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

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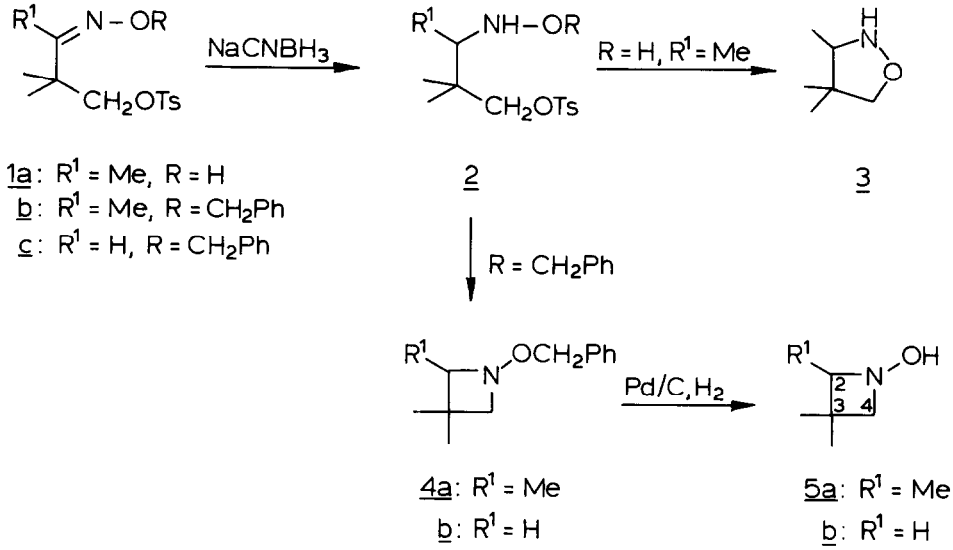
Abstract: 1-Hydroxyazetidines (5), prepared by reductive cyclization of O-benzyl-β-tosyloxy oximes 1 and subsequent debenzylation, can be oxidized selectively either to four-membered cyclic nitrones (6 and 7) or to 1,4-diacetoxy-2-azetidinones (9).

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 yields[2]. 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 ynamines[3], 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-hydroxyazetidines[4].

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[5] 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 ($NaCNBH_3/CH_3COOH$, 16 h at room temperature[8]) 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 ($C_6H_{13}NO$). ^1H NMR δ($CDCl_3$) 0.97 and 1.11 (s, 6H,CH_3), 1.03 (d,3H,CH_3), 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[9]. Obviously the reduction of the oxime is followed by a surprizing facile cyclization of the hydroxylamine derivative 2a via intramolecular alkylation of the hydroxylamine moiety at oxygen.

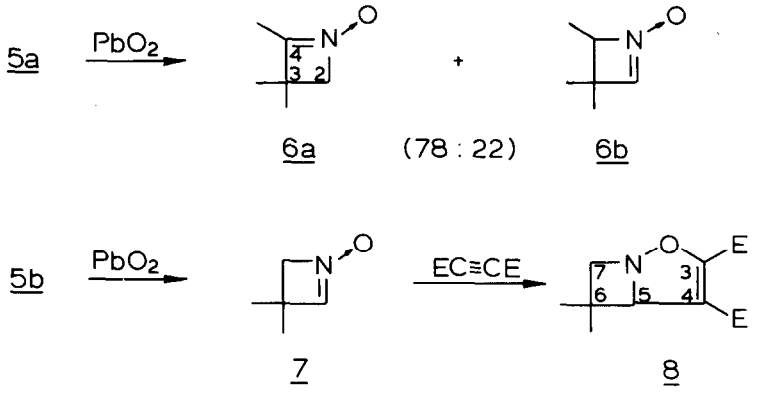
Therefore we prepared the *O*-benzyl oxime 1b from *O*-benzylhydroxylamine and 3,3-dimethyl-4-tosyloxy-2-butanone, in a yield of 96% (m.p. 83-84.5°C, from diisopropyl ether)[9]. Reduction of 1b with $NaCNBH_3$ in acetic acid (16 h, 35°C) gave the 1-ben-



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 ($C_{13}H_{19}NO$). ^{1}H 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 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 ($C_6H_{13}NO$). ^{1}H 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).

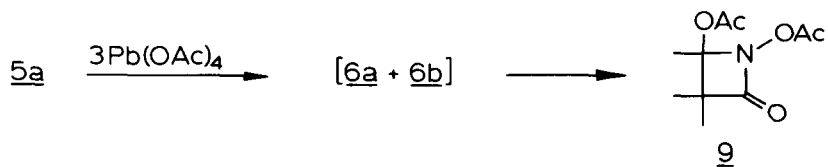
In a similar way, oxime 1c was prepared from 2,2-dimethyl-3-tosyloxypropanal[10] and *O*-benzylhydroxylamine in a yield of 96% (oil). Reduction of the crude oxime 1c as described for 1a gave the hydroxylamine derivative 2c in a yield of 92% (oil). However, 2c did not undergo cyclization even on prolonged 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 ($C_{12}H_{17}NO$). ^{1}H NMR δ($CDCl_3$) 1.17 (s,6H,CH_3), ∿ 3.3 (bs,4H,NCH_2). ^{13}C NMR δ($CDCl_3$) 28.5 (s,C-3), 70.3 (t,NCH_2). Debenzylation 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 ($C_5H_{11}NO$). ^{1}H NMR δ($CDCl_3$) 1.19 (bs,6H,CH_3), ∿ 3.4 (bAB,4H,NCH_2), ∿ 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 ^{1}H NMR spectroscopy contained ∿ 30% of the nitrone 6a. The absorptions in the ^{1}H 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 to drastic, since nitrone 6a was strongly contaminated (∿ 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 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, 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 ∿ 70%. ^{1}H NMR δ($CDCl_3$) 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 δ($CDCl_3$) 1.14 and 1.45 (s,6H,CH_3), 3.62 and 3.79 (dAB,2H,J=10 Hz,J∿1 Hz,H-7), 3.75 and 3.91 (s, 6H,OCH_3), 4.82 (t,1H,J∿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°)[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 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), (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 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 derivatives[18].

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