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One-Pot Synthesis of Ethyl 3-(2-Hydroxyalkyl)aminoalkanoates by Ring Opening of 1,3-Oxazolidines Using Reformatsky Reagent

Tomihiro NISHIYAMA,* Hiroshi KISHI, Kouji KITANO, and Fukiko YAMADA
Department of Applied Chemistry, Faculty of Engineering, Kansai University, Senriyama, Suita, Osaka 564

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Synopsis. Oxazolidines, obtained by the condensation of aldehydes with 2-anilino-1-alkanols, react with the Reformatsky reagent derived from ethyl bromoacetate under mild reaction conditions to afford ethyl 3-(2-hydroxyalkyl)-aminoalkanoates.

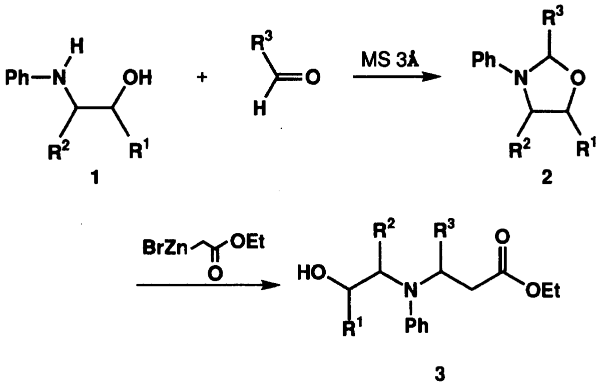
The synthesis of 2- or 3-(2-hydroxyalkyl)amino acids and their use in the synthesis of amino acids,[1] heterocyclic compounds[2] or crown ethers,[3] chelating reagents,[4] and hydrolyzable cationic polymers[5] are currently of particular interest since they have three different functional groups of the amino, hydroxyl, and carboxyl groups.

2-(2-Hydroxyalkyl)amino acids have been synthesized by the reaction of 2-aminoalkyl alcohols[6] or *α*-amino acids[7] with oxiranes, and that of 2-aminoalkyl alcohols with halo esters.[8] Contreras et al.[4] have also reported that *N*-(2-hydroxyethyl)glycines were prepared by the reaction of the corresponding 2-aminoethanols with glyoxal. This method, however, has a limitation since there is an equilibrium between the 2-morpholinone and the open-chain product.

On the other hand, 3-(2-hydroxyalkyl)amino acids are generally prepared by the ring opening reaction of *β*-propiolactone with 2-aminoalkyl alcohols[3] or *sec*-alkylamines.[9] A major problem of this method is the regioselectivity of the ring opening reaction of the lactone. Thus, there are two possible fissions of the alkyl oxygen bond or acyl oxygen bond during the ring opening reactions of *β*-propiolactone. Condensation reactions of 2-aminoalkyl alcohols with *β*-keto esters[10] followed by reduction of the formed double bond are also a well-established procedure for the preparation of 3-(2-hydroxyalkyl)amino acids.

Previously, we have studied the ring opening of 1,3-oxazolidines with Grignard reagents.[11] In this paper, we present a simple, one-pot procedure for the preparation of ethyl 3-(2-hydroxyalkyl)aminoalkanoates **3a**—**k** by a coupling of 1,3-oxazolidines **2** with Reformatsky reagent. Our method combines the ease of formation of 1,3-oxazolidines **2** from 2-aminoalkyl alcohols **1** and the lability of the newly formed carbon–oxygen bond toward the Reformatsky reagent to give the title compounds **3a**—**k**. An outline of this procedure is described in Scheme 1.

