# Triethylamine/Aluminum Chloride Promoted Aminolysis of Lactones: A Useful Method for the Preparation of ω-Hydroxyalkanamides

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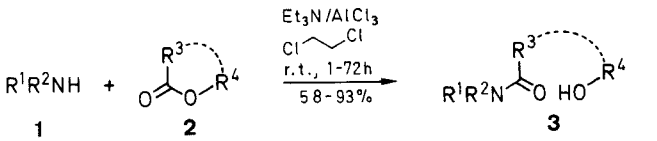
Primary and secondary aliphatic or aromatic amines react cleanly with medium-ring lactones in the presence of triethylamine/aluminum chloride to afford ω-hydroxyalkanamides in high yield.

A number of methods to facilitate the aminolysis of lactones have been described, including the use of high pressure,[1] lithium amides,[2] 2-hydroxypyridine,[3-6] dialkylaluminum amides,[7] and alkylaminostannanes.[8] In this context we recently reported[9] that medium-ring lactones react with 2.5–3 equivalents of primary or secondary amines in the presence of aluminum chloride to afford ω-hydroxyalkanamides in good yield. In most cases the use of excess amine has little incidence on cost or the ease of workup, but it may represent a serious drawback in the case of amines which are either expensive or not readily accessible.

We now report that ω-hydroxyalkanamides **3** may be prepared in good yield by the reaction of lactones **2** with a small excess of primary or secondary amine **1** in the presence of a triethylamine/aluminum chloride couple.

In a typical experiment the lactone **2** and amine **1** (1.1 equivalents) are added to a mixture of aluminum chloride (1.1 equivalents) and triethylamine (1.5 equivalents) in




**1**

| | $R^1$ | $R^2$ |
|---|---|---|
| **a** |  | |
| **b** | 2,6-$Me_2C_6H_3$ | H |
| **c** | *t*-Bu | H |
| **d** | Ph | Me |
| **e** |  | |

**2**

| | $R^3$–$R^4$ |
|---|---|
| **a** |  |
| **b** | $-(CH_2)_3-$ |
| **c** | $-(CH_2)_4-$ |
| **d** | $-(CH_2)_5-$ |

1,2-dichloroethane and the evolution of the reaction was followed by thin layer chromatography. As shown in Table 1, reactions with 1,2,3,4-tetrahydroisoquinoline (**1a**) and 1-phenylpiperazine (**1e**) were rapid and gave excellent yields of the corresponding ω-hydroxyalkanamides **3**. The reaction of *tert*-butylamine (**1c**) with phthalide (**2a**) was more sluggish but afforded **3c** in good yield. The weakly nucleophilic anilines **1b** and **1d** gave

**Table 1.** ω-Hydroxyalkanamides **3** Prepared using Aluminum Chloride/Triethylamine[a]

| Substrates | Time (h) | Product | Yield[b] (%) | mp (°C) (solvent) | Molecular Formula[c] or Lit. mp (°C) | IR[d] ν (cm$^{-1}$) OH, C=O | $^1$H NMR ($CDCl_3$/TMS) δ, J (Hz) |
|---|---|---|---|---|---|---|---|
| **1a + 2a** | 1 | **3a** | 93 | 110–111 ($ClCH_2CH_2Cl$/*i*-$Pr_2O$) | 111–112[9] | 3310, 1615 | 2.92 (m, 2H), 3.48 (s, 1H), 3.59 (t, 2H, $J$ = 6), 4.49 (d, 2H, $J$ = 5.5), 4.56 (m, 1H), 4.94 (m, 1H), 7.16 (m, 8H) |
| **1b + 2a** | 48 (30)[e] | **3b** | 58 (69)[e] | 142–143 ($ClCH_2CH_2Cl$/*i*-$Pr_2O$) | 142–143[f] | 3280, 1635 | 2.30 (s, 6H), 4.45 (s, 1H), 4.63 (s, 2H), 7.54 (m, 7H), 7.97 (s, 1H) |
| **1c + 2a** | 24 | **3c** | 83 | 89–90 ($ClCH_2CH_2Cl$/*i*-$Pr_2O$) | 88–89[9] | 3310, 1635 | 1.46 (s, 9H), 4.50 (s, 1H), 4.53 (s, 2H), 6.41 (s, 1H), 7.40 (m, 4H) |
| **1d + 2a** | 72 (18)[e] | **3d** | 68 (79)[e] | 99–100 ($ClCH_2CH_2Cl$/*i*-$Pr_2O$) | 100–101[9] | 3430, 1630 | 3.51 (s, 3H), 3.71 (s, 1H), 4.66 (s, 1H), 7.17 (m, 9H) |
| **1e + 2a** | 2 | **3e** | 93 | 119–121 ($ClCH_2CH_2Cl$/*i*-$Pr_2O$) | $C_{18}H_{20}N_2O_2$ (296.4) | 3330, 1765 | 3.12 (m, 2H), 3.27 (m, 2H), 3.55 (m, 3H), 4.00 (m, 2H), 4.58 (m, 2H), 6.94 (m, 3H), 7.37 (m, 6H) |
| **1a + 2b** | 1 | **3f** | 85 | oil | oil[9] | 3420, 1625 | 1.94 (m, 2H), 2.60 (t, 2H, $J$ = 6.5), 2.88 (m, 2H), 3.07 (s, 1H), 3.77 (m, 4H), 4.69 (m, 2H), 7.19 (m, 4H) |
| **1a + 2c** | 1 | **3g** | 89 | oil | oil[9] | 3420, 1630 | 1.63 (m, 2H), 1.80 (m, 2H), 2.46 (t, 2H, $J$ = 7), 2.66 (s, 1H), 2.88 (m, 2H), 3.72 (m, 4H), 4.68 (m, 2H), 7.23 (m, 4H) |
| **1a + 2d** | 1.5 | **3h** | 91 | oil | oil[9] | 3430, 1630 | 1.57 (m, 6H), 2.40 (t, 2H, $J$ = 7), 2.85 (m, 2H), 3.12 (s, 1H), 3.70 (m, 4H), 4.64 (m, 2H), 7.13 (m, 4H) |

