

Convenient One-Pot Synthesis of 2-Oxazolines from Carboxylic Acids

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Simple one-pot methods for preparation of 2-oxazolines have been developed using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM). Treatment of a mixture of carboxylic acids and 2-haloethylammonium salts with DMT-MM in methanol followed by refluxing in the presence of KOH gives oxazolines.

Key words oxazoline; carboxylic acid; 2-haloethylammonium salt; dehydrocondensation; cyclization

Preparation of 2-oxazoline, a versatile intermediate in synthetic chemistry, from carboxylic acids is a classical and useful method.^{1–5} Since 2-oxazolines can be readily re-converted into carboxylic acids, they can be used as a protecting group for carboxylic acids.^{3,6} Among various methods employed to convert derivatives of carboxylic acids to the oxazolines, intramolecular dehydrohalogenation of *N*-(β -haloethyl)amides to give 2-oxazolines is well established.^{1,4,5,7} Although the reaction readily takes place by treatment with either base or silver ion, such reactions have not adapted well to the preparation of 2-oxazolines, presumably because of the cumbersome method used to prepare *N*-(β -haloethyl)amides. For example, they have been prepared by Ritter reaction of nitriles with halohydrins or haloalkenes,⁸ chlorination of *N*-(β -hydroxyethyl)amides with thionyl chloride,⁹ and coupling of 2-haloethylammonium salts with acid chlorides^{10,11} or acid anhydrides.¹²

We report here a simple and general one-pot method to prepare 2-oxazolines from carboxylic acids; the reaction involves dehydrocondensation of carboxylic acids and 2-haloethylammonium salts leading to the formation of *N*-(β -haloethyl)amides, which then can be readily converted into 2-oxazolines by base treatment.

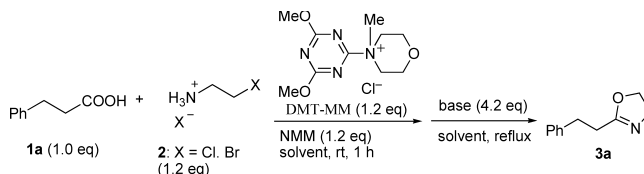
Results and Discussion

Because dehydrocondensation between carboxylic acids and amines using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) can proceed efficiently in water or alcohols,^{13,14} polar 2-haloethylammonium salts, which are insoluble in common less polar organic solvents, are directly available by using methanol as a solvent. First, we attempted a reaction using 3-phenylpropionic acid **1a** and 2-chloroethylammonium chloride (**2** (X=Cl)) as model compounds (Table 1). A methanol solution of **1a** (1.0 eq), **2** (X=Cl) (1.2 eq), and *N*-methylmorpholine (NMM: 1.2 eq) was treated with DMT-MM (1.2 eq) at room temperature for 1 h followed by addition of KOH (4.2 eq) dissolved in methanol. The resulting mixture was refluxed for 1.5 h to give 2-(2-phenethyl)-2-oxazoline **3a** in 74% yield. 2-Bromoethylammonium bromide (**2** (X=Br)) is also available for the reaction and gives a similar result (run 2). Reaction with Et₃N, a weaker base than KOH, resulted in decreasing the yield of **3a** despite prolongation of refluxing time to 4 h.

Since *N*-(β -chloroethyl)amide **4a** (X=Cl) was isolated in 91% yield after finishing the first step using DMT-MM, the reaction proceeds by the mechanism shown in Chart 1. Employing solvents in which the ammonium salt **2** is soluble is essential. Thus, the oxazoline was obtained in a good yield in polar solvents, DMF as well as methanol, whereas the yield was very low in a less polar THF, in which **2** is insoluble.

