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Chemoselective *N*-acylation of amino alcohols promoted by magnesium oxide in aqueous organic solution

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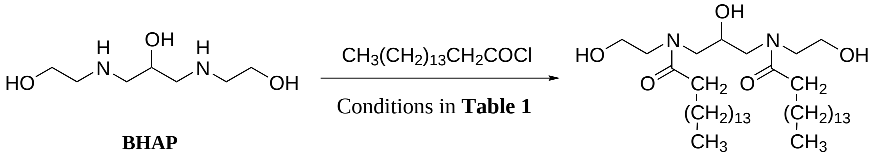
Abstract—The reaction of hydrophilic amino alcohols with acid chlorides in the presence of magnesium oxide in aqueous organic solution (THF/H_2O = 4:1) cleanly provided alkanolamides. © 2002 Elsevier Science Ltd. All rights reserved.

Among a number of amidation methods, condensation of acid chloride with amine has been routinely employed in laboratories. Although this method is highly reactive and successful for the preparation of simple amide, the lack of chemoselectivity limits its uses for the *N*-acylation of amino alcohols.[1] Long chain alkanolamides find importance as cosmetics[2] and surfactants[3,4] owing to their intrinsic surface active properties. In the course of the synthesis of alkanolamide compounds, control of chemoselective amide formation over competing *O*-acylation of neighboring hydroxyl groups plays as a key step. Although the application of enzymatic synthesis for these reactions have been reported in a few cases,[3–5] no efficient chemical method for the selective *N*-acylation of amino alcohols has been established for the preparations of alkanolamides.

Now we report a useful procedure for the efficient and chemoselective amidation of hydrophilic amino alcohols with acid chlorides in the presence of MgO in a THF/H_2O (v/v = 4:1) solution. To find and develop a chemoselective and efficient amidation method of amino alcohols, we chose to use 1,3-bis[(hydroxymethyl)amino]propan-2-ol (BHAP, **1**)[6] as a model amino alcohol substrate and tested selective *N*-acylation (Scheme 1) with palmitoyl chloride in the presence of various bases which include triethylamine, pyridine, and NaOH (Schotten–Baumann conditions). However, these attempted reaction conditions gave only slight amounts of desired amidation product, as shown in Table 1. After a number of experiments we found that magnesium oxide in a THF/H_2O (v/v = 4:1) solution efficiently promoted the amidation reaction and the desired alkanolamide (**2**) was obtained in 85% yield.[7] To the best of our knowledge, this is the first example of the successful use of magnesium oxide as a base in the acylation reaction of amines with acid chlorides. Treatment of BHAP with magnesium oxide (5.0 equiv.) in a THF/H_2O (4:1) solution with vigorous stirring at 20°C followed by addition of palmitoyl chloride gave the desired amide. The *N*-acylation of BHAP was achieved in high yield while hydroxyl groups remained mostly unaffected under the reaction conditions employed. The isolation of *N*-acylated



1

2

Scheme 1.

Keywords: acid chloride; amides; amine; aqueous solution.

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Table 1. Conditions for chemoselective amide (**2**) formation

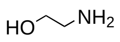
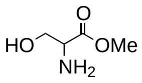
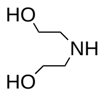
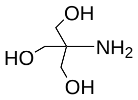
Entry	Solvent	Base[a]	Time (h)	Yield (%)[b]
1	CH_2Cl_2	TEA (2.2)	4	0
2	DMF	TEA (2.2)	5	10
3	DMF	Pyridine (2.2)	4.5	15
4	H_2O	NaOH (2.2)	4.5	5
5	THF/H_2O	NaOH (2.2)	4.5	12
6	THF/H_2O	MgO (5.0)	4.5	85

[a] The molar equivalents are given in parentheses.

