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A simple and general synthetic route to *N*-alkylazetidines from 1,2-amino alcohols

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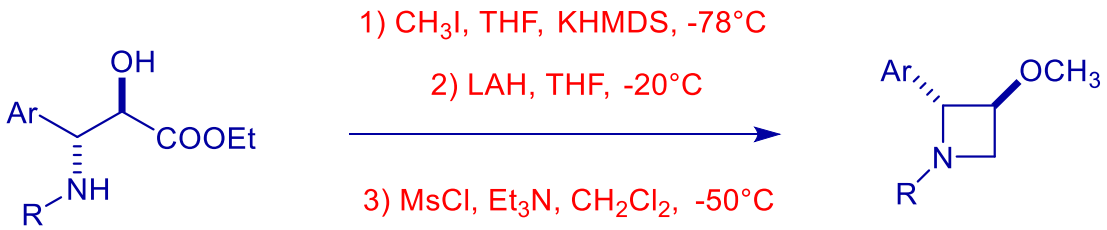
Abstract

Azetidines and their derivatives are of major interest since they exhibit important biological activities besides their utility as synthetic intermediates. Herein we describe a mild and efficient method for the formation of functionalized *N*-alkyl-azetidines in moderate-to-good yields starting from 1,2-aminoalcohols. This azetidine synthesis proceeds through three steps involving O-methylation of the starting 1,2-amino alcohols, reduction of the ester group of the resulting 1,2-aminoethers, and subsequent mesylation/intracyclization of the 1,3-amino alcohol intermediates.



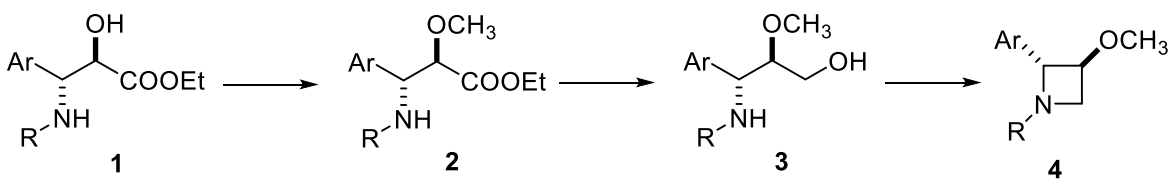
Keywords: O-methyl-1,2-amino alcohols, O-methyl-1,3-amino alcohols, ring-expansion reactions, trans-N-alkylazetidines.

Introduction

Azetidines are an important class of four-membered ring systems in modern synthetic chemistry.[1,2] They have received much attention as starting precursors in the synthesis of several nitrogen-containing compounds of synthetic[3-6] and biological[7-9] interest. Furthermore, these small heterocycles are of great interest since they represent the structural core of various natural products and pharmaceutical agents. For instance, they are potential nicotinic acetylcholine receptors (nAChRs),[10] anticancer agents (CDK8 inhibitors),[11] inhibitors of monoacylglycerol lipase (MAGL).[12] They are also used as relaxants,[13] antibiotics[14] and for cardiovascular desease.[15] Recently, Schreiber *et al.*[16] reported the synthesis of an azetidine having antimalarial properties (BRD3914). Conversely, their inherent ring strain makes them excellent candidates for both nucleophilic ring opening and ring-expansion reactions.[17-18] All of these reasons have enhanced the value of azetidine derivatives in the synthesis of nitrogen-containing compounds. Indeed, during the last few years, the chemistry of azetidines has gradually been developed, and a wide range of synthetic methods for the preparation of these compounds have been reported. Reduction of β-lactams[19-20] is considered to be one of the most convenient approaches for the synthesis of azetidines. The most common methods to obtain substituted azetidines involves the cyclization of allylamines,[21] γ-amino alcohols,[22-25] γ-halo amines,[26-27] 1,3-diols,[28] aldimines,[29] trifluoroacetoacetate[30], and through anionic C-alkylation.[31] The synthesis of azetidines can also be accomplished by either the expansion of aziridines[32] or oxiranes[33] with a variety of nucleophiles or by the contraction[34] of pyrrolydinones. Important progress has been recently made, and new methodologies based on organocatalysis have appeared for the preparation of these heterocycles in enantio-enriched form.[35-37] One of the most economic and easiest ways to obtain a racemic mixture of N-alkyl 2-substituted azetidines, however, is the use of 1,2-amino alcohols[38-40] as starting materials.

