Synthesis of 3-functionalized 3-methylazetidines

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Abstract – 1-t-Butyl- and 1-(4-methylbenzyl)-3-bromo-3-methylazetidines were prepared from the corresponding N-(2,3-dibromo-2-methylpropylidene)alkylamines and their propensity to undergo nucleophilic substitution at the 3-position by different nucleophiles was assessed, providing a convenient access to novel 3-alkoxy-, 3-aryloxy-, 3-hydroxy-, 3-cyano-, 3-carboxy-, 3-(aminomethyl)- and 3-(hydroxymethyl)azetidines.

Key words: aziridines, azetidines, aziridinium salts, imines, substitution

Within azaheterocyclic chemistry, azetidines represent a valuable class of strained nitrogen-containing compounds from both a biological\(^1\) and a synthetic point of view.\(^2\) In particular, 3-substituted azetidines have attracted considerable interest because of the diverse biological activities associated to this type of compounds. For example, 3-alkoxy- and 3-aryloxyazetidines have been described as G-protein coupled receptor agonists,\(^3\) inhibitors of stearoyl-coenzyme d-9 desaturase,\(^4\) and antibacterial agents.\(^5\) Moreover, 3-haloazetidines (without an additional alkyl group at the 3-position) are generally recognized as good substrates in organic chemistry for the preparation of other 3-functionalized azetidines.\(^6\)

Recently, the convenient synthesis of 3-methoxy-3-methylazetidines 3 through ring rearrangement of 2-bromomethyl-2-methylaziridines 2, obtained by NaBH\(_4\)-mediated reduction of the corresponding α,β-dibromo imines 1, upon treatment with NaBH\(_4\) in methanol under reflux has been described by us.\(^7\) The same azetidines 3 have also been prepared via a different route through NaBH\(_4\)-mediated cyclization of N-alkylidene-(3-bromo-2-methoxy-2-methylpropyl)amines.\(^8\) In general, halogenated imines comprise useful intermediates for the preparation of azaheterocyclic compounds such as aziridines and azetidines.\(^9\)
Furthermore, if aziridines 2 were heated in acetonitrile under reflux, 3-bromoazetidines 4 were obtained as the thermodynamic products (Scheme 1). Until then, the peculiar rearrangement of 2-(halomethyl)aziridines to 3-haloazetidines had been observed in the literature in only two specific cases.

Scheme 1. Reactivity of 2-bromomethyl-2-methylaziridines 2.

In general, the reactivity profile of 3-bromo-3-methylazetidines as useful synthons in organic chemistry has not been studied so far. In this Letter, the synthesis of 3-bromo-3-methyl-1-(4-methylbenzyl)azetidine and 3-bromo-1-t-butyl-3-methylazetidine will be covered, as well as their propensity to undergo nucleophilic substitution at the 3-position to access a window of novel 3-functionalized azetidines.

The synthesis of 3-bromo-3-methyl-1-(4-methylbenzyl)azetidine 9 was performed via thermal ring expansion of 2-bromomethyl-2-methylaziridine 8 upon heating in acetonitrile under reflux according to a literature protocol (Scheme 2). Aziridine 8 was prepared by reductive cyclization of α,β-dibromoaldimine 7a (R = 4-MeC₆H₄CH₂), obtained via bromination of 2-methylpropenal 5 and subsequent condensation with 4-methylbenzylamine in the presence of titanium(IV) chloride and triethylamine. In the same work, it has been shown that 3-methoxy-3-methylazetidines 3 were obtained upon treatment of imines 7 (R = CH₂Ar) with sodium borohydride in methanol under reflux. Considering this smooth imine 7 (R = CH₂Ar) to azetidine 3 transformation, different reaction conditions were evaluated to obtain 3-bromoazetidine 9 directly from imine 7a. The reaction of imine 7a with 1 molar equiv of LiAlH₄ in diethyl ether for 18 hours under reflux resulted only in aziridine 8, while the same reaction in tetrahydrofuran for a prolonged reaction time (5 days) gave a mixture of ring-opened amines derived from the hydride-induced ring opening of aziridine 8. The reduction of imine 7a, either with 1 molar equiv of LiAlH₄ in dioxane for 15 hours under...
reflux or with 2 molar equiv of NaBH₄ in isopropanol for 15-24 hours under reflux, gave
complex reaction mixtures, in which no 3-bromoazetidine 9 could be detected. Therefore, the
most efficient synthesis of azetidine 9 was shown to occur via thermal rearrangement of
aziridine 8.

