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

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<u>Abstract</u> 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  $\beta$ -lactam 4.

Preliminary results of our studies on the chemical reactivity of 4-membered cyclic nitrones (2,3-dihydroazete l-oxides) have revealed the extreme reactivity of the 4-membered ring system. Among other reactions we discovered the oxidative transformation of these compounds into  $\beta$ -lactam derivatives<sup>1</sup>. However, a relative facile synthesis of these 4-membered cyclic nitrones is hitherto limited to the reactions of nitro(cyclo)alkenes with aminoacetylenes<sup>2,3</sup>. 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<sup>4</sup> 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 (<u>1</u>) 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 <u>la</u> with sodium borohydride in methanol gave the *N*-hydroxyazetidine <u>2a</u> in a yield of 93% (m.p.  $\sim$  141°C, dec. starts at 130°C, from petroleum ether 60-80°; see table)<sup>6</sup>. Reduction of <u>1b</u> under similar conditions occurs stereospecifically and gave the azetidine <u>2b</u> in a yield of 92% (dec. > 135°C, from disopropyl ether). In the <sup>1</sup>H NMR spectrum of 2b the methyl group at C-4 gives



rise to a doublet at high field ( $\delta$  0.91 ppm), due to the shielding by the *cis*substituted phenyl group. Both azetidines (<u>2a</u> and <u>2b</u>) 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 <u>la</u> and <u>lb</u>.

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 <u>la</u> with two equivalents of methylmagnesium iodide in diethyl ether gave the *N*-hydroxyazetidine <u>3a</u>, with the stereochemistry as shown in a yield of 77%, as the only product (m.p. 119-120.5°C (dec), from disopropyl ether, see table). In the <sup>1</sup>H NMR spectrum of <u>3a</u>, the methyl group at C-4 absorps at a lower field ( $\delta$  1.29 ppm), than the methyl group of the corresponding isomer 2b. When la was reacted with potas-



sium cyanide in methanol the 4-cyano-N-hydroxyazetidine <u>3b</u> was isolated in a yield of 75% (m.p. 173-175°C (dec), from chloroform/petroleum ether  $60-80^{\circ}$ ). The transsubstitution at C-3 and C-4 is obvious from the small coupling constant (J=3.4 Hz) of the two hydrogen atoms<sup>7</sup>. Oxidation of <u>3a</u> with mercury(II)oxide yielded the known nitrone <u>1b</u> (76%) and from the oxidation of <u>3b</u>, nitrone <u>1c</u> was isolated in a yield of 80% (m.p. 119.5-121.5°C, from chloroform/petroleum ether  $60-80^{\circ}$ ). MS: M<sup>+</sup> 285.15 (C<sub>16</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>). <sup>1</sup>H NMR  $\delta$ (CDCl<sub>3</sub>): 2.00 (s,3H,CH<sub>3</sub>), 4.35 (s,1H,H-3)ppm. <sup>13</sup>C NMR  $\delta$ (CDCl<sub>3</sub>): 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 <sup>2b</sup>, 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 <u>la</u> can be oxidized with lead tetraacetate in benzene to give the *N*-acetoxy  $\beta$ -lactam derivative <u>4</u> in a yield of 51%<sup>1</sup>, and therefore we were interested whether the *N*-hydroxyazetidines can also be oxidized to the corresponding nitrones with lead tetraacetate. When <u>2a</u> was reacted with <u>two</u> equivalents of lead tetraacetate in benzene solution at 6°C, oxidation took place; however under these reaction conditions the initially formed nitrone <u>la</u> was further oxidized to the *N*-acetoxy  $\beta$ -lactam <u>4</u>, which was isolated in a yield of 44%.



Compared with the synthesis of *N*-acetoxy  $\beta$ -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<sup>2a</sup>, and because of this instability the great advantage of the direct oxidation of *N*-hydroxyazetidines to  $\beta$ -lactams is that the nitrones have not to be isolated, but are oxidized *in situ* to *N*-acetoxy  $\beta$ -lactams.

## TABLE

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

Characteristic NMR absorptions of N-hydroxyazetidines 2 and 3

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

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## References and Notes

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- 6. Satisfactory elemental analyses were obtained for all new compounds (C,H,N + 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 <u>2b</u> and <u>3a</u>).

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