# SYNTHESIS OF AZETIDINE FROM 1-SUBSTITUTED AZETIDIN-3-OLS

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Abstract ——— From readily available 1-substituted azetidin-3-ols, azetidine was prepared in high yield by removal of the hydroxyl group and N-substituents.

Although considerable interest in the use of azetidine or of its simpler derivatives as the amine moiety of pharmacologically active molecules has been aroused in recent years by new drug research programs,[1] existing methods for the preparation of azetidine itself are characterized by low yields and cumbersome preparative procedures.[2] Our interest in this area of drug development prompted us to exploit a convenient and useful method for the preparation of azetidine. In this paper, we describe the facile synthesis of azetidine from readily available 1-substituted azetidin-3-ols, as shown in Chart 1.

First, we chose 1-benzhydrylazetidin-3-ol (1)[3] as a starting material. Reductions of the mesylate (3)[3] and the tosylate (4)[3] with sodium borohydride in polar aprotic solvents such as DMF, DMSO, and HMPA were examined in order to obtain 1-benzhydrylazetidine (6). Thus, sodium borohydride was added to a solution of 3 in DMF at 40°C with stirring. The resulting mixture was kept at 100°C for 3 h. After usual work-up and recrystallization of the crude product from 70% ethanol, 6 was obtained in 81% yield as colorless needles (mp 109-110°C). The structure of 6 was established on the basis of its nmr spectral data and elemental analysis (Table I). Similar reduction of 4 could be performed at 70°C for 3 h to give 6 in 95% yield. Using DMSO or HMPA as solvent, 6 was also formed at 70°C from 3 and 4 in high yields. Interestingly, the reduction of 4 at 100°C in HMPA resulted in the reductive cleavage of the ring to give a considerable amount (50%) of N-propylbenzhydrylamine as a colorless oil along with 6 (38%).

Attempts to remove the benzhydryl group of 6 in refluxing in aqueous HCl[4] failed:

6 was recovered unchanged. However, removal of the benzhydryl group was accomplished by catalytic hydrogenolysis to yield cleanly azetidinium chloride (8). Thus, 10% HCl was added to a solution of 6 in methanol. Then, the resulting mixture was treated with hydrogen in the presence of 20% $Pd(OH)_2$ on charcoal[3,5] at 3 atm for 3 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was diluted with water, and then the mixture was extracted with ether. From the ethereal layer, diphenylmethane was obtained in 91% yield. The aqueous layer was washed with ether and concentrated under reduced pressure to give almost quantitatively 8 as a hygroscopic solid, mp 140-145°C. The picrate melted at 171.5-172.5°C (lit.,[6] mp 166-169°C). The structure of 8 was established on the basis of its nmr spectrum and additionally of the elemental analysis of the picrate (Table I).

As an alternative approach, we examined the synthesis of azetidine from 1-ethoxycarbonylazetidine (13) in which the alkoxycarbonyl group can be usually removed by simple acidic hydrolysis. Treatment of 4 with ethyl chloroformate in benzene gave 10 as a colorless oil in 78% yield along with 3-benzhydryl-5-chloromethyloxazolid-2-one (12) (mp 154-155.5°C, 11%) resulting from ring cleavage of 4 into 11

