The Use of 2-Oxazolidinone as a Latent Aziridine Equivalent. I. A Facile Method for the Preparation of 2-Substituted Oxazolines

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Ring-opening reaction of 2-oxazolidinone with acid chlorides followed by treatment with aqueous sodium hydroxide yields 2-substituted oxazolines.

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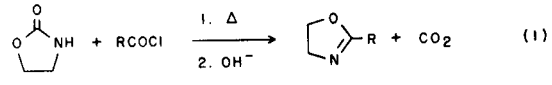
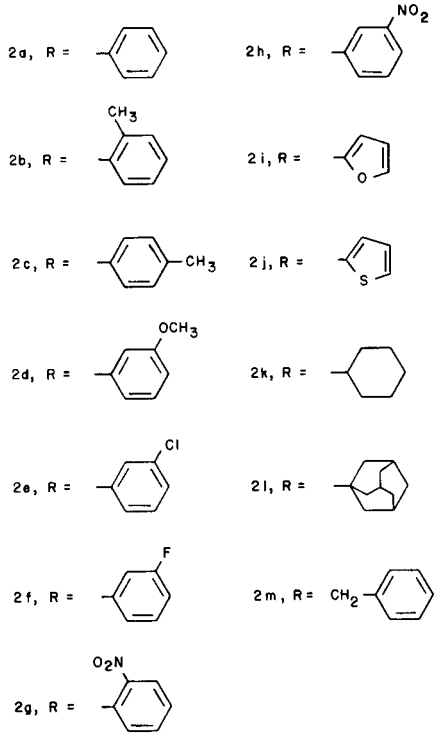
A recent note in this journal [1] has prompted us to report this alternative method to prepare 2-substituted oxazolines from 2-oxazolidinone (**1**). Herein, our method is based on the ability of 2-oxazolidinone (**1**) to function as a latent aziridine equivalent on reaction with certain electrophiles. A mixture of 2-oxazolidinone (**1**) and benzoyl chloride was heated at 140° for several hours to yield an 83:17 mixture of *N*-(2-chloroethyl)benzamide (**7a**) and 3-benzoyl-2-oxazolidinone (**4a**). Treatment of this mixture with a refluxing sodium hydroxide solution afforded, after work-up, 2-phenyloxazoline (**2a**) and an 83% distilled yield. In an analogous manner, other aromatic, heteroaromatic, and aliphatic oxazolines (**2b-2m**) were prepared in yields ranging from 21 to 83% by employing the appropriate acid chloride. The overall method is illustrated below (Equation 1).



1 **2**



Aromatic acid chlorides generally furnished the highest yields of oxazoline and aliphatic acid chlorides the lowest. The sequence could be conveniently carried out in one reaction vessel and thus obviated the need for isolation and/or purification of intermediates. Representative examples of this novel procedure are summarized in the Experimental.

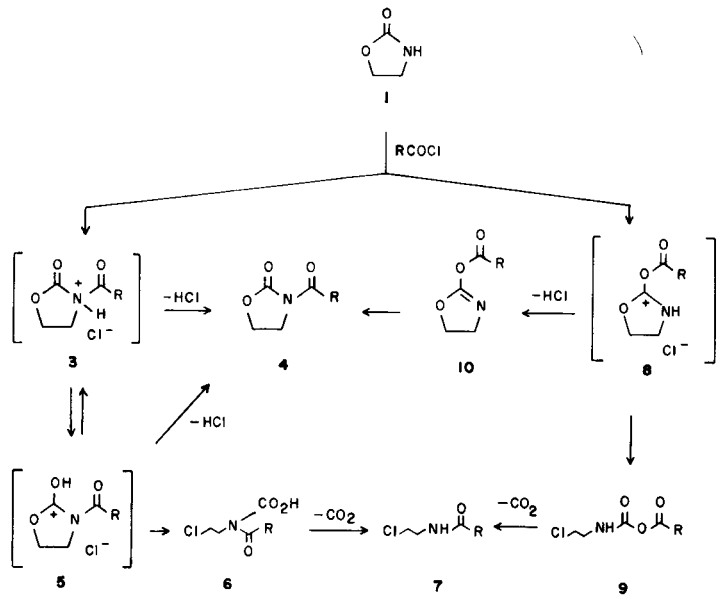
The major side reaction in this sequence is production of 3-acyl substituted 2-oxazolidinones **4** (Scheme I) resulting from elimination of hydrogen chloride. However, other than affecting yield, these products do not present any difficulties in the final purification of the oxazolines. During hydroxide treatment, cleavage of **4** occurs to give **1** and the corresponding acid salts which are readily separated from **2** by aqueous extraction during work-up.

