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Facile Formation of N-Alkyl-oxazolidin-2-ones from N-Alkyl-nitroxyethylamines and Carbonate Anion in Biphasic Media.

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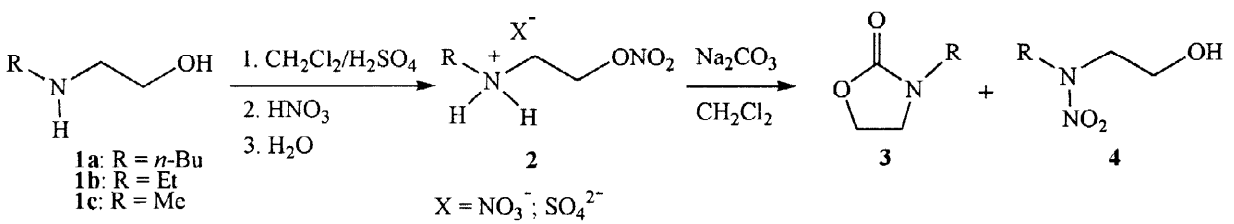
Abstract: Nitration of N-alkyl ethanolamines (**1**) followed by treatment of their corresponding N-alkyl-N-(2-nitroxyethyl)amine salts (**2**) in a biphasic CH_2Cl_2/aqueous Na_2CO_3 or $NaHCO_3$ mixture at 25 °C gives N-alkyl-oxazolidin-2-ones (**3**). This represents a new method that allows the preparation of oxazolidinones at ambient temperature with the use of aqueous carbonate. Published by Elsevier Science Ltd.

Oxazolidin-2-ones have found widespread use as chiral auxiliaries, but typical synthesis procedures for oxazolidin-2-ones employ anhydrous reaction conditions, high temperatures and toxic reagents.[1] Herein, we report N-alkyl-oxazolidin-2-ones **3a-c** can be prepared simply by nitrating N-alkyl ethanolamines **1a-c** and treating the nitroxyethylamine salts **2a-c** in biphasic CH_2Cl_2/aqueous Na_2CO_3 mixture at room temperature.



In a typical procedure, **1a** (2.7 g, 0.023 mol) in CH_2Cl_2 (20 mL) was stirred at < 10 °C during the dropwise additions of conc. H_2SO_4 (6 mL, 0.113 mol) followed by HNO_3 (98 %, 3 mL, 0.071 mol). After 45 min, the mixture was poured onto ice (60 g) and the aqueous phase was separated and stirred with CH_2Cl_2 (30 mL) at 25 °C while adding Na_2CO_3 (22 g, 0.207 mol). After 20 h at rt, the CH_2Cl_2 layer was separated, dried ($MgSO_4$) and concentrated to give 2.92 g (89 %) of **3a** along with a small amount of nitramine alcohol **4a**.[2,3] Yields of oxazolidinones **3a-c** are given in Table 1 along with relative amounts of nitramines **4a-c**.[4]

Table 1. Synthesis of N-Alkyl-oxazolidin-2-ones **3a-c**.

Entry	Substrate	Products (relative %)[a]		Yield (%)[b]
1	**1a**	**3a**:**4a**	97:3	89
2	**2a** ($X = NO_3^-$)[c]	**3a**:**4a**	98:2	93
3	**1b**	**3b**:**4b**	90:10	73
4	**1c**	**3c**:**4c**	90:10	30[d]

[a]**3**:**4** ratios determined by ^1H NMR. [b]isolated yields, unoptimized process. [c]For preparation and reaction of **2a** see reference 5. [d]Low yield may be partially due to product volatility.

The free amine nitrate ester **5a** was isolated from the neutralization of salts **2a**, but upon standing, neat **5a** underwent self condensation to produce N,N'-dibutyl-1,4-diazacyclohexane, dinitrate salt (**6a**) along with

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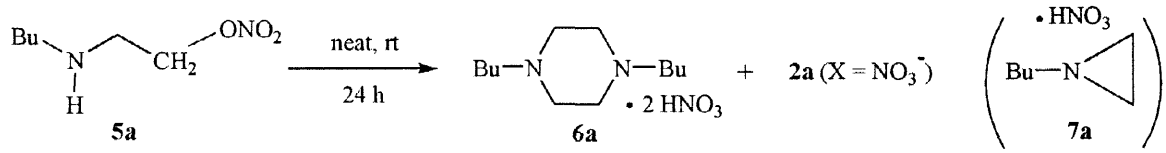
2a.[5,6,7] Elemental analysis was consistent with either **6a** [from condensation of two molecules of **5a**], or N-butylaziridine, nitrate salt (**7a**) [from intramolecular displacement of nitrate by the amine]. The structure assignment of **6a** was based on the ^{13}C NMR chemical shifts of the neutralized condensation product (14.0, 20.8, 29.0, 53.3, 58.6 ppm) via comparison to known compounds: 1,4-diazacyclohexane (47.9 ppm), aziridine (18.2 ppm), and tributylamine (14.2, 21.0, 30.3, 54.3 ppm).[8]



Interestingly, when **2a** was stirred in aqueous solution with magnesium oxide to try to completely convert it into **6a**, a high yield (93 %) of essentially pure nitramine alcohol **4a** was obtained instead.

