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OXIDATION OF *N*-HYDROXYAZETIDINES: A NOVEL SYNTHESIS OF *N*-ACETOXY β-LACTAMS AND FOUR-MEMBERED CYCLIC NITRONES

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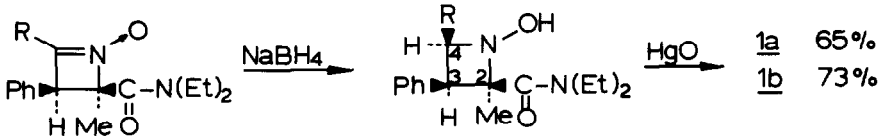
Abstract *The* N-*hydroxyazetidines* 2 *and* 3 *are prepared starting from 2,3-dihydroazete 1-oxides (*1a *and* 1b*) by reduction with sodium borohydride and by reaction with a nucleophile, respectively The* N-*hydroxyazetidines* 2 *and* 3 *can be oxidized with mercury(II)oxide to the corresponding nitrones* 1*, oxidation of the* N-*hydroxyazetidine* 2a *(unsubstituted at C-4) with* two *equivalents of lead tetraacetate yields the* N-*acetoxy* β-*lactam* 4.

Preliminary results of our studies on the chemical reactivity of 4-membered cyclic nitrones (2,3-dihydroazete 1-oxides) have revealed the extreme reactivity of the 4-membered ring system. Among other reactions we discovered the oxidative transformation of these compounds into β-lactam derivatives[1]. However, a relative facile synthesis of these 4-membered cyclic nitrones is hitherto limited to the reactions of nitro(cyclo)alkenes with aminoacetylenes[2,3]. Therefore we are currently investigating various possibilities of alternative synthesis routes for 4-membered cyclic nitrones.

A general route for the synthesis of nitrones comprises the oxidation of the corresponding hydroxylamine derivatives. Several oxidative reagents have been used for this conversion and Thesing and Sirrenberg[4] have reported the formation of pyrroline 1-oxide by oxidation of *N*-hydroxypyrrolidine using yellow mercury-(II)oxide. We wish to report here the synthesis of 4-membered cyclic nitrones by the oxidation of *N*-hydroxyazetidines.

N-hydroxyazetidines are virtually unknown heterocycles; the only representative has been prepared by a laborious method from methyl 2,4-dibromobutyrate and hydroxylamine in a yield of only 10%[5]. Since we had a number of easily accesible 4-membered cyclic nitrones (1) available, we have investigated an alternative synthesis of *N*-hydroxyazetidines *via* 4-membered cyclic nitrones. These *N*-hydroxyazetidines could then serve as model compounds in the oxidation reactions.

Reduction of 1a with sodium borohydride in methanol gave the *N*-hydroxyazetidine 2a in a yield of 93% (m.p. ∿ 141°C, dec. starts at 130°C, from petroleum ether 60-80°; see table)[6]. Reduction of 1b under similar conditions occurs stereospecifically and gave the azetidine 2b in a yield of 92% (dec. > 135°C, from diisopropyl ether). In the ^{1}H NMR spectrum of 2b the methyl group at C-4 gives

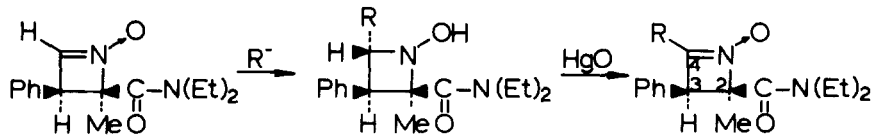


1a R=H
b R=Me

2a R=H
b R=Me

rise to a doublet at high field (δ 0.91 ppm), due to the shielding by the *cis*-substituted phenyl group. Both azetidines (2a and 2b) could be oxidized with yellow mercury(II)oxide in dichloromethane at room temperature to the corresponding nitrones, which were proven to be identical with the starting nitrones 1a and 1b.