In contrast to Mundy's calcium oxide-mediated rearrangement of 3-acyl-2-oxazolidinones **4** [1], our method involves a novel, acid chloride initiated ring-opening of **1** with concomitant loss of carbon dioxide to furnish *N*-2-chloroethylamides **7** as *in situ* intermediates [2]. Subsequent treatment of these amides with base affects the well known cyclo-eliminative ring-closure to afford the oxazolines **2** [3].

Two conceptual mechanistic routes for the formation of the intermediate *N*-2-chloroethylamides **7** and 3-acyl-2-oxazolidinones **4** are possible and are illustrated below in Scheme I. Initial *N*-acylation of 2-oxazolidinone (**1**) with acid chlorides would give rise to the intermediate *N*-acylium species **3** which on loss of hydrogen chloride would afford the observed 3-acyl-2-oxazolidinone **4**. Competitive prototropic rearrangement of **3** would generate the ambident, dioxazolinium species **5** which can suffer nucleophilic ring-opening by chloride ion to yield the carbamic acid intermediate **6**. Loss of carbon dioxide would furnish the observed amide **7**.

Alternatively, 2-oxazolidinone (**1**) can undergo initial *O*-acylation to yield the intermediate dioxazolinium species **8**. Hydrogen chloride elimination would yield the acyloxyoxazoline **10** which in the presence of acid chloride, could suffer Lander rearrangement to produce oxazolidinone **4**. Competitive *N*-2-chloroethylamide **7** formation would result by nucleophilic attack by chloride ion on **8** to give the ring-opened carbamic anhydride **9** followed by decarb-

SCHEME I



oxylation [4]. At this time it is uncertain which route is responsible for product formation. It is also unclear whether product formation is the exclusive result of only one pathway or whether perhaps a combination of both are operative.

In summary, our method has shown 2-oxazolidinone (**1**) to act as a latent aziridine equivalent on reaction with acid chlorides to furnish intermediate *N*-2-chloroethylamides **7** [5]. *Via* these amides, our one-pot method provides a facile synthesis of oxazolines from readily available starting materials. Additional studies directed towards the utilization of 2-oxazolidinone and substituted 2-oxazolidinones as aziridine synthons for other aminoethylation applications are currently in progress.

EXPERIMENTAL

The ir spectra were recorded on a Nicolet MX-1 FT spectrophotometer. The ^1H nmr spectra were recorded at 90 MHz on a Perkin-Elmer R32 spectrometer. Data are reported in the following manner: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broadened, and m = unresolved multiplet), integration, coupling constant. The ^{13}C nmr spectra were recorded on a Varian FT-80A spectrometer at 22.5 MHz using an internal deuterium lock. Data are reported as follows: $\{^1H\}^{13}C$ chemical shifts and multiplicity as obtained from the coupled spectra (s = singlet, d = doublet, t = triplet, q = quartet). Melting points were determined by using a Thomas-Hoover capillary apparatus and are both uncorrected and uncalibrated.

2-Oxazolidinone (**1**) was purchased from Aldrich Chemical Co., Milwaukee, WI, USA. The acid chlorides were either obtained from commercial sources or prepared by standard procedures from the corresponding acid.

General Method for the Preparation of Oxazolines **2a-2m**.

Equimolar quantities (0.10 mole) of 2-oxazolidinone (**1**) and the respective acid chloride were placed into a 500-ml round-bottomed flask equipped with magnetic stirring bar, condenser, and mineral oil bubbler (to monitor effluent gases). The contents were then heated while stirring in a 140° oil bath during which time the mixture became homogenous and gas evolution began (caution: hydrogen chloride and carbon dioxide gases are liberated). After several hours the gas evolution had ceased and the reaction mixture was allowed to cool to ambient temperature where the crude amide generally solidified. A solution of 100 ml of 10% aqueous sodium hydroxide (wt:vol) and 100 ml of ethanol was then added and the mixture allowed to reflux for 2 hours. After cooling, the phases were separated and the organic portion was washed with water and dried over anhydrous potassium carbonate. Filtration and removal of the volatiles *in vacuo* yielded the crude oxazolines **2** which were purified by either Kugelrohr distillation or recrystallization from the indicated solvents. The following oxazolines were prepared by this procedure:

4,5-Dihydro-2-phenyloxazole (**2a**).

