

## Zinc Mediated facile Amide Formation : Application to Alkyl, Aryl, Heterocycle, Carbohydrate and Amino Acids

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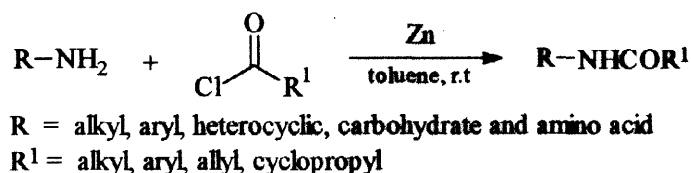
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**Abstract** : Synthesis of alkyl, aryl, heterocyclic, carbohydrate and amino acid amides using activated zinc is described. The recovery and reuse of the zinc makes the procedure more economic. © 1998 Published by Elsevier Science Ltd. All rights reserved.

The amide function is ubiquitous in organic and biological chemistry. Amides are important as pharmaceuticals<sup>1</sup> as well as agrochemicals.<sup>2</sup> They are used as protecting groups in synthetic organic chemistry,<sup>3</sup> because they offer the advantage of very good stability to a wide range of conditions.<sup>4</sup> More recently, they have been found to give high selectivities in carbonyl directed catalysis.<sup>5</sup> Amides are commonly prepared using anhydrides, but in terms of "atom economy" this produces one mole of acid as waste. Therefore, acyl chlorides may be preferable. There are numerous methods for amide formation using acyl chlorides but most of these procedures utilize triethylamine as a base. These methods have their own limitations for aliphatic or benzylic or amino acid amides. Some of the methods use DMF as solvent, which is inconvenient to remove from the reaction mixture (high temperature). Moreover, the use of triethylamine can lead to the problems with epimerization during amino acid amide formation.<sup>6</sup> In this context there is still a need to devise a general method under neutral conditions. Recently we have demonstrated the zinc mediated esterification of acid chloride,<sup>7</sup> and carbamate formation<sup>8</sup> and Friedel Crafts acylation.<sup>9</sup> In continuation of our work in this connection, we wish to report a zinc mediated general method for amide formation.

### Scheme



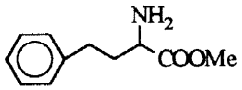
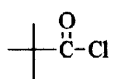
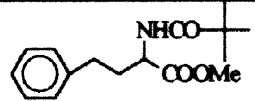
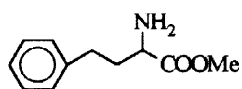
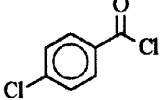
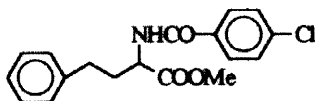
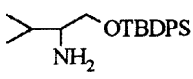
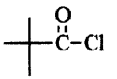
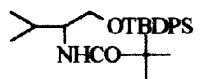
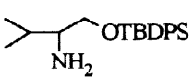
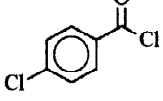
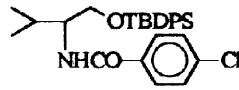
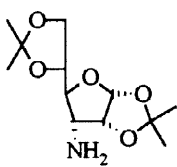
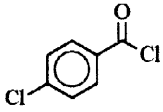
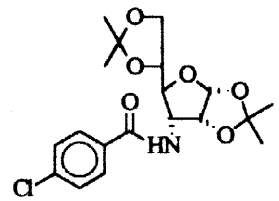
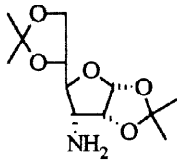
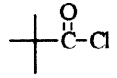
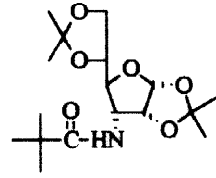
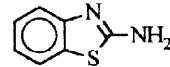
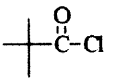
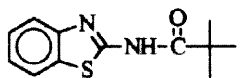
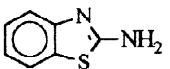
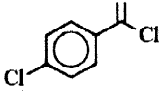
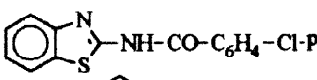
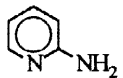
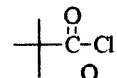
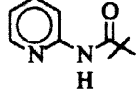
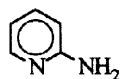
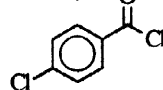
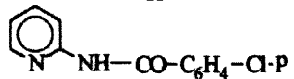
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Table-1 : Preparation of Amides from simple Amines

