Pergamon

Tetrahedron Vol. 51, No. 18, pp. 5465-5478, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00208-1

A Convenient Synthesis of 3-Alkoxyazetidines

Norbert De Kimpe* and Dirk De Smaele

Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, University of Gent, Coupure Links 653, B-9000 Gent, Belgium

Dedicated to Prof. Dr. Richard Neidlein on the occasion of his 65th birthday

Abstract : N-(Alkylidene or arylidene)-2-substituted-2-propenylamines were regiospecifically functionalized into novel N-(alkylidene or arylidene)-2-alkoxy-3-bromo-2-substituted-propylamines, which were proven to be excellent sources for 3-alkoxyazetidines through sodium borohydride reduction of the imino bond and subsequent intramolecular nucleophilic substitution.

INTRODUCTION

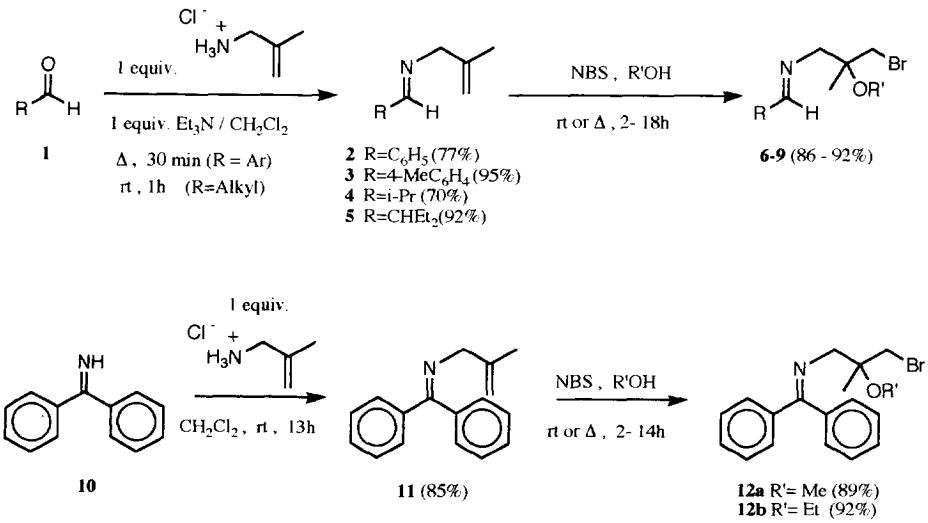
Imines, carrying reactive halogens in the side chains, have been rarely used in organic synthesis because of the unstable nature of the association of an imino bond and a halogen in the same molecule. Most often such bifunctional compounds suffer from decomposition due to a plethora of reactions. However, the selective introduction of halogens in imino substrates has been proven in recent years to give rise to compounds with a high synthetic potential, as exemplified amply for α-haloimines.[1]

In the present article, a novel and mild functionalization of olefinic imines into regiospecifically halogenated imines is described, and their synthetic value is underlined by means of a straightforward synthesis of 3-alkoxyazetidines.

RESULTS AND DISCUSSION

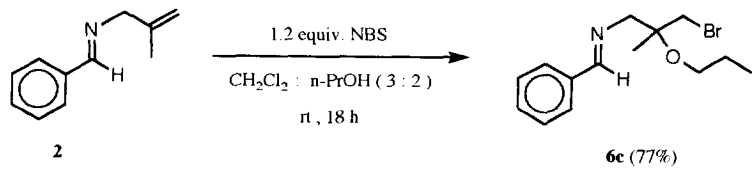
Aliphatic and aromatic aldehydes **1** were reacted with 2-methyl-2-propenylamine hydrochloride in dichloromethane in the presence of triethylamine under reflux to give N-(alkylidene or arylidene)-2-methyl-2-propenylamines **2-5** in 70-95% yield. Alternatively, N-(diphenylmethylidene)-2-methyl-2-propenylamine **11** was synthesized by transimination of diphenylketimine **10**, obtained from the addition of phenylmagnesium bromide to benzonitrile,[2] with 2-methyl-2-propenylamine hydrochloride in dichloromethane at room temperature. The N-(2-methyl-2-propenyl)imines **2-5** and **11** were regiospecifically alkoxybrominated by reaction with N-bromosuccinimide in alcohols, *e.g.* methanol,

ethanol, 1-propanol and 1-butanol, affording N-(alkylidene or arylidene)-2-alkoxy-3-bromo-2-methylpropylamines **6-9** and **12** in 86-92% yield (Scheme 1). The new functionalized imines **6-9** and **12** were obtained in high purity (> 95%) and could be used directly for further elaboration. Purification in high vacuum is possible. Only N-(2-methyl-1-propylidene)-2-methyl-2-propenylamine **4** did not react without side reactions when treated with N-bromosuccinimide in methanol. Functionalized aldimine **8** (R=i-Pr; R'=Me) was the major product in the reaction mixture but it was contaminated with several side products.



Scheme 1

The alkoxybrominations of **2-5** were performed in a 10% w/v solution of the appropriate alcohol. Several attempts with 1 to 6 equivalents of the alcohol in acetonitrile or tetrahydrofuran in the presence of 1.1 equivalents of NBS afforded compounds **6** in only 12-53% yield after 15-20 h at room temperature. In each case, substantial amounts of starting material (24-36%) were present in the reaction mixture, in addition to various undetermined side products. However, N-(benzylidene)-3-bromo-2-methyl-2-propoxypropylamine **6c** was synthesized in 77% yield from imine **2** by the use of 1-propanol : dichloromethane 2:3 (w/v) (Scheme 2). This procedure was previously used for the alkoxybromination of (S)-carvone.[3]



Scheme 2

Hydroxybromination of imine **2** with sodium hydroxide in water or in aqueous tetrahydrofuran could not be performed, as partial hydrolysis to benzaldehyde was the only reaction observed. Also the reaction

of 2 with N-bromosuccinimide (1 equiv.) and sodium acetate (0.7 equiv.) in dichloromethane : acetic acid (10:1) at room temperature (5 h) only afforded partial hydrolysis into benzaldehyde and some conversion into unidentified compounds. No trace of the desired acetoxy brominated product was found.

Table 1 gives a survey of the synthesis of N-(alkylidene or arylidene)-2-alkoxy-3-bromo-2-methylpropylamines **6-9** and **12**. A complete spectral analysis (^{1}H NMR, ^{13}C NMR, IR, MS) is given in the experimental part.

Table 1. Synthesis of N-(Alkylidene or Arylidene)-2-alkoxy-3-bromo-3-methyl (or phenyl)propylamines **6-9**, **12**, **23** and 3-Alkoxy-1,3-disubstituted Azetidines **13-16**, **17**, **24**

	R	R'	Reaction Conditions[a] **2-5 → 6-9** **11 → 12** **22 → 23**	Yield **6-9, 12, 23**	Reaction Conditions[b] **6-9 → 13-16** **12 → 17** **23 → 24**	Yield[c] **13-16, 17,24**
a	C_6H_5	Me	r.t., 5 h	**6a** : 88%	Δ, 1 h	**13a** : 92%
b	C_6H_5	Et	Δ, 1 h	**6b** : 92%	Δ, 1 h	**13b** : 97%
c	C_6H_5	n-Pr	r.t., 18 h	**6c** : 90%	Δ, 1 h	**13c** : 93%
d	C_6H_5	n-Bu	r.t., 18 h	**6d** : 90%	Δ, 1 h	**13d** : 94%
	4-MeC_6H_4	Me	Δ, 2 h	**7** : 86%[c]	Δ, 1 h	**14** : 86%
	i-Pr	Me	Δ, 1 h	**8** : 71%[d]	Δ, 1 h	**15** : 72%
	$CHEt_2$	Me	Δ, 2 h	**9** : 75%[c]	Δ, 1 h	**16** : 67%
a	-	Me	Δ, 2 h	**12a** : 89%	Δ, 2 h	**17a** : 65%
b	-	Et	r.t., 14 h	**12b** : 92%	Δ, 2 h	**17b** : 67%
a	-	Me	r.t., 4 h	**23a** : 94%	Δ, 2 h	**24a** : 89%
b	-	Et	r.t., 14 h	**23b** : 95%	Δ, 2 h	**24b** : 85%

[a] : 10% w/v solutions of compounds **2-5**, **11** and **22** in the appropriate alcohol were treated with 1 equiv. of NBS at room temperature or under reflux.

