidin*-2-*one* (**1**).—(±)-4-But-3-enylazetidin-2-one (**2**)[15] (1.25 g, 10 mmol) in dry methyl iodide (20 ml) was stirred at 0 °C whilst adding, portionwise, powdered potassium hydroxide (0.56 g, 10 mmol). The reaction mixture was then stirred at room temperature overnight, filtered, and the solution dried and evaporated to leave an oil (1.30 g). A sample of this *N*-methylated material (0.75 g) was immediately hydrogenated at room temperature over 10% Pd/C (0.1 g). After hydrogen uptake had ceased (1.5 h), the catalyst was filtered off, the solvent removed by evaporation under reduced pressure, and the residue chromatographed through silica (40 g), using 3:97 ethanol–chloroform as eluant to afford the *title lactam* (0.55 g, 71%), $\nu_{max.}$(film) 1 750 cm^{-1}; δ 0.91 [3 H, br t, $CH_3(CH_2)_3$] 1.1—2.0 [6 H, m, $(CH_2)_3$], 2.48 (1 H, dd, *J* 2, 15 Hz, 3-H), 2.76 (3 H, s, NMe), 2.95 (1 H, dd, *J* 6, 15 Hz, 3-H), 3.45 (1 H, m, 4-H); *m/z* 142 (M^+ + 1), 141, 113, 98, 84, 70, 56, and 42 (Found: *M*, *m/z* 141.1152. $C_8H_{15}NO$ requires *M*, 141.1154).

(±)-3-*Methylaminoheptan*-1-*ol* (**3**).—The lactam (**1**) (0.35 g, 2.5 mmol) in dry THF (30 ml) at −10 °C was treated with a stream of diborane gas, generated from sodium borohydride (0.16 g, 4.2 mmol) and boron trifluoride–diethyl ether (1 g, 7.1 mmol) in diglyme. The mixture was stirred at −10 °C for 4 h and then overnight at room temperature before being stirred with saturated aqueous ammonium chloride for 30 min and extracted with ether (× 2); the extracts were dried and the solvent removed under reduced pressure. The resulting oil showed an intense i.r. band at 2 360 cm^{-1} (B–H) so it was treated with 1M-HCl; the solution was then made basic to pH 11 with 2M-NaOH, saturated with sodium chloride, and extracted with ether (× 3). The original aqueous extract was likewise treated with 2M-HCl and the ether extracts combined, dried, and the solvent removed to give the *title compound* as an oil (0.28 g, 77%), $\nu_{max.}$(film), 3 300 cm^{-1}; δ 0.92 (3 H, t, *J* 6 Hz, Me), 1.1—1.9 (8 H, m, 4 × CH_2), 2.42 (3 H, s, MeN), 2.65 (1 H, m, 3-H), 3.60 (2 H, br s, exch. D_2O, OH and NH), 3.80 (2 H, t, *J* 6 Hz, CH_2OH); *m/z* 146 (M^+ + 1), 145, 100, 88, 70, 58, and 44 (Found: *M*, *m/z* 145.1462. $C_8H_{19}NO$ requires *M*, 145.1466). The alcohol (50 mg) in ether (2 ml) was treated with oxalic acid dihydrate (43 mg) in ether (2 ml) and ethanol (3 drops) to give a crystalline salt of the *half-acid oxalate*, m.p. 82—83 °C (EtOH–ether) (Found: C, 51.3; H, 9.0; N, 6.1. $C_8H_{19}NO{\cdot}C_2H_2O_4$ requires C, 51.1; H, 9.0; N, 6.0%).

Benzhydryl (αR,3S)-α-*Isopropyl*-3-*t*-*butoxycarbonylamino*-2-*oxoazetidin*-1-*ylacetate* (**4**).—6-t-Butoxycarbonylaminopenicillanic acid (20 g, 63 mmol) was dissolved in a solution of sodium hydrogen carbonate (5.3 g, 63 mmol) in water (500 ml) and the solution deoxygenated with a stream of nitrogen; freshly prepared Raney nickel (*ca.* 90 g) was then added and the mixture rapidly heated to reflux (7 min) and maintained at reflux for a further 10 min. The mixture was then rapidly cooled, filtered, and the catalyst washed with a small quantity of aqueous sodium hydrogen carbonate and then water. The filtrate was acidified to pH 3, extracted with EtOAc (3 × 250 ml) and the extract dried and evaporated to give (αR,3S)-α-*isopropyl*-3-*t*-*butoxycarbonylamino*-2-*oxazetidin*-1-*ylacetic acid* (11.7 g, 65%), m.p. 146—152 °C (decomp.), $[\alpha]_D^{22}$ +23° (*c* 0.28, $CHCl_3$) (Found: C, 54.5; H, 7.7; N, 9.7. $C_{13}H_{22}N_2O_5$ requires C, 54.5; H, 7.7; N, 9.8%).

