SYNTHESIS OF 1-HYDROXYAZETIDINES AND THEIR CONVERSION
INTO 1,4-DIACETOXY-2-AZETIDINONES

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Abstract: 1-Hydroxyazetidines (5), prepared by reductive cyclization of *O*-benzyl- β -tosyloxy oximes 1 and subsequent debenzylation, can be oxidized selectively either to four-membered cyclic nitrones (6 and 7) or to 1,4-diacetoxy-2-azetidinones (9).

Recently we have reported a novel route to *N*-acetoxy β -lactams by oxidation of the corresponding four-membered cyclic nitrones (2,3-dihydroazete 1-oxides)¹. We have also found that 1-hydroxyazetidines obtained by reduction of the corresponding four-membered cyclic nitrones, could be oxidized with HgO to the same nitrones in almost quantitative yields². Furthermore, the C-4 unsubstituted 1-hydroxyazetidine could be converted directly to the 1-acetoxy-2-azetidinone without isolating the intermediate nitrone by reaction with two equivalents of lead tetraacetate^{1b,2}. Since the synthesis of four-membered cyclic nitrones is virtually limited to the reaction of nitroalkenes with ynamines³, an alternative and more general route to these heterocycles seemed to be the oxidation of the corresponding 1-hydroxyazetidines. We wish to report here the preliminary results of a study on the synthesis and the oxidation of 1-hydroxyazetidines⁴.

We anticipated that 1-hydroxyazetidines might be synthesized by cyclization of γ -tosyloxy hydroxylamine derivatives, prepared by reduction of the corresponding oximes. Oximation of 3,3-dimethyl-4-tosyloxy-2-butanone⁵ gave the corresponding oxime 1a in a yield of 92% (m.p. 119.5-121.5°C, from diisopropyl ether)⁶. Reduction of this oxime under relatively mild conditions (NaCNBH₃/CH₃COOH, 16 h at room temperature⁸) afforded 3,4,4-trimethylisoxazolidine 3 in a yield of 61% (b.p. 62-64°C/13 mm Hg, n_D^{20} 1.4444). MS: M^+ 115.10 (C₆H₁₃NO). ¹H NMR δ (CDCl₃) 0.97 and 1.11 (s, 6H, CH₃), 1.03 (d, 3H, CH₃), 3.02 (q, 1H, H-3), 3.58 and 3.70 (AB, 2H, $J=7.3$ Hz, H-5), 4.6 (bs, 1H, NH). 3.HCl: dec. > 120°C, from chloroform/ethyl acetate⁹. Obviously the reduction of the oxime is followed by a surprising facile cyclization of the hydroxylamine derivative 2a via intramolecular alkylation of the hydroxylamine moiety at oxygen.

Therefore we prepared the *O*-benzyl oxime 1b from *O*-benzylhydroxylamine and 3,3-dimethyl-4-tosyloxy-2-butanone, in a yield of 96% (m.p. 83-84.5°C, from diisopropyl ether)⁹. Reduction of 1b with NaCNBH₃ in acetic acid (16 h, 35°C) gave the 1-ben-

zyloxy-2,3,3-trimethylazetidine 4a in a yield of 63% (b.p. 62–64°C/0.5 mm Hg; n_D^{20} 1.4909)⁹. MS: M^+ 205.15 ($\text{C}_{13}\text{H}_{19}\text{NO}$). ^1H NMR δ (CDCl_3) 3.27 (q, 1H, H-2), 3.02 and 3.35 (AB, 2H, $J=7$ Hz, H-4). ^{13}C NMR δ (CDCl_3) 30.4 (s, C-3), 68.3 (t, C-4), 73.8 (d, C-2). Catalytic debenzoylation of 4a with Pd/C in acetic acid afforded the 1-hydroxyazetidine 5a in a yield of 71% (b.p. 58–60°C/5 mm Hg, n_D^{20} 1.4363). MS: M^+ 115.10 ($\text{C}_6\text{H}_{13}\text{NO}$). ^1H NMR δ (CDCl_3) 3.25 (q, 1H, H-2), 3.06 and 3.37 (AB, 2H, $J=7.3$ Hz, H-4), 6.9 (bs, 1H, OH). ^{13}C NMR δ (CDCl_3) 30.7 (s, C-3), 69.3 (t, C-4), 74.7 (d, C-2).