[b] Isolated yields.

product was easily conducted by column chromatography. The reaction was then examined for its generality by performing it with a variety of acid chlorides with varying chain length. The results are shown in Table 2. The amidation products were obtained in good to excellent yields with small amounts of *O*-acylated forms which are easily separated by flash chromatography. As shown in Table 2, the reaction of amino alcohols with acid chloride, which contained more than carbon number C2 proved to be effective at present reaction conditions. In the case of amidation of acetyl chloride this method did not work at all and none of the desired product was obtained. The result can be explained by the rapid hydrolysis of acetyl chloride must be much faster than the amide formation. In the case of benzoyl chloride and the other long chain acid chlorides, which are more hydrophobic than acetyl chloride, the desired *N*-acylation products were obtained chemoselectively in high yields. Replacing MgO with NaOH at the same reaction conditions resulted in formation of only a small amount of *N*-acylation products. Therefore, it seems likely that the coordinating ability of magnesium ion, as has already been demonstrated on amidation of esters,[8] to the carbonyl function of acid chlorides plays a crucial role in the selective *N*-acylation of amino alcohols. More nucleophilic amino groups should react faster with reactive magnesium coordinated acid chlo-

Table 2. Chemoselective amidation of alkanolamines with various acid chlorides[a]

Entry	Substrate	Acid chloride	Yield(%)[b]
7	**1**	Acetyl chloride	0
8	**1**	Propionyl chloride	50
9	**1**	Hexanoyl chloride	85
10	**1**	Octanoyl chloride	90
11	**1**	Ethylhexanoyl chloride	75
12	**1**	Benzoyl chloride	80
13	**1**	Lauroyl chloride	88
14	**1**	Stearoyl chloride	94
15		Palmitoyl chloride	92
16		Palmitoyl chloride	89
17		Palmitoyl chloride	92
18		Palmitoyl chloride	76

[a] All the reactions were run with 2.2 equiv. of acid chloride in THF/H_2O (4:1).

[b] The yields are for isolated compounds.

ride than hydroxyl groups. The reaction also worked equally well for other hydrophilic amines such as ethanolamine, DL-serine methyl ester, diethanolamine, and tris(hydroxymethyl)-aminomethane (entries 15–18). In all of the cases investigated, as judged by HPLC, the *O*-acylated products were seen in minimal amounts (<5%), which can be readily eliminated by column chromatography. The notable feature of the reaction is that when the reaction temperature was elevated to above 20°C, substantial formation of the *O*-acylation side products has been observed. In addition, the nature of the solvent system used for the reaction is of the greatest importance. When the reaction is carried out in either THF or H_2O, only in the presence of MgO, no appreciable amidation products were detected. At present reaction conditions, the effective formation of long chain amide can be attributed to the high lipophilicity of acid chlorides which allow faster reaction with amine other than hydroxide, a phenomenon that should become more pronounced with increasing carbon chain length of acid chlorides.

In summary, we have developed an efficient and chemoselective amidation reaction by the reaction of amino alcohols with acid chloride in the presence of magnesium oxide, which will be a promising alternative to the classical Schotten–Baumann reaction. Moreover, this method offers wide applicability for the preparations of a range of other industrially useful alkanolamides. Further applications of this protocol in the synthesis are currently in progress.

Acknowledgements

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6. BHAP was readily prepared in 90% yield from reaction between epichlorohydrin and an excess of ethanolamine with reflux.
7. Typical procedure: To a solution of BHAP (1.0 g, 5.6 mmol) in H_2O (2 mL) was added MgO (1.13 g, 28.0 mmol), THF (6 mL), and stirred vigorously for 30 min at 20°C. To a suspension of reaction mixture, palmitoyl chloride (3.4 g, 12.3 mmol) in THF (2 mL) was added dropwise for 1 h. After additional stirring for 1 h at 20°C, the reaction mixture was filtered through a bed of Celite. The filtrate was evaporated and extracted with ethyl acetate (50 mL) and washed with water. The solvent was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH = 15:1) to give the desired product (3.1 g, 85%) as a white solid. Mp 71–72°C; IR ν_{max} (KBr) 3358, 2910, 2860, 1609 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) 0.86 (6H, t, J = 6.6 Hz), 1.16–1.38 (48H, m), 1.52–1.65 (4H, m), 2.35 (4H, t, J = 7.2), 3.21–3.42 (4H, m), 3.44–3.62 (4H, m), 3.72–3.86 (4H, m), 4.18–4.26 (1H, m); anal. calcd for $C_{39}H_{78}N_2O_5$: C, 71.51; H, 12.00; N, 4.28. Found: C, 71.40; H, 11.92; N, 4.32.
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