Preparation of 3-Azetidinols with Non-Bulky 1-Alkyl Substituents [1]

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Cyclization of either the tetrahydropyranyl or trimethylsilyl ether of 1-(alkylamino)-3-chloro-2-propanols **1** followed by cleavage of the azetidinyl ether provides a general method for the preparation of 1-alkyl-3-azetidinols. Unhindered amines provide a more facile preparation of derivatives of **1**, or its ethers, than do hindered amines, while hindered derivatives of **1** undergo more facile ring closure.

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Introduction.

Since 1967, when Gaertner [2] reported his elegent synthesis of azetidin-3-ols by condensation of epichlorohydrin with primary amines, few improvements in the preparation of these compounds have been made. Okutani, Kaneko and Masuda [3] reported that 1-(alkylamino)-3-chloro-2-propanols **1**, where the alkyl substituent is secondary or tertiary, rapidly cyclize in acetonitrile to the hydrochloride salts of azetidinols in good yields (55-75%).

Gaertner's method fails completely, however, for *N*-alkyl substituents less bulky than isopropyl. Almost simultaneously with Gaertner's [2] suggestion that substituents on the oxygen atom in derivatives of **1** would also favor cyclization, Gaj and Moore [4] reported preparation of ethers of 1-methyl and 1-ethyl-3-azetidinols. Indeed, ring-closure of ethers of **1** appears to be more facile [4,5] than that of the corresponding **1**. Probably the best method, to date, for preparation of azetidinols with non-bulky *N*-alkyl substituents involves condensation-cyclization of **2b** with primary amines and subsequent hydrogenolysis of the benzhydryl substituent [5].

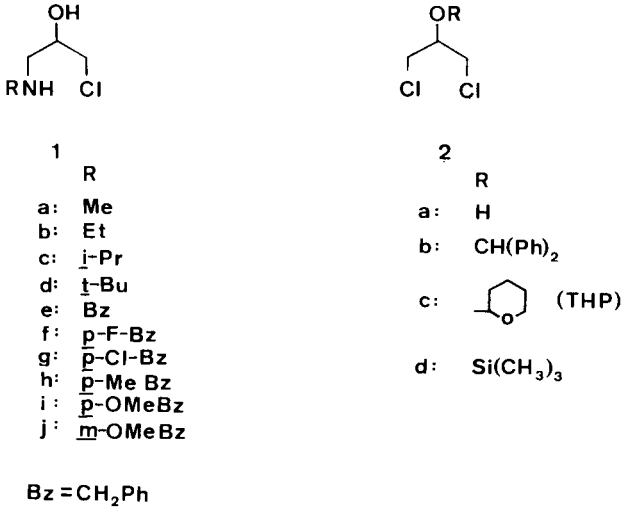


Figure 1

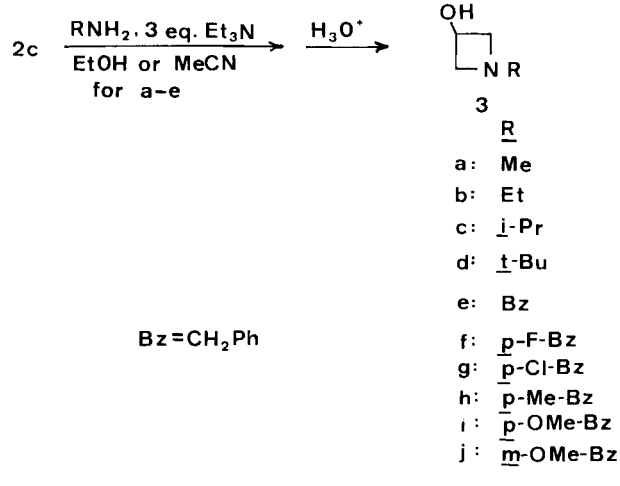
Results and Discussion.