In a similar way, oxime 1c was prepared from 2,2-dimethyl-3-tosyloxypropanal¹⁰ and *O*-benzylhydroxylamine in a yield of 96% (oil). Reduction of the crude oxime 1c as described for 1a gave the hydroxylamine derivative 2c in a yield of 92% (oil). However, 2c did not undergo cyclization even on prolonged reaction in acetic acid, and could be characterized as the hydrochloride (m.p. 110–119°C, dec., from chloroform/ethyl acetate)⁹. Without further purification 2c was cyclized in diethyl ether at 20°C by the rapid addition of a *n*-butyl lithium solution in hexane, to the 1-benzyloxyazetidine 4b in a yield of 53% (b.p. 62–64°C/0.6 mm Hg, n_D^{20} 1.4960)⁹. MS: M^+ 191.13 ($\text{C}_{12}\text{H}_{17}\text{NO}$). ^1H NMR δ (CDCl_3) 1.17 (s, 6H, CH_3), $\sim$ 3.3 (bs, 4H, NCH_2). ^{13}C NMR δ (CDCl_3) 28.5 (s, C-3), 70.3 (t, NCH_2). Debenzoylation of 4b afforded 3,3-dimethyl-1-hydroxyazetidine (5b) in a yield of 61% (b.p. 56–58°C/5 mm Hg, n_D^{20} 1.4359). MS: M^+ 101.08 ($\text{C}_5\text{H}_{11}\text{NO}$). ^1H NMR δ (CDCl_3) 1.19 (bs, 6H, CH_3), $\sim$ 3.4 (bAB, 4H, NCH_2), $\sim$ 7.6 (bs, 1H, OH). ^{13}C NMR δ (CDCl_3) 28.1 (s, C-3), 71.3 (t, NCH_2)¹³.

Oxidation of 1-hydroxyazetidine 5a with yellow mercury(II)oxide in dichloromethane gave an oil, which according to ^1H NMR spectroscopy contained $\sim$ 30% of the nitron 6a. The absorptions in the ^1H NMR spectrum at δ 1.32 (s), δ 1.93 (t, $J=1.95$ Hz, and δ 3.96 (q, $J=1.95$ Hz) are in good agreement with those reported previously by Black et al.⁷. Obviously this method of oxidation is too drastic, since nitron 6a was strongly contaminated ($\sim$ 70%) with products that arise from decomposition or polymerization. Oxidation of 5a with "active lead(IV)oxide"¹⁴, which has been used for the preparation of sensitive and unstable nitrones from the corresponding hydroxylamines, gave a mixture of two isomeric four-membered cyclic nitrones in quan-

titative yield. According to ^1H NMR spectroscopy in addition to **6a** (78%) a second nitrone (**6b**) was formed (22%) by a different mode of hydrogen abstraction. ^1H NMR δ (CDCl_3) 1.23 and 1.36 (s, 6H, CH_3), 1.41 (d, 3H, CH_3), 4.14 (q, 1H, H-2), 6.74 (s, 1H, $\text{N}=\text{CH}$).

Oxidation of 1-hydroxyazetidine **5b**, in which there is only one possible way of hydrogen abstraction gave the four-membered cyclic nitrone **7** as an oil in a yield of $\sim 70\%$. ^1H NMR δ (CDCl_3) 1.39 (s, 6H, CH_3), 4.04 (s, 2H, H-2), 6.86 (s, 1H, $\text{N}=\text{CH}$). Reaction of this crude oxidation product with dimethyl acetylenedicarboxylate (DMAD) quantitatively gave the cycloadduct **8** (oil, purified by filtration of an ethyl acetate solution through florisil). The structure of **8** was proven by comparison of the ^1H and ^{13}C NMR spectroscopic data with those of similar cycloadducts of four-membered cyclic nitrones with DMAD¹⁵. MS: M^+ 241.09 ($\text{C}_{11}\text{H}_{15}\text{NO}_5$). ^1H NMR δ (CDCl_3) 1.14 and 1.45 (s, 6H, CH_3), 3.62 and 3.79 (dAB, 2H, $J=10$ Hz, $J\sim 1$ Hz, H-7), 3.75 and 3.91 (s, 6H, OCH_3), 4.82 (t, 1H, $J\sim 1$ Hz, H-5).

Oxidation of 1-hydroxyazetidine **5a** with three equivalents of lead tetraacetate in toluene at 0°C , produces the 1,4-diacetoxy-2-azetidinone **9** in a yield of 71% (m.p. $68.5\text{--}70^\circ\text{C}$, from petroleum ether $60\text{--}80^\circ$)⁹. MS: M^+ +1 230.10 ($\text{C}_{10}\text{H}_{16}\text{NO}_5$); IR (KBr) 1810 (NOCOCH_3), 1785 ($\text{C}=\text{O}$) and 1745 cm^{-1} (OCOCH_3); ^1H NMR δ (CDCl_3) 1.36 (s, 6H, CH_3), 1.78 (s, 3H, CH_3), 2.07 and 2.19 (s, 6H, COCH_3). ^{13}C NMR δ (CDCl_3) 55.0 (s, C-3), 97.2 (s, C-4), 169.0 (s), 168.3 (s) and 167.1 (s), ($\text{C}=\text{O}$ and $\text{OC}=\text{O}$). It has been reported in the literature that oxidation of *N,N*-dibenzylhydroxylamine proceeds via the nitrone and also gives the corresponding diacetoxy amide derivative^{16,17}.

The above results show that 1-hydroxyazetidines can be synthesized by cyclization of γ -tosyloxy hydroxylamine derivatives, and that they can be oxidized in good yields to the corresponding nitrones with "active PbO_2 ". Oxidation with lead tetraacetate gives a 4-acetoxy-2-azetidinone derivative, a type of 2-azetidinone that is a precursor for biologically important bicyclic β -lactam derivatives¹⁸.

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References and Notes

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