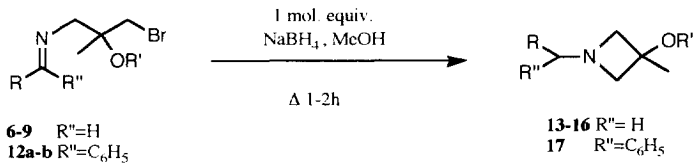
[b] : 10% w/v solutions of compounds **6-9**, **12** and **23** in methanol were treated with 1 molar equiv. of sodium borohydride under reflux.

[c] : yield of the isolated compounds, purified by distillation (**7** : 92-103°C/0.04 mmHg; **9** : 58-64°C/0.04 mmHg); all other compounds **6-9**, **12** and **23** were pure enough (> 95%) to be used in further reactions, except for compound **8** (see note d).

[d] : the reaction mixture was composed of 85% of compound **8**; some unidentified compounds were present; based on ^{1}H NMR, no α-bromination took place.

[e] : Compounds **13-17** and **24a-b** were formed in high purity (> 98%). Further purification of some 3-alkoxyazetidines was performed by flash chromatography on silicagel, *e.g.* **14** : ether, R_f = 0.65; **17a** : pentane-ether (91-9), R_f = 0.17; **17b** : pentane-ether (95-5), R_f = 0.15; **24b** : hexane-EtOAc (9-1), R_f = 0.17. Isolation of compound **15** was performed by preparative gaschromatography from a reaction mixture containing about 80% of **15**.

Functionalized aldimines **6-9** and ketimines **12** were proven to be excellent starting materials for the synthesis of functionalized azetidines. Reaction of bromo imines **6-9** and **12** with sodium borohydride in methanol under reflux (1-2 h) afforded 3-alkoxy-1,3-disubstituted azetidines **13-16** and **17** in 65-97% yield (Scheme 3). No side products were observed. 3-Alkoxyazetidines **13-16** and **17** were mostly isolated as pure materials but, if necessary, could be further purified by flash chromatography.



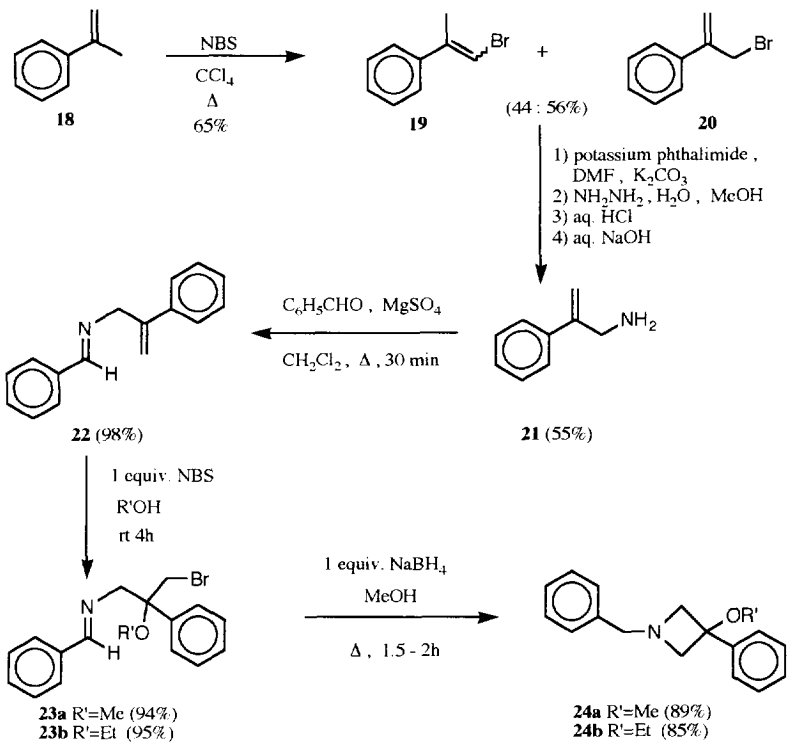
6-9 R''=H
12a-b R''=C_6H_5

13-16 R''= H
17 R''=C_6H_5

Scheme 3

The three-step synthesis of 3-alkoxyazetidines **13-16** and **17** from a suitable carbonyl compound (ketone or aldehyde) was also applied to the synthesis of 3-alkoxy-3-phenylazetidines **24**.

2-Phenyl-2-propenylamine **21** was obtained from α-methylstyrene **18** by a sequence of reactions involving bromination with NBS,[4] reaction of the resulting mixture of bromides (**19**, **20**) with potassium phthalimide, hydrazinolysis, treatment with hydrogen chloride and regeneration of the free base.[5] Condensation of this allylamine **21** with benzaldehyde gave the corresponding aldimine **22** in nearly quantitative yield. Bromoalkoxylation of the N-allyl imine **22** with N-bromosuccinimide in methanol or



18

19

20

22 (98%)

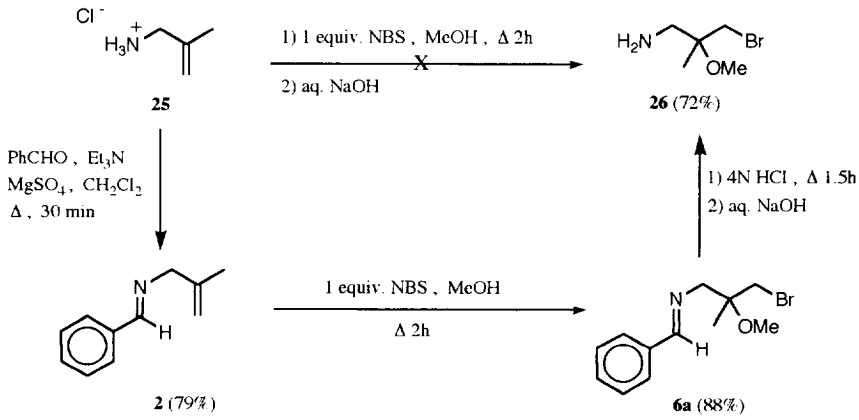
21 (55%)

23a R'=Me (94%)
23b R'=Et (95%)

24a R'=Me (89%)
24b R'=Et (85%)

Scheme 4

ethanol afforded cleanly aldimines **23** in 94-95% yield. The reductive ring closure of the functionalized imines **23** with sodium borohydride in methanol under reflux procuded 3-alkoxy-1-benzyl-3-phenylazetidines **24** in 85-89% yield, free from any side product (Scheme 4). Attempts to perform a methoxybromination of 2-methyl-2-propenylamine hydrochloride **25** by reaction with NBS in methanol failed. 3-Bromo-2-methoxy-2-methylpropylamine **26** could be prepared by hydrolysis of N-(benzylidene)-3-bromo-2-methoxy-2-methylpropylamine **6a**, obtained from 2-methyl-2-propenylamine hydrochloride by imination and methoxybromination *(vide supra)* (Scheme 5). These results demonstrate that imination of allylamines can be useful as nitrogen protective group, which allows further functionalizations of the double bond to take place without interference of the nitrogen nucleophile.



