Preparation of Trimethylsilyl Ethers of 3-Azetidinols. Scope and Limitations [1]

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Dedicated to Professor Norman H. Cromwell

Preparation of the trimethylsilyl ethers of 1-alkyl-3-azetidinols from non-hindered primary amines and epichlorohydrin by conversion of the intermediate 1-(alkylamino)-3-chloro-2-propanols to their trimethylsilyl ethers by either *N*-(trimethylsilyl)acetamide or by 1-(trimethylsilyl)imidazole followed by ring closure in acetonitrile is described. This sequence of reactions fails for aromatic amines, but appears to be general for all primary aliphatic amines, although the condensation of hindered amines with epichlorohydrin occurs slowly. Several novel azetidinols, in which the *N*-alkyl substituent itself contains a second heterocyclic system, are reported. In addition, the pK_A's of several *m*- and *p*-substituted 1-benzylazetidinols correlates well with the Hammett equation.

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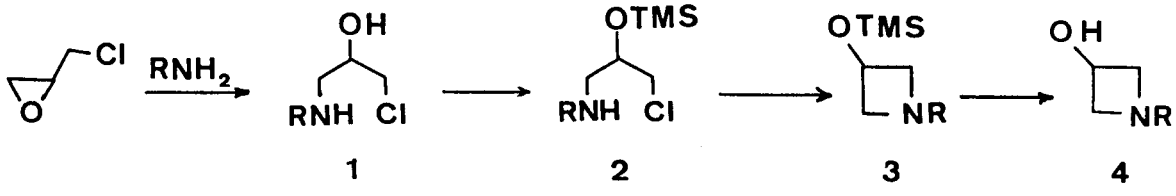
Since Gaertner's [2] classic preparation of azetidinols from epichlorohydrin and sterically hindered amines, there have been relatively few, but never-the-less significant, improvements in the preparation of these interesting compounds. Okutani, Kaneko and Masuda [3] conducted ring-closures of hindered amines in acetonitrile and substantially decreased the time for ring-closure and increased the yield of products (isolated as salts).

3-Azetidinyl ethers have been prepared by reaction of unhindered amines with ethers of 1,3-dichloro-2-propanol. Gaj and Moore [4] prepared several 1-(primary alkyl)-3-(methoxymethoxy)azetidines; Jenkins and Cale [5] prepared the 1-methyl and 1-ethylazetidinols (isolated as hydrochlorides) by hydrogenolysis of the corresponding 3-(diphenylmethoxy) or (phenylmethoxy)methoxy ethers which had been prepared by treatment of the appropriate ether of 1,3-dichloro-2-propanol with amine; while the tetrahydropyranyl and trimethylsilyl ethers were prepared in our laboratory from unhindered amines and appropriate ethers of 1,3-dichloro-2-propanol, which were readily



a. Methyl
b. Ethyl
c. i-Propyl
d. t-Butyl
e. Cyclohexyl
f. Benzyl
g. p-Fluorobenzyl
h. p-Chlorobenzyl
i. p-Methylbenzyl
j. p-Methoxybenzyl
k. m-Methoxybenzyl
l. 3,4-dimethoxybenzyl
m. racemic α-phenethyl
n. (R)-α-Phenethyl
o. (S)-α-Phenethyl
p. α-Picolinyl
q. β-Picolinyl
r. γ-Picolinyl
s. 2-(1-Ethylpyrrolidinyl)methyl

Figure 1

cleaved to the azetidinols [6].

While various primary alkylamines react with the trimethylsilyl ether of 1,3-dichloro-2-propanol, the reaction of hindered amines with this reagent occurs too slowly to be synthetically useful [6]. We, therefore, investigated the possibility of conversion of 1-(alkylamino)-3-chloro-2-propanols (**1**, obtained by the condensation of amine with epichlorohydrin--generally in petroleum ether) to their trimethylsilyl ethers, **2**, followed by ring-closure to the azetidinyl trimethylsilyl ethers, **3**, and found this method to be efficient in circumventing the slow displacement of chloride by hindered amines (Figure 1) [6].

