The Effect of the Steric Requirements of Trialkylsilyl Ethers on Ring Closure of 1-(Benzylamino)-3-chloro-2-(trialkylsiloxy)propanes

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The ring closure of 1-(benzylamino)-3-chloro-2-(trialkylsiloxy)propanes to 1-benzyl-3-(trialkylsiloxy)azetidines was investigated. There appears to be little or no advantage in the use of trialkylsilyl substituents larger than trimethylsilyl.

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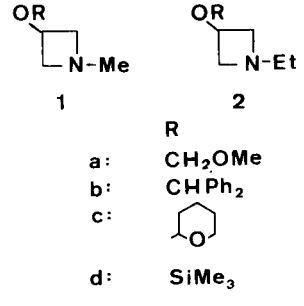
It has been well extablished that bulky *N*-alkyl substituents facilitate ring closure of γ-haloalkylamines to azetidines. This effect has been observed by Bottini and Roberts in ring closure to a alkylazetidines [1], by Gaertner in that of 1-(alkylamino)-3-chloro-2-propanols [2], by Cromwell and co-workers in closure to 1-alkyl-2-phenyl-3-benzoylazetidines and to 1-alkyl-2-carboalkoxyazetidines [3,4], and recently in our laboratory in the ring closure of the tetrahydropyranyl and of the trimethylsilyl ethers of 1-(alkylamino)-3-chloro-2-propanols to the corresponding ethers of 1-alkyl-3-azetidinols [5].

Gaertner [3] had proposed, without experimental support, that bulky substituents at C-2 should also aid in this type of ring closure. Since then, it has become increasingly clear that these types of substituents do, indeed, facilitate closure. This effect has been successfully exploited in the preparation of ethers of even methylazetidinols. Thus, Gaj and Moore [6] successfully prepared **1a** and **2a**, Jenkins and Cale [7] prepared **1b** and **2b**, while we recently reported the preparation of **1c,d** and **2c,d** as well as numerous substituted derivatives of the trimethylsilyl ether of 1-benzylazetidinols [5]. This effect has been rationalized [3,6] on the basis that of the three *gauche* conformation **3a-c**, large C-2 substituents should favor conformation **3a**, which is one of the two *gauche* conformations from which ring closure can occur.



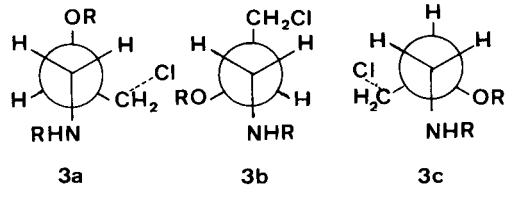
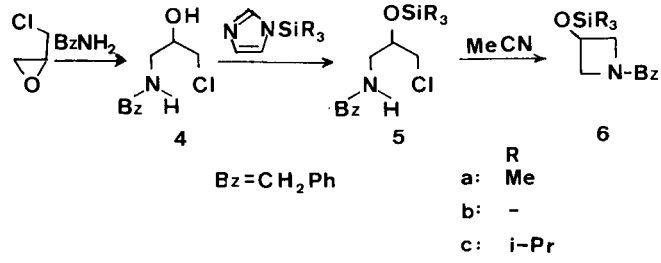


Figure 1

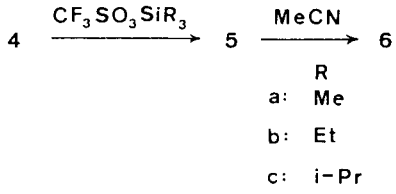
In view of our interest in the use of azetidinols as synthons for pharmacologically active compounds, it seemed logical to further exploit this effect. Thus, the triisopropylsilyl derivative was prepared by the method outlined in Scheme I. Interestingly, the yields of the trimethylsilyl and the triisopropylsilyl derivatives, **6a** and **6c** respectively, were identical (39% overall) when prepared in this manner.

Scheme I (Method 1)



In an effort to ascertain whether this steric effect had peaked at or below the steric bulk of trimethylsilyl (with no further advantage being gained by further increases in the bulk of the trialkylsilyl substituent) or whether this effect reached a maximum somewhere between the bulk of the trimethylsilyl and that of the triisopropylsilyl substituents, it seemed necessary to prepare the triethylsilyl derivative, **6b**. Owing to the unavailabiltiy of triethylsilyl chloride from our preferred supplier and to the desire to examine alternative methods for silating derivatives of **4**, we chose to examine the feasability of employing trialkylsilyl trifluoromethanesulfonates (triflates) as silating agents (Scheme II).

Scheme II (Method 2)



The crude products were analyzed by pmr spectroscopy before distillation. From the weights of the crude products and the integrated pmr signals, it was determined that the yield of **6b** appeared to be slightly greater than that of **6a** (although this difference is probably within experimental error), while that of **6c** is significantly lower than either **6a** or **6b** (see Table). The low yield of **6c** is possibly a reflection of an unfavorable equilibrium established between the *O*-silated amine and the triflate. Unfortunately, while all compounds underwent some decomposition on distillation, **6b** and **6c** underwent extensive decomposition such that the isolated yields were far lower than that of **6a**.

Table

Yield of Trialkylsilyl Azetidinyl Ethers

6	Method 1	Method 2 [a]	Method 2 [b]
a	39	52	32
b	--	58	14
c	39	25	12

[a] Yield based on weight of crude material and integrated pmr spectrum. [b] Isolated after distillation.

In conclusion, while data tend to suggest that there may be maximum ring closure with the triethylsilyl substituent, the high cost of silating agents bulkier than trimethylsilyl plus the extensive decomposition observed with the bulky triflates argue in favor of employing the trimethylsilyl substituent.