Scheme 5

Azetidines are an interesting class of four-membered heterocyclic compounds, which have been shown to exhibit various biological activities.[6-8] 3-Alkoxy-, 3-hydroxy- or 3-aryloxyazetidines are important small ring azaheterocycles which are accessible by ring transformation of epichlorohydrin with primary amines,[9-11] rearrangement of 2-(aziridinyl)methyl tosylates[12] or N-tosyl-2-(chloromethyl)aziridines,[13] addition of organometallic reagents to 3-azetidinones,[14] reduction of 3-alkoxy-2-azetidinones,[15] photochemical ring closure of β-aminoketones,[16,18] and nucleophilic substitution of 3-chloroazetidines.[19] However, several of these procedures have been exemplified only for one example[12,13] and some reactions could not be duplicated.[16,17]Some 3-alkoxy- or 3-aryloxyazetidines display a pronounced physiological activity, *e.g.* anticonvulsant activity[20,21] and antiepileptic activity.[20]

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded with Varian T-60 (60 MHz), Jeol PMX 60 SI (60 MHz), Jeol JNM EX 270 (270 MHz) or Bruker Aspect (500 MHz) NMR spectrometers. ^{13}C NMR spectra were measured with a Jeol JNM EX 270 (68 MHz), Varian FT-80A (20 MHz), or a Bruker Aspect (90 MHz) NMR spectrometer. The type of carbon was determined either by the DEPT mode or by the off resonance

decoupled spectra. Infrared spectra were obtained from a Perkin Elmer model 1310 spectrophotometer while mass spectra were recorded with a Varian MAT 112 (70 eV) utilizing the GC-MS technique or *via* the direct inlet system. Gas chromatographic analyses were done with Varian 1400 using a capillary column (fused silica, 20 m, glass capillary column, i.d. 0.53 mm, H_2 carrier gas) and Varian 920 (5-10% SE-30, Chromosorb W 60-80, 1.5 m, H_2 carrier gas). Ether, THF and dichloromethane were freshly distilled from sodium wire, sodium benzophenone ketyl and calcium hydride, respectively. Flash chromatography was performed using Merck Kieselgel 60 (40-63 μm). Solvent systems were determined via initial tlc analysis (Merck Kieselgel 60 F_{254}, precoated).

Synthesis of N-(Alkylidene or arylidene)-2-methyl-2-propenylamines 2-5

The synthesis of N-(benzylidene)-2-methyl-2-propenylamine **2** is representative of all preparations of imines **2-5**.

A solution of 1.06 g (0.01 mol) of benzaldehyde in 12 ml of dichloromethane was treated successively with 1.01 g (0.01 mol) of triethylamine, 1.08 g (0.01 mol) of 2-methyl-2-propenylamine hydrochloride and 2 g of magnesium sulfate. The mixture was stirred under reflux for 30 minutes. After cooling, the drying agent was filtered off and the solvent was evaporated *in vacuo*. After the addition of 15 ml of dry ether, the white precipitate was filtered and washed with dry ether. The filtrate was evaporated to give crude aldimine **2**. Distillation *in vacuo* afforded 1.26 g (79%) of pure compound **2**, bp. 68-70 °C, 0.05 mmHg. The crude product (purity > 96%) can be used directly in further reactions.

N-(Benzylidene)-2-methyl-2-propenylamine 2

IR (NaCl) : 1641 cm^{-1} (C=N). ^1H NMR (60 MHz, CCl_4) δ 1.80 (3H, s, Me); 4.05 (2H, s, CH_2N); 4.84 (2H, m, CH_2=C); 7.1-7.4 (3H, m, m/p-C_6H_3); 7.6-7.8 (2H, m, o-C_6H_2); 8.16 (1H, t, J=1.2 Hz, CH=N). Mass spectrum m/z (%) : 159 (M^+; 65); 158(100); 144(18); 143(8); 142(4); 141(4); 131(9); 130(10); 129(4); 128(4); 118(38); 117(50); 116(8); 115(8); 104(70); 91(55); 90(50); 89(23); 82(18); 80(5); 78(5); 77(20); 68(10); 65(13); 63(8); 56(25); 55(40); 53(10); 52(5); 51(15); 50(5); 41(15).

N-(4-Methylbenzylidene)-2-methyl-2-propenylamine 3

IR (NaCl) : 1646 cm^{-1} (C=N). ^1H NMR (60 MHz, CCl_4) δ 1.81 (3H, s, $C\underline{H}_3C=CH_2$); 2.33 (3H, s, $C\underline{H}_3C_6H_4$); 4.10 (2H, s, CH_2N); 4.8-5.1 (2H, m, CH_2=C); 7.20 and 7.74 (each 2H, each d, J=10.4 Hz, C_6H_4); 8.24 (1H, s, br, CH=N). Mass spectrum m/z (%) : 173 (M^+; 75); 172(88); 158(46); 157(9); 132(33); 131(42); 130(33); 118(100); 117(27); 116(16); 105(67); 104(33); 103(21); 91(42); 90(15); 86(25); 84(37); 82(25); 78(29); 77(25); 76(8); 68(17); 65(33); 63(13); 56(38); 55(79); 54(13); 53(21); 52(13); 51(33); 50(8); 49(50); 44(29); 42(13); 41(33).

N-(2-Methyl-1-propylidene)-2-methyl-2-propenylamine 4

Bp. 42-47 °C/18 mmHg. IR (NaCl) : 1675 cm^{-1} (C=N). ^1H NMR (60 MHz, CCl_4) δ 1.08 (6H, d, J=6.8 Hz, Me_2); 1.73 (3H, s, CH_3-C=); 2.1-2.6 (1H, m, C$\underline{H}$-C=N); 3.80 (2H, s, br, CH_2N); 4.74 (2H, s, br, CH_2=C); 7.50 (1H, d, J=3.9 Hz, CH=N). Mass spectrum m/z (%) : 125 (M^+; 2); 124(2); 110(11); 97(2); 96(2); 84(7); 83(4); 82(29); 70(11); 68(7); 67(4); 56(26); 55(100); 53(6); 43(13); 42(6); 41(16).

N-(2-Ethyl-1-butylidene)-2-methyl-2-propenylamine 5

IR (NaCl) : 1672 cm^{-1} (C=N). ^1H NMR (60 MHz, $CDCl_3$) δ 0.91 (6H, ~t, $(C\underline{H}_3CH_2)_2$); 1.1-1.7 (4H, m, 2xCH_2); 1.9-2.3 (1H, m, C<u>H</u>-C=N); 1.74 (3H, s, CH_3-C); 3.93 (2H, s, CH_2-N); 4.85 (2H, ~s, CH_2=C); 7.48 (1H, dxt, J_1=5.8 Hz, J_2=1.0 Hz, CH=N). Mass spectrum m/z (%) : 153 (M^+; 0.5); 138(5); 125(19); 124(14); 110(98); 97(7); 96(14); 95(5); 94(5); 93(5); 86(5); 84(8); 83(6); 82(32); 71(5); 70(10); 69(5); 68(10); 67(5); 55(100); 54(10); 53(14); 49(7); 44(10); 43(26); 42(12); 41(24).

Synthesis of N-(Diphenylmethylene)-2-methyl-2-propenylamine 11

A solution of 1.81 g (0.01 mol) of diphenylketimine **10**, obtained from the addition of phenylmagnesium bromide to benzonitrile,[2] and 1.08 g (0.01 mol) of 2-methyl-2-propenylamine hydrochloride in 20 ml dichloromethane was stirred at room temperature for 13 h. The reaction mixture was poured into a 1% sodium bicarbonate solution (100 ml) and extracted three times with dichloromethane. After washing with a saturated sodium bicarbonate solution the combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo* to obtain 2.00 g (85%) of pure N-(diphenylmethylene)-2-methyl-2-propenylamine **11**.

N-(Diphenylmethylene)-2-methyl-2-propenylamine 11

IR (NaCl) : 1616 cm^{-1} (C=N). ^1H NMR (270 MHz, $CDCl_3$) δ 1.79 (3H, s, $C\underline{H}_3C$=); 3.86 (2H, s, CH_2N); 4.7-5.0 (2H, m, CH_2=C); 7.0-7.8 (10H, m, $(C_6H_5)_2$). Mass spectrum m/z (%) : 235 (M^+, 89); 234(100); 220(11); 219(7); 218(7); 217(7); 194(22); 193(22); 180(11); 167(11); 166(33); 165(56); 164(11); 163(7); 159(11); 158(59); 156(7); 152(7); 144(7); 117(15); 116(15); 115(15); 104(22); 91(70); 77(35); 65(11); 55(59); 53(11); 51(22); 44(11); 41(11).