Results and Discussion.

The basicity constants for azetidinols **3a-k** are reported in Table 1. It is apparent that an aromatic nucleus attached to the nitrogen-bearing carbon of the 1-alkyl substituent markedly decreases the basicity of these compounds. This effect runs parallel to that observed in the comparison of the basicity of benzylamines with alkylamines [7], and probably reflects the inductive electron-withdrawal of electrons by the sp^2 hybridized carbon attached to the nitrogen-bearing carbon. Only relatively minor variations are observed from anticipated results in the Hammett plot of basicities for the benzylamines (Figure 2).

In view of the similar effective sizes of methyl and phenyl substituents [8], it is difficult to rationalize the previously reported poorer yield for **3b** (with respect to those for the benzylazetidinols, **3f-k**) on conformational effects alone. In view of the fact that the basicity (and presumably nucleophilicity) of ethylamine is greater than that of the benzylamines and that the same order of basicities is observed for azetidinols, we felt that ring-closure of **2b** to **3b** should have occurred more rapidly than that of the benzyl compounds **2f-k**. This seems to suggest that the problems are related to the poor solubility of ethylamine in petroleum ether.

Gaertner [9] has shown that 1-(alkylamino)-3-chloro-2-propanols **1** rapidly undergo cyclodehydrohalogenation to form 1-(alkylamino)-2,3-epoxypropanes in methanol. Previous isolations of derivatives of **1** have been accomplished only in hydrocarbon solvents [2,9]. The fact that

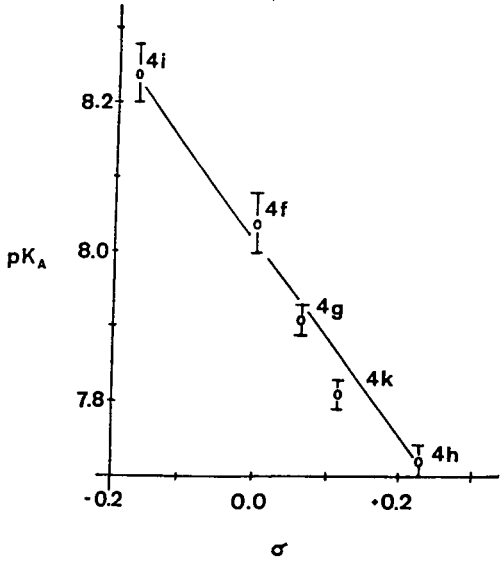


Figure 2. Plot of pK_A versus Hammett substituent constants (σ) for azetidinols **4f-i** and **4k**.

Table 1

pK_A's for Some Azetidinols at 20° [a]

Compound	pK_A	Compound	pK_A
3a	9.10 ± 0.01 [b]	**3f**	8.08 ± 0.08
3b	8.68 ± 0.03	**3g**	7.91 ± 0.02
3c	8.89 ± 0.04	**3h**	7.72 ± 0.02
3d	9.24 ± 0.02	**3i**	8.24 ± 0.04
3e	9.02 ± 0.04	**3j**	8.17 ± 0.02
		3k	7.81 ± 0.02
		3m	7.82 ± 0.02 [b,c]

[a] Unless otherwise specified, results in at least triplicate. [b] Results of duplicate determinations. [c] Determined on the racemic modification.