As shown in Table 2, preparation of 2-oxazolines **3b–g** from various carboxylic acids was conducted using methanol, which has advantages over DMF in terms of cost and boiling point; methanol can be readily removed by a rotary evaporator. Benzoic acid **1b**, α,β -unsaturated carboxylic acid **1e**, and secondary carboxylic acids **1c** or **1f** could be converted into the corresponding oxazolines in fair to good yields. In contrast to the ring-closing reaction of β -hydroxyamide, which

Table 1. One-Pot Synthesis of 2-(2-Phenethyl)oxazoline Using DMT-MM



Run	X	Solvent	Base	Refluxing time (h)	Yield (%) ^{a)}
1	Cl	MeOH	KOH	2.0	74
2	Br	MeOH	KOH	1.0	73
3	Br	MeOH	Et ₃ N	4.0	52
4	Br	DMF	KOH	1.3	81
5	Br	THF	KOH	1.0	15

a) Isolated yield.

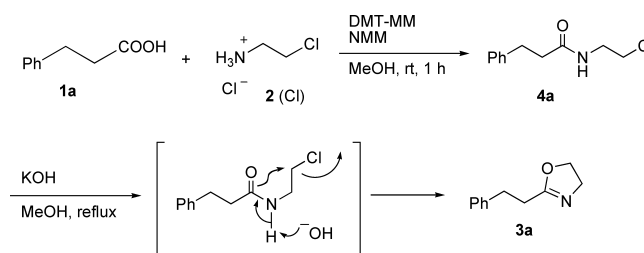


Chart 1

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generally proceeds under acidic conditions, the present reaction proceeds under basic conditions. Thus, the Boc group, which is subject to decomposition under acidic conditions, is compatible with our reaction conditions (Run 7).

Chiral oxazolines are utilized as chiral metal ligands, such as C2-symmetric chiral bis(oxazolines), as well as a chiral auxiliaries.¹⁵⁾ We succeeded in synthesizing chiral oxazolines **6** from chiral 2-chloroethylammonium salts **5**, which were readily prepared from chiral aminoethanols (Table 3).¹⁶⁾ When the reaction performed from *N*-Cbz-L-phenylalanine and (*S*)-1-chloro-2-aminopropane hydrochloride, a trace amount of the diastereomer (<1%) resulting from racemization at the asymmetric α -carbon was observed by NMR analysis (Chart 2).¹⁷⁾ A similar result was observed with *N*-Boc-L-phenylalanine and (*S*)-1-chloro-2-aminopropane hydrochloride (yield 77%, racemization <1%).

In summary, we present a simple one-pot method for the synthesis of 2-oxazolines by using DMT-MM, which involves dehydrocondensation of carboxylic acids and 2-haloethylammonium salts followed by base-promoted ring closure of the resulting β -haloethylamide.

Table 2. Synthesis of 2-Alkylloxazolines from Carboxylic Acids by the One-Pot Procedure

Run	Carboxylic acid	X	Product	Refluxing time (h)	Yield (%) ^{a)}
1	PhCOOH	1b Br	3b	3.5	83
2		1c Cl	3b	4.0	58
3	Me Ph-COOH	1c Br	3c	3.0	70
4		1d Br	3d	1.5	100 ^{b)}
5		1e Br	3e	2.5	74
6		1f Br	3f	1.5	62
7	Boc-Phe-OH	1g Br	3g	1.0	83

a) Isolated yield. b) Determined by GC.

Table 3. Synthesis of Chiral Oxazolines

Run	R	Refluxing time (h)	Yield (%) ^{a)}
1	L-CH ₃	2.0	81 (86 ^{b)})
2	L-PhCH ₂	2.0	86
3	L-(CH ₃) ₂ CH	2.5	95

a) Isolated yield. b) Determined by GC.

readily applicable to various kinds of carboxylic acids.