Synthesis of N-(Benzylidene)-2-phenyl-2-propenylamine 22

Compound **22** was prepared from benzaldehyde (30 mmol) and 2-phenyl-2-propenylamine **21**[4,5] (30 mmol) in dichloromethane in a way as described for the synthesis of compounds **2-5**. Yield 98%. Mp. 41°C. IR (NaCl) : 1644 cm^{-1} (C=N). ^1H NMR (60 MHz, $CDCl_3$) δ 4.63 (2H, m, NCH_2); 5.35 and 5.58 (each 1H, each m, C=CH_2); 7.3-8 (10H, m, 2xPh); 8.45 (1H, t, J=1.5 Hz, CH=N). This compound was used as such in the next haloalkoxylation reactions.

Alkoxybromination of N-(2-Methyl-2-propenyl)imines 2-5, 11 and 22

The preparation of N-(4-methylbenzylidene)-3-bromo-2-methoxy-2-methylpropylamine **7** is representative to all preparations.

A solution of 1.73 g (0.01 mol) of N-(4-methylbenzylidene)-2-methyl-2-propenylamine **3** in 20 ml of absolute methanol was treated with 1.78 g (0.01 mol) of N-bromosuccinimide. The solution was refluxed for 2 h and the solvent was then evaporated *in vacuo*, after which 30 ml of pentane was added to the residue. The precipitated succinimide was filtered off and the solid was washed with pentane. The combined filtrates were evaporated *in vacuo* to afford pure N-(4-methylbenzylidene)-3-bromo-2-methoxy-2-methylpropylamine **7** as an oil (purity > 96%). Distillation *in vacuo* gave 2.44 g (86%) of compound **7**, bp. 92-103°C/0.04 mmHg.

N-(4-Methylbenzylidene)-3-bromo-2-methoxy-2-methylpropylamine 7

IR (NaCl) : 1650 cm^{-1} (C=N). ^1H NMR (60 MHz, CCl_4) δ 1.29 (3H, s, CH_3); 2.29 (3H, s, 4-$\underline{C}H_3C_6H_4$); 3.21 (3H, s, OMe); 3.2-3.9 (4H, m, CH_2Br and CH_2N); 7.07 and 7.51 (each 2H, each d, J=8 Hz, C_6H_4); 8.10 (1H, s, broad, CH=N). ^{13}C NMR (20 MHz, $CDCl_3$) δ 20.14 and 21.49 (each q, 2xMe); 38.06 (t, CH_2Br); 49.83 (q, OMe); 66.09 (t, CH_2N); 75.87 (s, $\underline{C}$-O); 128.17 and 129.25 (each d, C_o and C_m); 133.49 (s, $\underline{C}$qCH=N); 141.08 (s, $\underline{C}qCH_3$); 162.73 (d, CH=N). Mass spectrum m/z (%) : no M^+; 268/70 (M^+-Me; 0.5); 252/4(1); 204(10); 190(8); 174(23); 158(5); 151/3(20); 133(40); 132(100); 131(5); 130(5); 118(10); 117(8); 105(70); 103(9); 95(5); 91(8); 79(8); 78(8); 77(10); 72(10); 65(5); 57(20); 55(5); 51(5); 45(5); 43(5); 42(11); 41(11). *Anal.* Calcd. for $C_{13}H_{18}BrNO$: N, 4.93. Found : N, 4.87.

N-(Benzylidene)-3-bromo-2-methoxy-2-methylpropylamine 6a

IR (NaCl) : 1650 cm^{-1} (C=N). ^1H NMR (60 MHz, $CDCl_3$) δ 1.33 (3H, s, CH_3CO); 3.26 (3H, s, OMe); 3.2-3.9 (4H, m, CH_2Br and CH_2N); 7.2-7.5 (3H, m, C_6H_3); 7.5-7.8 (2H, m, ortho =CH's, C_6H_2); 8.20 (1H, t, J=1.2 Hz, CH=N). ^{13}C NMR (20 MHz, $CDCl_3$) δ 20.14 (q, $\underline{C}H_3CO$); 37.99 (t, CH_2Br); 49.70 (q, OCH_3); 66.02 (t, CH_2N); 75.75 (s, $\underline{C}O$); 128.14 and 128.44 (d, Co and Cm); 130.64 (d, Cq); 136.14 (s, Cq); 162.48 (d, CH=N). Mass spectrum m/z (%) : no M^+; 190 (M^+-Br; 15); 176(7); 160(15); 151/3(92); 119(40); 118(100); 91(63); 72(18); 57(22); 42(11); 41(11). *Anal.* Calcd. for $C_{12}H_{16}BrNO$: N, 5.18. Found : N, 5.28.

N-(Benzylidene)-3-bromo-2-ethoxy-2-methylpropylamine 6b

IR (NaCl) : 1643 cm^{-1} (C=N). ^1H NMR (60 MHz, $CDCl_3$) δ 1.19 (3H, t, J=6.9 Hz, $C\underline{H}_3CH_2$); 1.37 (3H, s, $C\underline{H}_3CO$); 3.3-3.8 (6H, m, CH_2N and CH_2O and CH_2Br); 7.2-7.5 (3H, m, C_6H_3); 7.5-7.9 (2H, m, ortho =CH's, C_6H_2); 8.29 (1H, t, J=1.4 Hz, CH=N). ^{13}C NMR (20 MHz, $CDCl_3$) δ 15.89 (q, $\underline{C}H_3CH_2$); 20.91 (q, $\underline{C}H_3C$); 38.55 (t, CH_2Br); 57.21 (t, CH_2N); 66.50 (t, CH_2O); 75.61 (s, CO); 128.14 and 128.46 (each d, Co and Cm); 130.60 (d, $\underline{C}p$); 136.28 (s, Cq); 162.31 (d, CH=N). Mass spectrum m/z (%) : no M^+; 204 (M^+-Br; 1); 190(2); 165/7(38); 160(40); 137/9(40); 119(45); 118(100); 117(13); 104(13); 91(88); 90(19); 89(13); 86(31); 65(19); 58(48); 57(50); 55(13); 44(13); 43(36); 41(13). *Anal.* Calcd. for $C_{13}H_{18}BrNO$: N, 4.93. Found : N, 4.80.

N-(Benzylidene)-3-bromo-2-propoxy-2-methylpropylamine 6c

IR (NaCl) : 1648 cm^{-1} (C=N). ^1H NMR (60 MHz, $CDCl_3$) δ 0.93 (3H, ~t, Me); 1.35 (3H, s, MeCO); 1.3-2.0 (2H, m, $OCH_2\underline{C}H_2$); 3.2-4.0 (6H, m, OCH_2 and CH_2N and CH_2Br); 7.2-7.5 (3H, m, C_6H_3); 7.6-7.8 (2H, m, ortho =CH's, C_6H_2); 8.28 (1H, t, J=1.0 Hz, CH=N). ^{13}C NMR (20 MHz, $CDCl_3$) δ 10.76 (q, $\underline{C}H_3CH_2$); 20.84 (q, $\underline{C}H_3CO$); 23.54 ($\underline{C}H_2CH_3$); 38.73 (t, CH_2Br); 63.38 (t, CH_2N); 66.43 (t, CH_2O); 75.35 (s, $\underline{C}O$); 128.10 and 128.44 (each d, Co and Cm); 130.56 (s, Cq); 136.28 (d, Cp); 162.26 (d, CH=N). Mass spectrum m/z (%) : no M^+; 282/4 (M^+-Me; 0.9); 238/40(2); 218(12); 204(12); 179/81(31); 160(62); 137/39(65); 119(46); 118(100); 117(12); 91(85); 90(15); 89(15); 59(39); 58(19); 57(23); 55(23); 44(27); 43(54); 41(30).