This compound was isolated as a clear liquid (83%) by distillation (bp 68-70°/0.5 mm), lit [6] bp 77-75°/0.1 mm.

4,5-Dihydro-2-(2-methylphenyl)oxazole (**2b**).

This compound was obtained as a clear oil (70%) by distillation (bp 65°/0.1 mm), lit [7] bp 254-255°/756 mm.

4,5-Dihydro-2-(4-methylphenyl)oxazole (**2c**).

This compound was isolated as colorless needles (83%) after recrystallization from aqueous methanol (mp 70-71°), lit [8] mp 70-71°.

4,5-Dihydro-2-(3-methoxyphenyl)oxazole (**2d**).

This compound was obtained after distillation (bp 80°/0.5 mm) as a clear liquid (61%) which slowly solidified on standing at room temperature to a colorless solid, mp 53-55°; ir (potassium bromide): 1649, 1583, 1493, 1359, 1288, 1270, 1222, 1214, 1044, and 715 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.47 (m, 2), 7.24 (t, 1, J = 7.8 Hz), 6.97 (m, 1), 4.34 (m, 2), 3.98 (m, 2), and 3.77 (s, 3); ^{13}C nmr (deuteriochloroform): 164.4 (s), 159.6 (s), 129.4 (d), 129.2 (s), 120.6 (d), 117.7 (d), 112.8 (d), 67.6 (t), 55.2 (q), and 54.9 (t) ppm.

Anal. Calcd. for $C_{10}H_{11}NO_2 \cdot 0.5\ H_2O$: C, 67.44; H, 6.28; N, 7.86. Found: C, 67.24; H, 6.21; N, 8.14.

2-(3-Chlorophenyl)-4,5-dihydrooxazole (**2e**).

This compound was isolated after distillation (bp 65°/0.1 mm) as a colorless liquid (62%). On standing at room temperature, the liquid slowly solidified to a colorelss solid, mp 39-42°; ir (potassium bromide): 1651,

1575, 1358, 1255, 1077, 1063, 977, 947, 762, and 708 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.86 (m, 1), 7.74 (m, 1), 7.30 (m, 2), 4.32 (m, 2), and 3.95 (m, 2); ^{13}C nmr (deuteriochloroform): 163.3 (s), 134.4 (s), 131.2 (d), 129.7 (s), 129.6 (d), 128.3 (d), 126.3 (d), 67.8 (t), and 55.0 (t) ppm.

Anal. Calcd. for C_9H_8ClNO: C, 59.52; H, 4.40; N, 7.71. Found: C, 59.32; H, 4.42; N, 7.66.

2-(3-Fluorophenyl)-4,5-dihydrooxazole (**2f**).

This compound was isolated after distillation (bp 85°/1.2 mm) as a very pale yellow liquid (67%): ir (neat): 1653, 1586, 1493, 1454, 1362, 1269, 1189, 954, 846, and 714 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.70 (m, 2), 7.26 (m, 2), 4.40 (m, 2), and 4.03 (m, 2); ^{13}C nmr (deuteriochloroform): doublet at 163.4, J = 0.1 Hz (s), doublet at 162.7, J = 12.3 Hz (s), doublet at 130.3, J = 0.4 Hz (s), doublet at 130.0, J = 0.4 Hz (d), doublet at 124.1, J = 0.1 Hz (d), doublet at 118.1, J = 1.0 Hz (d), doublet at 115.2, J = 1.1 Hz (d), 67.9 (t), and 55.1 (t) ppm.

Anal. Calcd. for $C_9H_8FNO \cdot 0.1\ H_2O$: C, 64.74; H, 4.95; N, 8.39. Found: C, 64.56; H, 4.92; N, 8.26.

4,5-Dihydro-2-(2-nitrophenyl)oxazole (**2g**).

This compound was isolated as a yellow oil (64%) after distillation (bp 175°/5 mm). The oil slowly solidified to a pale yellow solid (mp 50-54°), lit [6] mp 52-53°.

4,5-Dihydro-2-(3-nitrophenyl)oxazole (**2h**).

