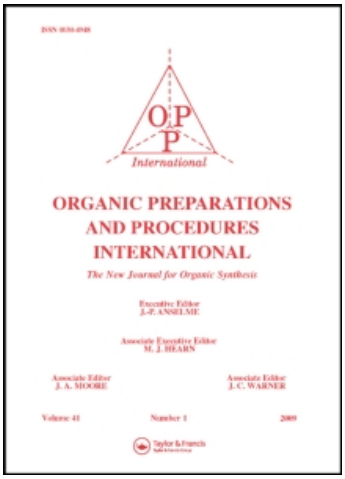

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REDUCTIVE CLEAVAGE OF N-NITROSOOXAZOLIDINES TO AMINES WITH Al-Ni ALLOY. REDUCTION TO SECONDARY N-ALKYLALKANOLAMINES†

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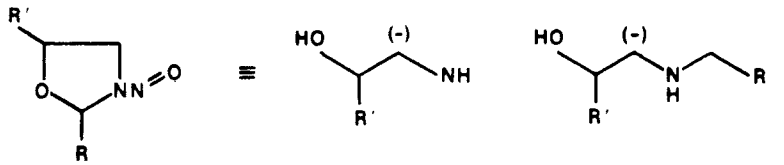
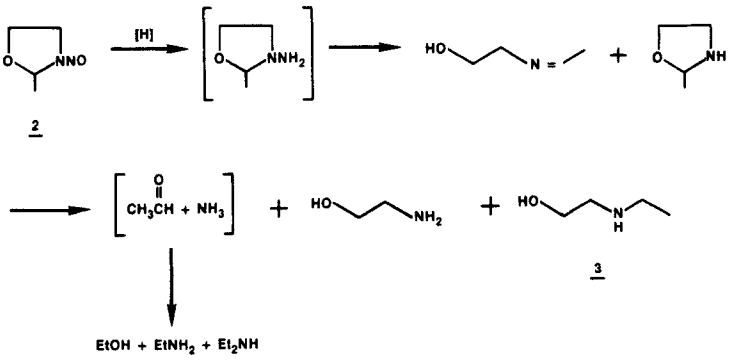
Recently, we demonstrated that α-nitrosaminoalkyl ethers undergo electrophilic addition at the α-position to give fair to excellent yields of the alkylated or hydroxyalkylated products.[1] This established a new method for umpolung reactivity of primary amines. Primary 1,2-alkanolamines can be readily converted to N-nitrosooxazolidines[2,3] which are cyclic congeners of α-nitrosaminoalkyl ethers. These compounds generally undergo deuterium exchange at the α-position.[3] Reactivity umpolung is plausible for this system; therefore a nitrosooxazolidine 1 is a β-hydroxy primary amino carbanion synthon (1a),[4] or a β-hydroxy secondary amino carbanion synthon (1b).



1 1a 1b

Our investigation of the umpolung reactivity of N-nitrosooxazolidines, led to the requirement of a method to transform these compounds to a primary or a secondary amine as a demasking step. Hydrolytic and reductive methods for the conversion of nitrosamines to their corresponding parent secondary amines have been developed by Seebach et al.[5] However, because of the alkylidine (O-C-N) functionality, nitrosooxazolidines exhibit a chemistry of their own and must be considered special

cases. These compounds are hydrolytically cleaved by acid to form the primary alkanolamine salt.[4,6] Nace and Goldberg demonstrated that nitrosooxazolidines are inert towards Adams platinum[8] and were totally reduced over Raney-Nickel catalyst to a mixture of primary and seconary amines.[7] However, this does not constitute a practical de-masking step due to its lack of selectivity. The method described by Lunn et al.[8] for the denitrosation of various nitrosamines proved to be very effective in reducing nitrosooxazolidines. This involved adding aluminum-nickel alloy to a basic solution of the nitrosamine. The catalyst generates Raney-nickel in situ with adsorbed hydrogen, making an external source of the gas unnecessary. In a typical experiment, N-nitroso-2-methyloxazolidine was dissolved in 0.25 N aqueous potassium hydroxide, a five-fold excess (by weight) of aluminum-nickel alloy was added slowly and the mixture stirred at room temperature. After 1.5 hr the products were analyzed by gas liquid chromatography and the yields calculated using n-butanol as the internal standard. Ethylamine (6%), diethylamine (2%), ethanol (19%), ethanolamine (44%), and 2-ethylaminoethanol 3 (31%) were formed. The mechanism shown in Scheme 1 accounts for all the products formed.