In our previous work, we reported on the transformation of *erythro*-1,2-amino alcohols **1** into a range of nitrogen heterocyclic compounds including 1,4-oxazin-2-ones, aziridine-2-carboxylates, 1,3-oxazolidin-2-ones, functionalized cyclic sulfamidates and oxazol-2-one-5-carboxylates.[41] These successful results motivated us to further explore the potential of compounds **1** to yield other types of azaheterocycles. Amino alcohols **1** were prepared, through controlled ring opening of ethyl trans-β-phenylglycidate with amines, as described previously.[42]

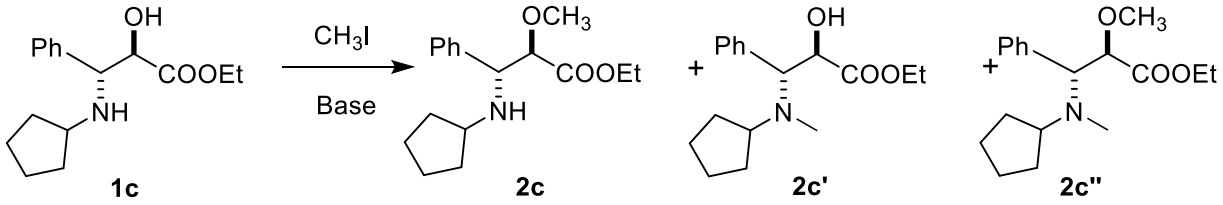
Compared to the widely explored chemistry of activated azetidines, the synthesis of their non-activated counterparts has received only limited interest in the literature. This prompted us to describe the synthesis of new diversely substituted non-activated azetidines **4** in this paper. This synthesis is carried out via a three-step sequence involving (a) O-methylation of 1,2-amino alcohols **1**, (b) reduction of the ester group of **2** and (c) a one-pot mesylation/intracyclization of **3**. This protocol yields the advantages of a general and efficient synthetic strategy involving simple procedure, mild reaction conditions, and metal-free conditions, from amino alcohols bearing an electron-donating group on the nitrogen atom. The synthetic route for the formation of the target compound **4** is shown in Scheme 1.



Scheme 1. Synthetic transformation of 1,2-amino alcohols.

Results and Discussion

The first step of this synthesis was the O-methylation of compounds **1** (see Table 1). To this end, our initial attempts were carried out using N-cyclopentyl-amino-alcohol **1c** as a starting material. A first attempt using 1.1 equiv of CH_3I with 1.1 equiv of base (NaH) at room temperature resulted in the formation of a mixture of O-methyl-1,2-amino-alcohol **2c** in 26% yield, N-methyl-1,2-amino alcohol **2c'** in 26% yield, and O,N-dimethyl-1,2-amino alcohol **2c"** in 4% yield, respectively (Scheme 2).

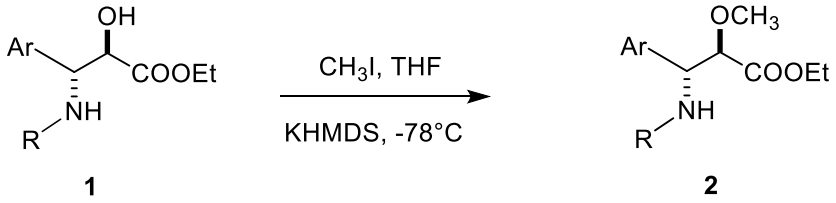


Base= NaH, rt	26%	26%	4%
Base= KHMDS, -78°C	75%	—	—

Scheme 2. Synthesis of O-methyl 1,2-amino-alcohol derivatives **2c**, **2c'** and **2c''**.

We then thought that using a bulkier base and operating at a lower temperature could improve the efficiency of this reaction and its chemoselectivity. Therefore, when potassium bis(trimethylsilyl) (KHMDS) was used in anhydrous tetrahydrofuran (THF) at -78 °C, only compound **2c** was obtained with a 75% yield with no competitive formation of the by-products **2c'** and **2c''**. Based on this promising result, our attention was turned to the generality of this O-methylation using a series of racemic 1,2-amino alcohols **1a-g**. The results are presented in Table 1.

Table 1. Preparation of O-methyl 1,2-amino alcohols **2**



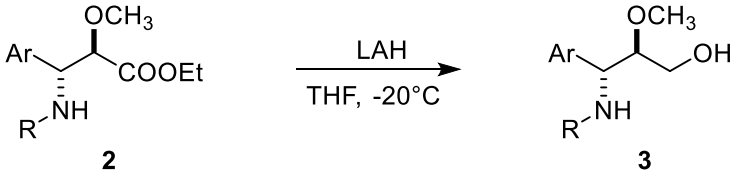
Entry	Product **2**	Ar	R	Yield[a] (%)
1	**2a**	C_6H_5	*i*-C_3H_7	76
2	**2b**	C_6H_5	*c*-C_3H_5	68
3	**2c**	C_6H_5	*c*-C_5H_9	75
4	**2d**	*p*-ClC_6H_4	*c*-C_5H_9	40
4	**2e**	C_6H_5	*c*-C_6H_{11}	82
6	**2f**	C_6H_5	*c*-C_7H_{13}	84
7	**2g**	C_6H_5	*c*-C_8H_{15}	92