Contrary to the reactivity of N-(arylmethyl)imine 7a, treatment of N-t-butylimine 7b with 2.5
molar equiv of NaBH₄ in methanol for 4 hours at room temperature selectively provided
amine 10 instead of 2-bromomethyl-1-t-butyl-2-methylaziridine (Scheme 2). These
observations are in accordance with the NaBH₄-mediated reduction of chlorinated imines
towards the synthesis of different 1-alkyl-2-chloromethyl-2-methylaziridines, except in the
case of the 1-t-butyl derivative where the formation of the corresponding aziridine was also
never observed.¹² When amine 10 was further heated in methanol or ethanol for 12 hours
under reflux, a mixture of azetidines 11 and 12a,b (as their hydrobromic salt) was obtained. It
should be noted that even if the corresponding 2-bromomethyl-2-methylaziridine was formed
in this step, it immediately rearranged into azetidines 11 and 12 as the thermodynamically
preferred products. Heating of amine 10 in a less nucleophilic solvent such as isopropanol for
16 hours under reflux provided only 3-bromoazetidine hydrobromide 11, which was then
isolated as a neutral compound upon treatment with a sodium hydroxide solution in 83%
yield. In addition, treatment of imine 7b with 1 molar equiv of LiAlH₄ in diethyl ether for 18
hours under reflux gave 3-bromoazetidine 11 as the major product (75%), together with some
non-identified side products (Scheme 2). Again, no traces of 2-bromomethyl-1-t-butyl-2-
methylaziridine were observed.
Scheme 2. Synthesis of 3-bromo-3-methylazetidines 9 and 11.

The formation of 3-alkoxyazetidines 12a,b from amine 10 is proposed to occur via nucleophilic attack of the solvent molecule (methanol or ethanol) at the more-substituted carbon atom of the intermediate bicyclic aziridinium ion 13 (Scheme 3). This strained intermediate 13 is most probably formed via intramolecular nucleophilic displacement of bromide in the initially formed 3-bromoazetidine 11. The proposed pathway concurs with the previously reported synthesis of 3-methoxy-3-methylazetidines 3 (R¹ = CH₂Ar, R² = Me, Scheme 3) comprising the smooth ring expansion of 2-bromomethyl-2-methylaziridines 2 via bicyclic aziridinium intermediates 14 upon heating in methanol in the presence of NaBH₄. In the same study, it has been shown that 3-methoxy-3-methylazetidines 3 can also be obtained starting from 3-bromoazetidines 4 applying the same reaction conditions (NaBH₄, MeOH, Δ).
The latter transformation served as a starting point to thoroughly investigate the synthetic potential of 3-bromo-3-methylazetidines for the preparation of novel 3-substituted azetidines. For this purpose, 3-bromo-3-methyl-1-(4-methylbenzyl)azetidine 9 and 3-bromo-1-t-butyl-3-methylazetidine 11 were selected as eligible substrates for reactions with different nucleophiles.

Upon heating of 3-bromo-1-t-butylazetidine 11 (R = tBu) in different alcohols (MeOH, EtOH, iPrOH) for 24-72 hours under reflux, the corresponding 3-alkoxyazetidines 12a-c were formed in pure form after basic work-up (Scheme 4). Furthermore, the reactions of azetidines 9 and 11 with 1-2.2 equiv of different phenols and 2-5 equiv of K$_2$CO$_3$ in tetrahydrofuran or acetonitrile for 4-48 hours under reflux provided the corresponding 3-aryloxyazetidines 15a-d in good yields, which were purified by means of column chromatography on silica gel in order to obtain analytically pure samples.$^{13}$ When substrates 9 and 11 were heated in water or water/CH$_2$Cl$_2$ (9/1) for 10-24 hours under reflux in the presence of 5 equiv of KOH or 2 equiv of K$_2$CO$_3$, 1-t-butyl-3-methyl-3-azetidinol 16a and 3-methyl-1-(4-methylbenzyl)-3-azetidinol 16b were obtained in high yields (Scheme 4).$^{14}$ The above-described findings support the suitability of 3-bromo-3-methylazetidines as substrates for nucleophilic substitutions by different oxygen-centered nucleophiles.

Scheme 4. Reactivity of 3-bromo-3-methylazetidines 9 and 11 towards oxygen nucleophiles.

In the literature, it is known that azetidine-3-carbonitriles can be prepared via nucleophilic substitution of 3-mesyloxy- and 3-tosyloxyazetidines.\textsuperscript{15} In that respect, 3-bromo-3-methylazetidines 9 and 11 were also shown to be good substrates for the synthesis of azetidine-3-carbonitriles 17a,b upon treatment with 1.5 equiv of KCN in dimethylsulfoxide or acetonitrile for 13-22 hours under reflux (Scheme 5). Azetidine 17a was purified via distillation and azetidine 17b by means of column chromatography on silica gel, which were then used for further derivatization.