2

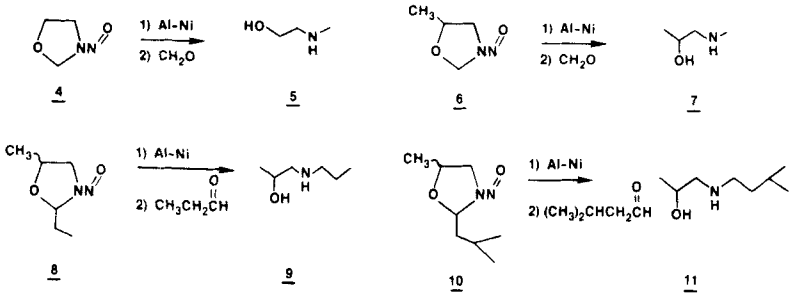
3

Scheme 1

The nitroso group is reduced to a hydrazine which, under these conditions, is short-lived,[8] losing ammonia to the oxazolidine Schiff base mixture. Loss of acetaldehyde gives ethanolamine, while reduction of oxazolidine provides the secondary amine 3. At this stage, it is possible to make the reductive degradation of nitrosooxazolidines into a useful reaction by forcing the formation of a Schiff base and concomitantly reducing it to the secondary alkanolamine. The following reaction is an example. A solution of 1.5 mmoles of 2 in 10 ml of 0.5 N KOH (1:1, methanol:water) was treated with 500 mg of aluminum-nickel alloy. The mixture was stirred at 25° for 2.5 hrs giving a 0.8:1 ratio of ethanol-amine:2-ethylaminoethanol. Two equivalents of acetaldehyde were added to the mixture and stirring was continued at 25° for 18 hrs to give 2-ethylaminoethanol 3 in near quantitative yield. Similarly, N-nitrosooxazolidine 4 was reduced to a mixture of ethanolamine 2 and 2-(methylamino)ethanol 5 with aluminum-nickel alloy in 0.5 N aqueous potassium hydroxide. For the second stage of the reduction, the mixture was treated with formalin to give 93% of 5. The two-stage reduction of N-nitroso-5-methyloxazolidine 6 gave a 98% yield of 3-(methylamino)-2-propanol 7. 3-(n-Propylamino)-2-propanol 9 and 3-(isoamylamino)-2-propanol 11 were obtained from 2-ethyl-5-methylnitrosooxazolidine 8 and 2-isobutyl-5-methylnitrosooxazolidine 10 respectively.

Aluminum-nickel alloy in base is a versatile catalyst for degrading N-nitrosooxazolidines. These nitroso compounds were reduced to a mixture of primary and secondary amines. For synthetic work a two-stage reduction procedure which leads to the conversion of the nitrosooxazolidine into a secondary amine in fair yield was developed. This conversion established that N-nitrosooxazolidines may be considered synthetic equivalents of β-hydroxy α-secondaryamino carbanions 1b.

WARNING! All the nitroso compounds herein described are carcinogenic and/or mutagenic.[9,10]



4 5 6 7 8 9 10 11

EXPERIMENTAL SECTION

Proton magnetic resonance spectra were measured on a Varian XL-100 or a Perkin-Elmer R-12B spectrometer with $CDCl_3$ or D_2O as the solvent. The IR spectra were obtained on a Perkin-Elmer 467 spectrometer. Low resolution mass spectra were taken on a Finnigan 3300 mass spectrometer equipped with a Finnigan 6000 MS data system. High-resolution spectra were obtained from a VG Micromass ZAB-2F mass spectrometer equipped with a VG 2000 data system. Gas chromatographic analyses were carried out on a Shimadzu Model 4BM gas chromatograph equipped with a Hewlett-Packard 18652A A/D converter coupled to the recorder of a flame ionization detector. A 2.5 m, 8% Hi-FFF-IBP-coated Gas Chrom Q, and a 2.5 m, Tenax GC 80/100 glass columns (Applied Science Division) were used, n-butanol was used as the internal standard. Melting points were determined on an Electrothermal capillary melting point apparatus and were not corrected. The starting materials were obtained from Aldrich Chemical Co. Silica Gel 60 (70-230 mesh, E. Merck) was used for dry-column separations.

