

Green and efficient method for the acylation of amines and phenols in the presence of hydrotalcite in water

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In this study a mild, efficient and environmentally friendly method has been developed for the synthesis of amides and esters in the presence of hydrotalcite in water at room temperature. Different types of amines and phenols have been used and in all cases the products were obtained in moderate to high yields after an easy work-up. This method follows the principles of green chemistry.

Keywords: hydrotalcite, water, acylation, amines, phenols, green synthesis

The acylation of phenols and amines is very important in various organic transformations.¹ Acylation is usually carried out by treating phenols or amines with carboxylic acid chlorides or anhydrides in the presence of acid or base catalyst in a suitable organic solvent. Recently, *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was used as base catalyst for acylation of alcohols and thiols.² On the other hand, Lewis acids such as metal halides and oxide,³ metal triflates,⁴ and metal perchlorates,⁵ and several solid acids such as zeolite⁶ have also been utilised to achieve the acylation of phenols and amines. However, these methods have some disadvantages such as exothermic reaction, the formation of by products, complicated conditions, excess acylating agents and toxic organic solvents. The main drawbacks of homogeneous process include lack of reusability of the catalyst, hazardous nature of liquid base like pyridine or DMAP (highly toxic *e.g.*, intravenous LD50 in the rat: 56 mg kg⁻¹) and post-reaction work-up of spent liquid bases. However, despite the efficiency of the latter protocols, the development of less expensive and environmentally benign reaction conditions is a major goal for organic synthesis.

Therefore, it was desirable to develop a solid base catalyst which would overcome these disadvantages and provide a commercial process involving easy handling of the catalyst, separation of products, decreased corrosion of the reactor, and possible regeneration and re-use of the catalyst.

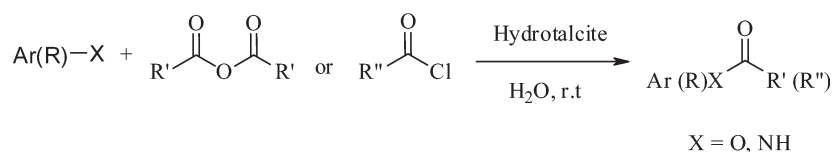
Hydrotalcite (HT) or hydrotalcite-like compounds (HTlc) are layered double hydroxides belonging to the class of anionic clays. The structure of these compounds are very similar to that of brucite, Mg(OH)₂, where some of Mg²⁺ represented as [M(II)] are isomorphously replaced by Al³⁺ represented as [M(III)] and the net positive charge is compensated by an inter-layered exchangeable anion (Aⁿ⁻). The general formula of these compounds can be represented as: [M(II)_{1-x}M(III)_x(OH)₂] Aⁿ⁻_{x/n}·mH₂O. Hydrotalcite has recently received much attention as a solid base catalyst. The basicity of the hydrotalcite could be modified either by changing the divalent to trivalent cations molar ratio [M(II)/M(III)] or by intercalation of a suitable anion in the interlayer space. These catalysts can be used for different purposes in organic chemistry, such as condensations reactions,⁷ alkylation of phenol,⁸ and *N*-arylation of amines.⁹

In recent years, organic reactions that can proceed in water have attracted great interest because of significant environmental and economic advantages over those occurring in organic solvents.¹⁰ As a part of our ongoing research project to develop newer synthetic methodologies, particularly in acylation reactions,¹¹ we now report our results on the hydrotalcite catalysed acylation of amines and phenols, with some carboxylic acid anhydrides and chlorides in water (Scheme 1). Due to its operational simplicity, generality and efficacy, this method may have wider applicability for the acylation reaction of amines and phenols and it represents a better, eco-friendly alternative to many existing procedures.