The hydrolysis of the cyano group in azetidines 17 can provide an access towards cyclic amino acids which can be considered as analogues of azetidine-2-carboxylic acid, a natural molecule isolated from \textit{Convallaria majalis} (lily-of-the-valley) and endowed with impressive biological activities such as the inhibition of the proliferation of \textit{Escherichia coli}, alteration of the structure of collagen, keratin and haemoglobin in human proteins, and teratogenic effects and various malformations in animals.\textsuperscript{16} Thus, the reaction of azetidine 17a with 5 equiv of KOH in ethanol under reflux resulted in the corresponding new amino acid 1-t-butyl-3-methylazetidine-3-carboxylic acid 18 (23\% after purification on a Dowex column) after a prolonged reaction time (120 hours) and without traces of the corresponding amide. The carboxy group in azetidine 18 was then successfully reduced using 2 molar equiv of LiAlH\textsubscript{4} in diethyl ether for 3 hours at room temperature to form 3-(hydroxymethyl)azetidine 19 in 90\% yield. Furthermore, 3-(aminomethyl)azetidine 20 was obtained after reduction of
the cyano group with 2 molar equiv of LiAlH₄ in diethyl ether for 14 hours at room temperature.¹⁶

A number of experiments were also performed concerning the hydrolysis of the cyano group in 1-(4-methylbenzyl)azetidine-3-carbonitrile 17b. The treatment of azetidine 17b with 5 equiv of KOH in EtOH/H₂O (5/1) under microwave irradiation (150 °C, 15 min, 150 W) and subsequent neutralization with a solution of hydrochloric acid (1M) gave the corresponding new amino acid 21. Interestingly, two isomeric structures (ratio 3/2) of azetidine 21 were observed upon NMR analysis (CD₃OD), which can be attributed to the zwitterionic nature of this compound providing two diastereomeric counterparts. The purification of amino acid 21 on Dowex H⁺ (NH₄OH) afforded ammonium 3-methyl-1-(4-methylbenzyl)azetidine-3-carboxylate 22 as a single isomer in pure form.¹⁷ These observations further support the synthetic utility of 3-bromo-3-methylazetidines as substrates for nucleophilic displacements, e.g. towards the synthesis of versatile 3-methylazetidine-3-carbonitriles.

In conclusion, efficient syntheses of 3-bromo-3-methylazetidines 9 and 11 were disclosed starting from 2-bromomethyl-2-methylaziridine 8 and β,γ-dibrominated amine 10, respectively. Through a number of examples, the azetidines 9 and 11 were shown to easily undergo nucleophilic substitution with different nucleophiles, providing a convenient method for the preparation of new synthetically and biologically attractive 3-substituted azetidines 23.
such as 3-alkoxy-, 3-aryloxy-, 3-hydroxy-, 3-cyano-, 3-carboxy-, 3-(aminomethyl)- and 3-(hydroxymethyl)azetidines (Scheme 6).

Scheme 6. 3-Bromo-3-methylazetidines 9 and 11 as building blocks for the preparation of 3-substituted 3-methylazetidines 23.

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References and notes

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As a representative example, the synthesis of 1-t-butyl-3-(4-ethylphenoxy)-3-methylazetidine 15b is described here. 3-Bromo-1-t-butyl-3-methylazetidine 11 (1.03 g, 5 mmol) was dissolved in THF (10 mL), after which 4-ethylphenol (0.61 g, 1 equiv) and K₂CO₃ (1.38 g, 2 equiv) were added, and the mixture was stirred for 48 hours under reflux. The reaction mixture was poured into an aqueous sodium hydroxide solution (1M, 15 mL) and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic extracts were washed with H₂O (2 x 15 mL) and brine (15 mL). Drying (MgSO₄), filtration of the drying agent and evaporation of the solvent afforded 1-t-butyl-3-(4-ethylphenoxy)-3-methylazetidine 15b (0.88 g, 71%), which was purified by column chromatography (CH₂Cl₂:MeOH 96/4, Rf = 0.15) in order to obtain an analytically pure sample. 1-t-Butyl-3-(4-ethylphenoxy)-3-methylazetidine 15b: Yield 71%; ¹H NMR (270 MHz, CDCl₃) δ 0.97 (9H, s), 1.21 (3H, t, J = 7.6 Hz), 1.68 (3H, s), 2.58 (2H, q, J = 7.6 Hz), 3.32 (2H, d x d, J = 6.9, 1.6 Hz), 3.45 (2H, d, J = 6.9), 6.64-7.07 (4H, m). ¹³C NMR (67.8 MHz, CDCl₃) δ 15.8, 22.0, 24.2, 27.9, 52.0, 58.8, 72.1, 116.7, 128.6, 136.5, 153.2. IR (NaCl, cm⁻¹) νmax = 2958, 1602, 1503, 1356, 1310, 1228, 828. MS (70 eV) m/z (%): 247 (M⁺, 5), 232 (16), 163 (15), 162 (100), 147 (12), 133 (36), 122 (21), 120 (14), 119 (57), 107 (44), 86 (28), 70 (30), 57 (18), 55 (14).

