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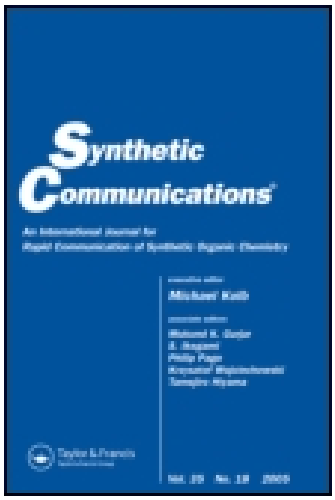

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A FACILE, HIGH YIELD SYNTHESIS OF γ- AND δ-HYDROXYAMIDES

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A FACILE, HIGH YIELD SYNTHESIS OF γ- AND δ-HYDROXYAMIDES

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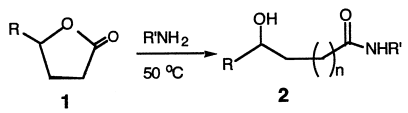
ABSTRACT

γ- and δ-Hydroxyamides can be prepared in high yields by heating a lactone with ammonia in a pressure tube. The ammonia can be removed by controlled evaporation with ice/acetone cooling.

We needed a series of racemic γ-hydroxyamides **2a**–**d** and **k** (eq 1 and **Table 1**) for biotransformation studies.[1] However, a review of the literature strongly indicated that a straightforward, general method for the preparation of these types of compounds was needed.[2]



(1)

Hydroxyamides have been synthesized recently by treating a γ-lactone with methylaluminumchloroamide (prepared from trimethyl aluminum and

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NH_4Cl).[3] We found this method to work nicely but only in only approximately 50% yield[4] (e.g. **1b** to **2b**, **Table 1**). This method is probably based on a popular, reliable preparation of amides from esters[5] utilizing the same or similar reagents.[6–8]

In looking at the difference between **1** and **2** ($R' = H$), we reasoned that the only difference was NH_3. Reported methods using NH_3 equivalents include reacting a lactone with conc. NH_4OH,[9] conc. $NH_4OH/EtOH$,[10] NH_4OH/NH_4Cl,[11] NH_3 at 50°C[12] or elevated temperatures (120°C),[2b] or simple amines,[13–15] but they can be described as inconsistent in the conditions used.[15] We don't favor the use of aqueous or ethanolic NH_4OH for hydroxyamide preparation from γ-lactones because in limited studies, we only achieved low yields of hydroxyamide products. We also note that in some cases where these methods were used, no yields were reported.[9,10]

The following method gave consistently high yields of the desired hydroxyamide products from a variety of lactone substrates *via* a simple, direct procedure. We sealed lactones in a pressure tube with NH_3 and warmed them for about a week at 50–60°C, opened the tube and allowed the ammonia to evaporate slowly with ice/acetone cooling (~ -20°C). Excellent, white crystalline 4- and 5-hydroxyamide products were obtained in high yields from five- and six-membered ring lactones. Recrystallization from ethyl acetate produced very pure crystals that gave excellent analytical results. **Table 1** lists the compounds investigated. All lactone precursors were commercially available. The yields were typically $\geq 90\%$ for γ- and δ-lactones and both were treated similarly, even though δ-lactones react slower.[15] This caused no problem, and it showed the generality of the reaction procedures.

Table 1. Hydroxyamide Preparations

Entry	Lactone	n=	R=	R′=	Hydroxyamide	Yield %
1	**1a**	1	$-CH_2CH_3$	H	**2a**	87
2	**1b**	1	$-(CH_2)_3CH_3$	H	**2b**	92
3	**1c**	1	$-(CH_2)_4CH_3$	H	**2c**	94
4	**1d**	1	$-(CH_2)_7CH_3$	H	**2d**	99
5	**1e**	1	Ph–	H	**2e**	92
6	**1f**	1	$-(CH_2)_3CH_3$	CH_3	**2f**	81
7	**1g**	1	$-(CH_2)_4CH_3$	CH_3	**2g**	89
8	**1h**	1	$-(CH_2)_4CH_3$	$-CH_2CH_3$	**2h**	98
9	**1i**	2	$-(CH_2)_4CH_3$	H	**2i**	69
10	**1j**	2	$-(CH_2)_5CH_3$	H	**2j**	90
11	**1k**	2	$-(CH_2)_6CH_3$	H	**2k**	89

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General methods to make γ-hydroxynitriles are available,[16] and numerous attempts were made to partially hydrolyze the γ-hydroxynitriles to γ-hydroxyamides, but only low yields were achieved. Typical methods[17] using H_2O_2/NaOH led to lactones. KF/alumina[18] nicely did the partial hydrolysis, but we only got a 20% yield, and liquid chromatography was necessary to separate the reactants and products. This method was abandoned in favor of the procedure described herein.