This compound was obtained as pale yellow solid (67%) after recrystallization from aqueous ethanol (mp 117-118°), lit [6] mp 118-119°.

2-(2-Furanyl)-4,5-dihydrooxazole (**2i**).

This compound was isolated as a pale tan solid (74%) after recrystallization from ethyl acetate-hexane (mp 75-77°), lit [9] mp 83°.

4,5-Dihydro-2-(2-thienyl)oxazole (**2j**).

This compound was isolated after distillation (bp 120°/10 mm) as a colorless solid (42%), mp 57-58°; ir (potassium bromide): 1649, 1432, 1257, 1057, 1017, 928, 855, and 738 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.58 (d, 1, J = 3.8 Hz), 7.41 (d, 1, J = 5.0 Hz), 7.04 (d of d, 1, J = 3.8 and 5.0 Hz), 4.40 (m, 2), and 4.00 (m, 2); ^{13}C nmr (deuteriochloroform): 160.2 (s), 130.6 (s), 130.1 (d), 129.7 (d), 127.5 (d), 68.0 (t), and 55.0 (t).

Anal. Calcd. for C_7H_7NOS: C, 54.89; H, 4.61; N, 9.15. Found: C, 54.92; H, 4.53; N, 9.35.

2-Cyclohexyl-4,5-dihydrooxazole (**2k**).

This compound was obtained after distillation (bp 120°/15 mm) as a clear oil (28%), lit [8] bp 90-92°/9 mm.

4,5-Dihydro-2-(tricyclo[3.3.1^{3,7}]dec-1-yl)oxazole (**2l**).

This compound was obtained as a colorless solid (72%) after distillation (bp 125°/2.5 mm), mp 39-40°; ir (potassium bromide): 1658, 1453, 1348, 1226, 1056, 987, and 951 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.12 (m, 2), 3.75 (m, 2), 1.97 (m, 3), 1.88 (m, 6), and 1.70 (m, 6); ^{13}C nmr (deuteriochloroform): 174.2 (s), 67.0 (t), 54.3 (t), 39.7 (t), 36.7 (t), 35.3 (s), and 28.1 (d) ppm, lit [10] no data available.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.76; H, 9.28; N, 6.80.

4,5-Dihydro-2-(phenylmethyl)oxazole (**2m**).

This compound was isolated after distillation (bp 65°/0.1 mm) as a clear liquid (21%), lit [8] bp 94-100°/0.3 mm.

3-Benzoyl-2-oxazolidinone (**4a**) and *N*-(2-Chloroethyl)benzamide (**7a**).

In a manner similar to that as described above, a mixture of 10 mmoles each of **1** and benzoyl chloride was heated while stirring in a 140° oil bath. After 1.5 hours, the gas evolution had ceased and the clear solution was allowed to cool to room temperature where it solidified to a colorless solid. Analysis (^1H nmr) of the solid revealed an 83:17 mixture of **7a**:**4a**. The mixture was carefully recrystallized from ethyl acetate to yield 0.20 g (11%) of **4a** as colorless plates, mp 167-168°; ir (potassium bromide): 1778, 1678, 1380, 1358, 1341, 1214, 1203, 1109, 758, and 753 cm^{-1}; ^1H nmr (perdeuteriodimethylsulfoxide): δ 7.50 (m, 5), 4.42 (m, 2), and 4.03 (m, 2); ^{13}C nmr (perdeuteriodimethylsulfoxide): 169.1 (s), 153.2 (s), 133.7 (s), 131.5 (d), 128.6 (d), 127.6 (d), 62.5 (t), and 43.5 (t) ppm, lit [1] mp 167-167.5°. The filtrate was concentrated and recrystallized from ethyl acetate to furnish 1.21 g (63%) of **7a** as a colorless solid; mp 103-104°; ir (potassium bromide): 1637, 1603, 1580, 1542, 1493, 1313, 1255, 1187, and 692 cm^{-1}; ^1H nmr (perdeuteriodimethylsulfoxide/deuteriochloroform): δ 7.78 (m, 2), 7.45 (m, 3), 6.65 (bs, 1), and 3.74 (m, 4); ^{13}C nmr (perdeuteriodimethylsulfoxide/deuteriochloroform): 167.7 (s), 134.3 (s), 131.3 (d), 128.2 (d), 127.3 (d), 42.8 (t), and 41.8 (t) ppm, lit [11] mp 102-103.5°.

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