Experimental

General Procedure for Preparation of 2-Oxazoline from Carboxylic Acid: 2-(2-Phenethyl)-2-oxazoline **3a**¹⁸⁾ DMT-MM (111 mg, 0.40 mmol) was added at room temperature to a solution of 3-phenylpropionic acid **1a** (50.0 mg, 0.33 mmol), 2-bromoethylammonium bromide **2** (X=Br) (81.9 mg, 0.40 mmol), and NMM (40.4 mg, 0.40 mmol) in methanol (3 ml). After stirring for 1 h, a methanol solution of KOH (1 M, 1.40 ml, 1.40 mmol) was added, and the resulting mixture was refluxed for 1.5 h. The reaction mixture was poured into water and extracted with ether. The organic phase was combined and washed successively with 1 M HCl, NaHCO₃, and brine, and then dried over MgSO₄. The crude product was purified by alumina column chromatography (Neutral, super V) to give 2-(2-phenethyl)-2-oxazoline (**3a**) (42.3 mg) in 73% yield. Pale yellow oil; IR (neat) 2952, 1668 cm⁻¹; ¹H-NMR (CDCl₃) δ : 2.55–2.62 (m, 2H), 2.93–3.00 (m, 2H), 3.79–3.87 (m, 2H), 4.20–4.27 (m, 2H), 7.17–7.24 (m, 3H), 7.26–7.32 (m, 2H); HR-MS Calcd for C₁₁H₁₃NO (M⁺) 175.0997, Found 175.0997.

2-(1-Phenethyl)-2-oxazoline (**3b**)¹⁹⁾: Pale yellow oil; IR (neat) 2930, 1650 cm⁻¹; ¹H-NMR (CDCl₃) δ : 4.06 (t, *J*=9.5 Hz, 2H), 4.43 (t, *J*=9.5 Hz, 2H), 7.38–7.50 (m, 3H), 7.92–7.98 (m, 2H); HR-MS Calcd for C₉H₉NO (M⁺) 147.0684, Found 147.0686.

2-(1-Phenethyl)-2-oxazoline (**3c**)²⁰⁾: Pale yellow oil; IR (neat) 2977, 1663 cm⁻¹; ¹H-NMR (CDCl₃) δ : 1.55 (d, *J*=7.2 Hz, 3H), 3.74 (q, *J*=7.2 Hz, 1H), 3.82–3.89 (m, 2H), 4.15–4.27 (m, 2H), 7.22–7.36 (m, 5H); HR-MS Calcd for C₁₁H₁₃NO (M⁺) 175.0997, Found 175.0997.

2-(3-Butenyl)-2-oxazoline (**3d**)²¹⁾: Colorless oil; IR (neat) 2979, 1667 cm⁻¹; ¹H-NMR (CDCl₃) δ : 2.33–2.44 (m, 4H), 3.82 (t, *J*=9.5 Hz, 2H), 4.22 (t, *J*=9.5 Hz, 2H), 4.97–5.12 (m, 2H), 5.78–5.92 (m, 1H); ESI-MS *m/z*: 126 [(M+H)⁺].

2-(*trans*-2-Phenylethyl)-2-oxazoline (**3e**)²²⁾: Pale yellow oil; IR (neat) 3024, 2928, 1653 cm⁻¹; ¹H-NMR (CDCl₃) δ : 3.99 (t, *J*=9.3 Hz, 2H), 4.35 (t, *J*=9.3 Hz, 2H), 6.64 (d, *J*=16.3 Hz, 1H), 7.30–7.41 (m, 4H), 7.45–7.52 (m, 2H); HR-MS Calcd for C₁₁H₁₁NO (M⁺) 173.0841, Found 173.0839.

2-Cyclohexyl-2-oxazoline (**3f**)²³⁾: Pale yellow oil; IR (neat) 2931, 1662 cm⁻¹; ¹H-NMR (CDCl₃) δ : 1.15–1.49 (m, 5H), 1.60–1.81 (m, 3H), 1.88–1.97 (m, 2H), 2.24–2.34 (m, 1H), 3.81 (t, *J*=9.3 Hz, 2H), 4.20 (t, *J*=9.3 Hz, 2H); HR-MS Calcd for C₉H₁₅NO (M⁺) 153.1154, Found 153.1158.