Results and discussions

In order to optimise the reaction conditions, we chose the reaction of 4-methoxyaniline, and 4-nitrobenzoyl chloride as a reaction model. To start with, the reaction was screened in different solvents. Water provided excellent yields and proved to be the solvent of choice as a green solvent. Next this conversion was carried out at room temperature using different amount of water including 3 mL (70%), 2 mL (78%), and 1 mL (83%). However the best yield of product (89%) was obtained when 0.5 mL of water was used as solvent. The effect of the amount of catalyst on the reaction was also investigated. The yield of amide increased with increasing the amounts of the hydrotalcite from 0.05 to 0.2 g. No improvement in the yield was found with a further increase of the catalyst. Hence, the optimal amount of hydrotalcite was chosen as 0.2 g based on 1.0 mmol of 4-methoxyaniline and 1.2 mmol of 4-nitrobenzoylchloride (1.0 mmol of benzoic anhydride, 4.0 mmol of acetic anhydride) for further study.

To demonstrate the scope of these reaction conditions, a variety of phenols and amines were acylated to form the corresponding ester and amide in good to high yields and high purity at ambient temperature in water. Several examples illustrating the usefulness of this efficient and rapid acylation procedure are summarised in Table 1. Various functional groups such as Me, Cl, OMe, NO₂, and Br were tolerated under these conditions. In spite of the fact that the presences of the chloro and nitro group(s) in the aromatic amines and phenols make the amino and hydroxy group of these substrates poor nucleophiles, good to excellent yields of the corresponding



Scheme 1 Acylation of phenols and amines in water.

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Table 1 Acylation of amines and alcohols in water

Entry	Substrate	Acyating agent	Time/min	Yield/%	M. p. [lit. m. p. °C]
1	4-Methylaniline	Acetic anhydride	5	93	151–153 [151] ¹³
2	Aniline	Acetic anhydride	10	87	113–115 [115] ¹³
3	4-Chloroaniline	Acetic anhydride	5	85	180–182 [179] ¹³
4	2,4-Dichloroaniline	Acetic anhydride	8	85	143–145 [144] ¹⁴
5	4-Bromoaniline	Acetic anhydride	5	85	168–170 [168] ¹⁶
6	3-Nitroaniline	Acetic anhydride	10	89	154–155 [154–155] ¹⁵
7	4-Nitroaniline	Acetic anhydride	12	73	216–218 [215–216] ¹⁵
8	1-Naphthylamine	Benzoic anhydride	8	75	161–163 [164–165] ¹⁷
9	4-Methylaniline	Benzoic anhydride	5	81	157–159 [157–158] ¹⁶
10	4-Methoxyaniline	4-Nitrobenzoylchloride	8	89	197–199 [196–197] ¹⁸
11	4-Bromoaniline	4-Nitrobenzoylchloride	13	80	237–239 [238–240] ¹⁹
12	Aniline	4-Nitrobenzoylchloride	8	78	210–212 [211–212] ¹⁶
13	2,4-Dichloroaniline	4-Nitrobenzoylchloride	25	76	169–171 [171–172] ²⁰
14	4-Nitroaniline	4-Nitrobenzoylchloride	35	75	267–269 [268–270] ¹⁸
15	4-Methylphenol	Benzoyl chloride	5	83	69–71 [71–73] ²¹
16	4-Chlorophenol	Benzoyl chloride	5	80	85–87 [84–86] ²¹
17	3-Nitrophenol	Benzoyl chloride	5	80	92–94 [95] ²²
18	4-Nitrophenol	Benzoyl chloride	5	72	127–130 [128–129] ²¹
19	Phenol	Benzoyl chloride	5	77	67–68 [68–69] ²¹
20	2,4-Dichlorophenol	Benzoyl chloride	5	70	92–94 [91–92] ²³
21	2,4-Dichlorophenol	Benzoic anhydride	15	70	92–94 [91–92] ²³
22	4-Chlorophenol	Benzoic anhydride	10	77	85–87 [86–88] ²¹
23	4-Nitrophenol	Benzoic anhydride	10	79	145–147 [143–145] ²¹
24	Phenol	Benzoic anhydride	15	76	67–68 [68–69] ²¹
25	Phenol	4-Nitrobenzoylchloride	5	75	131–133 [127–130] ²¹
27	4-Methylphenol	4-Nitrobenzoylchloride	5	78	100–102 [99–100] ²¹

amides and esters were obtained at room temperature in the presence of hydrotalcite. Also, in order to generalise the catalytic efficiency of hydrotalcite for other acylating agents, we tried the acylation of some phenols and amines with different carboxylic acid anhydrides and chlorides while most literature methods for acylation employ only acetic anhydride.