We have repeated the preparation of the benzhydryl ethers of 1-methyl and 1-ethyl-3-azetidinols employing 40% and 70% aqueous solutions of methylamine and ethylamine, respectively, in refluxing ethanol with **2b** and suffered only modest losses in yield compared to those reported by Jenkins and Cale [5]. Several fires during hydrogenolysis and the desire to obtain a general method for the preparation of compounds possessing *N*-alkyl substituents, which are labile to hydrogenolysis conditions, prompted us to investigate *O*-alkyl substituents which are removable by hydrolysis.

Our initial efforts centered around use of **2c**, since tetrahydropyranyl ethers possess a fair degree of steric bulk in the vicinity of the oxygen atom, are readily prepared, are stable in basic solution, and are readily cleaved by warming with dilute acid [6].

The appropriate primary amine was condensed with **2c** and three equivalents of triethylamine in either ethanol or acetonitrile. Acidic hydrolysis afforded **3a-e** in fair yields (Scheme I, Method A). Interestingly, the isolated yields of **3a-d** were relatively insensitive to the bulk of the alkyl

SCHEME I (Method A)



substituent which would appear contrary to effects observed by others [2,7]. However, a more detailed analysis of the product mixtures indicates this apparent anomaly may result from opposing effects, see Table 1.

Table 1

Yields of **3a-e** by Method A

Compound	% Yield [a]	% **2c** Recovered	% Yield [b]
3a [c]	8.8	42	15
3b [c]	8.1	46	15
3c	25	54	53
3d	15	84	95
3e [c]	22	37	35

[a] Overall. [b] Corrected for recovered **2c**. [c] The pmr spectrum of this compound as prepared by this method indicated about 10-15% of the tetrahydropyranyl ether as an impurity.

The yield of recovered **2c** increases regularly as the steric bulk of the alkylamine increases. This probably obtains primarily from the degree of difficulty in achieving the transition state necessary for displacement of the first chloride ion — the transition state is apparently reached with less steric interactions with small *N*-alkyl than with more bulky *N*-alkyl substituents [8-10].

A second effect, ease of ring-closure of the intermediate, seems to follow the generalizations proposed by Gaertner [2] and Moore [4] concerning the total steric bulk of the *N*-alkyl and *O*-alkyl substituents. It may be seen that yields, based on the amount of recovered **2c**, increase from relatively poor for methyl and ethyl to nearly quantitative for *t*-butyl — in agreement with effects observed by others [2,7]. Part of the loss in yield for the lower molecular weight compounds can be attributed to greater water solubility of these compounds and their subsequent loss during the extraction process; however, it is also apparent that side-reactions are also more prevalent with the less bulky amines — larger quantities of resinous pot-residues are obtained.

No difficulties were encountered in the hydrolysis of the 1-isopropyl and *t*-butyl derivatives; however, hydrolysis of the 1-methyl, ethyl, and benzyl derivatives did not proceed as smoothly. One possible explanation involves steric acceleration of the hydrolysis of the azetidinyl ether when large *N*-alkyl substituents are present [11], thus minimizing the likelihood of ring cleavage in the strongly acidic medium [12] required for hydrolysis.

If Gaertner's hypothesis is correct, larger *O*-alkyl substituents should aid in ring closure. Since trimethylsilyl ethers are bulkier and undergo cleavage more readily than tetrahydropyranyl ethers, we chose to examine the possibility of employing this ether of 1,3-dichloro-2-propanol, **2d**. When **2d** was allowed to react with the appropriate benzylamine in acetonitrile containing triethylamine (Scheme II, Method B), the expected azetidinyl trimethylsilyl ethers, **4e-j**, were formed in respectible yields (Table 2). The pmr spectra of the crude reaction mixtures obtained from treatment of **2d** with either isopropylamine or with *t*-butylamine in the normal manner indicated very little reaction had occurred, although it was apparent that isopropylamine had reacted to a larger extent than had *t*-butylamine. In both cases, however, the only discernible product was the azetidinyl trimethylsilyl ether, **4c** or **4d**.