EXPERIMENTAL

All racemic lactones were commercially available. The NH_3 used was reagent grade anhydrous ammonia. All proton NMR spectra were performed on a 400 MHz spectrometer, and carbon-13 spectra were done (at 100.6 MHz) with high signal/noise ratio to prove product purities: C, H analyses were also done to prove product purities. Mass spectral analyses led to ambiguous fragmentations, and are not included.

The vacuum and high pressure procedures (sealed tubes) should be done behind a safety shield!

General Procedure for γ- and δ-Hydroxyamide Preparations from Lactones

4-Hydroxyhexanamide (2a). A vacuum (10^{-2} torr) was applied to a thick-walled 100 mL reaction tube containing 1.02 g (8.9 mmol) γ-caprolactone that was cooled with liquid N_2. Approximately 20 mL of NH_3 was condensed into the tube *via* a glass T. The tube was then sealed off with a flame and was allowed to warm to room temperature and sit for 10 days. The tube was then cooled with liquid N_2 and opened, and the ammonia was allowed to evaporate slowly at room temperature (sometimes this evaporation method led to bumping and the loss of some product). After evaporation, the tube contained white solid, which was dissolved and rinsed out with a total of approximately 7 mL of hot EtOAc. Upon cooling, white crystals of 4-hydroxyhexanamide were isolated (0.95 g). From the filtrate, an additional 0.065 g were obtained, 1.015 g (87%), mp 76–77.5°C (lit.[19] 74°C). A 1.00 g sample of γ-caprolactone was sealed in a tube similarly, only this time it was warmed to 50°C for 6 days and then opened after cooling with liquid N_2. The NH_3 was allowed to evaporate with ice/acetone cooling applied to the tube. This cooling method allowed a very controlled evaporation of the NH_3, prevented bumping, and was the preferred procedure. A total of 0.986 g (86%) of solid, mp 76–77.5°C, was obtained from the combined

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crystallizations. A tube sealed and warmed similarly for two days still had unreacted lactone in it. IR (mineral oil) 3700–3000, 1674 (C=O), 1616, 1471, 1121, 938 cm^{-1}. ^1H NMR (d_6 DMSO) δ 7.25 (s, 1H), 6.7 (s, 1H), 4.4 (d, J = 5.4 Hz, OH), 3.3 (m, 1H), 2.2 (m, 2H), 1.6-1.2 (m, 4H), 0.85 (t, J = 7.5 Hz, 3H). ^{13}C NMR (d_6 DMSO) δ 175 (C=O), 71.4, 33.1, 32.4, 30.5, 10.8. Anal Calcd for $C_6H_{13}NO_2$: C, 54.94; H, 9.99. Found C, 54.83, H, 10.03.

4-Hydroxyoctanamide (2b). γ-Octanoic lactone (1.66 g, 11.2 mmol) was sealed in a thick-walled reaction tube with 22 mL of NH_3 as above, and the solution was warmed to 50°C for 6 days. Opening the tube at liquid N_2 temperature and evaporating the NH_3 off with ice/acetone cooling led to 1.682 g of white crystals, and the filtrate yielded 25 mg more **2b** (total 1.707 g, 91.7%), mp 84–86°C (lit.[2a] 84–84.5°C). IR (mineral oil) 3400–3160, 1680 (C=O), 1600, 1456, 1080 cm^{-1}. ^1H NMR (d_6 DMSO) δ 7.25 (s, 1H), 6.7 (s, 1H), 4.4 (d, J = 5.1 Hz, 1H), 3.4 (m, 1H), 2.2–2.0 (m, 2H), 1.6 (m, 1H), 1.5 (m, 1H), 1.2-1.4 (m, 6H), 0.86 (t, J = 7 Hz, 3H). ^{13}C NMR (d_6 DMSO) δ 176.1, 70.8, 38.5, 34.5, 33.3, 29.22, 24.0, 15.8. Anal Calcd for $C_8H_{17}NO_2$: C, 60.35; H, 10.76. Found C, 60.44; H, 10.97.

4-Hydroxynonanamide (2c). γ-Nonanoic lactone (0.945 g, 6 mmol) was combined with 20 mL ammonia and heated as above at 50–60°C for 7 days. Evaporation with ice/acetone cooling led to 0.987 g **2c** (94%), mp 82–84°C (lit.[2a] 85–86°C). IR (mineral oil) 3500–3100, 1680 (C=O), 1603, 1458 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.7 (s, 1H), 5.5 (s, 1H), 3.6 (m, 1H), 2.5 (d, J = 5 Hz, 1H), 2.4 (t of d, J = 6.5 and 1.5 Hz, 2H), 1.9–1.8 (m, 1H), 1.62–1.71 (m, 2H), 1.5–1.2 (m, 7H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR (d_6 DMSO) δ 180.8, 75.6, 43.5, 39.3, 38.1, 37.9, 31.4, 28.6, 20.4. Anal Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05. Found C, 62.33; H, 11.23.