The acid (11.2 g, 39 mmol) in dichloromethane (200 ml) was cooled to +5 °C before a solution of diphenyldiazomethane in hexane was added dropwise. After 4 h, when a slight pink colour remained, the solvent was removed to afford the *title compound* (12.8 g, 73%), m.p. 125—156 °C, $[\alpha]_D$ +29° (*c* 0.25, $CHCl_3$), $\nu_{max.}$ 3 240, 1 730, and 1 705 cm^{-1}; δ 0.90 and 0.99 (6 H, 2 × d, *J* 6 Hz, Me_2CH), 1.43 (9 H, s, Me_3C), 2.20 (1 H, m, $CHMe_2$), 3.30 (1 H, m, 4-H), 3.76 (1 H, m, 4-H), 4.26 (1 H, d, *J* 8 Hz, α-H), 4.70 (1 H, m, 3-H), 5.05 (1 H, br d, *J ca.* 8 Hz, CONH), 6.89 (1 H, s, Ph_2CH), 7.30 (10 H, s, ArH) (Found: C, 69.1; H, 7.1; N, 6.3. $C_{26}H_{22}N_2O_5$ requires C, 69.0; H, 7.1; N, 6.2%).

Benzhydryl (2′S,2R)-2-[(2′-*t*-*Butoxycarbonylamino*-3′-*hydroxy*)*propylamino*]-3-*methylbutanoate* (**5**).—The amide (**4**) (10 g, 22 mmol) in THF (170 ml) was reduced with diborane, generated from boron trifluoride–diethyl ether (7.1 g, 50 mmol) and sodium borohydride (1.1 g, 30 mmol), in the manner described above. After the usual treatment with aqueous ammonium chloride, the product was chromatographed through silica (350 g), using 1:2 EtOAc–light petroleum as eluant to give the *title amino alcohol* (2.21 g, 22%), m.p. 86—90 °C, $[\alpha]_D^{20}$ +22° (*c* 0.42, $CHCl_3$), $\nu_{max.}$ 3 440, 1 730, and 1 710 cm^{-1}; δ 0.83, 0.92 (6 H, 2 × d, *J* 6 Hz, Me_2CH), 1.44 (9 H, s, Me_3C), 2.0 (1 H, m, $CHMe_2$), 2.47 (1 H, dd, *J* 4.5, 12 Hz, 1′-H), 2.92 (1 H, dd, *J* 5, 12 Hz, 1′-H), 2.70 (2 H, br s, exch. D_2O, CH_2OH), 3.12 (1 H, d, *J* 6 Hz, $CHCO_2R$), 3.5—3.9 (3 H, m, CH_2OH and 2′-H), 5.20 (1 H, d, *J* 6 Hz, CONH), 6.94 (1 H, s, Ph_2CH), 7.31 (10 H, s, ArH) (Found: C, 68.4; H, 7.8; N, 5.9. $C_{26}H_{36}N_2O_5$ requires C, 68.4; H, 7.9; N, 6.1%).

1-*Benzylamino*-3-*bromopropane* (**15**).—3-Benzoylaminopropanoic acid[16] (9.65 g, 0.05 mol) in dry THF (60 ml) was

added dropwise, during 30 min, to an ice-cooled solution of lithium aluminium hydride (3.8 g, 0.1 mol) in dry THF (80 ml). The mixture was then stirred at room temperature overnight before being heated to reflux for 9 h. Ether (100 ml), followed by water (4 ml), 4M-NaOH (4 ml), and water (12 ml) were sequentially added, giving a white precipitate which was filtered off. The filtrate was evaporated and then distilled under reduced pressure to give 1-benzylaminopropan-3-ol (**6**) (5.5 g, 67%), b.p. 105 °C/0.3 mmHg (lit.,[17] 132 °C/3 mmHg).