Reductive Degradation of N-nitroso-2-methyloxazolidine (2) with Aluminum-Nickel Alloy. - To a solution of 120 mg (1.03 mmol) of 2 in 0.25N aqueous potassium hydroxide was added 500 mg of nickel-aluminum alloy. All the nitrosamine was reduced within 15 min. GLC analysis revealed a 44% yield of ethanolamine 2, 31% of 2-ethylaminoethanol 3, 6% of ethylamine, 19% ethanol, and 2% diethylamine.

Two-stage reduction of N-nitroso-2-methyloxazolidine (2).- A solution of 135 mg (1.16 mmol) of 2 in 10 ml of 0.25 N aqueous potassium hydroxide was treated with 500 mg of aluminum-nickel catalyst, and stirred at room

temperature for 30 min. To the mixture was added 200 µl of acetaldehyde and stirred at 25° for 18 hrs. n-Butanol (16 mg) was added as an internal standard and the mixture was analyzed on GLC giving a 97% yield of 2-ethylaminoethanol 3. There is no evidence of tertiary amine formation.

On a preparative scale, 1.56 g (0.013 mmol) of 2 in 140 ml of 0.25 N aqueous potassium hydroxide was reduced with 7 g of nickel-aluminum alloy for 30 min. To the reaction mixture was added 616 mg (0.014 mol) of acetaldehyde and the mixture was stirred at room temperature overnight. The mixture was filtered through Celite and the filtrate continuously extracted with methylene chloride for 24 hrs. The organic layer was dried over sodium sulfate, filtered through a layer of magnesium sulfate and the solvent removed on a rotary evaporator. The residue was distilled in vacuo to give 847 mg (73%) of 2-ethylaminoethanol (3) bp. 102-103°/100 mm Hg, lit[12] 102-103° at 100/mm Hg; nmr ($CDCl_3$): δ 1.13 (t, 3H), 2.66 (q, 2H), 2.75 (m, 2H), 3.17 (b, 3H) NH_2OH, 3.68 (t, 2H).

Reduction of N-nitrosooxazolidine (4).-A solution of 137 mg (1.34 mmol) of N-nitrosooxazolidine[9] 4 in 10 ml of 0.5 N aqueous potassium hydroxide was treated with 500 mg of aluminum-nickel alloy, and stirred at room temperature for 1 h. Two hundred ml of formalin was added and the mixture was stirred at 25°C for 4 h. The reaction mixture was filtered through Celite, and n-butanol (16 mg) was added as an internal standard. GLC analysis of the solution gave 93% yield of 2-(methylamino) ethanol 5.

Reduction of N-nitroso-5-methyloxazolidine (6).-This reduction was carried out in two stages as described for N-nitrosooxazolidine 4. GLC analysis of the resulting solution revealed a 98% yield of 3-(methylamino)-2-propanol 7 which was identical to an authentic sample.[11]

Reduction of isomeric N-nitroso-2-ethyl-5-methyloxazolidine (8).-A solution of 212 mg (1.5 mmol) of 8[4] in 0.25 N aqueous KOH was reduced as

described for compound 2. At the second stage of the reduction 0.144 ml (2 mmol) of propionaldehyde were added to the mixture, which was then stirred at 25°C for 1 h. The mixture was filtered through Celite and the product extracted continuously with methylene chloride. The solution was dried over sodium sulfate and filtered through a layer of magnesium sulfate. Evaporation of the solvent gave 93 mg (53%) of 3-(n-propylamino)-2-propanol 9. This compound was identical to the authentic sample of 9 (vide infra).