During the first step, 2-anilinoethanol (**1a**), 1-anilino-2-propanol (**1b**), 1-anilino-2-butanol (**1c**), 2-methyl-1-*p*-toluidino-2-propanol (**1d**), 2-anilino-1-propanol (**1e**) or 2-anilino-2-phenylethanol (**1f**) (Chart 1) was reacted with aldehyde in dry ether or CH_2Cl_2 at room temperature over molecular sieves 3 Å. After 3 h, most of the 2-aminoalkyl alcohols had been converted to the corresponding 1,3-oxazolidine **2** as indicated by gas chromatography. 2-Aminoalkyl alcohols, **1c** and **1f**, having bulky substituents did not react with aldehyde at room temperature, therefore, it was necessary to reflux the reaction mixture in CH_2Cl_2 for 5 to 7 h. During the azeotropic distillation method in benzene, however, the cyclization reaction of **1** with acetaldehyde, propinoaldehyde, isobutyraldehyde or benzaldehyde at reflux temperature resulted in formation of 2-substituted 1,3-oxazolidine **2** in low yields (ca. 5%). Since 1,3-oxazolidines are an analogue of cyclic acetal analogues with one oxygen replaced by a nitrogen atom, they might be significantly decomposed at reflux temperature.



Scheme 1.

1,3-Oxazolidines **2** smoothly reacted in situ with the zinc derivative of ethyl bromoacetate under mild conditions (room temperature, sonication, 2—3 h) to afford the corresponding ethyl 3-(2-hydroxyalkyl)aminoalkanoates **3**. However, the reactions with ethyl bromoacetates having a sterically bulky substituent at the 2-position did not give **3**, and **2** was recovered in almost

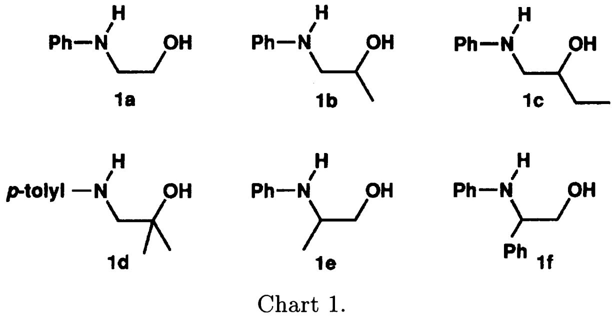
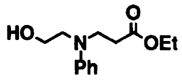
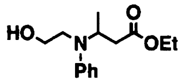
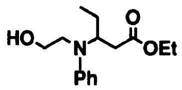
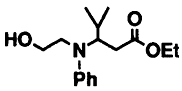
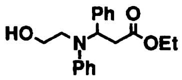
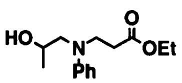
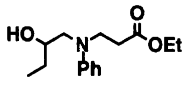
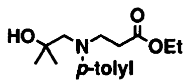
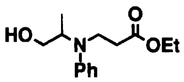
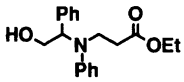
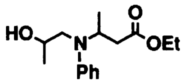


Chart 1.

Table 1. One-Pot Synthesis of Ethyl 3-(2-Hydroxyalkyl)aminoalkanoates Using Reformatsky Reagent

Entry	Amino alcohol	Aldehyde[a)]	Solvent	Overall[b)] yield/%	Product	
1	**1a**	A	Et_2O	69		**3a**
2	**1a**	B	CH_2Cl_2	72		**3b**
3	**1a**	C	CH_2Cl_2	60		**3c**
4	**1a**	D	CH_2Cl_2	82		**3d**
5	**1a**	E	CH_2Cl_2	85		**3e**
6	**1b**	A	Et_2O	63		**3f**
7	**1c**	A	CH_2Cl_2	82		**3g**
8	**1d**	A	Et_2O	67		**3h**
9	**1e**	A	CH_2Cl_2	90		**3i**
10	**1f**	A	CH_2Cl_2	82		**3j**
11	**1b**	B	CH_2Cl_2	76		**3k**

a) A: paraformaldehyde, B: acetaldehyde, C: propinonaldehyde, D: isobutyraldehyde, E: benzaldehyde. b) Isolated yield based on **1**.

quanitiative yield. Furthermore, when 2,4-dimethyl-1,3-oxazolidine was employed in the reaction, the corresponding **3** ($R^2=R^3=CH_3$, $R^1=H$ in Scheme 1) was obtained in 65% yield (yield was determined by GC). However, isolation of pure compound **3** by column chromatography was not possible.