Finally, we were interested to study the re-use of the catalyst for economic and environmental aspects. For this purpose, the reaction of 4-methoxyaniline with acetic anhydride was chosen as a model reaction in the presence of hydrotalcite in water. At the end of each run, the catalyst was recovered from the reaction mixture and washed with ethyl acetate and dried at 100 °C. The recycled hydrotalcite was used for further runs and its activity did not show any significant decrease after three runs.

In conclusion, hydrotalcite has been found to be a highly efficient and low-cost basic catalyst for acylation of phenols, and amines in water at room temperature. Operational simplicity, use of water as a green solvent, exceptionally fast reaction, low cost and non-toxic nature of the catalyst, and reusability of the catalyst, are the key features of this method. In terms of environmental and economic factors, hydrotalcite is also a promising alternative to organic bases.

Experimental

All chemicals were purchased from the Merck and Fluka chemical companies. IR spectra were recorded on Nicolet (impact 400D model) FT-IR spectrometer. ¹H NMR and ¹³C NMR spectra were recorded on Bruker DRX 400 Avance Spectrometer in CDCl₃ and DMSO-d₆. All yields refer to isolated yield. The Mg–Al hydrotalcite catalyst was synthesised by co-precipitation method at constant pH.¹²

The Mg–Al hydrotalcite samples with Mg/Al molar ratio in the range of 2–3.5 were synthesised by co-precipitation method at constant pH. For example, during the synthesis of hydrotalcite of Mg/Al molar ratio 2.5, an aqueous solution (A) of Mg (NO₃)₂·6H₂O (0.22 mol) and Al (NO₃)₃·9H₂O (0.088 mol) was prepared in 200 mL of double distilled deionised water. The solution A was added dropwise into a second solution (B) containing NaOH (0.72 mol) and Na₂CO₃ (0.21 mol) in 200 mL double distilled deionised water, in around 2 h with vigorous stirring at room temperature. The content was then transferred to a Teflon coated stainless steel autoclave and aged at

70 °C for 14h under normal pressure. After 14h, the precipitate which formed was filtered and washed thoroughly with hot distilled water until the pH of the filtrate was 7.0. The washed precipitate was dried in an oven at 80 °C for 14h and activated at 450 °C for 4h in a muffle furnace. The solid material was then cooled and stored under vacuum prior to using as catalyst for acylation of phenols and amines.

Synthesis of *N*-phenyl-4-nitrobenzamide; typical procedure for acylation of amines

4-Nitrobenzoyl chloride (1.2 mmol) was added to a stirred mixture of hydrotalcite (0.2 g) and aniline (1 mmol) in water (0.5 mL). The reaction mixture was stirred for a certain period of time as required to complete the reaction (monitored by TLC) at room temperature. Ethyl acetate (20 mL) was added and the solid mass (hydrotalcite) was then eluted with more ethyl acetate (10 mL). The ethyl acetate extract was then washed with an aqueous solution of sodium bicarbonate (15 mL) and water (15 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent furnished pure *N*-phenyl-4-nitrobenzamide in 78% yield, m.p. 210–212 °C; FT-IR (KBr): 3343, 3100, 1657, 1586, 1530, 1339, 1321, 751, cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) = 7.12 (t, 1H, *J* = 7.2 Hz), 7.37 (t, 2H, *J* = 7.8 Hz), 7.76 (d, 2H, *J* = 8.0 Hz), 8.16 (d, 2H, *J* = 8.4 Hz), 8.37 (d, 2H, *J* = 8.8 Hz), 10.57 (s, 1H); ¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) = 120.9, 124.0, 124.6, 129.1, 129.6, 139.1, 141.1, 149.5, 164.3 ppm.