[a] isolated yields

As shown in Table 1, the reactions of racemic 1,2-amino alcohols **1** with CH_3I/KHMDS proceeded chemoselectively, and were complete within 2h to produce, in all cases, the corresponding compounds **2** in moderate-to-good yields as the sole reaction products. When the phenyl moiety was substituted with an electron-withdrawing group (entry 4, Ar = *p*-ClC_6H_4), the expected product **2d** was formed in a moderate yield (40%). This may be due to the formation of undesired by-products (TLC).

The second step of the synthesis was the reduction of compounds **2**. Indeed, when the reaction was carried out in the presence of 0.8 equiv of lithium aluminium hydride (LAH), under the standard reaction conditions (i.e., anhydrous THF, low temperature), the starting O-methyl 1,2-amino alcohols **2** were cleanly converted in a few minutes into the corresponding O-methyl-1,3-amino-alcohols **3** (Table 2).

Table 2. Preparation of O-methyl 1,3-amino alcohols **3**



2 **3**

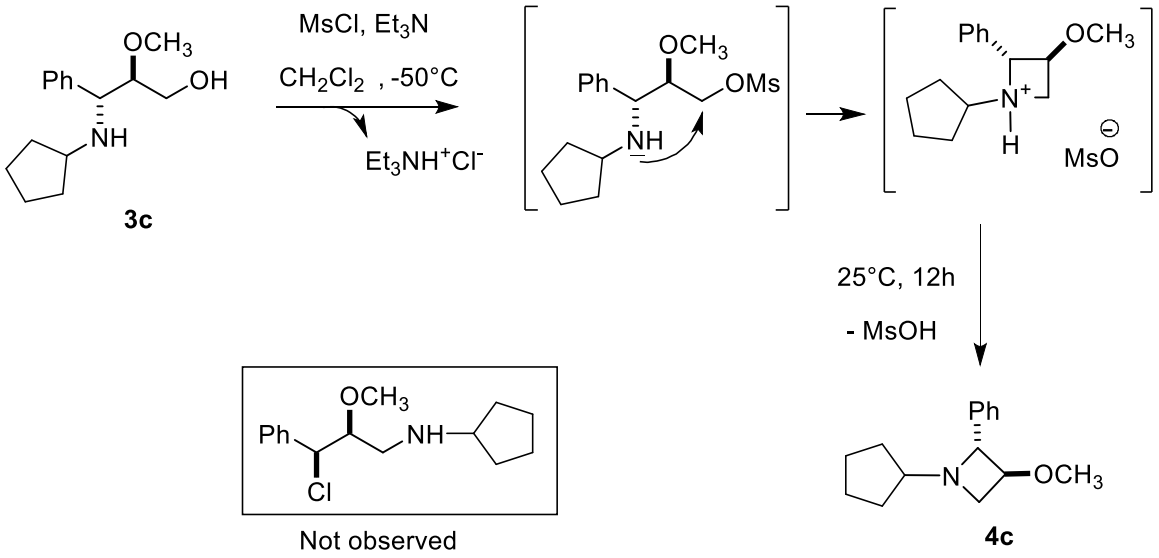
Entry	Product **3**	Ar	R	Yield[a] (%)
1	**3a**	C_6H_5	*i*-C_3H_7	82
2	**3b**	C_6H_5	*c*-C_3H_5	58
3	**3c**	C_6H_5	*c*-C_5H_9	82
4	**3d**	*p*-ClC_6H_4	*c*-C_5H_9	92
5	**3e**	C_6H_5	*c*-C_6H_{11}	88
6	**3f**	C_6H_5	*c*-C_7H_{13}	75
7	**3g**	C_6H_5	*c*-C_8H_{15}	86

[a] isolated yields

In all cases in Table 2, the yields are good-to-excellent and appear to not depend on the N-substituent of the starting **2**.

Finally, the transformation of O-methyl-1,3-amino alcohols **3** into azetidines **4** was investigated. Inspired by the reported successful and efficient synthesis of azetidines,[13] and assuming that the main key of this synthesis is the transformation of the alcohol group of **3** into a suitable leaving group, we envisaged that the mesylation of the amino alcohol **3c** (MsCl 1.2 equiv, Et_3N 2.5 equiv, CH_2Cl_2, -50 °C), taken as a model reaction, would be amenable to the cyclization and generation of the azetidine **4c**. Disappointingly, however, the reaction did not afford the expected cyclic product under these conditions. Unlike the results reported by Couty et al.,[31] it is proposed that this reaction resulted probably in the formation of the mesylate intermediate which was unstable, and therefore, not isolable.

