Synthesis of Pyrrolidines and Piperidines *via* Intramolecular Cyclisation of ω-Azidoalkyl Boronic Esters

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Intramolecular cyclisation of ω-azidoalkyl boronic esters occurs in the presence of boron trichloride and leads, after hydrolysis, to the corresponding pyrrolidines or piperidines.

Pyrrolidine and piperidine ring systems are common skeletal features in several alkaloid families.[1] Of particular interest are new methods for the construction of these nitrogen heterocycles. We now report such a synthesis where the ring closure occurs by formation of a carbon–nitrogen bond *via* the reaction of an azide with *in situ* generated chloroborane.

Brown and co-workers showed that azides react with boranes to give secondary amines,[2] but little attention was paid to this pioneering work. It led us to define the scope and limitations, and explore further synthetic possibilities of this method.[3] First, we proposed a new and general synthesis of polyamines based on the reaction of dichloroboranes with azides,[4] and then we investigated an intramolecular variant of this reaction which had not previously been described.

The successful realisation of this approach involves a selective migration of the ω-aminoalkyl group (path a) rather than two other R groups (path b), as shown in Scheme 1.

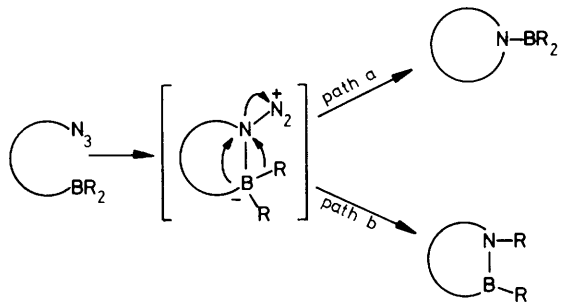
The results of our systematic study of the intermolecular version of this reaction[5] led us to choose R = halogen as the non-migrating group. While this work was in progress, Evans and co-workers showed an example where R = cyclohexyl which may also be used.[6] Pyrrolidines and piperidines have been synthesised according to Scheme 2.

Boronic acids (**1**) are easily prepared by the hydroboration

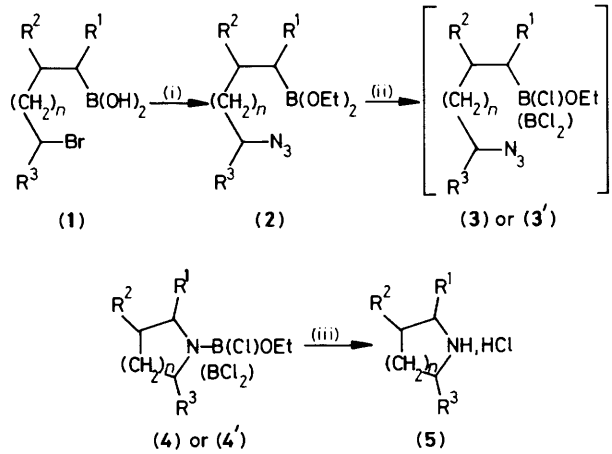
Table 1. Pyrrolidines and piperidines from ω-bromoalkenes.[a,b]

Entry	*n*	R^1	R^2	R^3	(1) Yield (%)[b]	(2) Yield (%)[b]	(5) Yield (%)[b]
a	1	H	H	H	78	75	89
b	1	H	Me	H	80	66	80
c	1	Pr^i	H	Me	90[c]	68[c]	86[c]
d	2	H	H	H	83	78	79
e	2	H	H	Me	83	75	75

[a] All new compounds gave satisfactory elemental analysis and spectral data (^1H and ^{13}C n.m.r., i.r.). [b] Isolated yields. For (**1**), yields are calculated from the starting ω-bromoalkenes. For (**5**), yields are based on the *N*-benzoyl compounds (**6**), prepared by benzoylation of the crude cyclisation product. [c] A 1 : 1 mixture of two diastereoisomers was obtained.



Scheme 1



Scheme 2. *Reagents and conditions*: i, NaN_3, EtOH, reflux overnight; ii, BCl_3, CH_2Cl_2, −78 to 25 °C; iii, EtOH, room temp.

of the corresponding alkenic bromides with $HBBr_2.SMe_2$, followed by hydrolysis. The usual reactivity and regioselectivity were observed.[7] The treatment of (**1**) with sodium azide in refluxing ethanol afforded the ω-azidoalkyl boronic esters (**2**). The addition of 1 equiv. of boron trichloride to a solution of (**2**) in CH_2Cl_2 generated the chloro derivatives (**3**) or (**3′**)†‡ which, by an intramolecular cyclisation, gave (**4**) or (**4′**). After methanolysis the corresponding pyrrolidine or piperidine hydrochlorides (**5**) were obtained (Table 1).

In a typical procedure, a mixture of ω-bromoalkyl boronic acid (**1**) (10 mmol, prepared by known methods[7]) and sodium azide (15 mmol) was refluxed in ethanol (15 ml) for 18 h. After cooling and addition of ether (15 ml), the solid was filtered. The solvent was removed under reduced pressure (15 mmHg) and the resulting residue dissolved in hexane (15 ml) in the presence of ethanol (0.5 ml). Filtration and elimination of the solvent afforded the crude boronic ester (**2**) which was purified by distillation (Kugelrohr, 0.01 mmHg). To a solution of (**2**) (10 mmol) in dichloromethane (5 ml) was added, at −78 °C, a solution of boron trichloride in dichloromethane (1.4 M; 7.1 ml). The mixture was allowed to reach room temperature overnight. After addition of methanol (2 ml) and removal of the solvent, the crude material was directly benzoylated by a known procedure. *N*-Benzoylpyrrolidines (or piperidines) (**6**) were purified by chromatography on silica gel.

In conclusion, the method described in this communication represents a convenient and versatile procedure for the construction of nitrogen heterocycles. A wide variety of diastereoisomeric (or enantiomeric) pure boronic esters can easily be prepared *via* asymmetric hydroboration[9] or (and) homologation.[10] The use of these compounds as starting materials should allow the synthesis of the pyrrolidines and piperidines with complete control of stereochemistry.

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† In the presence of boron trichloride, boronic esters $RB(OR')_2$ afford first the monochloroalkoxyborane RB(OR′)Cl and then the dichloroborane $RBCl_2$ *via* a redistribution reaction.[8] Cyclisation can occur from one of these two intermediates.

‡ Direct hydroboration of the alkenic azide with $HBCl_2{\cdot}SMe_2$ leads mainly to reduction of the azido group.

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