Table 2

Isolated Yields of **3a-s**

3	from Trimethylsilylacetamide in ligroin	from Trimethylsilylacetamide in ethyl ether	from Trimethylsilylimidazole in ligroin	from Trimethylsilylimidazole in ethyl ether
a	0 [a]	16 [a]	--	--
b	20 [a]	41	--	--
c	42 [b]	--	--	38 [c]
d	59 [b]	--	--	26 [c,d]
e	58	--	24 (48 [e])	--
f	38 [a]	--	30 (35 [e])	--
g	45 (55 [e])	--	48 (53 [e])	--
h	54 [a]	--	37 (57 [e])	--
i	34 [a]	--	28 (44 [e])	--
j	30 [a]	--	--	23
k	28 [a]	38	--	33
l	34 [f]	--	--	19
m	17 (44 [g])	--	26	--
n	64 [g]	--	--	--
o	63 [g]	--	--	--
p	24	26	--	23
q	18	29	--	12
r	2	11	--	8
s	39	--	33	--

[a] From reference [6]. [b] From reference [6], with two weeks for initial condensation. [c] Epichlorhydrin and amine condensed for two weeks. [d] Contains about 10-20% of an unidentified impurity. [e] Results based on isolated **2**. [f] Mostly ethyl ether. [g] Amine and epichlorohydrin condensed for seven days.

we have been able to isolate ring-closed products **3a**, **3j**, and **3k**, even though the condensation of amine with epichlorohydrin was accomplished in ether or in solutions containing ether [6], led us to attempt to improve yields of derivatives of **3** by conducting the condensations in ether solvent. Generally, little or no increase in these yields was obtained by use of ether solvent with one notable exception (Table 2). A rather dramatic increase in the yield of the 1-ethyl derivative **3b** was observed. It appears likely that this increase is due to the improved solubility of ethylamine in ethyl ether with subsequent minimization of condensation of **1** with additional epichlorohydrin.

We have extended our method to the preparation of 1-(3,4-dimethoxybenzyl)-3-azetidinol (**31**), to the preparation of 1-α-phenethyl-3-azetidinol (both racemic **3m** and both optically pure enantiomers **3n** and **3o**), to the preparation of several new azetidinols in which the *N*-alkyl substituent is exocyclic to a second heterocyclic system **3p-3s**, as well as to the preparation of the known 1-cyclohexyl-3-azetidinol (**3e**) [2]. The pmr spectroscopy on the crude product obtained by refluxing aniline with epichlorohydrin indicates very little condensation has occurred, even after one month. The fact that all primary aliphatic amines that we have examined have yielded the azetidinyl ethers indicates that cyclization of trimethylsilyl ethers of **1** (*ie.* **2**) provides the most general and versatile method for the preparation of azetidinols yet developed.

In view of the high cost of the *N*-(trimethylsilyl)acetamide and of our success in preparing the trimethylsilyl ether of 1-benzyl-3-azetidinol by use of trimethylsilylimidazole (**5**), which had been prepared *in situ* from chlorotrimethylsilane (Figure 3) [10], we chose to investigate whether this considerably less costly reagent was competitive with the more expensive reagent for the preparation of azetidinyl trimethylsilyl ethers. A comparison of the results obtained by the two methods is shown in Table 2. While there are some instances in which the yields of the azetidinyl ethers prepared by the acetamide reagent exceed those obtained by the imidazole reagent, it appears that the imidazole method is also a general method for the preparation of **2** and, therefore, of **3**.

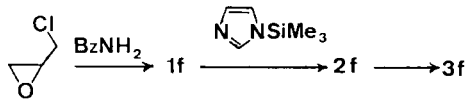


Figure 3

In an additional experiment, epichlorohydrin and benzylamine were added in equivalent molar quantities to a previously prepared acetonitrile-triethylamine unfiltered solution of **5** [10]. The mixture was brought to reflux, and aliquots were periodically withdrawn for pmr analysis. No azetidinyl ether was observed, suggesting that benzylamine possibly underwent *N*-silation with subsequent lack of reactivity with epichlorohydrin.