The alcohol (**6**) (1 g, 6 mmol) was placed in a flask equipped with magnetic stirrer, reflux condenser, and ice-cooling. Hydrobromic acid (47%, *d* 1.5; 20 ml) was added, the cooling bath removed, and the solution heated to reflux for 5 h. The mixture was reduced to a volume of 9 ml by distillation and the resulting solution cooled to afford crystals of 1-benzylamino-3-bromopropane hydrobromide, m.p. 185—189 °C (lit.,[18] 190—191 °C). The free base was obtained by adding 2M-NaOH to an aqueous solution of the salt until it was just basic (pH 7.5) and extracting with chloroform. The free base showed δ 1.78 (1 H, s, exch. D_2O, NH), 2.03 (2 H, quintet, $CH_2CH_2CH_2$), 2.81 (2 H, t, *J* 7 Hz, CH_2N), 3.52 (2 H, t, *J* 7 Hz, CH_2Br), 3.82 (2 H, s, $PhCH_2$), and 7.42 (5 H, s, Ph). (The oil was unstable to storage, extensive decomposition occurring at 20 °C within 4 days.)

Diethyl N-(3-Benzylaminopropyl)hydrazodicarboxylate (**7**).—To the alcohol (**6**) (0.83 g, 5 mmol) in dry benzene (100 ml) containing triphenylphosphine (1.83 g, 7 mmol), cooled to 10 °C, was added diethyl azodicarboxylate (1.22 g, 7 mmol) in benzene (15 ml). After the solution had been stirred at room temperature for 2.5 days, the solvent was removed and ether added. The precipitated triphenylphosphine oxide was removed by filtration and the residue chromatographed through silica (140 g), using 1:19 methanol–EtOAc as eluant, to remove the remaining side products; elution then with 1:2 methanol–EtOAc gave the *title compound* as a viscous oil (1.2 g, 74%), $\nu_{max.}$(film) 3 300 and 1 700—1 750 cm^{-1}; δ 1.25 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.27 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.78 (2 H, m, $CH_2CH_2CH_2$), 2.72 (2 H, t, *J* 6 Hz, CH_2NH), 3.63 (2 H, m, CH_2NCO), 3.81 (2 H, s, $PhCH_2$), 4.23 (4 H, q, *J* 7 Hz, 2 × CH_3CH_2O), 7.42 (5 H, s, ArH); *m/z* 323 (M^+) 235, 192, 143, 132, 120, 106, 91, and 56 (Found: *M*, *m/z* 323.1809. $C_{16}H_{25}N_3O_4$ requires *M*, 323.1845). The *half acid oxalate salt* had m.p. 159—162 °C (Found: C, 52.6; H, 6.6; N, 9.9. $C_{16}H_{25}N_3O_4 \cdot C_2H_2O_4$ requires C, 52.3; H, 6.5; N, 10.2%).

General Procedure for Alkylations (*Table*).—The amine, or its salt, alcohol, and triphenylphosphine were mixed together in the appropriate solvent, cooled in ice, and diethyl azodicarboxylate added dropwise, with stirring; the mixture was then left at room temperature overnight. Between 1 and 1.5 mol equiv. of the dehydrating reagent were used, the amine and alcohol being used in equimolar quantities. The reaction was worked-up by adding EtOAc and extracting with 2M-HCl. The aqueous phase was washed with EtOAc, basified to pH 10 with concentrated NaOH, extracted with light petroleum (× 3), and the organic extract dried (K_2CO_3) and the solvent removed.

N-Benzylazetidine (**9**).—*Method a.* Sodium hydride (60% suspension in oil; 65 mg, 1.6 mmol) was washed with dry benzene and suspended in dry DMF (20 ml). Dry THF (3 ml) was added and the suspension cooled to −55 °C before a solution of 1-benzylamino-3-bromopropane hydrobromide (0.25 g, 0.8 mmol) in DMF (5 ml) was added. The mixture was allowed to warm to room temperature before being stirred for 2 h. The bulk of the DMF was removed under reduced pressure and the residue taken up in EtOAc; the latter was then washed with water, dried, and evaporated, to give the crude *N*-benzylazetidine (0.09 g, 75%), b.p. 65—70 °C/4 mmHg (lit.,[11] 71—75 °C/5 mmHg), δ 2.07 (2 H, m, CH_2), 3.20 (4 H, m, CH_2), 3.55 (2 H, s, $PhCH_2$), and 7.25 (5 H, s, ArH). The *half acid oxalate* had m.p. 127—130 °C (Found: C, 60.8; H, 6.3; N, 5.9. $C_{10}H_{13}N \cdot C_2H_2O_4$ requires C, 60.8; N, 6.3; N, 5.9%).