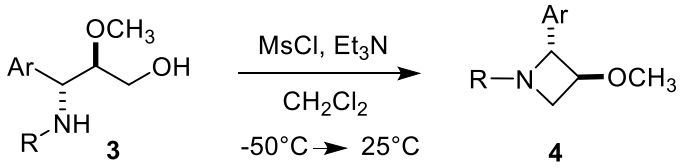
When this mesylation was conducted under the same reaction conditions, and the resulting mesylate was stirred for 12 h at room temperature, the azetidine **4c** was isolated in good yield (79%) without any traces of the corresponding chloride[30] (Scheme 3). The cyclic structure of **4c** was confirmed by NMR spectroscopic analyses. The coupling constant of the H-2 and H-3 protons (~5 – 6 Hz) indicated their *trans*-orientation.[43]



Scheme 3. Synthesis of N-cyclopentyl azetidine **4c.**

With optimized reaction conditions in hand, the scope of the transformation reaction was investigated. The results are presented in Table 3.

Table 3. Preparation of N-alkyl azetidines **4**



Entry	Product **4**	Ar	R	Yield[a] (%)
1	**4a**	C_6H_5	*i*-C_3H_7	75
2	**4b**	C_6H_5	*c*-C_3H_5	80
3	**4c**	C_6H_5	*c*-C_5H_9	79
4	**4d**	*p*-ClC_6H_4	*c*-C_5H_9	82
5	**4e**	C_6H_5	*c*-C_6H_{11}	-
6	**4f**	C_6H_5	*c*-C_7H_{13}	58
7	**4g**	C_6H_5	*c*-C_8H_{15}	65

[a] Isolated yields

As can be seen from Table **3**, a good conversion of the starting 1,3-amino alcohols **3** to the corresponding azetidines **4** was observed. There is a slight difference, however, in the reactivity that essentially depended on the nucleophilic character of the amino alcohol, which was influenced by the nature of the *N*-substituent. Indeed, in entries 1-4, reactions proceeded smoothly, and compounds were isolated in good yields (75-82%). The reaction of 1,3-amino alcohols (entries 6 and 7) did take place and the cyclic compounds were isolated in moderate yields (58% and 65%, respectively). All attempts to transform N-cyclohexyl amino alcohol **3e** into the

corresponding azetidine **4e** were unsuccessful (entry 5), however, instead affording a complex mixture of products with no sign of the starting material.

Conclusions

1,2-amino alcohols proved to be useful starting materials for the production of four-membered azaheterocycles. A general and efficient three-step protocol for the synthesis of structurally diverse N-cycloalkyl azetidines in moderate-to-good yields has been developed. Reactions were performed using simple chemistry, under mild conditions, from easily available starting materials. We believe that these azetidines could be very useful for constructing nitrogen-containing molecules such as 1,3-oxazinan-2-ones, which have diverse biological activities. Further work in this regard is under investigation in our laboratory.

Experimental Section

General. All reagents were purchased from Sigma-Aldrich. Reaction progress was monitored by TLC on silica gel plates (Fluka Kieselgel 60 F_{254}). For column chromatography, Fluka Kieselgel 70-230 mesh was used. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV 300 spectrometer in $CDCl_3$ as solvent and TMS as the internal standard. High-resolution mass spectra were obtained using an Autoflex III (Bruker) with electron impact (EI) ionization methods.

General procedure for the synthesis of (*Erythro*)-O-methyl-1,2-amino alcohols 2(a-g). KHMDS (3.9 mmol) was slowly added to a stirred solution of 1,2-Amino alcohols **1** (1.95 mmol) and iodomethane (3.9 mmol) in anhydrous THF (10 mL) under nitrogen at -78 °C and the mixture was allowed to stir for 2 hours. After completion of the reaction (as indicated by TLC), the mixture was filtered and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography using a mixture of dicholoromethane/EtOAc (7:3) as eluent to give **2** as colorless oils.

Ethyl 3-isopropylamino-2-methoxy-3-phenylpropionate (2a). Yield (392 mg, 76%); NMR ^{1}H (300 MHz $CDCl_3$) δ: 0.98, 1.00 (2d, 6H, *J* 6.1 Hz, *J* 5.9 Hz), 1.15 (t, 3H, *J* 7.1 Hz), 1.86 (brs, 1H, NH), 2.58 (m, 1H), 3.39 (s, 3H), 4.01 (d, 1H, *J* 5.3 Hz), 4.13 (q, 2H, *J* 7.1 Hz), 4.10 (d, 1H, *J* 5.3 Hz), 7.27 (m, 5H); NMR ^{13}C (75 MHz $CDCl_3$) δ: 14.2, 21.6, 24.0, 45.0, 59.0, 60.7, 61.3, 84.6, 127.5, 128.1, 128.2, 139.9, 170.70; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{15}H_{24}NO_3$: 266.1750, found 266.1761.

