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N-CHLORAMINE REARRANGEMENTS. THE USE OF CYCLOBUTYLAMINE AS A PYRROLIDEINE PRECURSOR.

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Abstract: Exposure of N-chloro-N-cyclobutyl-3,4-dimethoxyphenethylamine to silver ion in benzene results in efficient ring expansion to a pyrrolideine that can be trapped via Pictet-Spengler reaction.

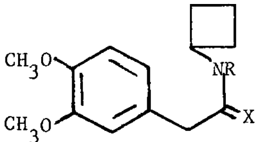
As part of a continuing study of N-chloramine rearrangements[1] we decided to explore the reactivity of a simple cyclobutyl amine derivative. Gassman and Carrasquillo[2] previously investigated the rearrangement of N-chloro-N-methyl-1-phenylcyclobutylamine in methanol solution containing silver trifluoroacetate. After sodium borohydride treatment of the reaction mixture, N-methyl-2-phenylpyrrolidine was obtained in 35% yield.

We were especially interested in the reactions of N-chlorocyclobutylamines in benzene solutions of silver tetrafluoroborate, since this medium provided superior results in other cases.[1] We hoped to obtain higher yields in the rearrangement, but, also to trap the immonium ion in a useful fashion. The low yield in the previous case was of concern, especially since the aromatic substituent should provide added stability to the intermediate ion. Nevertheless, we decided to start with a potentially more difficult case; namely, cyclobutylamine itself equipped only with a trapping appendage on nitrogen. Thus the silver ion induced reaction of 3 was studied.

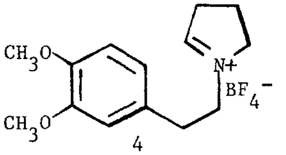
Acylation of cyclobutylamine[3] with homoveratryl chloride[4] provided amine 1 (m.p. 130-131). Reduction with borane-dimethyl sulfide[5] in THF proved to be far superior to lithium aluminum hydride reduction and cleanly produced amine 2 (b.p. 125° (0.01 torr, kugelrohr) in excellent yield. Treatment of 2 with 1 eq NCS in methylene chloride followed by washing the reaction mixture with sodium bicarbonate solution, drying with sodium sulfate and removal of the solvent, provided the N-chloramine 3 as a colorless oil. This was used without further purification.

When a benzene solution of 3 was added to a warn (∿ 50°) anhydrous benzene solution of silver tetrafluoroborate, there was immediate precipitation. The reaction was monitored with tlc and 3 was consumed in less than 0.5 h. Furthermore, the product had oiled out and there was essentially no benzene soluble organic material at this point. This is consistent with the desired rearrangement product 4.

Pictet-Spengler cyclization of intermediate 4 was easily carried out by addition of concentrated HCl to the benzene solution as soon as the N-chloramine disappeared. Standard basic work-up of the reaction after 1 h provided a red oil, which solidified on standing, in 95% yield. Carbon nmr of the crude product clearly indicated that the major product was the desired tricycle 5. This was contaminated with approximately 10-12% of the secondary amine 2, as well as an unidentified third product in similar quantity. Chromatography on silica followed by crystallization from hexane provided pure 5 (m.p. 87-89°, lit.[6] m.p. 88-90; ^{1}H nmr, δ 6.53 (s, 2H), 3.78 (s, 6H), 3.5-1.6 (m, 11H); ^{13}C nmr, C carbons at δ 147.0 (2C), 130.8, 126.0; CH carbons at δ 111.2, 108.8, 62.5; CH$_2$ carbons at δ 52.7, 48.0, 30.1, 27.7, 21.9; CH$_3$ carbons at δ 55.6, 55.5) in 67% yield.



1 R=H; X=O
2 R=H; X=H$_2$
3 R=Cl; X=H$_2$



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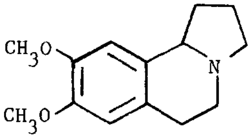

5

Significantly more secondary amine was produced in this reaction than in other rearrangements in benzene solution.[1] While we had previously assumed that this was due to inefficient production of N-chloramine, that is not reasonable in this case. Analysis of the crude N-chloramine 3 by tlc showed that it was free of amine 2. Thus, the aprotic solvent did not completely supress the dechlorination reaction.

The reaction of 3 in a methanol solution of silver tetrafluoroborate differed dramatically Addition of concentrated acid after disappearance of the N-chloramine followed by a normal basic work-up provided a crude product which contained none of the desired 5, although amine 2 was a major constituent.

It is clear that cyclobutyl amine can serve as a pyrrolideine precursor. The range of nucleophiles that can be used to usefully trap the rearrangement product has yet to be established. Furthermore, the details of the dechlorination reaction are of special interest. Relevant studies are underway.

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References and Notes

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