adds as a nucleophile to the carbonyl group rather than undergoing electron transfer to either the carbonyl group or the nitro group of 1.

Experimental Section

2-Methyl-2-nitrocyclopropyl methyl ketone (1) was prepared in 71% yield by the reaction of 5-chloro-5-nitrohexan-2-one with NaH in DMF, bp 103 °C (25 torr).[15]

3-(2-Nitro-2-propyl)-5-nitro-2-hexanone (2) was isolated from the reaction of 4.6 mmol of 1 and 4.6 mmol of $Me_2C{=}NO_2Li$[16] in 10 mL of DMF after irradiation under N_2 for 22 h with a 275-W sunlamp ca. 16 cm from the reaction flask. Hydrolysis of the reaction mixture followed by ether extraction and Kugelrohr distillation, 85 °C (29 torr), gave 51% of 2: ^{1}H NMR ($CDCl_3$) δ 4.55 (m, 1), 2.82 (m, 2), 2.32 (s, 3), 1.90 (s, 3), 1.83 (s, 3), 1.50 (d, 3, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 204.59, 141.44, 132.27, 82.07, 35.26, 30.95, 22.89, 21.59, 18.59; IR (neat) 3000, 2980, 1690 (s), 1550 (s), 1460, 1400, 1360, 1300, 1195, 1145, 1105, 860 cm^{-1}; HRMS calcd for $C_9H_{15}O$ (P – HN_2O_4) 139.11229, found 139.11235; calcd for $C_8H_{12}NO_3$ (P – CH_3, HNO_2) 170.08172, found 170.08228.

1-(2-Methyl-2-nitrocyclopropyl)ethanol was prepared in 80% yield by reaction of 1 with $NaBH_4$ in Me_2CHOH at reflux for 1 h mp 89–90 °C; ^{1}H NMR ($CDCl_3$) δ 3.40 (m, 1), 1.83 (s, 3), 1.35 (d, 3); ^{13}C NMR ($CDCl_3$) δ 68.28, 64.38, 37.14, 23.10, 22.39, 14.87; IR (KBr) 3250 (br s), 2990, 1570 (s), 1450, 1390, 1370, 1350 (s), 1170, 1110, 1080 (s), 1060, 965, 880 (s), 860, 720; HRMS calcd for $C_5H_8NO_3$ (P – CH_3) 130.05042, found 130.05018.

The alcohol was also prepared by the reaction of 6 mmol of the ketone with 12 mmol of $Na_2S_2O_4$ and 24 mmol of $NaHCO_3$ in a mixture of 14 mL of DMF and 6 mL of H_2O at 110 °C for 2 h. Hydrolysis and CH_2Cl_2 extraction gave a crude product that was analyzed by ^{1}H NMR as 29% of recovered ketone and a 45% yield of 1-(2-methyl-2-nitrocyclopropyl)ethanol.

Registry No. 1, 96194-32-0; 2, 96194-33-1; $Me_2C{=}NO_2^-$, 20846-00-8; 1-(2-methyl-2-nitrocyclopropyl)ethanol, 96194-34-2.

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Synthesis of 2,2-Disubstituted *N*-Nitrosooxazolidines wiih Nitrosyl Chloride†

Joseph E. Saavedra

LBI-Basic Research Program, Laboratory of Chemical and Physical Carcinogenesis, NCI-Frederick Cancer Research Facility, Frederick, Maryland 21701

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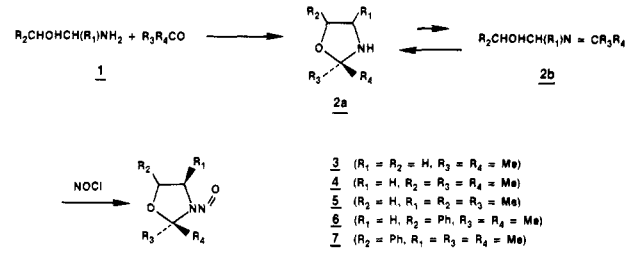
Recently, we reported a method in which α-nitrosaminoalkyl ethers serve as α-primary amino carbanion synthons.[1] β-Alkanolamines form *N*-nitrosooxazolidines, with a substituent on the C-2 position, in the presence of aldehydes and nitrous acid.[2,3] These compounds, which are cyclic congeners of α-nitrosaminoalkyl ethers, have acidic protons on the C-4 position and can serve as umpoled synthons of β-alkanolamines.[3,4] However, the single substitution on the C-2 position does involve some problems. One of these is the existence of 2-substituted nitrosooxazolidines as a mixture of *E* and *Z* rotamers,[3] which