Although this reaction was carried out in ether and CH_2Cl_2, higher yields were obtained in CH_2Cl_2. The increased effectiveness of CH_2Cl_2 solvent can be attributed to the solubility of the reaction mixture. Examples featuring the versatility of the procedure are summarized in Table 1.

In summary, this paper has shown a new methodology for nucleophilic ring opening of oxazolidines providing a one-pot synthesis of ethyl 3-(2-hydroxyalkyl)aminoalkanoates **3** under mild conditions.

Experimental

^1H and ^{13}C NMR spectra were recorded using a JEOL GSX-400 spectrometer in $CDCl_3$ solution with $(CH_3)_4Si$ as the internal standard. Gas chromatography was performed using a Hewlett–Packard 5890A instrument fitted with an OV101 capillary column. Mass spectra were recorded with a Perkin– Elmer Model 910 gas chromatographic mass spectrometer at 70 eV.

Materials. 1-Anilino- (**1b**) and 2-methyl-1-*p*-toluidino-2-propanol (**1d**) were prepared by the regioselective ring opening of propylene oxide or isobutylene oxide with the corresponding amines in the presence of a metal salt.[12)] 2-Anilino-2-phenylethanol (**1f**) was isolated by column chromatography. 1-Anilino-2-butanol (**1c**) and 2-anilino-1-propanol (**1e**) were prepared by the reaction of 2-hydroxybutyric acid or methyl 2-chloropropionate with aniline followed by reduction with $\mathrm{LiAlH_4}$.

General Method for the Synthesis of 3. A solution of 1.0 g of 2-aminoalkyl alcohol **1a** (R^1=R^2=H) (7.29 mmol) and 0.76 g of paraformaldehyde (25.4 mmol) in dry ether (30 ml) in the presence of molecular sieves 3 Å was stirred at room temperature under nitrogen. After 3 h, all of **1a** had been converted to 1,3-oxazolidine **2a** (R^1=R^2=R^3=H) as indicated by gas chromatography. A suspension of 1.9 g of zinc (29.1 mg atom), 4.86 g of ethyl bromoacetate (26.6 mmol), and a trace of iodine in dry ether (15 ml) was then added dropwise. The resulting suspension was sonicated at room temperature under an atmosphere of nitrogen. After sonication for 2 h, the molecular sieves were removed by filtration. The filtrate was washed with saturated $\mathrm{NH_4Cl}$. The aqueous layer was extracted with ether, and the combined ether extracts were dried over $\mathrm{Na_2SO_4}$ and concentrated to leave a pale yellow oil. Column chromatography (hexane and then 10 : 1 hexane/ethyl acetate) of the crude material afforded **3a** (R^1=R^2=R^3=H) (1.2 g, 69%) as an oil.

Ethyl 3-[*N*-(2-Hydroxyethyl)-*N*-phenyl]aminopropanoate (3a). ^{13}C NMR δ=14.1, 32.2, 47.3, 53.4, 59.6, 60.6, 112.7, 116.8, 129.3, 147.5, and 172.6; ^{1}H NMR δ=1.17 (t, J=7.1 Hz, 3H), 2.52 (t, J=7.1 Hz, 2H), 3.37 (t, J=5.9 Hz, 2H), 3.60 (t, J=7.1 Hz, 2H), 3.65 (t, J=5.9 Hz, 2H), 4.04 (t, J=7.1 Hz, 2H), 6.63—6.68 (m, 3H), and 7.13—7.17 (m, 2H); MS m/z (rel intensity) 237 (M^+, 10). Found: C, 65.70; H, 7.97; N, 5.80%. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90%.