Preparation of an authentic sample of 1-(n-propylamino)-2-propanol (9).- A solution of 2 ml (0.0286 mol) of propylene oxide in 10 ml (0.12 mol) of n-propylamine was stirred at 25°C overnight. The excess amine was evaporated in vacuo to give a viscous oil. The crude product was vacuum distilled to give 500 mg (15%) of 9: bp 50-51°C at 3 mm Hg; m.p. 24-5°C; IR (film) 3410 cm^{-1}, 2960, 1458, 1380, 1121, 1078, 840; NMR ($CDCl_3$) δ 0.94 (t, 3H), 1.16 (d, 3H), 1.49 (sextet, 2H), 2.32-2.73 (m, 4H), 3.76 (m, 1H).

N-Nitroso-2-isobutyl-5-methyloxazolidine (10).-A solution of 11.3 g (0.15 mol) of 1-amino-2-propanol in 50 ml of water was cooled to 0°C and acidified with 14 ml (0.23 mol) of glacial acetic acid. To the cold solution was added 15 g (0.17 mol) of isovaleraldehyde and the mixture was stirred for 1 h. Sodium nitrite (31 g, 0.45 mol) in 50 ml of water was added and the reaction mixture kept at 4°C overnight. The mixture was made basic by the slow addition of potassium hydroxide pellets, and the product extracted into methylene chloride. The solution was filtered through a pad of magnesium sulfate and the solvent removed on a rotary evaporator. The residual oil was vacuum distilled to give 12.8 g (50%) of a cis and trans mixture of N-nitroso-2-isobutyl-5-methyloxazolidine: bp 64-5°C at 0.2 mm Hg; IR (film) 2942 cm^{-1}, 2880, 1415, 1295, 1250, 1087; NMR ($CDCl_3$): the ratio of cis:trans was calculated to be 1.6:1. The stereo-

chemical assignments were based on previously reported observations on other congeners.[3] The cis isomer shows an upfield chemical shift for the C-2 proton at δ 5.64 (t, 1.2 H) and a down field chemical shift for the C-5 methyl substituent at δ 1.43 (d, 1.86 H). The trans isomer exhibits a downfield shift for the C-2 proton at δ 5.93 (t, 0.8 H) and an upfield shift for the C-5 methyl group at δ 1.32 (d, 1.14 H). Common shifts are: δ 1.02 (d, 6H), 1.96 (m, 2H), 2.0-4.72 (m, 4H); MS, m/z (%) 172 (M^+, 1.3), 116 (6.47), 115 (7.91), 97 (2.27), 96 (1.88), 85 (3.09), 84 (2.01), 83 (2.83), 81 (2.40), 69 (4.33), 57 (6.61), 44 (6.80); exact mass (M^+) 172.1226, required for $C_8H_{16}N_2O_2$ (M^+) 172.229.

Reduction of 10 to 1-(isoamylamino)-2-propanol (11). - To a partial solution of 1.76 gm (0.0102 mol) of N-nitroso-2-isobutyl5-methyloxazolidine 10 in 100 ml 0.25 N aqueous potassium hydroxide was added 7 g of aluminum-nickel alloy over a 10 min period. The mixture was stirred for 1 h at 25°C. GLC analysis at this stage indicated a 1.5:1 ratio of 3-(isoamylamino)-2-propanol 11:1-amino-2-propanol with no trace of starting nitrosamine being detected. Isobutyraldehyde 1.3 g (0.015 mol) was added to the mixture, and stirred at room temperature overnight. The mixture was filtered through Celite and the filtrate extracted with methylene chloride. The organic layer in turn was extracted with 20 ml of 10% hydrochloric acid. The aqueous layer was made basic with aqueous sodium hydroxide and extracted with methylene chloride. The solution was filtered through a layer of magnesium sulfate, the solvent evaporated and the residual oil vacuum distilled to give 816 mg (56%) of 11: bp 69-70°C at 2 mm Hg (lit[12] 70-1°C at 2.3 mm Hg); the amine crystallized on standing, mp = 157-9°C; IR (film) 3380 cm^{-1}, 2955, 2800, 1466, 1130, 735; NMR ($CDCl_3$) δ 0.94 (d, 6H), 1.30 (d, 3H), 1.75 (m, 2H), 3.09 (m, 5H), 4.34 (sextet, 1H); MS, m/z (%) 145 (M^+, 3.9), 114 (3.3), 100 (41), 88 (18), 81 (26.6), 80 (25), 70 (16), 44 (100), 30 (37.8).

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