Scheme I



leads to complications in the nuclear magnetic resonance analysis of the products. Moreover, no regioselectivity of alkylation is observed in the reaction, and multiple alkylation occurs to a large extent.[4] To overcome some of these problems oxazolidines with symmetrical 2,2-disubstitutions were prepared. That is, symmetrical ketones were used in lieu of aldehydes during the condensation reaction with the alkanolamine. The standard nitrous acid method used for the high yield syntheses of nitrosooxazolidines[2,3] with mono, or no, substitution at C-2 gives either low yields or no production of *N*-nitroso 2,2-disubstituted oxazolidines. Even when the compound is formed in low yields, there is always contamination with nitroso compounds derived from self-condensation of the parent amine and degradation products.[3]

We report here an efficient preparation of *N*-nitroso 2,2-disubstituted oxazolidines via in situ condensation of a primary alkanolamine (1) with a ketone in methylene chloride–anhydrous potassium carbonate, followed by nitrosation with nitrosyl chloride. The condensation takes place within 6 h at room temperature to give an oxazolidine (**2a**)-Schiff base (**2b**) equlibrium mixture, the ratio **2a**:**2b** depending on the structure. However, the oxazolidine is always the predominant form[5] —see Experimental Section. Nitrosyl chloride is added to the reaction mixture at 0 °C and after minimal workup the product is isolated and distilled.[6] Only a single nitroso compound is detected in the reaction, and the yields are fairly high (Scheme I). Here, the potassium carbonate serves a dual purpose—as a water scavenger in the condensation reaction and as an hydrochloric acid trap during nitrosation.

Condensation of ethanolamine and acetone, followed by nitrosation with nitrosyl chloride at 0 °C gave on workup and purification a 72% yield of *N*-nitroso-2,2-dimethyloxazolidine (**3**). *N*-Nitroso-2,2,3-trimethyloxazlidine (**4**) was obtained from 1-amino-2-propanol in 75% yield. This is a vast improvement over the 11% yield reported previosly[3] from nitrosation in aqueous media. Other yields were *N*-nitroso-2,2,4-trimethyloxazolidine (**5**, 58%), *N*-nitroso-2,2-dimethyl-5-phenyloxazolidine (**6**, 73%), and *N*-nitroso-2,2,4-trimethyl-5-phenyloxazolidine (**7**, 72%).

The lack of byproducts in these reactions indicates that the small amounts of Schiff bases present in the mixtures are also converted to the nitrosooxazolidine. It is well-documented that imines react with nitrosyl chloride to form the corresponding α-chloronitrosamine, where the chloro derivative undergoes rapid nucleophilic displacement by methanol and acetic acid giving α-methoxy- and

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acetoxynitrosamines.[7] In this case, intramolecular nucleophilic displacement of the chloro by the hydroxyl group gives the cyclic nitrosamine.

N-Nitroso 2,2-disubstituted oxazolidines can now be prepared cleanly and in good yields with nitrosyl chloride and anhydrous potassium carbonate. it is not known at this time whether symmetrical 2,2-disubstitutions have any effect on the regioselectivity of alkylation or if it prevents multiple alkylations. However, the nuclear magnetic resonance data indicates that these nitrosamines exist as the *E* rotamers. *N*-nitroso-2,2,4-trimethyloxazolidine (**5**) is an exception, with the *Z* rotamer representing 3% of the mixture.

Experimental Section

Proton and NMR spectra were recorded on a Nicolet NT-300 spectrometer with $CDCl_3$ as the solvent containing 0.5% tetramethylsilane. The IR spectra were obtained on a Perkin-Elmer 467 spectrometer. Low-resolution mass spectra were taken on a Finnigan 330 mass spectrometer equipped with a Finnigan 6000 MS data system. Gas chromatographic analyses were carried out on a Shimdazu 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 Tenax 80/100 GC column (Applied Science Division) was used.