Ethyl 3-[*N*-(2-Hydroxyethyl)-*N*-phenyl]aminobutanoate (3b). ^{13}C NMR δ=14.2, 17.6, 40.1, 46.4, 56.5, 59.6, 60.8, 117.5, 119.6, 129.1, 129.4, 148.3, and 172.4; ^{1}H NMR δ=1.17 (d, J=6.6 Hz, 3H), 1.23 (t, J=7.1 Hz, 3H), 2.39 (q, J=5.7 and 14.3 Hz, 1H), 2.66 (q, J=9.2 and 14.3 Hz, 1H), 3.22—3.29 (m, 1H), 3.35 (t, J=4.4 Hz, 1H), 3.38 (t, J=4.4 Hz, 1H), 3.59—3.73 (m, 3H), 4.12 (q, J=7.1 Hz, 2H), 4.26—4.32 (m, 1H), 6.81—6.92 (m, 3H), and 7.21—7.26 (m, 2H); MS m/z (rel intensity) 251 (M^+, 63). Found: C, 66.77; H, 8.38; N, 5.53%. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.43; N, 5.57%.

Ethyl 3-[*N*-(2-Hydroxyethyl)-*N*-phenyl]aminopentanoate (3c). ^{13}C NMR δ=11.6, 14.1, 26.4, 38.8, 45.7, 59.2, 60.8, 60.9, 116.2, 118.6, 129.1, 148.9, and 172.9; ^{1}H NMR δ=0.85 (t, J=7.3 Hz, 3H), 1.22 (t, J=7.3 Hz, 3H), 2.49 (dd, J=4.8 and 13.9 Hz, 1H), 2.62 (dd, J=10.3 and 13.9 Hz, 1H), 2.93—2.88 (m, 1H), 3.24—3.31 (m, 1H), 3.41—3.47 (m, 1H), 3.57—3.64 (m, 1H), 3.73—3.79 (m, 1H), 4.04—4.13 (m, 2H), 4.09 (q, J=7.3 Hz, 2H), and 6.76—7.26 (m, 5H); MS m/z (rel intensity) 265 (M^+, 45). Found: C, 67.66; H, 8.89; N, 5.21%. Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.28%.

Ethyl 3-[*N*-(2-Hydroxyethyl)-*N*-phenyl]amino-4-methylpentanoate (3d). ^{13}C NMR δ=14.1, 20.7, 20.8, 32.4, 37.5, 59.2, 61.0, 65.5, 114.8, 117.7, 129.1, 149.2, and 173.6; ^{1}H NMR δ=0.78 (d, J=7.0 Hz, 3H), 0.97 (d, J=6.6 Hz, 3H), 1.21 (t, J=7.3 Hz, 3H), 2.59 (dd, J=11.2 and 13.7 Hz, 1H), 2.72 (dd, J=3.7 and 13.7 Hz, 1H), 3.18—3.25 (m, 1H), 3.28—3.36 (m, 1H), 3.48—3.65 (m, 1H), 3.78—3.82 (m, 1H), 3.85—3.91 (m, 1H), 4.05 (q, J=7.3 Hz, 2H), 4.06—4.11 (m, 1H), and 6.70—7.26 (m, 5H); MS m/z (rel intensity) 279 (M^+, 56). Found: C, 68.55; H, 8.95; N, 5.10%. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01%.