In an effort to circumvent this stereochemically demanding preparation of ethers of **1** (Method B), derivatives of **1** were prepared by treating the appropriate primary amine with epichlorohydrin in petroleum ether. Methylamine afforded only very small quantities of **1a** when the reaction was conducted in petroleum ether, presumably as a result of its low solubility; consequently,

SCHEME II

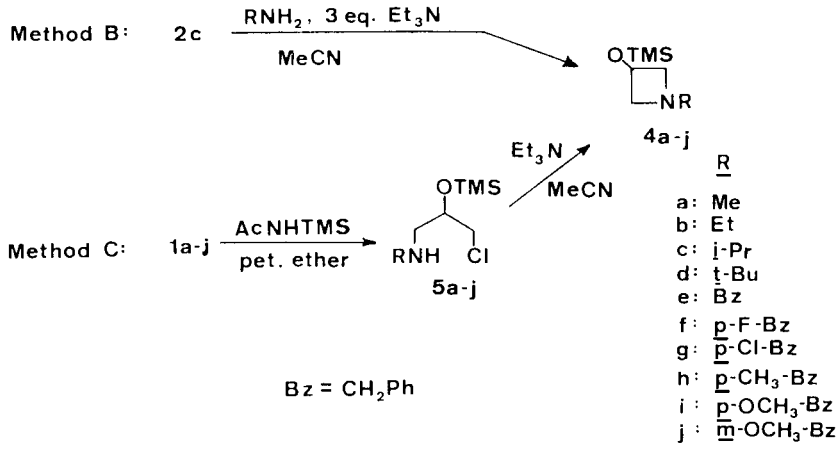


Table 2

Comparison of Methods B and C

Compound	% Yield (Method B)	% Yield (Method C)
4a	—	16
4b	—	20
4c	6	42
4d	*ca.* 0	59
4e	16	38
4f	26	26
4g	23	54
4h	22	34
4i	5.5	30
4j	22	28

ethyl ether was substituted as a solvent for this amine. *m*-and *p*-Methoxybenzylamines are also insoluble in petroleum ether, thus sufficient ethyl ether was added to the petroleum ether to effect solution of these amines. The resulting derivatives of **1** were readily converted to those of **5** by warming with *N*-(trimethylsilyl)acetamide in petroleum ether.

Pmr analysis of the crude reaction mixtures (after filtration to remove the bulk of the acetamide) of all amines examined indicated good to excellent yields of **5a-j**, which underwent closure to **4a-j** in fair to good yields upon refluxing for 2-3 days in acetonitrile containing 3 equivalents of triethylamine (Table 2) — see Scheme 2, Method C.

Hydrolysis of **4e-j** with dilute acid at room temperature afforded **3e-j** in excellent yields. A second method for cleavage of the trimethylsilyl ethers, which gave comparable results, involved treatment with a catalytic quantity of sodium methoxide in methanol. The latter method has the advantage of avoiding acid-base extractions. Hence, it was the method chosen for cleavage of **4a** and **4b** to **3a** and **3b** (Table 3).

Table 3

Cleavage of the Trimethylsilyl Ethers

Compound	Acidic Hydrolysis	Methoxide
3a	—	84% [a]
3b	—	75% [a]
3e	88%	73%
3f	57%	75%
3g	74%	61%
3h	71%	78%
3i	90% [a]	95% [a]
3j	88%	71%

[a] Appears to be pure by pmr, even though efforts to crystallize were unsuccessful.

In summary, it appears that the principles advanced by Gaertner [2] and Moore [4] concerning the total steric bulk of the *N*-alkyl and *O*-alkyl substituents of **1** towards facile synthesis of 1-alkyl-3-azetidinols are meritorious. In view of the ease of purification and facility of removal of the trimethylsilyl ether substituent, we feel that Method C (or minor variations thereof) as outlined in Scheme 2 presents a general and versatile method for preparation of 1-alkyl-3-azetidinols.