Method b. 1-Benzylaminopropan-3-ol (0.5 g, 3 mmol) in acetone (5 ml) was treated with hydrobromic acid (47%, 0.35 ml, 3 mmol). Removal of solvent under reduced pressure afforded the hydrobromide salt, as a white powder, m.p. 66—72 °C. The salt (0.61 g, 2.5 mmol) in dry DMF (20 ml) and benzene (10 ml) was treated with triphenylphosphine (0.92 g, 35 mmol) followed by diethyl azodicarboxylate (0.61 g, 3.5 mmol) in benzene (10 ml). The mixture was stirred at room temperature overnight before it was reduced to a volume of *ca.* 4 ml. Extraction with ether removed most of the by-products. The residue was treated with 2M-NaOH and brine, before re-extraction with ether. The ethereal extract was dried over solid NaOH and distilled to give *N*-benzylazetidine (0.18 g, 40%).

Method c. Silver tetrafluoroborate (0.2 g, 1 mmol) in methanol (2 ml) was added to the hydrobromide salt of the amino alcohol (0.25 g, 1 mmol) in methanol (4 ml). Filtration and evaporation of the filtrate and drying of the residue *in vacuo* afforded the tetrafluoroborate salt (0.24 g, 97%) as a very hygroscopic solid. Cyclisation to the azetidine was achieved under the same conditions as described in method b, except that dry THF only was used as solvent. The crude yield was 0.18 g but this was contaminated with a little triphenylphosphine oxide; attempted distillation afforded a reduced quantity of the pure azetidine (0.073 g, 51%), characterised as the half acid oxalate, m.p. 127—130 °C.

(±)-*2-Butyl-1-methylazetidine* (**10**).—The alcohol (**3**) (0.15 g, 1.0 mmol) in acetonitrile (10 ml) was treated with

Table.[a] Amine alkylations using triphenylphosphine and diethyl azodicarboxylate

Amine	Alcohol	Acid	Solvent	Product	Yield (%)	Derivative m.p. (°C)
Aniline	Pr^nOH	HCl	THF–DMF		0	
Aniline	$PhCH_2OH$	HCl	THF–DMF	$PhNHCH_2Ph$	10	
Piperidine	$PhCH_2OH$	HCl	THF–DMF	*N*-Benzylpiperidine	43	Hydrochloride, 176—179 (lit.,[c] 176—178)
Piperidine	$PhCH_2OH$		THF–DMF	*N*-Benzylpiperidine	56	Hydrochloride, 174—177
Piperidine	$PhCH_2OH$		C_6H_6	*N*-Benzylpiperidine	55	Hydrochloride, 174—177
Benzylamine	MeOH	HCl	DMF	Mixture		
$HO(CH_2)_3NHCH_2Ph$			C_6H_6	(**7**)	74	Acid oxalate, 159—166
$HO(CH_2)_3NHCH_2Ph$		HBr	DMF–C_6H_6	(**9**)	40[b]	Acid oxalate, 127—130
$HO(CH_2)_3NHCH_2Ph$		HBF_4	THF	(**9**)	51	Acid oxalate, 127—130
$NH_2(CH_2)_5OH$		HCl	DMF	Piperidine	23	Hydrochloride, 242—244 (lit.,[d] 245)

[a] See Experimental section for conditions. [b] Yield after distillation. [c] P. J. Stone, J. C. Craig, and H. W. Thompson, *J. Chem. Soc.*, 1958, 52. [d] 'Dictionary of Organic Compounds,' 5th edn., Chapman and Hall, London, 1982, p. 4719.

triphenylphosphine (0.38 g, 1.3 mmol), followed by freshly recrystallised carbon tetrabromide (0.49 g, 1.5 mmol). An immediate exothermic reaction occurred, the mixture turning slightly brown. The mixture was stirred at room temperature overnight before EtOAc and dilute HCl were added. The aqueous extract was made basic with 2M-NaOH, solid potassium carbonate was added and the whole extracted with ether (× 5). The extract was dried and evaporated to give the *title azetidine* (0.10 g, 78%) as an oil, δ 0.90 (3 H, t, *J* 6 Hz, Me), 1.0—2.2 (8 H, m, 4 × CH_2), and 2.7—3.7 (3 H, m, 2-H and 4-H_2). The *half acid oxalate* had m.p. 79—82 °C (Found: C, 55.3; H, 8.7; N, 6.6. $C_8H_{17}N{\cdot}C_2H_2O_4$ requires C, 55.3; H, 8.8; N, 6.5%).