Ethyl 3-[*N*-(2-Hydroxyethyl)-*N*-phenyl]amino-3-phenylpropanoate (3e). ^{13}C NMR δ=14.1, 37.2, 48.3, 59.2, 61.1, 61.3, 116.9, 119.4, 127.0 127.6, 128.5, 129.2, 139.1, 148.3 and 172.4; ^{1}H NMR δ=1.21 (t, J=7.3 Hz, 3H), 2.96 (dd, J=5.3 and 14.1 Hz, 1H), 3.08—3.13 (m, 2H), 3.10 (dd, J=10.6 and 14.1 Hz, 1H), 3.39—3.44 (m, 1H), 3.59—3.65 (m, 1H), 4.12 (q, J=7.3 Hz, 2H), 5.43 (dd, J=5.5 and 9.9 Hz, 1H), 6.82—6.93 (m, 3H), and 7.11—7.30 (m, 7H); Ms m/z (rel intensity) 313 (M^+, 43). Found: C, 72.70; H, 7.42; N, 4.40%. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.39; N, 4.47%.

Ethyl 3-[*N*-(2-Hydroxypropyl)-*N*-phenyl]aminopropanoate (3f). ^{13}C NMR δ=14.2, 20.0, 32.1, 48.1, 60.3, 60.7, 65.1, 114.4, 118.3, 129.3, and 172.4; ^{1}H NMR δ=1.21 (d, J=6.2 Hz, 3H), 1.24 (t, J=7.3 Hz, 3H), 2.59 (t, J=7.1 Hz, 2H), 3.14 (q, J=14.7 and 9.2 Hz, 1H), 3.32 (q, J=14.7 and 3.3 Hz, 1H), 3.68 (q, J=7.1 Hz, 2H), 4.04—4.14 (m, 1H), 4.12 (q, J=7.3 Hz, 2H), 6.78—6.82 (m, 3H), and 7.22—7.26 (m, 2H); MS m/z (rel intensity) 251 (M^+, 100). Found: C, 66.68; H, 8.38; N, 5.31%. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.43; N, 5.57%.

Ethyl 3-[*N*-(2-Hydroxybutyl)-*N*-phenyl]aminopropanoate (3g). ^{13}C NMR δ=10.0, 14.1, 27.4, 32.1 48.1, 58.7, 60.7, 70.3, 114.3, 118.0, 129.3, 148.3, and 172.5; ^{1}H NMR δ=1.01 (t, J=7.5 Hz, 3H), 1.24 (t, J=7.1 Hz, 3H), 1.47—1.54 (m, 2H), 2.59 (t, J=7.3 Hz, 2H), 3.11 (dd, J=9.2 and 14.7 Hz, 1H), 3.37 (dd, J=3.1 and 14.7 Hz, 1H), 3.67 (t, J=7.3 Hz, 2H), 3.79—3.85 (m, 1H), 4.11 (q, J=7.1 Hz, 2H), 6.75—6.80 (m, 3H), and 7.21—7.25 (m, 2H); MS m/z (rel intensity) 265 (M^+, 8). Found: C, 67.70; H, 8.88; N, 5.22%. Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.28%.

Ethyl 3-[*N*-(2-Hydroxy-2-methylpropyl)-*N*-*p*-tolyl]aminopropanoate (3h). ^{13}C NMR δ=14.2, 20.2, 27.6, 31.4, 48.5, 60.6, 63.3, 72.4, 115.0, 127.2, 129.7, 146.9, and 172.8; ^{1}H NMR δ=1.23 (s, 6H), 1.23 (t, J=7.3 Hz, 3H), 2.24 (s, 3H), 2.57 (t, J=7.1 Hz, 2H), 3.22 (s, 2H), 3.69 (t, J=7.1 Hz, 2H), 4.11 (q, J=7.3 Hz, 2H), 6.76 (d, J=8.6 Hz, 2H), and 7.02 (d, J=8.6 Hz, 2H); MS m/z (rel intensity) 279 (M^+, 7). Found: C, 68.71; H, 9.00; N, 4.99%. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01%.