N-(Benzylidene)-3-bromo-2-butoxy-2-methylpropylamine 6d

IR (NaCl) : 1646 cm^{-1} (C=N). ^1H NMR (60 MHz, CCl_4) δ 0.88 (3H, ~t, Me); 1.30 (3H, s, $C\underline{H}_3CO$); 1.2-

2 (4H, m, CH_2CH_2); 3.2-4.2 (6H, m, CH_2O and CH_2N and CH_2Br); 7.1-7.5 (3H, m, C_6H_3); 7.5-7.8 (2H, m, ortho =CH's, C_6H_2); 8.20 (1H, t, J=1.1 Hz, CH=N). ^{13}C NMR (20 MHz, $CDCl_3$) δ 13.88 (q, $\underline{C}H_3CH_2$); 19.33 (t, $\underline{C}H_2CH_3$); 20.83 (q, $\underline{C}H_3C$); 32.40 (t, $\underline{C}H_2CH_2CH_3$); 38.69 (t, CH_2Br); 61.42 (t, CH_2N); 66.42 (t, CH_2O); 75.36 (s, Co); 128.12 and 128.44 (each d, Co and Cm); 130.58 (s, Cq); 136.25 (d, Cp); 162.29 (d, CH=N). Mass spectrum m/z (%) : no M^+; 193/5 (M^+-118; 20); 162(15); 161(65); 160(60); 137/9(6); 119(40); 118(100); 117(20); 104(15); 99(20); 92(20); 91(99); 90(20); 89(20); 84(18); 77(15); 59(30); 58(28); 57(90); 56(28); 55(30); 51(20); 49(20); 44(72); 43(35); 41(75).

N-(2-Methyl-1-propylidene)-3-bromo-2-methoxy-2-methylpropylamine 8

IR (NaCl) : 1703 cm^{-1} (C=N). ^1H NMR (270 MHz, $CDCl_3$) δ 1.07 (6H, d, J=6.9 Hz, $(C\underline{H}_3)_2CH$); 1.32 (3H, s, MeC); 2.4-2.5 (1H, m, $C\underline{H}(CH_3)_2$); 3.30 (3H, s, OMe); 3.4-3.6 (4H, m, CH_2Br and CH_2N); 7.58 (1H, dxt, J_1=5.3 Hz, J_2=1.3 Hz, $C\underline{H}$=N). ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.25 ($(\underline{C}H_3)_2CH$); 20.02 ($\underline{C}H_3C$); 34.16 ($\underline{C}HCH$=N); 37.81 (CH_2Br); 49.76 (OMe); 65.80 (CH_2N); 75.52 (CO); 172.34 (CH=N).

N-(2-Ethyl-1-butylidene)-3-bromo-2-methoxy-2-methylpropylamine 9

IR (NaCl) : 1670 cm^{-1} (C=N). ^1H NMR (60 MHz, $CDCl_3$) δ 0.89 (6H, ~t, $(C\underline{H}_3CH_2)_2$); 1.1-1.8 (4H, m, $(CH_3C\underline{H}_2)_2$); 1.33 (3H, s, M$\underline{e}$CO); 2.03 (1H, pentuplet, $C\underline{H}CH_2$); 3.30 (3H, s, OMe); 3.1-3.8 (4H, m, CH_2N and CH_2Br); 7.50 (1H, dxt, J_1=5.8 Hz, J_2=1.2 Hz, CH=N). ^{13}C NMR (20 MHz, $CDCl_3$) δ 11.56 (q, 2x$\underline{C}H_3CH_2$); 20.13 (q, $\underline{C}H_3C$); 24.91 (t, 2x$CH_3\underline{C}H_2$); 37.81 (t, CH_2Br); 48.24 (d, $\underline{C}HC$=N); 49.64 (q, OCH_3); 66.18 (t, CH_2N); 75.53 (s, C); 171.02 (d, CH=N). Mass spectrum m/z (%) : no M^+; 207/9 (M^+-56;2); 192/4(3); 170(10); 154(15); 153(15); 151(20); 128(10); 113(20); 112(80); 98(8); 97(5); 96(8); 85(7); 84(45); 83(35); 82(15); 73(5); 72(25); 71(13); 70(20); 69(10); 68(11); 67(5); 63(17); 57(35); 56(26); 55(70); 54(8); 53(11); 45(15); 44(15); 43(26); 42(100); 41(50).

N-(Diphenylmethylene)-3-bromo-2-methyl-2-methoxypropylamine 12a

IR (NaCl) : 1621 cm^{-1} (C=N). ^1H NMR (270 MHz, $CDCl_3$) δ 1.37 (3H, s, CH_3C); 3.22 (3H, s, OMe); 3.31 and 3.56 (each 1H, AB, J=14.8 Hz, CH_2N or CH_2Br); 3.66 and 3.75 (each 1H, AB, J=10.9 Hz, CH_2Br or CH_2N); 7.1-7.8 (10H, m, $(C_6H_5)_2$). ^{13}C NMR (68 MHz, $CDCl_3$) δ 20.14 ($\underline{C}H_3C$); 38.13 (CH_2Br); 49.72 (OMe); 58.80 (CH_2N); 76.58 (CO); 127.62, 128.01, 128.26, 128.35, 128.48, 128.57, 130.04, 130.10 and 132.40 (arom. =$\underline{C}$H's); 136.64 and 139.53 ($C_{quat.}$); 169.18 (C=N). Mass spectrum m/z (%) : no M^+; 315/7 (M^+ -30, 0.5); 272(0.5); 267(0.5); 253(0.7); 238(2); 237(5); 228(1); 199(3); 198(11); 196(4); 195(8); 184(8); 183(41); 182(8); 166(4); 154(7); 153(5); 152(6); 151(6); 105(100); 91(16); 86(14); 84(22); 77(61); 76(8); 75(15); 72(4); 57(3); 56(4); 55(3); 51(21); 50(6); 49(6); 47(8); 45(5); 43(6); 42(4); 41(4). *Anal.* Calcd. for $C_{18}H_{20}BrNO$: C, 62.44, H, 5.82, N, 4.05. Found : C, 62.36, H, 5.89, N, 4.01.

N-(Diphenylmethylene)-3-bromo-2-ethoxy-2-methylpropylamine 12b

IR (NaCl) : 1623 cm^{-1} (C=N). ^1H-NMR (270 MHz, $CDCl_3$) δ 1.15 (3H, t, J=6.9 Hz, $C\underline{H}_3CH_2$); 1.38 (3H, s, CH_3C); 3.31 and 3.60 (each 1H, AB, J=14.7 Hz, CH_2N or CH_2Br); 3.43 (2H, q, J=6.9 Hz, CH_2O); 3.67 and 3.77 (each 1H, AB, J=10.9 Hz, CH_2Br or CH_2N); 7.2-7.8 (10H, m, $(C_6H_5)_2$). ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.80 ($\underline{C}H_3CH_2$); 20.86 ($\underline{C}H_3C$); 38.54 (CH_2Br); 57.00 (CH_2N); 59.19 (CH_2O); 76.35 (CO); 127.60, 127.98, 128.21, 128.28, 128.41, 128.53, 129.97 and 132.34 (arom. =CH's); 136.64 and 139.57 (each

$C_{quat.}$); 168.84 (C=N). Mass spectrum m/z (%) : no M^+; 315/7 (M^+-44; 1); 238(3); 237(10); 236(2); 235(2); 212(5); 196(6); 195(5); 184(9); 183(42); 182(9); 181(6); 178(3); 176(6); 155(12); 154(6); 153(6); 106(11); 105(100); 103(6); 99(5); 91(23); 78(6); 77(62); 76(9); 75(5); 57(5); 56(5); 51(23); 50(6); 47(5); 43(9). *Anal.* Calcd. for $C_{19}H_{22}BrNO$: C, 63.34, H, 6.15, N, 3.89. Found : C, 63.45, H, 6.23, N, 3.99.