Ethyl 3-cyclopropylamino-2-methoxy-3-phenylpropionate (2b). Yield (349 mg, 68%); NMR ^{1}H (300 MHz $CDCl_3$) δ: 0.23- 0.37 (m, 4H), 1.07 (t, 3H, *J* 7.1 Hz), 1.81-1.88 (m, 1H), 2.32 (brs, 1H, NH), 3.32 (s, 3H), 3.99 (s, 2H), 4.01 (q, 2H, *J* 7,1 Hz), 7.18 (m, 5H); NMR ^{13}C (300 MHz $CDCl_3$) δ: 6.2, 6.7, 14.1, 28.1, 59.0, 60.7, 64.1, 83.9, 127.5, 128.1, 128.2, 139.6, 171.0; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{15}H_{22}NO_3$: 264.1594, found 264.1604.

Ethyl 3-cyclopentylamino-2-methoxy-3-phenylpropionate (2c). Yield (426 mg, 75%); IR (ν cm^{-1}): 1749, 3335; NMR ^{1}H (300 MHz $CDCl_3$) δ: 1.16 (t, 3H, *J* 7.1 Hz), 1.28-1.50 (2m, 4H), 1.65 (m, 4H), 1.90 (brs, 1H, NH), 2.85 (m, 1H), 3.35 (s, 3H), 3.99 (s, 2H), 4.09 (q, 2H, *J* 7.1 Hz), 7.25 (s, 5H); NMR ^{13}C (300 MHz $CDCl_3$) δ: 14.2, 24.0, 32.3, 33.9, 56.4, 58.9, 60.7, 62.7, 84.7, 127.4, 128.1, 139.8, 171.0; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{17}H_{26}NO_3$: 292.1907, found 292.1894.

Ethyl 3-cyclopentylamino-2-methoxy-3-parachorophenylpropionate (2d). Yield (254 mg, 40%); NMR ^{1}H (300 MHz $CDCl_3$) δ: 1.17 (t, 3H, *J* 7.1Hz), 1.2-1.68 (m , 8H), 2.00 (brs, 1H, NH), 2.78 (q , 1H , *J* 6.4 Hz), 3.39 (s, 3H),

3.99 (d,1H, *J* 5.3 Hz), 4.04 (q, 2H, J 7.1 Hz), 4.01 (d, 1H, *J* 5.3 Hz), 7.22 and 7.28 (A_2B_2, 4H, *J* 8.7 Hz); NMR ^{13}C (300 MHz $CDCl_3$) δ: 14.2, 23.9, 31.9, 32.2, 33.8, 56.3, 59.0, 60.9, 62.0, 84.2, 128.3, 129.4, 133.2, 138.1, 170.8; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{17}H_{25}ClNO_3$: 326.1517, found 326.1522.

Ethyl 3-cyclohexylamino-2-methoxy-3-phenylpropionate (2e). Yield (487 mg, 82%); IR (ν cm^{-1}): 1749, 3337; NMR ^1H (300 MHz $CDCl_3$) δ: 1.00-1.15 (m, 2H), 1.13 (t, 3H, *J* 7.1 Hz), 1.53 (brs, 1H, NH), 1.61-1,67 and 1.80-1.90 (2m, 8H), 2.24 (m, 1H), 3.36 (s, 3H), 3.98 (d, 1H, *J* 5.6 Hz), 4.09 (q, 2H, *J* 7.1 Hz), 4.13 (d, 1H, *J* 5.6 Hz); 7.20-7.33 (m, 5H); NMR ^{13}C (300 MHz $CDCl_3$) δ: 14.2, 24.5, 24.9, 26.1, 32.4, 34.4, 53.0, 58.9, 59.0, 60.7, 84.7, 127.4, 128.0, 128.1, 139.8, 171,0. HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{18}H_{28}NO_3$: 306.2064, found 306.2062.