Ethyl 3-[*N*-(2-Hydroxy-1-methylethyl)-*N*-phenyl]aminopropanoate (3i). ^{13}C NMR δ=12.5, 14.1, 32.8, 38.5, 60.0, 60.7, 63.8, 118.5, 119.9, 129.1, 129.3, 148.8, and 172.9; ^{1}H NMR δ=0.98 (d, J=6.6 Hz, 3H), 1.21 (t, J=7.1 Hz, 3H), 2.46 (ddd, J=16.2, 6.2, and 5.1 Hz, 1H), 2.59 (ddd, J=16.2, 8.1, and 6.9 Hz, 1H), 3.35—3.47 (m, 2H), 3.52 (dd, J=11.6 and 4.8 Hz, 1H), 3.68 (dd, J=11.6, 9.5 Hz, 1H), 3.80—3.87 (m, 1H), 4.10 (q, J=7.1 Hz, 2H), 6.83—6.95 (m, 3H), and 7.22—7.29 (m, 2H); MS m/z (rel intensity) 251 (M^+, 1). Found: C, 66.59; H, 8.51; N, 5.50%. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.43; N, 5.57%.

Ethyl 3-[*N*-(2-Hydroxy-1-phenylethyl)-*N*-phenyl]aminopropanoate (3j). ^{13}C NMR δ=14.1, 32.4, 40.6, 60.7, 61.4, 118.5, 120.1, 127.5, 128.4, 129.2, 148.8, and 172.9; ^{1}H NMR δ=1.19 (t, J=7.0 Hz, 3H), 2.38 (ddd, J=16.0, 6.8, and 4.4 Hz, 1H), 2.58 (ddd, J=16.0, 8.4, and 6.8 Hz, 1H), 3.18 (ddd, J=14.4, 6.8 and 4.4 Hz, 1H), 3.40 (ddd, J=14.4, 8.4, and 6.8 Hz, 1H), 4.00 (dd, J=12.0, and 5.2 Hz, 1H), 4.08 (q, J=7.0 Hz, 2H), 4.24 (dd, J=12.0 and 9.6 Hz, 1H), 4.88 (dd, J=9.6 and 5.2 Hz, 1H), 6.86—6.94 (m, 3H), 7.05—7.07 (m, 2H), and 7.22—7.26 (m, 5H); MS m/z (rel intensity) 313 (M^+, 1). Found: C, 72.59; H, 7.28; N, 4.39%. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.39; N, 4.47%.

Ethyl 3-[*N*-2-Hydroxypropyl)-*N*-phenyl]aminobutanoate (3k). ^{13}C NMR δ=14.1, 14.2, 16.9, 18.7, 19.8, 19.9, 39.3, 40.4, 52.2, 53.5, 55.4, 56.1, 60.6, 60.9, 63.5, 64.1, 118.8, 119.8, 120.4, 120.8, 129.0, 172.6, and 172.0; ^{1}H NMR δ=1.09 (d, J=6.9 Hz, 3H), 1.16 (d, J=6.9 Hz, 3H), 1.18 (d, J=6.9 Hz, 3H), 1.18 (d, J=7.1 Hz, 3H), 1.26 (d, J=6.9 Hz, 3H), 1.27 (t, J=7.1 Hz, 3H), 2.30 (dd, J=6.9 and 14.8 Hz, 1H), 2.40 (dd, J=5.0 and 14.2 Hz, 1H), 2.56 (dd, J=7.6 and 14.8 Hz, 1H), 2.72 (dd, J=9.9 and 14.2 Hz, 1H), 2.77 (dd, J=9.5 and 13.2 Hz, 1H), 2.88 (dd, J=9.5 and 13.2 Hz, 1H), 3.20—3.28 (m, 2H), 3.69—3.89 (m, 1H), 3.94—4.13 (m, 1H), 4.18 (q, J=7.1 Hz, 4H), 4.16—4.26 (m, 2H), 6.85—7.00 (m, 6H), and 7.21—7.36 (m, 4H); MS m/z (rel intensity) 265 (M^+, 5). Found: C, 67.62; H, 8.83; N, 5.36%. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28%

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