As a representative example, the synthesis of 3-methyl-1-(4-methylbenzyl)-3-azetidinol 16b is described here. 3-Bromo-3-methyl-1-(4-methylbenzyl)azetidine 9 (1.27 g, 5 mmol) was added to a two-phase solvent system (H₂O/CH₂Cl₂ 9/1, 15 mL), after which KOH (1.40 g, 5 equiv) was added, and the mixture was stirred for 10 hours under reflux. The reaction mixture was poured into water (15 mL) and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic extracts were washed with H₂O (2 x 15 mL) and brine (15 mL). Drying (MgSO₄), filtration of the drying agent and evaporation of the solvent afforded 3-methyl-1-(4-methylbenzyl)-3-azetidinol 16b as white crystals (0.92 g, purity > 95% based on NMR analysis). 3-Methyl-1-(4-methylbenzyl)-3-azetidinol 16b: White crystals; Mp = 85.3 °C. Yield 96%; ¹H NMR (300 MHz, CDCl₃) δ 1.40 (3H, s), 2.25 (3H, s), 2.99 and 3.20 (4H, 2 x d, J = 6.9 Hz), 3.53 (3H, s), 7.02-7.10 (4H, m). ¹³C NMR (75 MHz, ref = CDCl₃) δ 21.2, 26.1, 63.2, 68.0, 68.9, 128.6, 128.8, 134.9, 136.8. IR (neat, cm⁻¹) νOH = 3359. MS (70 eV) m/z (%): 192 (M⁺ + 1, 100).

16 Synthesis of 3-aminomethyl-1-t-butyl-3-methylazetidine 20. To an ice-cooled solution of 1-t-butyl-3-methylazetidine-3-carbonitrile 17a (0.76 g, 5 mmol) in dry diethyl ether (10 mL), LiAlH₄ (0.38 g, 2 equiv) was slowly added, and the reaction mixture was stirred first for 3 hours at 0 °C, and then for 14 hours at room temperature. The resulting mixture was poured cautiously into water (15 mL) and extracted with Et₂O (3 x 15 mL). The combined organic extracts were washed with H₂O (2 x 15 mL) and brine (15 mL). Drying (MgSO₄), filtration of the drying agent and evaporation of the solvent afforded 3-aminomethyl-1-t-butyl-3-methylazetidine 20 (0.76 g, 97%) in high purity (purity > 95% based on NMR analysis).

3-Aminomethyl-1-t-butyl-3-methylazetidine 20: Yield 97%; ¹H NMR (270 MHz, CDCl₃) δ 0.94 (9H, s), 1.18 (3H, s), 1.63 (2H, broad s), 2.78 (2H, s), 2.91 and 3.03 (4H, 2 x d, J = 7.3 Hz). ¹³C NMR (67.8 MHz, CDCl₃) δ 22.7, 24.1, 33.4, 50.9, 51.6, 55.2. IR (NaCl, cm⁻¹) νNH₂ = 3680-3000. MS (70eV) m/z (%) no M⁺, 141 (M⁺-Me, 58), 84 (36), 72 (72), 70 (100), 57 (69), 55 (47), 49 (35).

17 Synthesis of ammonium 3-methyl-1-(4-methylbenzyl)azetidine-3-carboxylate 22. 1-(4-Methylbenzyl)azetidine-3-carbonitrile 17b (0.20 g, 1 mmol) was dissolved in EtOH/H₂O (5/1, 5 mL), after which KOH (0.28 g, 5 equiv) was added. The mixture was placed in an 6-mL sealed glass vessel, provided with an appropriate stirring bar and subjected to microwave conditions (150 °C, 15 min, 150 W). The reaction mixture was neutralized with a solution of hydrochloric acid (1M) to pH = 7 and water was evaporated under high vacuum. Purification of amino acid 21 (two isomeric forms confirmed by NMR analysis) by means of ion-exchange chromatography on Dowex H⁺ (50 x 8-100) afforded ammonium 3-methyl-1-(4-methylbenzyl)azetidine-3-carboxylate 22 (0.20 g, 85%). White crystals; Mp > 350 °C. Yield 85%; ¹H NMR (300 MHz, CD₃OD) δ 1.41 (3H, s), 2.24 (3H, s), 3.73 and 4.20 (4H, 2 x d, J = 10.7 Hz), 4.20 (2H, s), 7.16-7.27 (4H, m). ¹³C NMR (75 MHz, CD₃OD) δ 21.3, 23.3, 42.3, 59.4, 63.7, 128.6, 131.0, 131.1, 141.2, 180.5. IR (neat, cm⁻¹) νCO = 1603. MS (70eV) m/z (%) 218 (M⁺ + 1, 100).