4-Hydroxydodecanamide (2d). γ-Dodecanoic lactone (1.44 g, 7.26 mmol) was sealed with 20 ml of NH_3 and warmed to 50°C for 7 days. A total of 1.54 g (99%) of **2d** was obtained, mp 103–105°C (lit.[20] 105°C). IR (mineral oil) 3500–3100 (2 bands), 1682, 1605, 1456, 1093 cm^{-1}. ^1H NMR (d_6 DMSO) δ 7.2 (s, 1H), 6.7 (s, 1H), 4.38 (d, J = 5 Hz, 1H), 3.4 (m, 1H), 2.1 (m, 2H), 1.5 (m, 1H), 1.4 (m, 1H), 1.4–1.2 (m, 14H), 0.86 (t, J = 7 Hz, 3H). ^{13}C NMR (d_6 DMSO) δ 176.1, 70,9, 38.8, 34.5, 33.3, 33.0, 30.9, 30.8, 30.4, 27.0, 23.8, 15.7. Anal Calcd for $C_{12}H_{25}NO_2$: C, 66.94; H, 11.70. Found C, 66.92; H, 11.76.

4-Phenyl-4-hydroxybutanamide (2e). γ-Phenyl-γ-butyrolactone (1.29 g, 7.95 mmol) was sealed with 20 ml of NH_3 for 3 days at 50°C (the reaction solution began to turn brown and was stopped: The color was removed with decolorizing charcoal). A total of 1.39 g of **2e** was obtained (97%), mp 80–82°C (lit.[21] 84–85°C). IR (mineral oil) 3500–3090, 1683 (C=O), 1614, 1452, 1444, 1089 cm^{-1}. ^1H NMR (d_6 DMSO) δ 7.31 (s, 2H), 7.29 (s, 2H), 7.28 (s, NH), 7.2 (m, 1H), 6.74 (s, NH), 5.28 (d, J = 3.2 Hz, OH),

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4.5 (q, J = 5.2 Hz, 1H), 2.1 (t, J = 7 Hz, 2H), 1.8 (q, J = 6.8 Hz, 2H). ^{13}C NMR (d_6 DMSO) δ 175.1, 146.7, 128.6 (2C), 127.3, 126.4 (2C), 72.5, 35.7, 32.3. Anal Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31. Found C, 67.26; H, 7.26.

N-Methyl-4-hydroxyoctanamide (2f). γ-Octanoic lactone (1.45 g, 10 mmol) was placed in an Ace Pressure tube with 20 mL of 2M CH_3NH_2 in THF and the solution was warmed to 50°C for 24 hours. It was cooled to room temperature, and the liquid was allowed to evaporate overnight. The solid was recrystallized from EtOAc/hexane (7 mL of 5:2 EtOAc:hexane), giving 1.434 g of hydroxyamide **2f** (81%), mp 51–53°C. IR (mineral oil) 3600–3000, 1653 (C=O), 1564, 1412, 1049 cm^{-1}. ^{1}H NMR (d_6 DMSO) δ 6.4 (s, 1H), 3.68 (s, 1H), 3.55 (m, 1H), 2.7 (d, J = 4.7 Hz, 3H), 2.3 (m, 2H), 1.7 (m, 2H), 1.35 (m, 6H), 0.85 (t, J = 7.1 Hz, 3H). ^{13}C NMR (d_6 DMSO) d 173.6 (C=O), 70, 37.6, 33.8, 32.7, 28.3, 26.2, 23.1, 14.8. Anal Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05. Found C, 62.41, H, 10.94.

N-Methyl-4-hydroxynonanamide (2g). γ-Nonanoic lactone (1.0 g, 6.4 mmol) was combined with 20 mL of 2M CH_3NH_2 in THF in an Ace Pressure tube at 65°C for 7 days. After evaporation, 1.07 g of white crystals were obtained (89%), mp 44–46°C. IR (mineral oil) 3600–3000, 1638 (C=O) cm^{-1}. ^{1}H NMR (d_6 DMSO) δ 6.0 (s, 1H), 3.58 (m, 1H), 3.23 (s, 1H), 2.77 (d, J = 4.7 Hz, 3H), 2.3 (m, 2H), 1.8 (m, 1H), 1.62 (m, 1H), 1.3 (m, 8H), 0.86 (t, J = 6.9 Hz, 3H). ^{13}C NMR (d_6 DMSO) δ 173.5 (C=O), 70, 37.8, 33.8, 32.7, 32.3, 26.2, 25.7, 23, 14.8. Anal Calcd for $C_{10}H_{21}NO_2$: C, 64.13: H, 11.30. Found C, 64.37; H, 11.35.