We have been unable to reproduce yields reported for the preparation of **2c-d** [3]. Upon reexamination of our data for the preparation of **3c-d**, we find that we erroneously reported the time for the condensation of epichlorohydrin with the appropriate amines to be three days; in fact, two weeks [6] were used for these two compounds. Apparently, the steric requirements of isopropyl and *t*-butylamine are such as to decrease the facility of epoxide ring opening. In addition, the preparation of **3m-o** required 7 days for the condensation of epichlorohydrin with α-phenethylamine in order to obtain the yields reported in Table 2. Furthermore, the qualitative rates of formation of **2f-k** and the resulting yields of **3f-k** do not seem to follow the pattern expected based on the basicity (and presumably nucleophilicity) of the benzylamines. As a result, we have begun to examine the nature of effects operative in the ring opening of epichlorohydrin by amines.

The corresponding azetidinols were obtained by base catalyzed cleavage of all azetidinyl trimethylsilyl ethers investigated in goods yields (Table 3).

Table 3

Yields of **4** from **3** by Methoxide in Methanol Method

4	%	4	%
e	67	p	105 [a]
l	44	q	104 [a]
n	78	r	48
o	70	s	84

[a] The pmr data indicates a small quantity of unreacted **3**.

EXPERIMENTAL

Melting points are uncorrected. Nuclear magnetic resonance spectra were determined on a Perkin-Elmer R24-A instrument at 60 MHz in deuteriochloroform solution, with chemical shift data reported with respect to tetramethylsilane as internal standard. Optical rotation data were determined in methanol on a PolyScience Model SR6 polarimeter at room temperature. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Characterization data for new azetidinols are recorded in Table 4.

General Method for Condensation of Epichlorohydrin with Amines.

All condensations were accomplished with 1.0 *M* solutions of epichlorohydrin containing 1.0 equivalent of amine (in the solvent listed) at room temperature for three days (unless otherwise specified). When **1** was isolated, the solvent employed was ligroin, **1** being simply filtered, dried, and used without purification or characterization (see Table 5).

Table 4

Data for Characterization of New Azetidinols

			Analysis (Calcd./Found)			PMR Spectra [a]			
4	α_D [b]	mp	%C	%H	%N	R [c]	C2 (& C4) [d]	C3 [e]	OH [f]
l		135-136°	64.55	7.68	6.27	6.75 [g]	3.5	4.35	4.4
			64.62	7.83	5.99	3.84 [h]	2.91		
						3.48			
n	+104°	88-90°	74.54	8.53	7.90	7.20 [i]	3.64	4.35	4.0
			74.51	8.35	7.99	3.3 [j]	3.3 [j]		
						1.22 [k]			
o	-105°	89-90°	74.54	8.53	7.90	7.20 [i]	3.64	4.35	4.0
			74.39	8.47	7.54	3.3 [j]	3.3 [j]		
						1.22 [k]			
p [l]		150-151°	40.52	2.91	18.01	8.45 [m]	3.66	4.44	5.35
			40.84	3.11	18.08	7.0-7.8 [n]	3.01		
						3.76			
g [l]		171-172°	40.52	2.91	18.01	8.40 [o]	3.6 [j]	4.41	4.3
			40.58	3.07	17.95	7.1-7.7 [p]	2.92		
						3.60			
r [l]		168-169°	40.52	2.91	18.01	8.38 [o]	3.6 [j]	4.41	4.3
			40.50	3.12	17.99	7.15 [q]	2.95		
						3.60			
s [l]		177-178°	41.12	4.08	17.44	1.5-3.3 [r]	3.70	4.45	5.1
			40.91	4.08	17.10	1.10 [s]	1.5-3.3 [t]		

[a] Spectra were recorded in deuteriochloroform. [b] Specific rotations were determined at ambient temperature and are recorded in degrees. [c] Unless otherwise indicated this absorption consists of a 2H singlet. [d] 2H triplet of doublets. [e] 1H pentuplet. [f] 1H broad singlet. [g] 3H singlet. [h] 6H singlet. [i] 5H singlet. [j] Severe overlap prevents complete analysis. [k] 3H doublet. [l] Analysis and mp are for the dipicrate. [m] 1H doublet. [n] 3H multiplet. [o] 2H doublet with further fine structure. [p] 2H multiplet. [q] 2H doublet of doublets. [r] 11H of 13H complex multiplet. [s] 3H triplet. [t] 2H of 13H complex multiplet.