Benzylhydryl (αR)-α-*Isopropyl*-3-*t*-*butoxycarbonylamino*-*azetidin*-1-*ylacetate* (**12**).—The alcohol (**5**) (0.19 g, 0.44 mmol) in dry acetonitrile (4 ml) was treated with triphenylphosphine (0.17 g, 0.66 mmol) followed by carbon tetrabromide (0.22 g, 0.66 mmol) and, finally, triethylamine (90 mg, 0.9 mmol). The mixture was stirred overnight at room temperature before work-up in the normal manner. The product was chromatographed through silica (25 g) using 1:2 EtOAc–light petroleum as eluant. The major product was the *title compound* (0.09 g, 53%), obtained as an oil, $\nu_{max.}$ 3 410 and 1 705 cm^{-1}; δ 0.82 (3 H, d, *J* 6 Hz, *Me*CH), 0.95 (3 H, d, *J* 6 Hz, *Me*CH), 1.42 (9 H, s, Me_3C), 1.85 (1 H, m, C*H*Me_2), 2.81 (1 H, m, ring CH), 2.95 (1 H, d, *J* 7 Hz, C*H*CO_2R), 3.14 (1 H, m, ring CH), 3.54 (1 H, t, *J* 7 Hz, ring CH), 3.66 (1 H, t, *J* 7 Hz, ring CH), 4.26 (1 H, m, 3-H), 4.58 (1 H, d, *J* 6 Hz, NH), 7.00 (1 H, s, Ph_2CH), 7.35 (10 H, m, ArH); *m/z* 438 (M^+), 365, 296, 227, 171, 167, 84, and 56.

The *acid oxalate salt* had m.p. 82—84 °C (Found: C, 63.2; H, 6.7; N, 5.3. $C_{26}H_{34}N_2O_4{\cdot}C_2H_2O_4$ requires C, 63.6; H, 6.9; H, 5.3%).

Acknowledgements

We thank the S.E.R.C. and Hoechst (U.K.) Ltd. for a C.A.S.E. studentship (to S. S).

References

1 J. A. Moore and R. S. Ayers, in 'Small Ring Heterocycles,' Part 2, ed. A. Hassner, Wiley-Interscience, New York, *1983*, p. 1.
2 M. Yamashita and I. Ojima, *J. Am. Chem. Soc.*, 1983, **105**, 6339.
3 H. O. House, 'Modern Synthetic Reagents,' W. A. Benjamin Inc., Menlo Park, California, 2nd Edn., 1972.
4 N. G. Gaylord, 'Reduction with Complex Metal Hydrides,' Interscience, N.Y., 1956, pp. 544—626; H. C. Brown and P. Heim, *J. Org. Chem.*, 1973, **38**, 912.
5 M. E. Speeter and W. H. Maroney, *J. Am. Chem. Soc.*, 1954, **76**, 5810; F. F. Blicka and W. A. Gould, *J. Org. Chem.*, 1958, **23**, 1102.
6 E. Testa, L. Fontanella, and G. F. Cristiani, *Annalen*, 1959, **626**, 114; E. Testa, A. Bonati, G. Pagani, and E. Gatti, *Annalen*, 1961, **647**, 92.
7 J. N. Wells and O. R. Tarwater, *J. Pharmaceut. Sci.*, 1971, **60**, 156.
8 C. V. Nataraj, C. Mandal, and P. K. Bhattacharyya, *Proc. Ind. Acad. Sci.*, 1978, **87A**, 1.
9 P. G. Sammes and S. Smith, *J. Chem. Soc., Chem. Commun.*, 1981, 1143.
10 N. H. Cromwell and B. Phillips, *Chem. Rev.*, 1979, **79**, 331.
11 W. R. Vaughan, R. S. Klonowski, R. S. McElhinney, and B. B. Millward, *J. Org. Chem.*, 1961, **26**, 138.
12 O. Mitsunobu, *Synthesis*, 1981, 1.
13 P. G. Sammes, S. Smith, and G. T. Woolley, *J. Chem. Soc., Perkin Trans. 1*, in the press.
14 (*a*) J. B. Lee and I. M. Downie, *Tetrahedron*, 1967, **23**, 359; (*b*) V. N. Gogte, S. B. Kulkarni, and B. D. Tilak, *Tetrahedron Lett.*, 1973, 1867; (*c*) J. P. Freeman and P. J. Mondran, *Synthesis*, 1974, 894; (*d*) V. Stoilova, L. S. Trifonov, and A. S. Orahovats, *Synthesis*, 1979, 105.
15 T. Aida, R. Legault, D. Dugat, and T. Durst, *Tetrahedron Lett.*, 1979, 4993.
16 F. H. Holm, *Arch. Pharm.* (Weinheim, Ger.), 1904, **242**, 611.
17 J. Décombe, *Ann. Chim.*, 1932, **18**, 81 (*Chem. Abstr.*, 1933, **27**, 2136).
18 L. W. Deady, N. H. Pirzada, and R. D. Topsom, *J. Chem. Soc., Perkin Trans. 1*, 1973, 782.

Received 1*st March* 1984; *Paper* 4/344