2-(*N*-Boc-1-amino-2-phenylethyl)-2-oxazoline (**3g**)²⁴⁾: Pale yellow oil; IR (neat) 3357, 1691, 1665 cm⁻¹; ¹H-NMR (CDCl₃) δ : 1.41 (s, 9H), 2.95–3.20 (m, 2H), 3.70–3.86 (m, 2H), 4.23–4.35 (m, 2H), 4.65 (br s, 1H), 5.15 (br s, 1H), 7.14 (d, *J*=6.8 Hz, 2H), 7.19–7.30 (m, 3H); ESI-MS *m/z*: 291 [(M+H)⁺], 313 [(M+Na)⁺].

(*S*)-2-(2-Phenylethyl)-4-methyl-2-oxazoline: Pale yellow oil; [α]_D²² –31.8 (*c*=0.22, CHCl₃); IR (neat) 2967, 1669 cm⁻¹; ¹H-NMR (CDCl₃) δ : 1.22 (d, *J*=6.6 Hz, 3H), 2.55–2.60 (m, 2H), 2.91–3.00 (m, 2H), 3.75 (t, *J*=7.9 Hz, 1H), 4.09–4.20 (m, 1H), 4.32 (dd, *J*=8.0, 9.3 Hz, 1H), 7.17–7.32 (m, 5H); HR-MS Calcd for C₁₂H₁₅NO (M⁺) 189.1154, Found 189.1146.

(*S*)-2-(2-Phenylethyl)-4-phenylmethyl-2-oxazoline²⁵⁾: Pale yellow oil; [α]_D²² –10.6 (*c*=0.73, CHCl₃); IR (neat) 3026, 2927, 1668 cm⁻¹; ¹H-NMR (CDCl₃) δ : 2.54–2.64 (m, 3H), 2.95 (t, *J*=7.6 Hz, 2H), 3.05 (dd, *J*=5.2, 13.7 Hz, 1H), 3.94 (dd, *J*=7.1, 7.7 Hz, 1H), 4.15 (dd, *J*=8.5, 8.5 Hz, 1H), 4.31–4.41 (m, 1H), 7.15–7.32 (m, 10H); HR-MS Calcd for C₁₈H₁₉NO (M⁺) 265.1467, Found 265.1479.

(*S*)-2-(2-Phenylethyl)-4-*iso*-propyl-2-oxazoline²⁶⁾: Pale yellow oil; [α]_D²² –54.8 (*c*=0.19, CHCl₃); IR (neat) 3028, 2958, 1669 cm⁻¹; ¹H-NMR (CDCl₃) δ : 0.84 (d, *J*=6.8 Hz, 3H), 0.92 (d, *J*=6.8 Hz, 3H), 1.64–1.77 (m, 1H), 2.59 (t, *J*=8.1 Hz, 2H), 2.95 (t, *J*=7.8 Hz, 2H), 3.83–3.96 (m, 2H), 4.16–4.25 (t, *J*=9.2 Hz, 1H), 7.15–7.32 (m, 5H); HR-MS Calcd for C₁₄H₁₉NO (M⁺) 217.1467, Found 217.1464.

(*S,S*)-2-[*N*-(Benzoyloxycarbonyl)-1-amino-2-phenylethyl]-4-methyl-2-oxazoline: Pale yellow oil; ¹H-NMR (CDCl₃) δ : 1.18 (d, *J*=5.4 Hz, 3H), 2.93–3.22 (m, 2H), 3.82 (t, *J*=8.1 Hz, 1H), 3.99–4.17 (m, 1H), 4.36 (t, *J*=8.1 Hz, 1H), 4.63–4.80 (m, 1H), 5.10 (dd, *J*=10.8, 16.2 Hz, 2H), 5.35 (d,

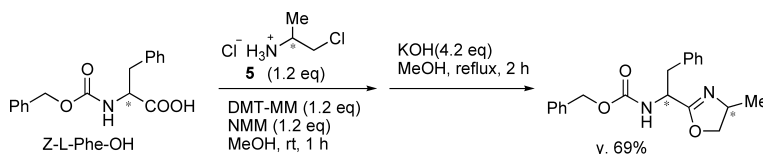


Chart 2

$J=8.1$ Hz, 1H), 7.08–7.42 (m, 10H); ESI-MS m/z : 339 [(M+H)⁺], 361 [(M+Na)⁺].

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