EXPERIMENTAL

The pmr spectra were determined on a Perkin-Elmer R24A spectrometer at 60 MHz. Chemical shift data are reported with respect to internal standard tetramethylsilane. In order to insure identical treatment, samples for comparison were run simultaneously. Commercial reagents (Aldrich Chemical Co.) were used without purification.

1-(Benzylamino)-3-chloro-2-propanol (**4**).

To a solution of epichlorohydrin in petroleum ether (in all experiments the concentration of epichlorohydrin was 1.0 mole per liter of petroleum ether) was added the appropriate quantity of benzylamine. The solutions were stirred at room temperature for 72 hours (**4** had begun to precipitate as a white solid overnight). The petroleum ether was removed *in vacuo*, the crude **4** being used for the silation studies.

General Procedure for Preparation of Trialkylsilylimidazoles.

These were prepared in a modification of the method employed by Cunico and Bedell [8]. A solution of 17.0 g (0.25 mole) of imidazole was prepared in 113 ml (0.80 mole) of triethylamine and 200 ml of acetonitrile. To the stirred solution, which was protected from moisture with a calcium chloride drying tube, was added (0.22 mole) of trialkylsilyl chloride, in a dropwise manner. The trimethylsilyl chloride was allowed to react fo 1.5 hours before addition to **4**, while the triisopropylsilyl chloride was allowed to react overnight before addition to **4**.

General Procedure for Preparation of **6a** and **6c** from the Trialkylsilylimidazoles (Method 1).

The unfiltered trialkylsilylimidazoles were added to **4** (prepared as above on the 0.20 mole scale). The mixtures were heated at reflux for 3 days, were filtered, and the solvents removed *in vacuo*. The residue was triturated two times with 200 ml portions of petroleum ether, the petroleum ether removed *in vacuo*, and the products distilled.

General Procedure for Preparation of **6a**, **6b**, and **6c** from Trialkylsilyl Trifluoromethanesulfonates (Method 2).

To the appropriate quantity of **4** in acetonitrile (all solutions were 1.0 *M*) was added three equivalents of triethylamine. To this solution was added 50.0 g of the trialkylsilyl triflate (based on a 1:1 reaction) in a dropwise fashion.

The resulting solutions were heated at reflux with stirring for three days. The solutions were allowed to cool, were filtered, and the solvents removed *in vacuo*. The residue was triturated twice with 200 ml portions of petroleum ether then with 100 ml of ethyl ether. The combined triturates were evaporated and the products distilled.

1-Benzyl-3-(trimethylsiloxy)azetidine (**6a**).

Method 1.

From 27.9 ml (23.9 g, 0.22 mole) of trimethylsilyl chloride was obtained 18.47 g (39%) of **6a**, bp 96-100° (0.4 torr); pmr: δ 7.29 (5H singlet, aromatic protons), δ 4.45 (1H pentuplet, azetidine C-3 proton), δ 3.64 (2H singlet, benzylic methylene protons), δ 3.6 (2H triplet with further fine splitting, C-2 and C-4 protons), δ 2.85 (2H triplet with further fine splitting, C-2 and C-4 protons), and δ 0.13 (9H singlet, trimethylsilyl protons), which is identical to that obtained previously [5].

Method 2.

From 17.6 ml (20.8 g, 0.225 mole) of epichlorohydrin and 24.6 ml (24.1 g, 0.225 mole) of benzylamine was obtained 42.27 g of crude yellow oil. The pmr spectrum of this indicated about 65% purity for **6a**. Distillation afforded 17.16 g (32%) of **6a**. The boiling point and pmr spectra were the same as above.

1-Benzyl-3-(triethylsiloxy)azetidine (**6b**).

Method 2.

From 14.8 ml (17.5 g, 0.19 mole) of epichlorohydrin and 20.6 ml (20.2 g, 0.19 mole) of benzylamine was obtained 46.51 g of crude yellow oil. The pmr spectrum of this indicated about 65% purity for **6b**. Distillation afforded 7.21 g (14%) of **6b** with decomposition occurring, bp 122-124° (0.3 torr); pmr: δ 7.25 (5H singlet), δ 4.45 (1H pentuplet), δ 3.61 (2H singlet), δ 3.6 (2H triplet with further fine splitting), δ 2.86 (2H triplet with further fine splitting) and δ 0.4-1.15 (15H complex multiplet).

Anal. Calcd. for $C_{16}H_{27}NOSi$: C, 69.3; H, 9.7; N, 5.05. Found: C, 69.21; H, 9.92; N, 5.05.

1-Benzyl-3-(triisopropylsiloxy)azetidine (**6c**) [9].

Method 1.

From 47.1 ml (42.4 g, 0.22 mole) of triisopropylsilyl chloride was obtained 24.62 g (39%) of **6c**, of boiling point 145-154° (0.4 torr); pmr data: δ 7.25 (5H singlet), δ 4.49 (1H pentuplet), δ 3.69 (2H singlet), δ 3.6 (2H triplet with further fine splitting), δ 2.83 (2H triplet with further fine splitting) and δ 1.04 (21H singlet).

Method 2.

From 12.7 ml (15.1 g, 0.163 mole) of epichlorohydrin and 17.8 ml (17.5 g, 0.163 mole) of benzylamine was obtained 26.29 g of yellow oil. The pmr spectrum indicated the purity of **6c** to be about 50%. Distillation afforded 6.51 g (12%) of **6c** with decomposition occurring, bp 144-148° (0.4 torr).

Acknowledgement.

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[9] Unsatisfactory elemental analyses were obtained on this compound--the sample prepared from triisopropylsilylimidazole appeared to be contaminated with some unreacted triisopropylsilylimidazole, while that prepared from the triisopropylsilyl triflate darkened on standing.