N-(Benzylidene)-3-bromo-2-methoxy-2-phenylpropylamine 23a

IR (NaCl) : 1650 cm^{-1} (C=N). ^1H NMR (60 MHz, $CDCl_3$) δ 3.16 (3H, s, OMe); 3.5-4.3 (4H, m, CH_2N and CH_2Br); 7.1-7.8 (10H, m, 2xPh); 8.13 (1H, s, br., CH=N). ^{13}C NMR (20 MHz, $CDCl_3$) δ 50.68 (q, OMe); 37.17 (t, CH_2Br); 65.70 (t, CH_2N); 79.70 (s, C-OMe); 136.09 and 140.06 (each s, 2x =$C_{quat.}$); 127.68 and 130.66 (each d, 2x =CH para); 127.03 (d, =CH); 128.17 (d, overlap, =CH); 128.41 (d, =CH); 163.04 (d, CH=N). Mass spectrum m/z (%) : no M^+; 252 (M^+-Br; 17); 251(28); 236(14); 213/15(28); 134(64); 133(21); 118(100); 106(21); 105(14); 104(21); 103(21); 91(100); 77(14); 44(42). *Anal.* Calcd. for $C_{17}H_{18}BrNO$: C, 61.46, H, 5.46, N, 4.22. Found : C, 61.58, H, 5.55, N, 4.14.

N-(Benzylidene)-3-bromo-2-ethoxy-2-phenylpropylamine 23b

IR (NaCl) : 1649 cm^{-1} (C=N); ^1H NMR (270 MHz, $CDCl_3$) δ 1.22 (3H, t, J=6.9 Hz, CH_3CH_2); 3.3-3.5 (2H, m, CH_3CH_2); 3.91 and 4.08 (2H, AB, J=10.7 Hz, CH_2Br or CH_2N); 3.94 and 4.22 (2H, AB, J=12.3 Hz, CH_2N or CH_2Br); 7.2-7.5 (8H, m, C_6H_5C and para =CH's); 7.8-7.9 (2H, m, ortho =CH's); 8.15 (1H, s, CH=N). ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.42 (CH_3CH_2); 37.56 (CH_2Br); 58.15 (CH_2O); 66.20 (CH_2N); 79.42 (CO); 126.84, 127.62, 128.16, 128.19, 128.44 (arom. =CH's); 130.67 and 140.79 (each $C_{quat.}$); 162.96 (C=N). Mass spectrum m/z (%) : no M^+; 266 (M^+-Br, 10); 227/9(36); 222(8); 199/201(27); 149(18); 148(72); 147(23); 121/3(36); 120(31); 119(27); 118(100); 117(25); 115(18); 105(43); 104(18); 103(18); 91(95); 90(9); 89(9); 84(9); 78(18); 77(27); 65(20); 51(18); 49(18); 44(40); 43(18). *Anal.* Calcd. for $C_{18}H_{20}BrNO$: C, 62.44, H, 5.82, N, 4.05. Found : C, 62.29, H, 5.85, N, 4.12.

Synthesis of N-(benzylidene)-3-bromo-2-methyl-2-propyloxypropane 6c

According to a modified general procedure *(vide supra)*, a stirred solution of 0.32 g (2 mmol) of N-(benzylidene)-2-methyl-2-propenylamine 2 in 1.9 ml of dichloromethane and 1.3 ml 1-propanol was treated portionwise with 0.43 g (2.4 mmol) of N-bromosuccinimide. After stirring for 18 h at room temperature, the solvents were evaporated and the residue was treated with pentane. After filtration of the precipitated succinimide, the filtrate was evaporated to give 0.46 g (77%) of compound **6c** (purity 95%), which was used further in the next cyclization.

Synthesis of 1,3-Disubstituted 3-Alkoxyazetidines 13-16, 17 and 24

The general synthesis is exemplified by the preparation of 1-(4-methylphenyl)methyl-3-methoxy-3-methylazetidine **14**. A stirred solution of 2.84 g (0.01 mol) of N-(4-methylbenzylidene)-3-bromo-2-methoxy-2-methylpropylamine 7 in 30 ml absolute methanol was treated portionwise with 0.38 g (0.01 mol) sodium borohydride. After a reflux period of 2 h, the reaction mixture was poured into 100 ml of water and extraction was performed three times with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to afford 1.76 g (86%) of very pure 1-(4-methylphenyl)methyl-3-methoxy-3-methylazetidine **14** after flash chromatography (Silica gel; ether; R_f = 0.65).

1-(4-Methylphenyl)methyl-3-methoxy-3-methylazetidine 14

IR (NaCl) : 1369-1355-1310-1235-1210-1063 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$) δ 1.42 (3H, s, $C\underline{H}_3CO$); 2.26 (3H, s, $C\underline{H}_3C_6H_4$); 2.29 and 3.14 (each 2H, AB, J = 7.2 Hz, CH_2NCH_2); 3.12 (3H, s, OMe); 3.56 (2H, s, $C_6H_4C\underline{H}_2N$); 7.11 (4H, s, C_6H_4). ^{13}C NMR (90 MHz, $CDCl_3$) δ 21.05 and 21.61 (each q, $\underline{C}H_3$-COMe and $\underline{C}H_3C_6H_4$); 50.32 (q, $\underline{C}H_3O$); 63.38 (t, $\underline{C}H_2C_6H_4$); 64.52 (t, $\underline{C}H_2N\underline{C}H_2$); 72.78 (s, $\underline{C}CH_3$); 128.37 and 128.93 (each d, Co and Cm); 135.25 and 136.40 (each s, 2xCq). Mass spectrum m/z (%) : 205 (M^+; 2); 190(2); 163(2); 134(32); 133(11); 105(100); 103(6); 79(9); 77(9); 73(17); 72(45); 43(9); 42(19); 41(7). *Anal.* Calcd. for $C_{13}H_{19}NO$: N, 6.82. Found : N, 6.95.

1-Benzyl-3-methoxy-3-methylazetidine 13a

IR (NaCl) : 2835 cm^{-1} (OMe). ^1H NMR (60 MHz, $CDCl_3$) δ 1.45 (3H, s, CCH_3); 2.9-3.3 (4H, AB, J = 7.5 Hz, CH_2NCH_2); 3.15 (3H, s, OMe); 3.66 (2H, s, CH_2N); 7.26 (5H, s, C_6H_5). ^{13}C NMR (20 MHz, $CDCl_3$) δ 21.66 (q, $\underline{C}H_3C$); 50.29 (q, OMe); 63.63 (t, $C_6H_5\underline{C}H_2N$); 64.63 (t, CH_2NCH_2); 72.83 (s, CO); 126.96 (d, Cp); 128.25 and 128.46 (each d, Co and Cm); 138.34 (s, Cq). Mass spectrum m/z (%) : 191(M^+; 2); 176(1); 120(50); 119(7); 91(62); 72(100); 65(10); 44(13); 43(10); 42(37); 41(7). *Anal.* Calcd. for $C_{12}H_{17}NO$: N, 7.32. Found : N, 7.19.

1-Benzyl-3-ethoxy-3-methylazetidine 13b

IR (NaCl) : 1451-1360-1235-1110-1071 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$) δ 1.13 (3H, t, J = 6.8 Hz, $C\underline{H}_3CH_2$); 1.43 (3H, s, $C\underline{H}_3C$); 2.9-3.6 (8H, m, OCH_2 and CH_2CH_2 and $C_6H_5C\underline{H}_2$); 7.20 (5H, s, C_6H_5). ^{13}C NMR (20 MHz, $CDCl_3$) δ 15.81 (q, $\underline{C}H_3CH_2$); 22.38 (q, $\underline{C}H_3C$); 58.11 (t, $\underline{C}H_2C$); 63.56 (t, $C_6H_5\underline{C}H_2N$); 65.21 (t, $\underline{C}H_2N\underline{C}H_2$); 72.12 (s, CO); 126.92 (d, Cp); 128.21 and 128.43 (each d, Co and Cm); 138.31 (s, Cq). Mass spectrum m/z (%) : 205 (M^+; 2); 176(3); 120(40); 119(11); 91(53); 86(53); 72(4); 65(8); 58(100); 43(30); 42(9); 40(50). *Anal.* Calcd. for $C_{13}H_{19}NO$: N, 6.82. Found : N, 6.93.