***N*-Nitroso-2,2-dimethyloxazolidine (3).** To a solution of 10 g (0.16 mol) of ethanolamine in 100 mL of methylene chloride were added 15 g of anydrous potassium carbonate and 18 mL (0.24 mol) of acetone. The mixture was stirred at 25 °C under nitrogen for 6 h. Since GLC analysis of the reaction mixture at this time indicated that no ethanolamine remained, an aliquot was removed, and the solvent evaporated. NMR analysis of the crude mixture showed a 5.7:1 ratio of oxazolidine **2a** ($R_1 = R_2 = H$, $R_3 = R_4 =$ Me):Schiff base **2b** ($R_1 = R_2 = H$, $R_3 = R_4 =$ Me). This was based on the area of *gem*-dimethyls, δ 1.38 for the oxazolidine and δ 2.28 for the Schiff base. The reaction mixture was cooled to 0 °C, and nitrosyl chloride was slowly bubbled in. After being stirred for 30 min at 5 °C, the solution was filtered, and the solvent was removed on a rotary evaporator. The residue was vacuum distilled to give 15 g (72%) of **3**: bp 60–61 °C (1.9 mmHg); IR (film) 2985, 2935, 2885, 1414, 1370, 1300, 1235, 1162, 1045, 818 cm^{-1}; NMR ($CDCl_3$, ^1H) δ 1.73 (s, 6 H), 3.73 (t, 2 H), 4.15 (t, 2 H); NMR ($CDCl_3$, ^{13}C) 94.14 ppm (C-2), 43.05 (C-3), 62.18 (C-4), 26.36 (CH_3 on C-2); MS, *m/z* (relative intensity) 130 (4.5 M^+), 115 (1.1), 91 (3.8), 86 (10.1), 84 (5.5), 59 (12.3), 58 (39), 56 (3.6), 50 (9), 43 (100), 42 (11).

Anal. Calcd for $C_5H_{10}N_2O_2$: C, 46.15; H, 7.69; N, 21.54. Found: C, 46.18; H, 7.72; N, 21.70.

***N*-Nitroso-2,2,5-trimethyloxazolidine (4).** A solution of 20 g (0.266 mol) of 1-amino-2-propanol in 250 mL of methylene chloride was condensed with acetone as described above. NMR analysis of the reaction mixture indicated a 6.1:1 ratio of the oxazolidine **2a** ($R_1 = H$, $R_2 = R_3 = R_4 =$ Me):Schiff base **2b** ($R_1 = H$, $R_2 = R_3 = R_4 =$ Me). The reaction mixture was cooled to 0 °C, treated with nitrosyl chloride, and worked up as described above. Distillation of the crude product gave 28.4 g (75%) of **4**: bp 61 °C (1.3 mmHg) (lit.[3] bp 64 °C (0.2 mmHg)); NMR ($CDCl_3$, ^{13}C), 18.64 ppm (CH_3 on C-5), 25.98 and 27.69 (CH_3 on C-2), 49.32 (C-4), 69.63 (C-5), 95.00 (C-2).

***N*-Nitroso-2,2,4-trimethyloxazolidine (5).** Condensation of 2 g (0.027 mol) of 2-amino-1-propanol with acetone was carried out as described above; 12 h were required to complete the reaction. The mixture was nitrosated and worked up as described above to give 2.2 g (58%) of **5**: bp 45–46 °C (1.5 mmHg); IR (film) 2985, 2935, 2880, 1450, 1410, 1368, 1275, 1228, 1000, 828 cm^{-1}; NMR ($CDCl_3$, ^1H) 1.27 (d, 3 H), 1.69 (s, 3 H), 1.76 (s, 3 H), 3.78 (q, 1 H), 4.12 (q, 1 H), 4.45 (m, 1 H); the *Z* isomer represented 3% of the total as calculated from the area of Me on C-4, δ 1.59 (d), and *gem*-dimethyls, δ 1.50 and δ 1.55; MS, *m/z* (relative intensity) 144 (20, M^+), 115 (2.3), 100 (12), 98 (28), 84 (24), 71 (14), 70 (5), 69 (11), 68 (30), 67 (13), 58 (58), 42 (100), 41 (63).

Anal. Calcd for $C_6H_{12}N_2O_2$: C, 49.98; H, 8.39; N, 19.43. Found: C, 49.98; H, 8.34; N, 19.35.

***N*-Nitroso-2,2-dimethyl-5-phenyloxazolidine (6).** A 0.5 M solution of 6.7 g (0.048 mol) of 2-amino-1-phenylethanol in methylene chloride was condensed with acetone over a 12-h period as described above. The ratio of the oxazolidine **2a** ($R_1 = H$, $R_2 =$ Ph, $R_3 = R_4 =$ Me):Schiff base **2b** ($R_1 = H$, $R_2 =$ Ph, $R_3 = R_4 =$ Me) was 27:1. Nitrosation and workup was carried out as described above. The crude product was purified through dry-packed silica gel (activity III), eluted with 6:1 hexane/tetrahydrofuran, to give 7.21 g (73%) of **6** as a yellow oil: bp 148–150 °C (1.2 mmHg) (purification by distillation of large quantities of this material is not recommended); IR (film) 3060, 3010, 2985, 2935, 2880, 1950, 1882, 1810, 1755, 1605, 1595, 1453, 1414, 1370, 1287, 1168, 1030, 842, 760, 700 cm^{-1}; NMR ($CDCl_3$, ^1H) δ 1.78 (s, 3 H), 1.91 (s, 3 H), 3.35 (q, 1 H), 4.30 (q, 1 H), 5.21 (q, 1 H), 7.34 (s, 5 H); MS, *m/z* (relative intensity) 206 (M^+, 0.1), 105 (17.6), 104 (100), 103 (9.3), 78 (13.8), 77 (9.3), 71 (5), 70 (27), 55 (20), 43 (17).