EXPERIMENTAL

Melting points were determined on a flame heated metal block and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R24A double resonance instrument. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

1,3-Dichloro-2-(6-(3,4,5,6-tetrahydro-2*H*-pyranoxy))propane (**2c**).

To a stirred mixture of 0.5 g strong acid ion-exchange resin (Rexyn 101H, Fisher Scientific) in 129 g (1.0 mole) of **2a** (Aldrich Chemical Co.) was added 84 g (1.0 mole) of 3,4-dihydro-2*H*-pyran (Aldrich). The mixture was stirred at room temperature for 12 hours and filtered through glass wool. The filtrate was distilled through a 40 cm glass bead column yielding 89.6 g (42%), bp 125-130° (25 torr), n_D^{20} 1.4818.

Anal. Calcd. for $C_8H_{14}Cl_2O_2$: C, 45.07; H, 6.57. Found: C, 45.02; H, 6.45.

1,3-Dichloro-2-(trimethylsiloxy)propane (**2d**).

To 23.9 ml (32.2 g, 0.25 mole) of **2a** was added 32.75 g (0.25 mole) of *N*-(trimethylsilyl)acetamide (Aldrich). The mixture was stirred at 80° for 1.0 hour while being protected from moisture by a calcium chloride drying tube. After being allowed to cool, the crystals of acetamide were removed by filtration through glass wool. A 200 ml portion of petroleum ether was added and the mixture again filtered. The filtrate was reduced *in vacuo* and distilled yielding 37.27 g (74%) of **2d**, bp 76-78° (25 torr), n_D^{20} 1.4480.

Anal. Calcd. for $C_6H_{14}Cl_2OSi$: C, 35.82; H, 7.01. Found: C, 35.35; H, 6.94.

General Method for Preparation of **3a-e** *via* **2c** (Method A).

To a stirred solution of 42.6 g (0.20 mole) of **2c** in 200 ml of either ethanol or acetonitrile was added three equivalents of the appropriate amine. The resulting solutions were refluxed for 3 days. The solvent and excess amine were removed *in vacuo*, the solvent replaced by benzene and extracted with a slight excess of dilute hydrochloric acid. The aqueous acidic extract was warmed on a steam bath for one hour, made strongly alkaline, and extracted with benzene. The benzene extract was then dried (sodium carbonate), the benzene removed *in vacuo*, and the product distilled under reduced pressure.

Trimethylsilyl Ethers of 3-Azetidinols.

These were prepared by either Method B or Method C as given below.

General Method for Preparation of **4e-j** *via* **2d** (Method B).

To a stirred solution of 40.2 g (0.20 mole) of **2d** in 200 ml of acetonitrile and 85 ml (0.60 mole) of triethylamine was added 0.20 mole of the appropriate amine. These solutions were heated at reflux with stirring for 2-3 days. The resulting mixtures were allowed to cool and were then filtered to remove precipitated triethylamine hydrochloride. The solvent was removed *in vacuo* and replaced with petroleum ether. The mixtures were again filtered and the petroleum ether removed *in vacuo*. The resulting oils were distilled under reduced pressure.

General Method for Preparation of **4a-j** *via* Epichlorohydrin (Method C).

To a stirred solution of 18.5 g (0.20 mole) epichlorohydrin (Aldrich) in

200 ml petroleum ether was added 0.20 mole of the appropriate amine, [**13a-c**]. The solutions were stirred at room temperature for 2 days (**1a-j** had separated either as crystals or as an oil), 26.2 g of *N*-(trimethylsilyl)-acetamide was added, and the mixture heated at reflux for 2 hours. Upon cooling, the crystals of precipitated acetamide were filtered; and the petroleum ether removed *in vacuo*. Acetonitrile (200 ml) and triethylamine (85 ml, 0.60 mole) were added, and the solution heated at reflux for 3 days. Upon cooling, the mixtures were filtered to remove the precipitated triethylamine hydrochloride. The acetonitrile was removed *in vacuo* and replaced with petroleum ether. The mixture was again filtered to remove additional triethylamine hydrochloride, the petroleum ether was then removed *in vacuo*, and finally the products distilled at reduced pressure. The region of the pmr spectra in which methyl protons of the trimethylsilyl group absorb often indicated a small amount of impurity (possibly dimethylsilyl); hence, these compounds were not subjected to elemental analysis.