N-Ethyl-4-hydroxynonanamide (2h). γ-Nonanoic lactone (1.41 g, 9 mmol) was added to a reaction tube and 15 mL of $EtNH_2$ was added to it. After 24 h at 50°C, the solution was cooled and evaporated leaving yellowish crystals which were recrystallized from toluene/hexane leaving 1.757 g (98%) of **2h**, mp 54–56°C (lit.[20] 56–56.5°C). The reaction was repeated with a 98% yield again. IR (mineral oil) 3450–3090, 1633 (C=O) cm^{-1}. ^{1}H NMR (d_6 DMSO) δ 7.84 (s, 1H), 4.36 (d, J = 5.9 Hz, 1H), 3.3 (s, 1H), 3.0 (pentet, J = 6.6 Hz, 2H), 2.07 (m, 2H), 1.56 (m, 1H), 1.41 (m, 1H), 1.25 (m, 8H), 0.96 (t, J = 7.3 Hz, 3H), 0.84 (t, J = 7.3 Hz, 3H). ^{13}C NMR (d_6 DMSO) δ 174.2 (C=O), 71.2, 37.9, 34.6, 33.4, 33.3, 32.2, 25.8, 22.9, 15.0, 14.3. Anal Calcd for $C_{11}H_{23}NO_2$: C, 65.63: H, 11.52. Found C, 66.02; H, 11.45.

5-Hydroxydecanamide (2i). A 1.67 g sample of δ-decanolactone (9.8 mmol) was sealed in a pressure tube with 30 mL of NH_3 and the solution was warmed to 50°C for 6 days. A total of 1.274 g (70%) of white crystals were obtained, mp 75–77°C. IR (mineral oil) 3400–3200, 1695, 1607, 1464, 1130, 910, 727 and 707 cm^{-1}. ^{1}H NMR (d_6 DMSO) δ 7.2 (s, 1H), 6.68 (s, 1H), 4.27 (d, J = 5.5 Hz, CHOH), 3.3 (m, 1H), 2.0 (t, J = 7.5 Hz, 2H), 1.6–1.2 (m, 12H), 0.86 (t, J = 7 Hz, 3H). ^{13}C NMR

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(d_6 DMSO) δ 173.9 (C=O), 69.1, 37.0, 36.6, 35.1, 31.4, 24.8, 22.1, 21.5, 13.9. Anal Calcd for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30. Found C, 64.20, H, 11.50.

5-Hydroxyundecanamide (2j). δ-Undecanolactone (0.98 g, 5.3 mmol) was combined with 5 mL of NH_3 at dry ice/acetone temperature in an Ace Pressure tube. After 6 days at 54°C, the NH_3 was evaporated at ice/acetone temperature, and recrystallization from EtOAc gave 0.92 g of white crystals: 44 mg more crystals were obtained from the filtrate (0.966 g, 90% yield), mp 81–83°C. IR (mineral oil) 3400–3200, 1661, 1615, 1460 cm^{-1} ^1H NMR (d_6 DMSO) δ 7.2 (s, 1H), 6.7 (s, 1H), 4.3 (d, J = 5.5 Hz, OH), 3.3 (m, 1H), 2.0 (t, J = 7 Hz, 2H), 1.6–1.2 (M, 14H), 0.85 (t, J = 7 Hz, 3H). ^{13}C NMR (d_6 DMSO) δ 173.9 (C = O), 69.1, 37.0, 36.6, 35.1, 31.2, 28.8, 25.1, 22.0, 21.4, 13.9. Anal Calcd for $C_{11}H_{23}NO_2$: C, 65.63; H, 11.52. Found, C, 65.47, H, 11.74.

5-Hydroxydodecananide (2k). δ-Dodecanoiclactone (0.18 g, 9 mmol) was combined with 10 mL of NH_3 in a pressure tube and the solution was kept at 50°C for 7 days. The white crystals obtained from EtOAc weighed 0.174 g (89%), mp 88–90°C. IR (mineral oil) 3400–3200, 1661, 1632, 1460, 1163, 922 cm^{-1} ^1H NMR (d_6 DMSO) δ 7.2 (s, 1H), 6.7 (s, 1H), 4.3 (d, J = 5 Hz, OH), 3.35 (m, 1H) 2.0 (t, J = 7 Hz, 2H), 1.6–1.2 (m, 16H), 0.86 (t, J = 7 Hz, 3H). ^{13}C NMR (d_6 DMSO) δ 173.9 (C = O), 69.1, 37.0, 36.6, 35.1, 31.2, 29.1, 28.7, 25.1, 22.0, 21.4, 13.9. Anal Calcd for $C_{12}H_{25}NO_2$: C, 66.93; H, 11.70. Found, C, 66.72, H, 11.99.

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