In conclusion, we have developed a facile way to prepare N-alkyl oxazolidin-2-ones from N-alkyl amine nitrate esters and carbonate anion. In addition, one might anticipate that the use of leaving groups other than the nitrate ester could produce oxazolidinones using carbonate anion in biphasic media.

Acknowledgements. Financial support from NSWC-IHD Technology Investment Program is acknowledged.

References and Notes:

1. For review and references see: (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.
2. Silica gel chromatography gave pure **3a**: ^1H NMR (200 MHz, $CDCl_3$): δ 0.95 (t, 3H), 1.27-1.63 (m, 4H), 3.26 (t, 2H), 3.55 (t, 2H), 4.32 (t, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5, 19.7, 29.3, 43.8, 44.4, 61.5, 158.4. IR (film): 1748 (C=O). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.51; H, 9.49; N, 9.70.
3. Compound **4a**'s identity was confirmed by comparison to pure **4a** synthesized from N-butyl-N-(2-nitroxyethyl)nitramine employing the hydrolysis method described in: Pews, R. G. *J. Org. Chem.* **1967**, *32*, 2914. Data for **4a**: ^1H NMR (200 MHz, $CDCl_3$): δ 0.96 (t, 3H), 1.27-1.46 (m, 2H), 1.62-1.78 (m, 2H), 3.79-3.92 (m, 7H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7, 20.0, 28.5, 53.0, 53.9, 59.5. IR (film): 3447 (OH), 1505 (NNO_2). Anal. Calcd for $C_6H_{14}N_2O_3$: C, 44.43; H, 8.70; N, 17.27. Found: C, 44.57, H, 8.78, N, 16.99.
4. Selected spectral data: **3b**. ^1H NMR (200 MHz, $CDCl_3$): δ 1.18 (t, 3H), 3.32 (q, 2H), 3.58 (t, 2H), 4.33 (t, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.5, 38.9, 44.0, 61.7, 158.3. IR (film): 1748 (C=O). **3c**. ^1H NMR (200 MHz, $CDCl_3$): δ 2.89 (s, 3H), 3.59 (t, 2H), 4.32 (t, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 31.1, 46.8, 61.6, 158.9. IR (film): 1747 (C=O). **4b**. ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, 3H), 3.80-3.92 (m, 7H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.4, 48.1, 53.5, 59.7. IR (film): 3429 (OH), 1504 (NNO_2). **4c**. ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.3, 55.3, 58.0. Observed as minor peaks in spectrum of **3c**.
5. N-butyl-N-(2-nitroxyethyl)amine nitrate salt **2a** was isolated as a pure material from the nitration of **1a** using 1 equivalent of HNO_3/acetic anhydride nitrating reagent (in addition to the one equivalent of HNO_3 required to form the amine salt). Data for **2a**: mp: 110-111 °C; ^1H NMR (200 MHz, DMSO-d_6): δ 0.90 (t, 3H), 1.33 (m, 2H), 1.55 (m, 2H), 2.95 (t, 2H), 4.80 (t, 2H), 8.75 (broad s). IR (KBr): 2957-2799 (CH), 2731-2426 (NH_2^+), 1648, 1277 (ONO_2), 1380 (NO_3^-). Anal. Calcd for $C_6H_{15}N_3O_6$: C, 32.00; H, 6.71; N, 18.66. Found: C, 31.28; H, 6.72; N, 18.92. Reaction of **2a** to give **3a** was as follows: To **2a** (1.1 g, 4.9 mmol) in CH_2Cl_2 (5 mL) and H_2O (5 mL) was added Na_2CO_3 (1.06 g, 10 mmol) at rt and the mixture was stirred for 24 h to give **3a** after work-up. Replacement of Na_2CO_3 with $NaHCO_3$ (5 mmol **2a**/15 mmol $NaHCO_3$) gave similar results.
6. A sample of **5a** was obtained by adding Na_2CO_3 to stirred aqueous **2a**/CH_2Cl_2 at 0 °C until the mixture was moderately basic (pH ~10), after which the CH_2Cl_2 solution was immediately separated, dried (Na_2SO_4) and the volatiles removed to give an oil: ^1H NMR (200 MHz, $CDCl_3$): δ 0.93 (t, 3H), 1.25-1.65 (m, 4H), 1.83 (NH + H_2O), 2.70 (t, 2H), 3.03 (t, 2H), 4.68 (t, 2H). IR (film): 3334 (NH), 1634, 1279 (ONO_2). The IR spectrum also showed a small peak near 1750 cm^{-1}, which was shown to be due to the presence of **3a**.
7. Data for **6a**: mp 212 °C (dec.); ^1H NMR (200 MHz, DMSO-d_6): δ 0.93 (t, 6H), 1.15-1.85 (m, 8H), 3.15-3.80 (m, 14H). IR (KBr): 3009-2874, 2684-2437 (NH^+), 1366 (NO_3^-). Anal. Calcd for $C_{12}H_{28}N_4O_6$: C, 44.43; H, 8.70; N, 17.27. Found: C, 44.49; H, 8.31; N, 17.10.
8. G. C. Levy, R. L. Lichter, and G. L. Nelson, "*Carbon-13 Nuclear Magnetic Resonance Spectroscopy*", John Wiley and Sons: New York, 1980.