Cleavage of Azetidinyl-Trimethylsilyl Ethers.

The trimethylsilyl ethers were cleaved by either aqueous acid or by basic methanol as outlined below. The pmr and analysis data are listed in Tables 4 and 5, respectively.

General Method for Acidic Hydrolysis of **4e-j**.

About 5 g samples of **4e-j** were dissolved in a solution of 20 ml of water containing 3 ml concentrated hydrochloric acid. After stirring at room temperature for 5 minutes the solutions were made alkaline with sodium hydroxide and extracted with benzene. The benzene solutions were dried (sodium carbonate), filtered, and the benzene removed *in vacuo*. The azetidinols were recrystallized from either benzene-petroleum ether or ethyl ether-petroleum ether.

General Method for Methoxide Cleavage of Trimethylsilyl Ethers of **4a-j**.

About 5 g samples of **4a-j** were dissolved in 50 ml of methanol containing a catalytic quantity (approximately 1 mg) of sodium methoxide. The solutions were stirred at room temperature for about 2 hours (usually 0.5 hour was sufficient) and the methanol removed *in vacuo*. The methanol was replaced with ethyl ether and the suspended sodium salts removed by filtration. The ether was removed *in vacuo* yielding the azetidinols in essentially quantitative yields in a nearly pure state.

Table 5

Analytical Data for New Azetidinols

Compound	Calcd./(Found) %C	%H	%N	mp
3f	66.28 (66.24)	6.68 (6.89)	7.73 (7.82)	57-58°
3g	60.90 (60.70)	6.12 (6.33)	7.09 (7.19)	82-84°
3h	74.54 (74.31)	8.53 (8.54)	7.90 (7.82)	53-54°
3i [a]	68.37 (66.63)	7.82 (7.69)	7.25 (7.77)	[a]
3j	68.37 (68.26)	7.82 (7.60)	7.25 (7.07)	63-63.5°

[a] Efforts to crystallize this compound have been unsuccessful and decomposition occurred on attempted distillation. The analysis is for the crude compound obtained by the methoxide in methanol method.

Acknowledgements.

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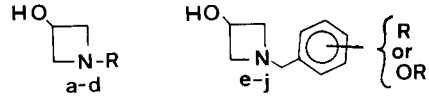
Table 4



PMR Data for 3-Azetidinols

Compound	δ H_2 and H_4 [a]	δ H_3 [b]	δ OH [c]	δ R	δ CH_2Ar [d]	δ Ar
3a	2.92, 3.62	4.33	6.0	2.35 (s)	—	—
3b	2.80, 3.64	4.32	6.3	0.96 (t) 2.45 (q)	—	—
3c	2.88, 3.58	4.36	5.5	0.93 (d) 2.36 (m)	—	—
3d	3.05, 3.42	4.30	5.8	1.00 (s)	—	—
3e	2.92, 3.56	4.34	4.3	—	3.58	7.24 (s)
3f	2.90, 3.52	4.34	3.8	—	3.53	7.2 (m)
3g	2.92, 3.52	4.36	5.0	—	3.54	7.17 (s)
3h	2.88, 3.48	4.3	4.5	2.30 [e]	3.52	7.12 (s)
3i	2.90, 3.53	4.37	4.0	3.78 [e]	3.53	7.02 [f]
3j	2.92, 3.56	4.37	4.3	3.77 [e]	3.57	7.0 (m)

[a] Each pair of identical hydrogen appears as two triplets (or double doublets) with further hyperfine splitting. [b] Appears as a five line multiplet (1 H). [c] Appears as a broad singlet which disappears upon addition of deuterium oxide. [d] Appears as a singlet (2 H). [e] 3 H singlet. [f] A-B pattern.

