On the Synthesis of Azetidines from 3-Hydroxypropylamines

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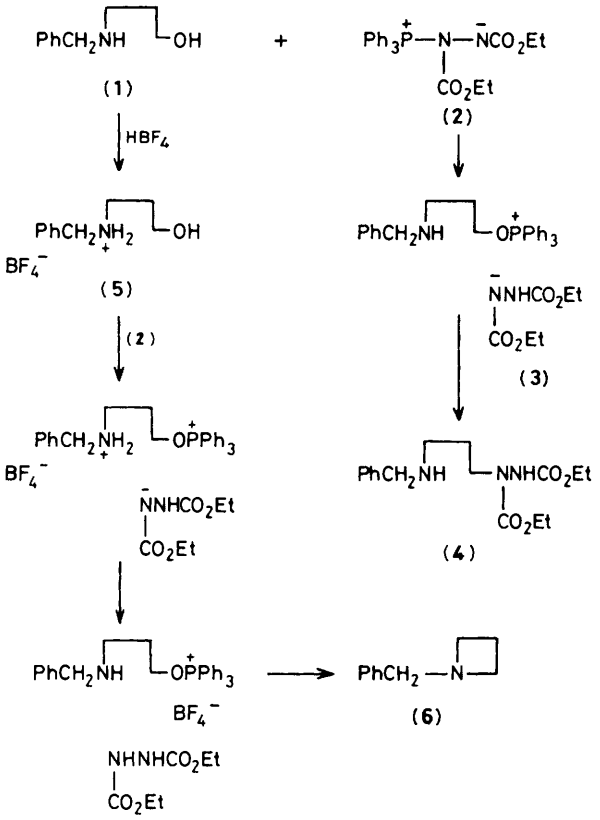
New methods are described for preparing azetidines from 3-hydroxypropylamines involving the use of triphenylphosphine and diethyl azodicarboxylate and related reagents.

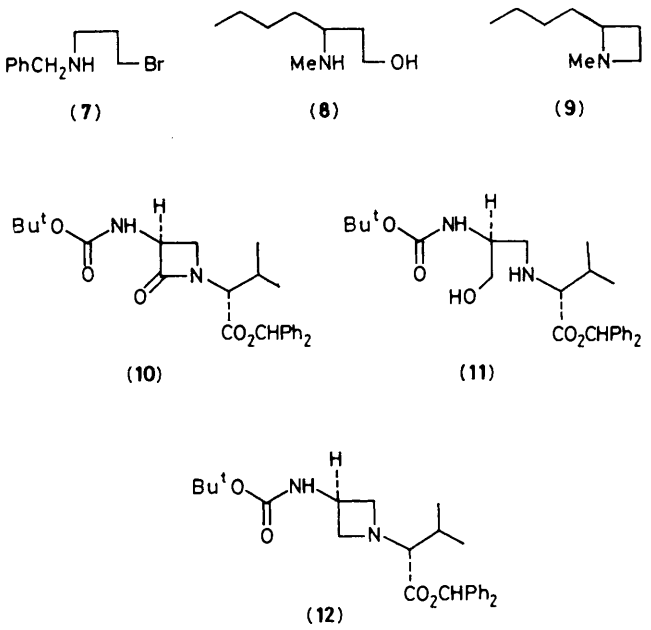
Although azetidine was first prepared in 1888,[1] ring strain makes this group of amines one of the most difficult to prepare.[2] Thus the cyclisation of 3-halogenopropylamines can be complicated by accompanying elimination, fragmentation, or



Scheme 1

dimerisation[3] and, furthermore, literature methods generally involve strong basic methods to effect cyclisation. Herein we describe a modified Mitsunobu reaction[4] and related processes for obtaining azetidines from 3-hydroxypropylamines.