Ethyl 3-cycloheptylamino-2-methoxy-3-phenylpropionate (2f). Yield (523 mg, 84%); NMR ^1H (300 MHz $CDCl_3$) δ: 1.09 (t, 3H, *J* 7.2 Hz), 1.20- 1.75 (m, 13H), 2.30-2.40 (m, 1H), 3.29 (s, 3H), 3.92 (d, 1H, *J* 5.6 Hz), 3.98 (d, 1H, *J* 5.6 Hz), 4.03 (q, 2H, *J* 7.2 Hz), 7.19 (m, 5H); NMR ^{13}C (300 MHz $CDCl_3$) δ: 14.2, 23.8, 24.3, 25.6, 28.1, 28.5, 33.0, 36.3, 54.9, 59.0, 60.7, 61.1, 84.7, 127.4, 128.0, 128.2, 139.6, 171.0; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{19}H_{30}NO_3$: 320.2220, found 320.2232.

Ethyl 3-cyclooctylamino-2-methoxy-3-phenylpropionate (2g). Yield (597 mg, 92%); NMR ^1H (300 MHz $CDCl_3$) δ:1.06 (t, 3H, *J* 7.1 Hz); 1.20-1.70 (m, 15H), 2.45 (m, 1H), 3.33 (s, 1H), 3.95 (d, 1H, *J* 5.8 Hz), 4.10 (q, 2H, *J* 7.1 Hz), 4.06 (d, 1H, *J* 5.8 Hz), 7.26 (s, 5H); NMR ^{13}C (300 MHz $CDCl_3$) δ: 14.2, 23.6, 23.8, 25.6, 27.2, 27.7, 34.0, 53.7, 58.8, 60.6, 61.2, 84.8, 127.4, 128.0, 128.1, 139.9, 171.0; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{20}H_{32}NO_3$: 334.2377, found 334.2364.

General procedure for the synthesis of (*Erythro*)-O-methyl-1,3-amino alcohols 3(a-f). Lithium aluminum hydride (1.55 mmol) was slowly added to a stirred solution of O-methyl-1,3-Amino Alcohols **2** (1.94 mmol) in anhydrous THF (10 mL) under nitrogen at -20 °C and then the mixture was allowed to stir for 30 min at room temperature. After completion of the reaction, the mixture was quenched with aqueous solution of ammonium chloride and extracted with CH_2Cl_2. The mixture was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using a mixture of n-hexane/EtOAc (6:4) as eluent to give **3** as colorless oils.

3-Isopropylamino-2-methoxy-3-phenylpropanol (3a). Yield (355 mg, 82%); NMR ^1H (300 MHz $CDCl_3$) δ: 1.01, 1.03 (2d, 6H, *J* 6.1 Hz, *J* 6.4 Hz), 2.69 (hept, 1H, *J* 6.3 Hz), 3.28 (s, 3H), 3.31 (m, 1H), 3.50 (brs, 2H, NH, OH), 3.62-3.79 (AB, 2H, J_1 11.6 Hz, J_2 5.7 Hz, J_3 3.6 Hz), 4.04 (d, 1H, *J* 6.5 Hz), 7.31 (s, 5H); NMR ^{13}C (300 MHz $CDCl_3$) δ: 21.1, 24.2, 45.5, 57.7, 62.6, 63.4, 83.0, 127.5, 127.6, 128.5, 140.3; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{13}H_{22}NO_2$: 224.1645, found 224.1639.

3-Cycloproylamino-2-methoxy-3-phenylpropanol (3b). Yield (249 mg, 58%); NMR ^1H (300 MHz $CDCl_3$) δ: 0.24-0.38 (m, 4H), 1.89 (m, 1H), 2.90 (brs, 2H, NH, OH), 3.18 (s, 3H), 3.20-3.27 (m, 1H), 3.50- 3.70 (AB, 2H, J_1 11.5 Hz, J_2 6.1 Hz, J_3 4.2 Hz), 3.85 (d, 1H, *J* 7.1 Hz), 7.24 (m, 5H); NMR ^{13}C (300 MHz $CDCl_3$) δ: 5.9, 7.1, 29.0, 58.0, 63.0, 66.7, 82.7, 127.4, 127.6, 128.5, 140.8; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{13}H_{20}NO_2$: 222.1488, found 222.1492.

3-Cyclopentylamino-2-methoxy-3-phenylpropanol (3c). Yield (396 mg, 82%); NMR ^1H (300 MHz $CDCl_3$) δ: 1.26-1.38 and 1.39-1.52 (2m, 4H), 1.62-1.76 (m, 4H), 2.93 (quint, 1H, *J* 6.6 Hz), 3.27 (s, 4H), 3.25-3.36 (m, 3H, NH, OH), 3.62-3.78 (AB, 2H, J_1 11.6 Hz, J_2 5.8 Hz, J_3 3.7 Hz), 3.96 (d, 1H, *J* 6.8 Hz), 7.25-7.39 (m, 5H); NMR ^{13}C (300 MHz $CDCl_3$) δ: 23.6, 31.9, 34.1, 56.7, 57.7, 62.8, 64.9, 83.1, 127.6, 127.8, 128.5, 140.6; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{15}H_{24}NO_2$: 250.1801, found 250.1810.