REFERENCES AND NOTES

[1] Portions have been presented at the: [1] 81st Annual Meeting of the North Carolina Academy of Science, Wake Forest University, Winston-Salem, NC, March, 1984; [b] 16th Annual Southeastern Sectional Conference of Undergraduate Student Chemists at Middle Tennessee State University, Murfreesboro, TN, April, 1984; [c] 12th Annual Minority Biomedical Research Support Symposium, Washington, DC, April, 1984; [d] 4th Annual Meeting of the Research Triangle Chapter of the National Technical Association, North Carolina A & T State University, Greensboro, NC, March, 1986; [e] Collegiate Academy, 83rd Annual Meeting of the North Carolina Academy of Science, East Carolina University, Greenville, NC, April, 1986; [f] 14th Annual Minority Biomedical Research Support Symposium, New Orleans, LA, April, 1986.

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[3] T. Okutani, T. Kaneko and K. Masuda, *Chem. Pharm. Bull.*, **22**, 1490 (1974).

[4] B. J. Gaj and D. R. Moore, *Tetrahedron Letters*, 2155 (1967).

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[6] See for example, L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol I, John Wiley & Sons, Inc., New York, NY, 1967, pp 256-257.

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[10] H. C. Brown, D. Gintis and L. Domash, *J. Am. Chem. Soc.*, **78**, 5387 (1956).

[11] It has been suggested that 1-3 interactions in azetidines are often more important than are 1-2 interactions and may help account for the observed puckering of the ring, see for example: [a] R. H. Higgins, N. H. Cromwell, and W. W. Paudler, *J. Heterocyclic Chem.*, **8**, 961 (1971); [b] R. H. Higgins and N. H. Cromwell, *J. Heterocyclic Chem.*, **8**, 1059 (1971). [c] R. H. Higgins, E. Doomes, and N. H. Cromwell, *J. Heterocyclic Chem.*, **8**, 1063 (1971). [d] R. M. Moriarty, *Topics Stereochem.*, **8**, 271 (1974).

[12] For a brief discussion of ring-opening of azetidines see J. A. Moore and R. S. Ayers, "Heterocyclic Compounds", Vol **42** (2), A. Hassner, ed, John Wiley and Sons, Inc., New York, NY, 1983, pp 64-69.

[13] Modifications were necessary for the 1-methyl, ethyl, *m*-methoxybenzyl and *p*-methoxybenzyl derivatives as follows: [a] Methylamine is not sufficiently soluble in petroleum ether to affect the desired reaction without polymerization. The epichlorohydrin was dissolved in 200 ml of ethyl ether in a 450 ml pressure reactor, and the system charged to a pressure of 4 atmospheres with methylamine. After 4 days the pressure had stabilized at 40 psi. The excess methyl amine was then allowed to evaporate, 26.2 g (0.20 mole) of *N*-(trimethylsilyl)acetamide added, and the mixture heated to 60° for 2 hours. After cooling, the ether was removed *in vacuo* and replaced with petroleum ether, yielding a two-layer mixture. The layers were separated, and the viscous, yellow, bottom layer discarded. The petroleum ether was removed *in vacuo*, replaced with acetonitrile and triethylamine, and the ring closure accomplished as in the general procedure. [b] Ethylamine is sufficiently volatile that the following modification was employed to minimize loss of ethylamine: the solution of epichlorohydrin in petroleum ether was refrigerated before the ethylamine was added. The resulting solution was then stoppered and shaken in a pressure bottle (capable of withstanding 4 atmospheres). [c] The methoxybenzylamines are insoluble in petroleum ether. Sufficient ethyl ether (40-50 ml) was added to the mixture of the methoxybenzylamine and petroleum ether to affect solution, and the general procedure followed.