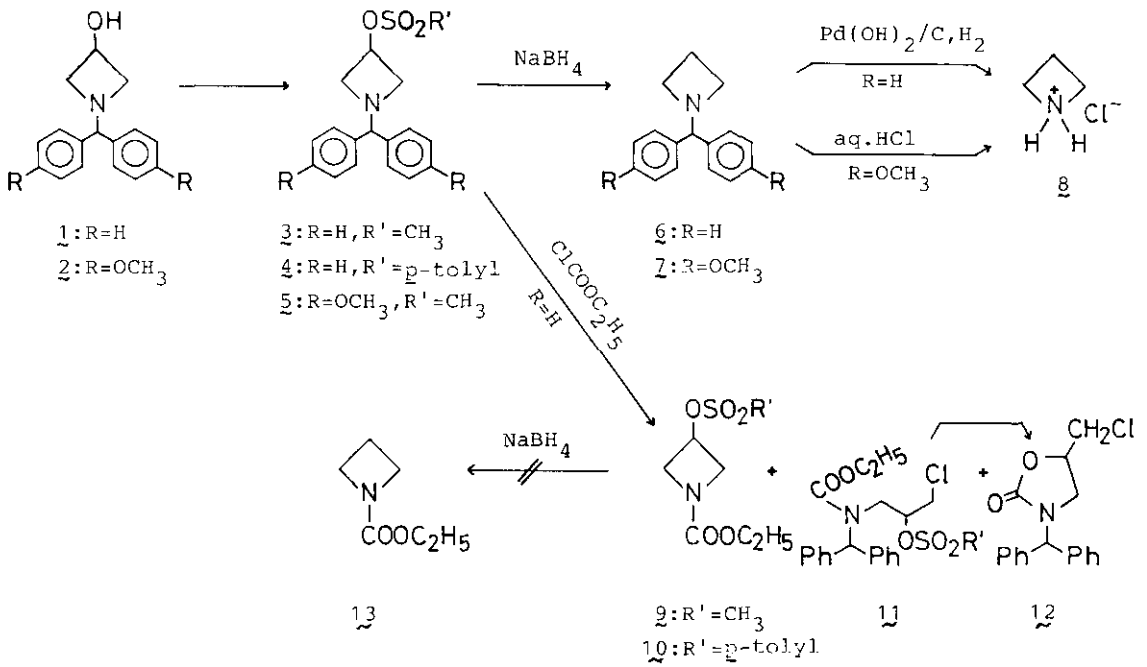


Chart 1

followed by cyclization. Similar treatment of 3 with ethyl chloroformate afforded 9 (41%) along with 12 (26%). Attempts to remove the mesyloxy group of 9 and the tosyloxy group of 10 by sodium borohydride reduction failed.

Recently, it has been reported by Greenlee[7] that removal of a 4,4'-dimethoxybenzhydryl protecting group in dialkylamines is nicely accomplished under conditions of the acidic hydrolysis to give primary amines. As the application of this procedure, we next examined the treatment of 1-(4,4'-dimethoxybenzhydryl)-azetidine (7) with aqueous HCl. The starting material, 2, mp 100-101°C, was prepared in 55% yield by the use of 4,4'-dimethoxybenzhydrylamine in place of benzhydrylamine in a manner similar to that for the preparation of 1. The N-substituted azetidine (7), mp 97-98°C, could be obtained in 95% yield via sodium borohydride reduction of the mesylate (5) which was readily derived from 2 by the usual procedure. The structure of 7 was established on the basis of its nmr spectral data and of elemental analysis (Table I). Subsequently, a solution of 7

Table I. $^1$H-NMR Spectral and Elemental-Analytical Data for 6, 7, and 8

| Compd. | Formula | $^1$H-NMR (solvent) $\delta$ | Analysis (%) Calcd/Found C | H | N |
|---|---|---|---|---|---|
| 6 | $C_{16}H_{17}N$ | ($CDCl_3$): 1.8-2.2 (2H, m, $CH_2CH_2CH_2$), 3.10 (4H, t, J=7.5Hz, $CH_2NCH_2$), 4.26 (1H, s, $Ph_2CH$), 7.0-7.4 (10H, m, aromatic H) | 86.06<br>86.13 | 7.67<br>7.68 | 6.27<br>6.28 |
| 7 | $C_{18}H_{21}NO_2$ | ($CDCl_3$): 1.8-2.2 (2H, m, $CH_2CH_2CH_2$), 3.08 (4H, t, J=7.5Hz, $CH_2NCH_2$), 3.72 (6H, s, 2x$OCH_3$), 4.20 (1H, s, $Ar_2CH$), 6.78 (4H, d, aromatic H), 7.28 (4H, d, aromatic H) | 76.26<br>76.38 | 7.47<br>7.52 | 4.94<br>4.91 |
| 8[a] | $C_3H_8NCl$ | (DMSO-$d_6$): 2.1-2.6 (2H, m, $CH_2CH_2CH_2$), 3.7-4.1 (4H, m, $CH_2NCH_2$), 8.8-10.0 (2H, br s, $^+NH_2$) | 37.77<br>37.90 | 3.25<br>3.25 | 19.58<br>19.57 |

a) The result of elemental analysis shown on the right column is the data for azetidine picrate ($C_9H_{10}N_4O_7$).

in 6N HCl was heated under reflux for 14 h. The reaction mixture was washed with ether and chloroform. Then, the aqueous layer was concentrated under reduced pressure to give 8 in 98% yield. Therefore, this procedure may be more suitable for the large scale preparation of 8 than that via 6.

In conclusion, the present method may have significant advantage over the other existing methods owing to the experimental simplicity and the high overall yield.

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Received, 23rd May, 1986