Synthesis of phenyl-4-nitrobenzoate; typical procedure for acylation of phenols

Phenyl-4-nitrobenzoate was synthesised according to the above procedure by using phenol instead of aniline, in 75% yield. The product was purified by recrystallisation in *n*-hexane, m.p. 131–133 °C; FT-IR (KBr): 1737, 1583, 1540, 1350, 1264, 1061, 936, 814, 706, cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ (ppm) = 7.44 (m, 2H), 7.57–7.72 (m, 3H), 8.25 (d, 2H, *J* = 7.6 Hz), 8.36 (d, 2H, *J* = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 122.7, 125.3, 128.5, 128.8, 130.3, 134.3, 145.4, 155.7, 164.3.

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References

- 1 T.W. Greene and P.G.M. Wuts, *Protective groups in organic synthesis*, 3rd edn. Wiley, New York, 1999, p. 150.
- 2 S.T. Kadam, H. Lee, S.S. Kim, *Bull. Korean Chem. Soc.*, 2009, **30**, 1071.
- 3 A.K. Chakraborti and R. Gulhane, *Tetrahedron Lett.*, 2003, **44**, 6749.
- 4 B. Karimi and J. Maleki, *J. Org. Chem.*, 2003, **68**, 4951.
- 5 G. Bartoli, M. Bosco, R. Dalpozzo, E. Marcantony, M. Massaccesi, S. Rinaldi and L. Sambri, *Synlett.*, 2003, 39.
- 6 R. Ballini, G. Bosica, S. Carloni, L. Ciarralli, R. Maggi and G. Sartory, *Tetrahedron Lett.*, 1998, **39**, 6049.
- 7 S.K. Sharma, P.A. Parikh and R.V. Jasra, *J. Mol. Catal. A: Chem.*, 2008, **286**, 55.
- 8 A.H. Padmasri, A. Venugopal, V. Durga Kumari, K.S. Rama Rao and P. Kanta Rao, *J. Mol. Catal. A: Chem.*, 2002, **188**, 255.
- 9 V.H. Jadhav, D.K. Dumbre, V.B. Phapale, H.B. Borate and R.D. Wakharkar, *Catal. Commun.*, 2007, **8**, 65.
- 10 P.A. Grieco, *Organic synthesis in water*; Blackie, London, 1998.
- 11 A.R. Massah, H. Adibi, R. Khodarahmi, R. Abiri, M.B. Majnooni, S. Shahidi, B. Asadi, M. Mehrabi and M.A. Zolfigol, *Bioorg. Med. Chem.*, 2008, **16**, 5465.
- 12 F. Cavani, F. Trifiro and A. Vaccari, *Catal. Today*, 1991, **11**, 173.
- 13 H. Eshghi, A. Hassankhani and E. Mosaddegh, *J. Chem. Res.*, 2006, 218.
- 14 S. Gowda and B.T. Gowda, *Z. Naturforsch.*, 2007, **62**, 84.
- 15 P. Gupta and S. Paul, *Green Chem.*, 2011, **13**, 2365.
- 16 I. Mohammadpoor-Baltork, H. R. Memarian and K. Bahrami, *Monatsh. Chem.*, 2004, **135**, 411.
- 17 H. Al-Awadi, M.R. Ibrahim, H.H. Dib, N.A. Al-Awadi and Y.A. Ibrahim, *Tetrahedron*, 2005, **61**, 10507.
- 18 S.B. Kang, *Bull. Korean Chem. Soc.*, 2008, **29**, 1025.
- 19 J. Gao, *J. Org. Chem.*, 2008, **73**, 2955.
- 20 F.D. Chattaway, *J. Chem. Soc. Transaction*, 1916, **109**, 89.
- 21 A. Khalafi-Nezhada, A. Parhami, A. Zare and A.R. Moosavi Zare, *J. Iran. Chem. Soc.*, 2008, **5**, 413.
- 22 C.K. Lee, *J. Heterocyclic Chem.*, 2002, **39**, 1207.
- 23 R.R. Sudarshan, *Org. Biomol. Chem.*, 2011, **9**, 3126.

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