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Boron(III) bromide-induced ring contraction of 3-oxygenated piperidines to 2-(bromomethyl)pyrrolidines

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Abstract

3-Methoxypiperidines were converted into 2-(bromomethyl)pyrrolidines by reaction with boron(III) bromide in dichloromethane. This reaction proceeds via an intermediate bicyclic aziridinium ion and features a rare conversion of piperidines into pyrrolidines.

Keywords: pyrrolidines; piperidines; ring transformation.

Pyrrolidines **1**, carrying a 2-(halomethyl)-substituent are easily converted into 3-functionalized piperidines **3** upon reaction with a variety of nucleophiles (Scheme 1).[1–4] This ring enlargement occurs via intramolecular substitution of the halide by nitrogen and subsequent opening of the bicyclic aziridinium ion **2** at the more substituted carbon by the nucleophile to give 3-functionalized piperidines **3**, which are sometimes accompanied by small amounts of the corresponding pyrrolidines carrying the CH_2Nu substituent at the 2-position (Scheme 1).[4] Also piperidines **4**, having a leaving group at the 3-position, have been shown to react similarly with nucleophiles to give rise to 3-functionalized piperidines **3**, via the same transient bicyclic aziridinium ions **2** (Scheme 1).[4–7] The general trend observed in these reactions is the facile formation of piperidines. The reverse ring transformation, i.e. the rearrangement of the piperidines into pyrrolidines, thus providing a useful synthetic reaction, is a rare process. Very often, the intermediate pyrrolidines are generated as transient species from different precursors. Examples of such pyrrolidine synthesis from piperidines include the transient formation of 3-halopiperidines from α-bromo iminium ions[8–11] and α,δ-dichloro aldimines.[12]

In the present report, a smooth conversion of 3-methoxypiperidines **6** into 2-(bromomethyl)pyrrolidines **7** via a boron(III) bromide-induced reaction is disclosed (Scheme 2). 3-Methoxypiperidines **6** are easily

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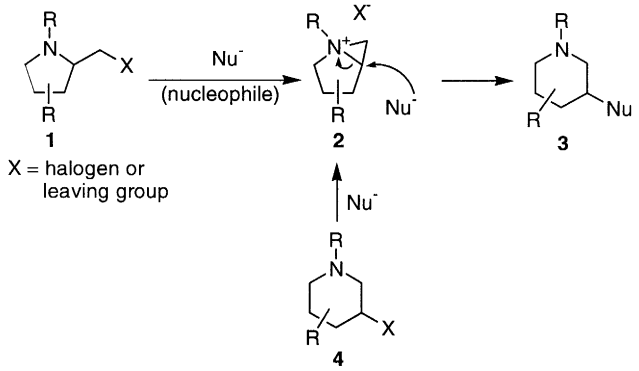
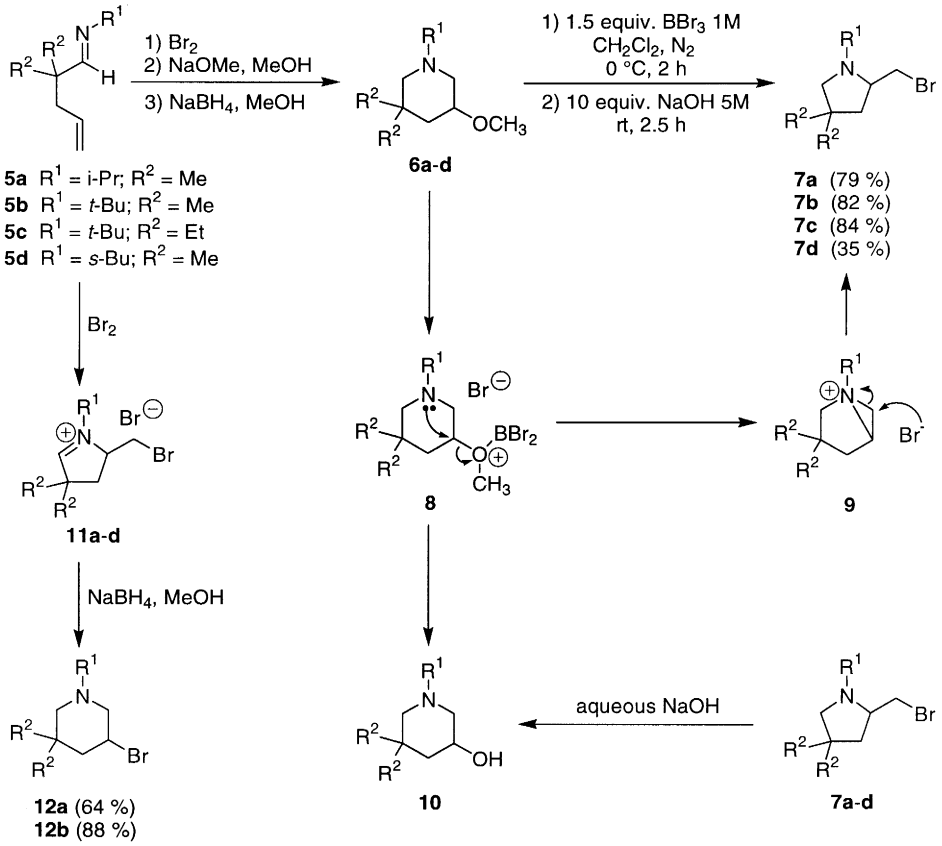


Scheme 1.