3-Cyclopentylamino-2-methoxy-3-parachorophenylpropanol (3d). Yield (506 mg, 92%); NMR ^1H (300 MHz $CDCl_3$) δ: 1.16-1.45 (m, 4H), 1.52-1.70 (m, 4H), 2.82 (quint, 1H, *J* 6.7 Hz), 3.21 (s, 4H), 3.17-3.22 (m, 3H, NH, OH), 3.52-3.70 (AB, 2H, J_1 11.6 Hz, J_2 5.8 Hz, J_3 3.7 Hz), 3.88 (d, 1H, *J* 6.7 Hz), 7.21 and 7.25 (A_2B_2, 4H, *J* 8.4); NMR ^{13}C (300 MHz $CDCl_3$) δ: 23.6, 23.7, 31.8, 33.9, 56.7, 57.7, 62.4, 64.1, 82.9, 128.6, 129.1, 133.1, 138.9; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{15}H_{23}ClNO_2$: 284.1411, found 284.1401.

3-Cyclohexylamino-2-methoxy-3-phenylpropanol (3e). Yield (510 mg, 88%); IR (ν cm^{-1}): NMR ^1H (300 MHz $CDCl_3$) δ: 1.08-1.26 (m, 6H), 1.53-2.03 (m, 4H), 2.38 (m, 1H), 3.26 (s, 3H), 3.38 (m, 1H), 3.61-3.82 (AB, 2H, J_1 11.7 Hz, J_2 5.7 Hz, J_3 3.5 Hz), 4.17 (d, 1H, *J* 6.7 Hz), 4.38 (brs, 2H, NH, OH), 7.28-7.40 (m, 5H); NMR ^{13}C (300 MHz $CDCl_3$) δ: 24.5, 25.0, 25.8, 31.4, 34.1, 53.4, 57.8, 62.3, 62.4, 82.3, 127.6, 127.7, 128.6, 139.6; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{16}H_{26}NO_2$: 264.1958, found 264.1962.

3-Cycloheptylamino-2-methoxy-3-phenylpropanol (3f). Yield (403 mg, 75%); NMR ^1H (300 MHz $CDCl_3$) δ: 1.20-1.90 (m, 13H), 2.48-2.58 (m, 1H), 3.25 (s, 3H), 3.23-3.29 (m, 3H, NH, OH), 3.60-3.80 (AB, 2H, J_1 11.6 Hz, J_2 8.0 Hz, J_3 3.6 Hz); 4.12 (d, 1H, *J* 7.0 Hz); 7.25-7.39 (m, 5H); NMR ^{13}C (300 MHz $CDCl_3$) δ: 23.6, 24.2, 28.3, 28.6, 32.5, 36.7, 54.8, 57.7, 62.8, 63.4, 83.0, 127.4, 128.2, 129.4, 140.7; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{17}H_{28}NO_2$: 278.2114, found 278.2119.

3-Cyclooctylamino-2-methoxy-3-phenylpropanol (3g). Yield (486 mg, 86%); NMR ^1H (300 MHz $CDCl_3$) δ: 1.22-1.80 (m, 14H), 2.55 (m, 1H), 3.19-3.32 (m, 3H, NH,OH), 3.26 (s, 1H), 3.62-3.78 (AB, 2H, J_1 11.6 Hz, J_2 5.8 Hz, J_3 3.4 Hz), 4.04 (d, 1H, *J* 6.7 Hz), 7.27-7.39 (m, 5H); NMR ^{13}C (300 MHz $CDCl_3$) δ: 23.5, 23.7, 25.6, 27.3, 27.7, 29.4, 29.7, 34.1, 53.8, 57.7, 62.9, 63.5, 83.1, 127.4, 127.5, 128.5, 140.8; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{18}H_{30}NO_2$: 292.2271, found 292.2274.

General procedure for the synthesis of *N*-alkylazetidines 4(a-d, f, g). To a stirred solution of amino alcohols **3** (0.76 mmol) and triethylamine (1.9 mmol) in CH_2Cl_2 (10 mL), cooled at -50 °C, methanesulfonyl chloride was slowly added (0.91 mmol). The solution was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was concentrated in vacuo and the residue was purified by silica gel column chromatography using a mixture of n-hexane/EtOAc (8:2) as eluent to give **4** as colorless oils.