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.20; H, 6.90; N, 13.48.

***erythro*-*N*-Nitroso-2,2,4-trimethyl-5-phenyloxazolidine (7).** A solution of 552 mg (3.5 mmol) of norephedrine in 8 mL of methylene chloride was stirred with 2 equiv of acetone for 6 h in the presence of anydrous potassium carbonate. The NMR spectrum indicates a ratio of 32:1 oxazolidine **2a** ($R_2 =$ Ph, $R_1 = R_3 = R_4 =$ Me):Schiff base **2b** ($R_2 =$ Ph, $R_1 = R_3 = R_4 =$ Me). The reaction mixture was nitrosated with nitrosyl chloride and worked up as described above. The product was purified on dry-packed silica gel (activity III), eluted with 6:1 hexane/THF to give 555 mg (72%) of **7**: bp (oil bath temperature) 108 °C (0.1 mmHg); IR (film) 3060, 3025, 2990, 1950, 1885, 1810, 1755, 1605, 1455, 1420, 1380, 1280, 1008, 860 cm^{-1}; NMR ($CDCl_3$, ^1H) δ 0.67 (d, 3 H), 1.84 (s, 3 H), 1.96 (s, 3 H), 4.80 (m, 1 H, $j = 5.3$ Hz), 5.26 (d, 1 H, $J = 5.3$ Hz); NMR ($CDCl_3$, ^{13}C) 134.63 ppm, 128.32, 128.07, 125.97, 94.84, 77.70, 54.71, 29.38, 26.51, 12.48; MS, *m/z* (relative intensity) 119 (10), 118 (100), 117 (47.7), 115 (5.9), 91 (14), 84 (26.4), 77 (12.3), 63 (14.5).

Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.45; H, 7.27; N, 12.72. Found: C, 65.60; H, 7.12; N, 12.86.

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Registry No. 1 (R^1, $R^2 =$ H), 141-43-5; 1 ($R_1 =$ H; $R_2 =$ Me), 78-96-6; 1 ($R_1 =$ Me; $R_2 =$ H), 78-91-1; 1 ($R_1 =$ H, $R_2 =$ Ph), 7568-93-6; **2a** (R_1, $R_2 =$ Hi R_3, $R_4 =$ Me), 20515-62-2; **2a** ($R_1 =$ H; R_2, R_3, $R_4 =$ Me), 52837-54-4; **2a** ($R_1 =$ H; $R_2 =$ Ph; R_3, $R_4 =$ Me), 87601-24-9; **2a** ($R_2 =$ Ph; R_1, R_3, $R_4 =$ Me), 60980-85-0; **2b** (R_1, $R_2 =$ H; R_3, $R_4 =$ Me), 44604-24-2; **2b** ($R_1 =$ H; R_2, R_3, $R_4 =$ Me), 96228-11-4; **2b** ($R_1 =$ H; $R_2 =$ Ph; R_3, $R_4 =$ Me), 96228-12-5; **2b** ($R_2 =$ Ph; R_1, R_3, $R_4 =$ Me), 96228-13-6; **3**, 96228-14-7; (*E*)-**4**, 77400-46-5; **5**, 96228-15-8; **6**, 96228-16-9; *cis*-**7**, 96228-17-0; Me_2CO, 67-64-1; norephedrine, 48115-38-4.

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The Role of Hydration and Stereoelectronic Effects in the Hydrolysis of cAMP

Marcel H. P. van Genderen,* Leo H. Koole, Raymond J. L. van Kooyk, and Henk M. Buck

Department of Organic Chemistry, Eindhoven University of Technology, Eindhoven, The Netherlands

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It is well-known that the coenzyme cyclic adenosine 3′,5′-monophosphate[1] is enzymatically hydrolyzed to adenosine 5′-monophosphate[1] with a large exothermic

(1) The abbreviations used are cAMP, cyclic adenosine 3′,5′-monophosphate; 5′-AMP, adenosine 5′-monophosphate.

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