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 (8).

Recently we have reported a novel route to N-acetoxy β-lactams by oxidation of
the corresponding four-membered cyclic nitrones (2,3-dihydroazete l-oxides). 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 yields. 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.

Since the synthesis of four-membered cyclic nitrones is virtually limited to the
reaction of nitroalkenes with ynamines, an alternative and more general route to
these heterocycles seemed to be the oxidation of the corresponding 1-hydroxyazeti-
dines. We wish to report here the preliminary results of a study on the synthesis
and the oxidation of 1-hydroxyazetidines.

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-butanone gave the corresponding
oxime la in a yield of 92% (m.p. 119.5-121.5°C, from diisopropyl ether). Reduction
of this oxime under relatively mild conditions (NaCNBH3/CH3COOH, 16 h at room tem-
perature) afforded 3,4,4-trimethylisoxazolidine 3 in a yield of 61% (b.p. 62-64°C/
13 mm Hg, nD 1.4444). MS: M+ 115.10 (C6H13NO). 1H NMR (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 acetate. Obviously the re-
duction of the oxime is followed by a surprizing facile cyclization of the hydrox-
ylamine 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). 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). MS: $M^+ 205.15$ (C$_{13}$H$_{19}$NO). $^1$H NMR $\delta$(CDCl$_3$) 3.27 (q,1H,H-2), 3.02 and 3.35 (AB,2H,$J=7$ Hz,H-4). $^{13}$C NMR $\delta$(CDCl$_3$) 30.4 (s,C-3), 68.3 (t,C-4), 73.8 (d,C-2). Catalytic debenzylation 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: $M^+ 115.10$ (C$_6$H$_{13}$NO). $^1$H NMR $\delta$(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 $\delta$(CDCl$_3$) 30.7 (s,C-3), 69.3 (t,NCH$_2$). Catalytic debenzylation of 4b afforded the 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: $M^+ 101.08$ (C$_5$H$_{11}$NO). $^1$H NMR $\delta$(CDCl$_3$) 1.19 (bs,6H,CH$_3$), 3.4 (AB,4H,NCH$_2$), 7.6 (bs,1H,OH). $^{13}$C NMR $\delta$(CDCl$_3$) 28.1 (s,C-3), 71.3 (t,NCH$_2$). 

Oxidation of 1-hydroxyazetidine 5a with yellow mercury(II)oxide in dichloromethane gave an oil, which according to $^1$H NMR spectroscopy contained $\approx 30\%$ of the nitron 6a. The absorptions in the $^1$H NMR spectrum at $\delta$ 1.32 (s), $\delta$ 1.93 (t,$J=1.95$ Hz, and $\delta$ 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 to drastic, since nitrone 6a was strongly contaminated ($\approx 70\%$) 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 $^1$H NMR spectroscopy in addition to $6a$ (78%) a second nitrone ($6b$) was formed (22%) by a different mode of hydrogen abstraction. $^1$H NMR $\delta$ (CDCl$_3$) 1.23 and 1.36 (s,6H,CH$_3$), 1.41 (d,3H,CH$_3$), 4.14 (q,1H,H-21), 6.74 (s,1H, N=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 $\approx 70\%$. $^1$H NMR $\delta$(CDCl$_3$) 1.39 (s,6H,CH$_3$), 4.04 (s,2H,H-2), 6.86 (s,1H,N=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 $^1$H and $^{13}$C NMR spectroscopic data with those of similar cycloadducts of four-membered cyclic nitrones with DMAD$^{15}$. MS: $M^+$ 241.09 ($C_{11}H_{15}NO_5$). $^1$H NMR $\delta$(CDCl$_3$) 1.14 and 1.45 (s,6H,CH$_3$), 3.62 and 3.79 (dAB,2H,$J_1=10$ Hz,$J_2=1$ Hz,H-7), 3.75 and 3.91 (s, 6H,0CH$_3$), 4.82 (t,1H,$J_1=1$ 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. 68.5-70°C, from petroleum ether 60-80°C$^9$. MS: $M^+$ +1 230.10 ($C_{10}H_{16}NO_5$); IR(KBr) 1810 (NOCOCH$_3$), 1785 (C=O) and 1745 cm$^{-1}$ (OCOCH$_3$); $^1$H NMR $\delta$(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 $\delta$(CDCl$_3$) 55.0 (s,C-3), 97.2 (s,C-4), 169.0 (s), 168.3 (s) and 167.1 (s), (C=O and OC=O). It has been reported in the literature that oxidation of $N,N$-dibenzylhydroxylamine proceeds via the nitrone and also gives the corresponding diacetoxyl amide derivative$^{16,17}$.

The above results show that 1-hydroxyazetidines can be synthesized by cyclization of $\gamma$-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 $\delta$-lactam derivatives$^{18}$. 

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Illustrations:

- A chemical reaction diagram showing the formation of $6a$ and $6b$ from $5a$.
- A chemical reaction diagram showing the formation of $7$ from $5b$.
- A chemical reaction diagram showing the formation of $9$ from $5a$.
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References and Notes

6. This compound has been described in the literature, but spectral and physical data were not reported7.
9. Satisfactory elemental analyses were obtained for this compound (C,H,N ± 0.3%).
10. This compound was prepared by oxidation of 2,2-dimethyl-3-tosyloxypropanol with pyridinium chlorochromate: m.p. 67-69°C (dec.), from diisopropyl ether; m.p. Lit. 61.3°C.
13. The methyl singlet in the 1H NMR spectrum of 5b at δ 1.19 broadened upon cooling of the CDCl3 solution, and further cooling to about 0°C gave rise to two sharp singlets at δ 1.16 and δ 1.22. From the coalescence temperature (Tc = 28°C) and the chemical shift difference of the two singlets (Δν = 4.6 Hz) a AGf value of 16.3 kcalmol-1 for the nitrogen inversion process was calculated; a detailed study will be reported elsewhere.

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