[a] Molar ratio **2/1** / $AlCl_3$/$Et_3N$ was 1 : 1.1 : 1.1 : 1.5 unless otherwise specified.
[b] Yield, based on **2**, of pure isolated product.
[c] Satisfactory microanalyses obtained for all solids: C ±0.40, H ±0.09, N ±0.12.
[d] KBr discs for solids, films for oils.
[e] Molar ratio of **2/1** / $AlCl_3$/$Et_3N$ was 1 : 1.3 : 1.5 : 2.0
[f] mp erroneously reported as 97–98 °C in Ref. 9.

**Table 2.** Influence of the Aprotic Base on the Formation of Product **3a**[a]

| Aprotic Base | Time (h) | Yield (%)[b] |
|---|---|---|
| $Et_3N$ | 1 | 93 |
| quinuclidine | 3 | 88 |
| hexamethylenetetramine | 3 | 88 |
| *i*-$Pr_2EtN$ | 3 | 86 |
| $Me_2NCH_2CH_2NMe_2$[c] | 3 | 83 |
| pyridine | 48 | 42 |
| DMAP | 48 | 37 |

[a] Molar ratio **2a/1a** / $AlCl_3$/aprotic base was 1 : 1.1 : 1.1 : 1.5 unless otherwise specified.
[b] Yield, based on **2a**, of pure isolated product.
[c] Molar ratio of **2a/1a** / $AlCl_3$/TMEDA was 1 : 1.1 : 1.1 : 0.75.

lower yields of **3b** and **3d**, respectively, but the reactions could be accelerated and the yields improved by increasing the amount of triethylamine/aluminum chloride and using a 30% excess of the aniline.

Aminolysis using other aprotic base/aluminum chloride couples was studied for the reaction between 1,2,3,4-tetrahydroisoquinoline (**1a**) and phthalide (**2a**) as shown in Table 2. The tertiary alkylamines examined, although very different in terms of basicity or steric hindrance, gave surprisingly similar results. The use of pyridine or 4-(dimethylamino)pyridine, however, markedly reduced the yield of ω-hydroxyalkanamide. None of the bases examined showed significant advantages over triethylamine in terms of yield, kinetics or ease of workup.

In conclusion, the use of a triethylamine/aluminum chloride couple promotes the aminolysis of a variety of 5–7 membered lactones by primary and secondary amines. The method presents the advantage, compared to the previously reported aluminum chloride method,[9] that only a small excess of the primary or secondary amine is required. The yields of ω-hydroxyalkanamides are good to excellent and the reaction conditions are mild.

$AlCl_3$ (Puriss) was purchased from Fluka Chemical Co. Other reagents and solvents were of reagent grade and were used without further purification. Column chromatography was carried out using silica chromagel 60 A-cc. Melting points were determined using a Kofler block (Heizbank WME) and are uncorrected. IR spectra were recorded on a Philips Unicam SP3-200S spectrometer and NMR spectra recorded using a Bruker AC-200 spectrometer. Microanalyses were obtained with a Carlo Erba Elemental Analyzer 1106.

***N*-[2-(Hydroxymethyl)benzoyl]-1,2,3,4-tetrahydroisoquinoline (3a); Typical Procedure:**

A solution of $Et_3N$ (10.7 mL, 75 mmol) in 1,2-dichloroethane (20 mL) was added dropwise with agitation and external cooling (*caution:* Exotherm) to a suspension of $AlCl_3$ (7.41 g, 55 mmol) in 1,2-dichloroethane (40 mL). The temperature was maintained at 15–25 °C during the addition and then allowed to warm to r.t. A solution of 1,2,3,4-tetrahydroisoquinoline (**1a**, 7.1 mL, 55 mmol) and phthalide (**2a**, 6.84 g, 50 mmol) in 1,2-dichloroethane (30 mL) was added over 15 min and the mixture stirred at r.t. for 1 h before quenching with a mixture of ice and $H_2O$ (250 mL). The mixture was stirred for a further 0.5 h and the resulting suspension filtered through Celite. 1,2-Dichloroethane (100 mL) was added and the organic phase separated, washed with $H_2O$ (150 mL), brine (100 mL) and dried ($Na_2SO_4$). After filtration and evaporation the solid obtained was triturated with *i*-$Pr_2O$, filtered, washed with *i*-$Pr_2O$ and dried under reduced pressure. Yield: 12.41 g (93%); mp 110–111 °C (Table 1).

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