Table 5

Yields of Crude Isolated **1**

1	Yield	**1**	Yield
e	55 [a]	**f**	85 [a]
g	92 [a]	**h**	65 [a]
i	60 [b]		

[a] Three days allowed for condensation. [b] Seven days allowed for condensation.

General Method for Preparation of **3** Employing Trimethylsilylacetamide.

From Isolated **1** (Method A).

The isolated **1** was dissolved in 200 ml of acetonitrile containing 85 ml triethylamine and 1.0 equivalents of trimethylsilylacetamide was added. The resulting solution was refluxed for 3 days, was allowed to cool, and was filtered. The solvent was removed *in vacuo* and replaced with ligroin. The resulting mixture was again filtered, the solvent was removed *in vacuo*, and the product was distilled.

In Ether (Method B).

To the solution (or mixture containing some precipitate) which resulted from use of ethyl ether as a solvent was added 1.0 equivalent of trimethylsilylacetamide. The solution was refluxed overnight, the ether was removed *in vacuo* and replaced with acetonitrile. Triethylamine (3.0 equivalents) was added, and the solution refluxed for 3 days. The solution was allowed to cool, was filtered, the solvent was removed *in vacuo* and replaced with petroleum ether. The resulting mixture was again filtered, the solvent removed *in vacuo*, and finally the product was distilled.

In Ligroin Without Isolation of **1** (Method C). (See reference 6, Method C). Trimethylsilylimidazole.

To the appropriate quantity of 1.0 *M* imidazole (based on a 1:1 reaction with **1**) in acetonitrile was added 4 equivalents of triethylamine. The solution was cooled in an ice bath while 1.0 equivalent of chlorotrimethylsilane was added dropwise. The resulting mixture was stirred for 1.0 hour and used without isolation of the trimethylsilylimidazole.

General Method for the Preparation of **3** Employing Trimethylsilylimidazole.

From Isolated **1** (Method D).

The crude isolated **1** was added to the solution of trimethylsilylimidazole as prepared above. The mixture was heated at reflux for 3 days, allowed to cool, and was filtered. The solvent was removed from the filtrate *in vacuo* and replaced with ligroin. The resulting mixture was again filtered, the solvent removed from the filtrate *in vacuo*, and the product distilled.

In Ligroin or in Ether (Method E).

The solvent was removed from the solution (or mixture containing some precipitate) obtained from the condensation of the appropriate amine with epichlorohydrin *in vacuo* with minimum application of heat. On at least two occasions a vigorous decomposition occurred. To the resulting material was added the trimethylsilylimidazole as prepared above. The resulting mixture was refluxed for 3 days, was allowed to cool, and was filtered. The solvent was removed from the filtrate and replaced with ligroin. The resulting mixture was filtered, the solvent was removed from the filtrate *in vacuo*, and the product distilled.

pK_A Determination.

Freshly distilled water was boiled for 30 to 60 minutes and allowed to cool while being protected from the atmosphere by means of lime water.

In those cases where the amine did not readily dissolve in water (we employed 50-100 mg of amine in 15-20 ml), the amine was dissolved in a few ml of methanol and then added to the water. Titrations were conducted at 25.00 ±0.02° under a nitrogen atmosphere by means of constant rate of addition (from a Sage Model 341A syringe pump) of 0.1 *M* hydrochloric acid. The *p*H was determined by means of a combination electrode and an Orion Model 701 meter and recorded on a Fisher Series 5000 Recordall recorder. Under these conditions the *p*H at half way to the equivalence point is the pK_A.

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