A second route to *N*-hydroxyazetidines involves the addition of carbon nucleophiles to the C=N bond of the 4-membered cyclic nitrones. Reaction of 1a with two equivalents of methylmagnesium iodide in diethyl ether gave the *N*-hydroxyazetidine 3a, with the stereochemistry as shown in a yield of 77%, as the only product (m.p. 119-120.5°C (dec), from diisopropyl ether, see table). In the ^{1}H NMR spectrum of 3a, the methyl group at C-4 absorps at a lower field (δ 1.29 ppm), than the methyl group of the corresponding isomer 2b. When 1a was reacted with potas-



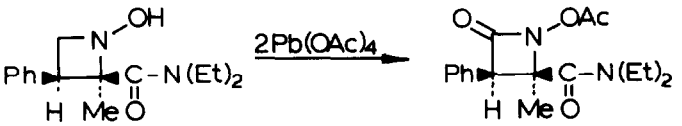
1a

3a R=Me
b R=CN

1b R=Me
c R=CN

sium cyanide in methanol the 4-cyano-*N*-hydroxyazetidine 3b was isolated in a yield of 75% (m.p. 173-175°C (dec), from chloroform/petroleum ether 60-80°). The *trans*-substitution at C-3 and C-4 is obvious from the small coupling constant (J=3.4 Hz) of the two hydrogen atoms[7]. Oxidation of 3a with mercury(II)oxide yielded the known nitrone 1b (76%) and from the oxidation of 3b, nitrone 1c was isolated in a yield of 80% (m.p. 119.5-121.5°C, from chloroform/petroleum ether 60-80°). MS: M^+ 285.15 ($C_{16}H_{19}N_3O_2$). ^{1}H NMR δ($CDCl_3$): 2.00 (s,3H,CH_3), 4.35 (s,1H,H-3)ppm. ^{13}C NMR δ($CDCl_3$): 52.5 (d,C-3), 94.0 (s,C-2), 108.2 (s,C≡N), 118.2 (s,C=N)ppm. It is rather remarkable that both in the reduction of the 4-membered cyclic nitrones and in the reaction with nucleophiles, the corresponding *N*-hydroxyazetidines are formed in a stereospecific manner. Obviously the 4-membered cyclic nitrone is that much crowded by the phenyl and carbamoyl group at one face of the almost flat ring[2b], that both the addition of the hydride and of the nucleophile (R) occur exclusively at the sterically less hindered face, which explains the observed stereochemistry of the *N*-hydroxyazetidines.

Our results show that the oxidation of *N*-hydroxyazetidines proceeds under mild conditions, and in almost quantitative yields to give 4-membered cyclic nitrones. Recently we have reported that nitrone 1a can be oxidized with lead tetraacetate in benzene to give the *N*-acetoxy β-lactam derivative 4 in a yield of 51%[1], and therefore we were interested whether the *N*-hydroxyazetidines can also be oxidized to the corresponding nitrones with lead tetraacetate. When 2a was reacted with two equivalents of lead tetraacetate in benzene solution at 6°C, oxidation took place; however under these reaction conditions the initially formed nitrone 1a was further oxidized to the *N*-acetoxy β-lactam 4, which was isolated in a yield of 44%.



2a 4

Compared with the synthesis of *N*-acetoxy β-lactams *via* oxidation of 4-membered cyclic nitrones, the two-step oxidation of *N*-hydroxyazetidines represents a more direct and convenient route to these biologically important heterocycles. 4-Membered cyclic nitrones, particularly those unsubstituted at C-4 are thermal unstable compounds[2a], and because of this instability the great advantage of the direct oxidation of *N*-hydroxyazetidines to β-lactams is that the nitrones have not to be isolated, but are oxidized *in situ* to *N*-acetoxy β-lactams.

TABLE

Characteristic NMR absorptions of *N*-hydroxyazetidines 2 and 3

Compd	^{1}H NMR		^{13}C NMR		
	H-3	H-4	C-2	C-3	C-4
2a	3.24 to 4.02 (ABX)		77.1	46.8	61.3
2b	3.39(d)	4.00(m) ($J_{3,4}$=9.0 Hz)	74.0	51.6	63.0
3a	2.85(d)	4.21(m) ($J_{3,4}$=8.8 Hz)	75.2	53.1	68.4
3b	3.67(d)	4.39(d) ($J_{3,4}$=3.4 Hz)	77.8	50.6	60.3

All chemical shifts were recorded in deuteriochloroform with TMS as internal standard

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6. Satisfactory elemental analyses were obtained for all new compounds (C,H,N $\pm$ 0.3%).

7. Because of the great flexibility of the azetidine ring, configurational analysis by the ^{1}H NMR coupling constants is often difficult (compare $J_{3,4}$ for 2b and 3a).

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