accessible in a three-step sequence from *N*-(4-penten-1-ylidene)amines **5**, i.e. α-allyl imines, via: (a) bromination to afford 1-pyrrolinium salts; (b) ring expansion with sodium methoxide in methanol to give 2,5-dimethoxypiperidines; and (c) subsequent demethoxylation with sodium borohydride in methanol.[13] Reaction of 5-methoxypiperidines **6** with boron(III) bromide (1.5 mol equivalent) in dichloromethane at 0°C for 2 h under a nitrogen atmosphere gave rise to a reaction mixture, which was treated with aqueous sodium hydroxide (5 M, 10 equivalents) at room temperature for 2.5 h in order to destroy the boron complexes (Scheme 2). Removal of the organic phase and drying ($MgSO_4$) afforded 2-(bromomethyl)pyrrolidines **7a**–**c** in 79–84% yield, accompanied by small amounts (about 5%) of 3-hydroxypiperidines **10**.[14] 1-*s*-Butyl-5-methoxy-3,3- dimethylpiperidine **6d** with boron(III) bromide afforded only 35% of 2-(bromomethyl)-1-*s*-butyl-4,4-dimethylpyrrolidine **7d**, in addition to 35% yield of 1-*s*-butyl-5,5-dimethyl-3-piperidinol **10d**. The formation of 2-(bromomethyl)pyrrolidine **7** can be explained in terms of a complexation of the methoxy moiety by boron(III) bromide.[15] After ionization of the boron–bromine bond, the intermediate **8** undergoes intramolecular nucleophilic substitution due to the leaving group capacity of the oxygen substituent. The resulting bicyclic aziridinium ion **9** is then subsequently opened at the less hindered position to provide pyrrolidines **7** (Scheme 2). Although it is difficult to explain in a clear-cut way why this regioselective opening takes place at the less hindered position, it is certainly linked to the use of the apolar medium (CH_2Cl_2), because more polar solvents (e.g. alcohols) favour the formation of piperidines. The latter is ascribed to the stabilization of the intermediate secondary carbenium ion, formed upon cleavage of the carbon–nitrogen bond. On the contrary, the opening of bicyclic intermediates **9** might be the result of an S_N2-type ring opening of the aziridinium ion at the methylene function without intervention of a pseudo-carbenium ion. The formation of 3-hydroxypiperidines **10** as side products can be explained either by demethylation of the methoxy substituent by boron(III) bromide or by sodium hydroxide-induced rearrangement of 2-(bromomethyl)-pyrrolidines **7** via transient species **9**. The importance of this boron tribromide-induced ring contraction is further illustrated by the fact that 2-(bromomethyl)-1-isopropyl-4,4-dimethylpyrrolidine **7a** cannot be obtained by simple reduction of the corresponding iminium compound, i.e. 2-(bromomethyl)-1-isopropyl-4,4-dimethyl-3,4-dihydro-2*H*-pyrrolium bromide **11a** with sodium borohydride in methanol (Scheme 2). Even at low temperatures and very slow addition of the reductant (−15°C, 10 min), the only reaction product isolated was 5-bromo-1-isopropyl-3,3-dimethylpiperidine **12a**. Distinction between the isomeric pyrrolidine **7a** and piperidine **12a** could be made by means of mass spectrometry. In the case of pyrrolidine **7a** the presence of an ion at *m/z* 140 accounted for the homolytic cleavage of a CH_2Br-group. The mass spectrum of **12a** did not show any trace of an *m/z* 140 fragment ion. In the ^1H NMR spectrum of **7a** the CHN was assigned to the broad singlet at δ 3.76–3.90. This signal is believed to be broad

because of the adjacent presence of the nitrogen atom. On the contrary, in compound **12a** the CHBr appears as a well-resolved multiplet.



Scheme 2.

In conclusion, a rare ring contraction of 3-methoxypiperidines **6** into 2-(bromomethyl)pyrrolidines **7** via a boron(III) bromide-induced reaction has been developed. The starting piperidines were synthesized by electrophile-induced cyclization of ω-alkenyl imines.

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14. As an example, the spectral data of 2-(bromomethyl)-1-isopropyl-4,4-dimethylpyrrolidine **7a** are given: ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.95 (6H, s, Me_2C), 0.97 and 1.00 (each 3H, each d, each *J*=6.6, CH*Me*$_2$), 1.02–1.14 (1H, m, *H*CH), 1.61 (1H, d×d×t, *J*=12.4, 4.4, 1.5 Hz, HC*H*), 1.95 (1H, d, *J*=11.0 Hz, *H*CHN), 2.05 (1H, d×d, *J*=10.3, 8.5 Hz, *H*CHBr), 2.21 (1H, d×t, *J*=11.0, 1.5 Hz, HC*H*N), 2.75 (1H, septet, *J*=6.6 Hz, C*H*Me_2), 2.81 (1H, d×d, *J*=10.3, 3.9 Hz, HC*H*Br), 3.76–3.90 (1H, br s, NC*H*CH_2Br); ^{13}C NMR (68 MHz, $CDCl_3$): δ 17.59 and 18.49 (CH*Me*$_2$), 26.88 and 29.51 (C*Me*$_2$), 31.46 (*C*Me_2), 46.85 (CH_2), 54.27 (*C*HMe_2), 57.36 (CH_2Br), 60.20 (NCH_2), 66.43 (NCH). IR (NaCl, cm^{-1}): ν_{max}=2960, 2795, 1361, 702. MS (70 eV) *m/z* (%): 233/235 (M^+, 2), 218/220 (18), 171 (12), 170 (22), 156 (100), 140 (18), 138 (10), 98 (10), 95 (8), 81 (12), 72 (12), 71 (19), 70 (11), 58 (21), 56 (52), 55 (21), 44 (27), 43 (43), 42 (22), 41 (35). B.p. 88–92°C/20 mmHg.
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