As a model amino-alcohol, 3-(*N*-benzyl)aminopropan-1-ol (**1**), b.p. 150 °C/0.3 mmHg (lit.[5] 132 °C/2 mmHg) was prepared (67% yield) by the reduction of *N*-benzoyl-β-alanine with lithium aluminium hydride. Treatment of the amino-alcohol (**1**) with the diethyl azodicarboxylate–triphenylphosphine adduct (**2**) in benzene for 16 h at room temperature afforded, as the major product, the hydrazine derivative (**4**).† Presumably this material forms according to the reactions outlined in Scheme 1, in which the mono-anion (**3**) must compete favourably as a nucleophile, compared to the relatively slow intramolecular amine attack, to displace the triphenylphosphine oxide. In order to avoid this unwanted reaction it was argued that either the nucleophilicity of the amine had to be increased, by generating the corresponding anion, or the nucleophilicity of the hydrazide anion had to be decreased by protonation. Since the pK_a of secondary amines suggests the need for a very strong base to produce the amine anion the latter argument prevailed. The method entails the initial formation of a salt of the starting amino-alcohol in order to provide a proton to quench the anion (**3**). Ideally a non-nucleophile is desirable and, initially, the tetrafluoroborate (**5**) was prepared. This salt was extremely hygroscopic and it was dried over phosphorus pentoxide before treating it with triphenylphosphine and diethyl azodicarboxylate in tetrahydrofuran. The reaction was worked-up by adding dilute HCl, extracting with diethyl ether to remove by-products, basifying with dilute NaOH, and diethyl ether extraction to yield the required azetidine (**6**) (50% yield), isolated as its half acid oxalate salt, m.p. 127—130 °C; none of the hydrazide (**4**) could be detected.



As an alternative to the use of the non-nucleophilic tetrafluoroborate salt (**5**), the hydrobromide salt of the amino-alcohol (**1**) could be employed. In this case reaction with the triphenylphosphine–diethyl azodicarboxylate reagent afforded, directly, the azetidine (**6**) (40%), initially formed as its hydrobromide salt. None of the bromo-amine (**7**) was detected in this reaction. The amine (**7**) could be prepared by treatment of the azetidine (**6**) with hydrogen bromide, followed by neutralisation of the hydrobromide salt thus obtained, but it did not cyclise to the azetidine (**6**) under the above reaction conditions. It appears, therefore, that the bromo-amine (**7**) is not involved in the cyclisation of the hydrobromide salt of (**1**).

The modified Mitsunobu reagent was also used to study some simpler amine alkylations. For example, piperidine hydrochloride could be treated with benzyl alcohol in the presence of one equivalent of triphenylphosphine and diethyl azodicarboxylate to produce *N*-benzylpiperidine hydrochloride (47%), m.p. 176—179 °C (lit.[6] 176—178 °C). However, in this particular case use of the hydrochloride salt is not imperative; reaction of the free amine with benzyl alcohol gave *N*-benzylpiperidine (56%) presumably because, in this instance, the amine can compete effectively with the anion (**2**) in the alkylation step.

Miller *et al.*[7] have reported the use of triphenylphosphine–carbon tetrachloride in the formation of β-lactams (azetidinones) and we have therefore examined use of the related triphenylphosphine–carbon tetrabromide reagent[8] for the formation of azetidines. In this process the only anion which can compete with the amino-function in the cyclisation step is liberated bromide anion (*cf.* Scheme 1). Treatment of the amino-alcohol (**8**) with 1.4 equiv. of the reagent in acetonitrile solution afforded the corresponding azetidine (**9**) (78% yield), half acid oxalate, m.p. 79—82 °C. Similarly the amino-alcohol (**11**), obtained by the diborane reduction of the dethiopenicillanate (**10**)[9] reacted with the carbon tetrabromide –triphenylphosphine reagent, in the presence of triethylamine, to give the corresponding azetidine (**12**) (56% yield), half acid oxalate, m.p. 82—84 °C.

† All new compounds gave satisfactory microanalytical and/or mass spectral data.

We thank Hoechst Pharmaceutical Research Laboratories, Milton Keynes, and the S.E.R.C. for a C.A.S.E. Studentship (to S. S.).

Received, 30th March 1983; Com. 416

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