3-Methoxy-2-phenyl-*N*-isopropylazetidine (4a). Yield (117 mg, 75%); NMR ^1H (300 MHz $CDCl_3$) δ: 0.71, 0.98 (2d, 6H, *J* 6.3 Hz, *J* 6.2 Hz), 2.47-2.51 (m, 1H), 2.68-2.71 (m, 1H), 3.22 (s, 3H), 3.67-3.73 (m, 2H), 3.81 (d, 1H, *J* 5.1 Hz), 7.23-7.48 (m, 5H); NMR ^{13}C (300 MHz $CDCl_3$) δ: 20.2, 20.9, 56.5, 56.7, 59.4, 76.3, 77.6, 127.0, 127.2, 128.3, 143.3; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{13}H_{20}NO$: 206.1540, found 206.1539.

3-Methoxy-2-phenyl-*N*-cyclopropylazetidine (4b). Yield (123 mg, 80%); NMR ^1H (300 MHz $CDCl_3$) δ: 0.11- 0.30 (m, 4H), 1.85 (m, 1H), 2.87 (m, 1H), 3.17 (s, 3H), 3.59- 3.69 (m, 2H), 3.97 (d, 1H, *J* 5.1 Hz), 7.18-7.36 (m, 5H); ^{13}C (300 MHz $CDCl_3$) δ: 3.8, 5.1, 37.7, 56.6, 57.6, 76.9, 77.8, 127.1, 127.4, 128.3, 141.7; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{13}H_{18}NO$: 204.1383, found 204.1389.

3-Methoxy-2-phenyl-*N*-cyclopentylazetidine (4c). Yield (139 mg, 79%); NMR ^1H (300 MHz $CDCl_3$) δ:1.10-1.68 (m, 8H), 2.67-2.74 (m, 1H), 2.82-2.86 (m, 1H), 3.21 (s, 3H), 3.67-3.73 (m, 2H), 3.80 (d, 1H, *J* 5.0 Hz), 7.22-7.47 (m, 5H); ^{13}C (300 MHz $CDCl_3$) δ: 23.8, 24.1, 30.3, 30.5, 56.5, 56.9, 70.2, 78.1, 127.1, 127.3, 128.3, 142.9; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{15}H_{22}NO$: 232.1696, found 232.1687.

3-Methoxy-2-parachlorophenyl-N-cyclopentylazetidine (4d). Yield (166 mg, 82%); NMR ^1H (300 MHz $CDCl_3$) δ:1.19-1.65 (m, 8H), 2.60-2.67 (m, 1H), 2.72-2.82 (m, 1H), 3.13 (s, 3H), 3.56-3.65 (m, 2H), 3.72 (d, 1H, *J* 5.0 Hz), 7.22 and 7.33 (m, 4H, *J* 8.4 Hz); ^{13}C (300 MHz $CDCl_3$) δ: 23.7, 24.0, 30.2, 30.4, 56.5, 56.9, 70.2, 76.0, 78.0, 128.4, 133.0, 141.2; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{15}H_{21}ClNO$: 266.1306, found 266.1315.

3-Methoxy-2-phenyl-*N*-cycloheptylazetidine (4f). Yield (114 mg, 58%); NMR ^1H (300 MHz $CDCl_3$) δ: 0.88-1.73 (m, 12H), 2.27-2.35 (m, 1H), 2.58-2.62 (m, 1H), 3.13 (s, 3H), 3.54-3.67 (m, 2H), 3.73 (d, 1H, *J* 5.5 Hz), 7.1-7.4 (2m, 5H). ^{13}C (300 MHz $CDCl_3$) δ: 24.0, 28.1, 28.6, 56.4, 57.0, 70.3, 76.3, 77.7, 127.0, 127.1, 128.3, 143.5; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{17}H_{26}NO$: 260.2009, found 260.2006.

3-Methoxy-2-phenyl-*N*-cyclooctylazetidine (4g). Yield (135 mg, 65%); NMR ^1H (300 MHz $CDCl_3$) δj: 1.07-1.29 (m, 2H), 1.26-1.51 (m, 10H), 1.61-1.74 (m, 2H), 2.36-2.43 (m, 1H), 2.64-2.69 (m, 1H), 3.20 (s, 3H), 3.62-3.75 (m, 2H), 3.79 (d, 1H, *J* 5.5 Hz); d: 7.20- 7.46 (m, 5H); ^{13}C (300 MHz $CDCl_3$) δ: 23.2, 24.00, 25.3, 27.2, 27.8, 28.3, 29.2,

56.4, 57.00, 69.4, 76.3, 77.8, 127.0, 127.1, 128.2, 143.6; HRMS (ESI/APCI) calcd for $(MH)^+$ $C_{18}H_{28}NO$: 274.2165, found 274.2160.

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Supplementary Material

Copies of ^1H and ^{13}C NMR spectra of compounds **2**, **3** and **4** are given in the Supplementary Material file associated with this manuscript.

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