1-Benzyl-3-methyl-3-propoxyazetidine 13c

IR (NaCl) : 1449-1362-1352-1228-1065 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$) δ 0.90 (3H, ~t, Me); 1.1-2.0 (2H, m, $CH_3C\underline{H}_2$); 1.42 (3H, s, CH_3CO); 2.8-3.3 (6H, m, CH_2NCH_2 and OCH_2); 3.52 (2H, s, $NC\underline{H}_2C_6H_5$); 7.16 (5H, s, br, C_6H_5). ^{13}C NMR (20 MHz, $CDCl_3$) δ 10.74 (q, $\underline{C}H_3CH_2$); 22.41 (q, $\underline{C}H_3CO$); 23.49 (t, $CH_3\underline{C}H_2$); 63.53 and 64.36 (each t, $C_6H_5\underline{C}H_2N$ and CH_2O); 65.13 (t, CH_2NCH_2); 71.99 (s, $CH_3\underline{C}O$); 126.85 (d, Cp); 128.14 and 128.41 (each d, Co and Cm); 138.44 (s, Cq). Mass spectrum m/z (%) : no M^+; 176 (M^+-43; 1); 120(15); 119(6); 101(6); 100(9); 92(6); 91(36); 86(7); 85(7); 84(9); 65(10); 60(6); 59(100); 58(54); 51(6); 49(12); 44(16); 43(27); 42(13); 41(13).

1-Benzyl-3-butoxy-3-methylazetidine 13d

IR (NaCl) : 1499-1460-1374-1316-1240-1082-1032. ^1H NMR (60 MHz, $CDCl_3$) δ 0.88 (3H, ~t, $C\underline{H}_3CH_2$); 1.2-2.0 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$); 1.40 (3H, s, OMe); 2.7-3.4 (6H, m, CH_2NCH_2 and CH_2O); 3.52 (2H, s, $NC\underline{H}_2C_6H_5$); 7.12 (5H, s, br, C_6H_5). ^{13}C NMR (20 MHz, $CDCl_3$) δ 13.88 (q, $\underline{C}H_3CH_2$); 19.41 (t, $CH_3\underline{C}H_2$); 22.41 (q, $\underline{C}H_3CO$); 32.40 (t, $CH_3CH_2\underline{C}H_2$); 62.40 and 63.53 (each t, CH_2O and $C_6H_5\underline{C}H_2N$); 65.13 (t, CH_2NCH_2); 72.02 (s, CH_3C); 126.84 (d, Cp); 128.14 and 128.37 (each d, Co and Cm); 138.48 (s, Cq). Mass spectrum m/z (%) : 233 (M^+; 2); 176(4); 120(29); 119(17); 115(13); 114(17); 99(42); 91(79); 65(17);

59(100); 58(67); 57(25); 56(58); 44(21); 43(17); 42(17); 41(38).

1-(2-Methylpropyl)-3-methoxy-3-methylazetidine 15

IR (NaCl) : 1469-1387-1371-1316-1230-1061. ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.88 (6H, d, J=6.1 Hz, Me_2); 1.3-1.8 (1H, m, $Me_2C\underline{H}$); 1.46 (3H, s, CH_3CO); 2.28 (2H, d, J=6.9 Hz, $CHC\underline{H}_2N$); 2.99 and 3.20 (each 2H, AB, J=7.5 Hz, CH_2NCH_2); 3.20 (3H, s, OMe). ^{13}C NMR (120 MHz, $CDCl_3$) δ 20.90 (q, $(\underline{C}H_3)_2$); 21.84 (q, $\underline{C}H_3$-C-O); 27.46 (d, CH); 50.31 (q, OCH_3); 65.42 (t, $\underline{C}H_2N\underline{C}H_2$); 68.53 (t, CH-$\underline{C}H_2$-N); 73.01 (s, $\underline{C}$-O). Mass spectrum m/z (%) : 157 (M^+; 1); 142(1); 114(19); 86(33); 85(4); 184(7); 72(100); 70(4); 57(7); 55(4); 43(20); 42(99); 41(15).

1-(2-Ethylbutyl)-3-methoxy-3-methylazetidine 16

IR (NaCl) : 1570-1461-1314-1239-1071-1069 cm^{-1}. ^{1}H NMR (60 MHz, $CDCl_3$) δ ($CDCl_3$) : 0.85 (6H, ~t, 2x$C\underline{H}_3CH_2$); 1.1-1.7 (5H, $C\underline{H}_2C\underline{H}C\underline{H}_2$); 1.40 (3H, s, $C\underline{H}_3CO$); 2.25 (2H, d, J=5.2 Hz, $NC\underline{H}_2CH$); 2.81 and 3.10 (each 2H, AB, J=6.5 Hz, CH_2NCH_2); 3.10 (3H, s, OMe). ^{13}C NMR (20 MHz, $CDCl_3$) δ 11.04 (q, 2x$\underline{C}H_3H_2$); 21.87 (q, $\underline{C}H_3C$); 24.34 (t, 2x$CH_3\underline{C}H_2$); 39.96 (d, $\underline{C}HMe_2$); 50.16 (q, $O\underline{C}H_3$); 63.90 (t, $CH\underline{C}H_2N$); 65.39 (t, $\underline{C}H_2N\underline{C}H_2$); 72.89 (s, $\underline{C}O$). Mass spectrum m/z (%) : 185 (M^+; 5); 170(2); 115(6); 114(57); 113(5); 85(4); 84(6); 73(18); 72(100); 57(5); 56(5); 55(7); 44(13); 43(27); 42(55); 41(10).

1-(Diphenylmethyl)-3-methoxy-3-methylazetidine 17a

m.p. 52°C; IR (KBr) : 1489-1449-1342-1225-1072-1060-1028. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.40 (3H, s, CH_3C); 3.03 (3H, s, OMe); 2.96 and 3.05 (each 2H, AB, J=8.1 Hz, CH_2NCH_2); 4.33 (1H, s, $(C_6H_5)_2C\underline{H}$); 7.0-7.4 (10H, m, $(C_6H_5)_2$). ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.71 ($\underline{C}H_3C$); 50.15 (CH_3O); 63.75 ($\underline{C}H_2N\underline{C}H_2$); 71.84 (CO); 78.00 ($C\underline{H}(C_6H_5)_2$); 126.93 ($C_{para}$); 127.35 and 128.28 ($C_{ortho}$ and C_{meta}); 142.41 ($C_{quat.}$). Mass spectrum m/z (%) : 267 (M^+; 3); 252(1); 197(8); 196(25); 195(8); 168(22); 167(100); 166(14); 165(28); 152(22); 100(6); 91(17); 73(19); 72(67); 49(8); 44(17); 43(17); 42(28); 41(17). *Anal.* Calcd. for $C_{18}H_{21}NO$: C, 80.86, H, 7.92, N, 5.24. Found : C, 80.82, H, 7.84, N, 5.18.

1-(Diphenylmethyl)-3-ethoxy-3-methylazetidine 17b

m.p. 76° C; IR (KBr) : 1492-1453-1314-1227-1072-1057. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.16 (3H, t, J=7.0 Hz, $C\underline{H}_3CH_2O$); 1.51 (3H, s, CH_3C); 2.97 and 3.12 (each 2H, AB, J=7.7 Hz, CH_2NCH_2); 3.33 (2H, q, J=6.9 Hz, $CH_3C\underline{H}_2O$); 4.38 (1H, s, $(C_6H_5)_2C\underline{H}$); 7.1-7.4 (10H, m, $(C_6H_5)_2$). ^{13}C NMR (68 MHz, $CDCl_3$) : 15.81 ($\underline{C}H_3CH_2O$); 22.57 ($\underline{C}H_3C$); 58.22 ($CH_3\underline{C}H_2O$); 64.44 (CH_2NCH_2); 71.39 (CO); 77.99 ($(C_6H_5)_2\underline{C}H$); 126.99 (C_{para}); 127.46 and 128.34 (C_{ortho} and C_{meta}); 142.53 ($C_{quat.}$). Mass spectrum m/z (%) : 281 (M^+; 0.2); 252(0.2); 196(20); 195(10); 168(20); 167(70); 166(15); 165(30); 152(25); 105(20); 91(10); 87(15); 86(55); 85(10); 77(20); 70(100); 59(20); 58(70); 43(22); 42(10); 41(10). *Anal.* Calcd. for $C_{19}H_{23}NO$: C, 81.10, H, 8.24, N, 4.98. Found : C, 80.94, H, 8.32, N, 5.07.

1-Benzyl-3-methoxy-3-phenylazetidine 24a

IR (NaCl) : 2830 cm^{-1} (OMe); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.97 (3H, s, MeO); 3.68 (2H, s, NCH_2); 3.40

and 3.58 (each 2H, d, J=8.0 Hz, $N(CH_2)_2$); 7.0-7.4 (10H, m, 2xPh). ^{13}C NMR (20 MHz, $CDCl_3$) δ 51.19 (q, OMe); 63.56 (t, $N\underline{C}H_2Ph$); 64.10 (t, $N(\underline{C}H_2)_2$); 77.00 (s, $\underline{C}$-OMe); 137.94 and 141.28 (each s, each $=C_{quat.}$); 128.80, 127.48, 127.96, 126.16, 128.28 and 128.50 (each d, arom.=$\underline{C}$H's). Mass spectrum m/z (%) : 253 (M^+; 2); 238(1); 134(95); 133(100); 120(2); 119(3); 105(7); 104(25); 103(12); 91(40); 78(10); 77(10); 65(10); 51(4); 44(7); 43(22); 42(4); 40(1). *Anal.* Calcd. for $C_{17}H_{19}NO$: C, 80.60, H, 7.56, N, 5.53. Found : C, 80.45, H, 7.69, N, 5.42.

1-Benzyl-3-ethoxy-3-phenylazetidine 24b

IR (NaCl) : 2965 - 1449 - 1212 - 1194 - 1117 - 1071 - 1028. ^1H NMR (270 MHz, $CDCl_3$) δ 1.12 (3H, t, J=7.1 Hz, $C\underline{H}_3CH_2O$); 3.10 (2H, q, J=6.9 Hz, $CH_3C\underline{H}_2$); 3.37 and 3.59 (each 1H, AB, J=8.1 Hz, CH_2NCH_2); 3.68 (3H, s, NCH_2Ph); 7.2-7.5 (10H, m, 2xPh). ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.44 ($\underline{C}H_3CH_2$); 59.08 ($CH_3\underline{C}H_2$); 63.68 ($N\underline{C}H_2Ph$); 64.74 (CH_2NCH_2); 76.23 (CO); 126.05, 126.97, 127.35, 128.26, 128.37 and 128.43 (arom. =CH's); 138.17 and 142.01 (each $C_{quat.}$). Mass spectrum m/z (%) : 267 (M^+, 3); 238(4); 149(17); 148(79); 147(36); 133(5); 131(7); 130(44); 105(100); 104(29); 103(6); 92(6); 91(13); 77(17); 78(15); 65(10); 51(5); 44(5); 43(10); 42(9); 41(4). *Anal.* Calcd. for $C_{18}H_{21}NO$: C, 80.86, H, 7.92, N, 5.24. Found : C, 80.69, H, 7.99, N, 5.29.

Synthesis of 3-Bromo-2-methyl-2-methoxypropylamine 26

A mixture of 1.62 g (6 mmol) N-(benzylidene)-3-bromo-2-methyl-2-methoxypropylamine **6a** in 6 ml 4N aqueous hydrogen chloride was stirred under reflux for 1.5 h. The reaction mixture was three times extracted with ether. The aqueous phase was made alkaline with the minimum amount of 50% aqueous sodium hydroxide, after which the aqueous phase was extracted three times with dichloromethane. The combined extracts were dried ($MgSO_4$), filtered and evaporated to afford 0.79g (72%) of compound **26** (purity > 95%).

3-Bromo-2-methyl-2-methoxypropylamine 26

IR (NaCl) : 3380 cm^{-1} (NH, weak). ^1H NMR (60 MHz, $CDCl_3$) δ 1.25 (3H, s, CH_3); 1.44 (2H, s, NH_2); 2.80 (2H, s, CH_2N); 3.24 (3H, s, OMe); 3.46 (2H, s, CH_2Br). ^{13}C NMR (20 MHz, $CDCl_3$) δ 19.10 (q, Me); 36.92 (t, CH_2Br); 46.96 (t, CH_2N); 49.76 (q, MeO); 76.20 (s, $\underline{C}$OMe). Mass spectrum m/z (%) : no M^+; 151/3 (M^+-30; 9); 128(5); 112(25); 86(9); 84(10); 72(10); 71(20); 70(100); 57(15); 55(10); 49(10); 44(23); 43(15); 42(20); 41(20).

ACKNOWLEDGEMENTS

The Belgian National Fund for Scientific Research is thanked for support of this research. We are indebted to Ciba for partial support of these investigations.

REFERENCES

1. De Kimpe, N.; Verhé, R. *The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines*; Patai S.; Rappoport Z. Eds.; John Wiley: Chichester, 1988.

2. P.L. Pickard, T.L. Tolbert *Org. Synth.* **1973**, Coll. Vol. V, 520-522.
3. Srikrishna, A.; Hemamalini, P. *J. Org. Chem.* **1990**, *55*, 4883-4887.
4. Reed, S.F., Jr. *J. Org. Chem.* **1965**, *30*, 3258.
5. Panzik, H.L.; Mulvaney, J.E. *J. Polym. Sci.* **1972**, *10*, 3469-3487.
6. Moore, J.A.; Ayers, R.S. In *Chemistry of Heterocyclic Compounds, Small Ring Heterocycles, Part 2*, Hassner, A. Ed.; 1983; Vol. 42, Chapter I, pp. 1-217.
7. Cromwell, N.H.; Phillips, B. *Chem. Rev.* **1979**, 331-358.
8. Davies, D.E.; Storr, R.C. In *Comprehensive Heterocyclic Chemistry, Part 5*; 1984; Vol 7, pp. 237-284.
9. Gaertner, V.R. *Tetrahedron Lett.* **1964**, 141-146.
10. Gaertner, V.R. *Tetrahedron Lett.* **1966**, 4691-4694.
11. Gaertner, V.R. *J. Org. Chem.* **1967**, *32*, 2972-2976.
12. Deyrup, J.A.; Moyer, C.L. *Tetrahedron Lett.* **1968**, 6179-6182.
13. Markov, V.I.; Doroshenko, V.A.; Klimenko, O.I.; Sachko, G.P. *Zh. Org. Khim.* **1972**, *8*, 1717-1722; *Chem. Abstr.* **1972**, *77*, 139853.
14. Morimoto, A.; Okutami, T.; Masuda, K. *Chem. Pharm. Bull.* **1973**, *21*, 228-231.
15. Ojima, I.; Zhao, M.; Yamamoto, T.; Nakahashi, K.; Yamashita, M.; Abe, R. *J. Org. Chem.* **1991**, *56*, 5263-5277.
16. Claisen, R.A.; Searles, S., Jr. *J. Chem. Soc. Chem. Commun.* **1966**, 289-290.
17. Gold, E.H. *J. Am. Chem. Soc.* **1971**, *93*, 2793-2795.
18. Lee, Y.J.; Lee, C.P.; Jeon, Y.T.; Mariano, P.S.; Yoon, U.C.; Kim, D.U.; Kim, J.C.; Lee, J.G. *Tetrahedron Lett.* **1993**, *34*, 5855-5858.
19. Gaertner, V. *J. Org. Chem.* **1970**, *35*, 3952-3959.
20. Taylor, C.R., Jr.; Cale, A.D., Jr.; Stauffer, H.F, Jr. U.S. US 4,956,359 (Cl. 514-210; A61K31/395), 11 Sep 1990, US Appl. 706,621, 28 Feb 1985; *Chem. Abstr.* **1991**, *114*, 163978.
21. Taylor C.R., Jr.; Cale A.D., Jr.; Stauffer H.F., Jr.; U.S. US 5,095,014 (Cl. 514-210; A61K31/395), 10 Mar 1992, Appl. 623,517, 07 Dec 1990; *Chem. Abstr.* **1992**, *116*, 255466.

(*Received in UK* 12 *December* 1994; *revised* 2 *March* 1995; *accepted* 10 *March* 1995)