Entry	Acid Chloride	Amine	Product	Time (min.)	Yield <sup>a</sup>
1.				10	96
2.		$\text{H}_2\text{N}-\text{C}_6\text{H}_5$		8	95
3.	$\text{C}_{15}\text{H}_{31}\text{COCl}$	$\text{H}_2\text{N}-\text{C}_6\text{H}_5$	$\text{C}_{15}\text{H}_{31}\text{CONH}-\text{C}_6\text{H}_5$	8	93
4.	$\text{C}_{15}\text{H}_{31}\text{COCl}$		$\text{C}_{15}\text{H}_{31}\text{CONH}-\text{CH(CH}_3\text{)-C}_6\text{H}_5$	10	94
5.	$\text{C}_{15}\text{H}_{31}\text{COCl}$		$\text{C}_{15}\text{H}_{31}\text{CONH}-\text{C}_6\text{H}_4(\text{OMe})(\text{NO}_2)$	60	97
6.	$\text{C}_{15}\text{H}_{31}\text{COCl}$		$\text{C}_{15}\text{H}_{31}\text{CONH}-\text{C}_6\text{H}_5$	10	83
7.		$\text{H}_2\text{N}-\text{C}_6\text{H}_5$		10	95
8.				13	94
9.				30	92
10.				15	90
11.				35	85
12.				10	92
13.				11	94
14.		$\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{OMe}$		8	93
15.				15	92
16.				14	90

a : All the products exhibited physical and spectral (NMR, IR, Mass) properties in accord with the assigned structure

**Table-2 : Preparation of Amides from Amino acid esters, Carbohydrates and Heterocycles**

Entry	Amine	Acid Chloride	Product	Time (min.)	Yield <sup>a</sup>
1.				10	96
2.				15	89
3.				15	91
4.				20	86
5.				18	91
6.				20	90
7.				15	89
8.				18	90
9.				12	89
10.				15	91

<sup>a</sup> : All the products exhibited physical and spectral (NMR, IR, Mass) properties in accord with the assigned structure

The reaction of acid chlorides with amines in the presence of zinc (metal grade) is remarkably fast and leads to high yields of products. Thus in a typical procedure the acid chloride (10 mmol) and activated zinc powder (10 mmol) is stirred in anhydrous toluene (25 ml) for 10 minutes at room temperature. An anhydrous toluene solution of amine (10 mmol in 15 ml) is added slowly, and the mixture stirred for the stipulated time (see table) at the same temperature. The progress of the reaction is monitored by tlc. After completion of the reaction, it is filtered and the solid washed with ether (100 ml). The combined filtrate is washed with 10% NaHCO<sub>3</sub> solution, water and dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gives the amide (85-98% yield) with high purity.

The reaction proceeds very smoothly at room temperature and within a few minutes. It is interesting though perhaps not surprising to note that electron donating groups facilitate the reaction whereas electron withdrawing groups slow down the reaction. As can be seen from Tables 1 and 2, the application of this method to a variety of different substrates shows the generality and versatility of the reaction. The importance of the procedure can be demonstrated by the tolerance of the acetonide protecting group. It is noteworthy to observe that the protecting groups like TBDPS, ester and acetate in amino acid are unchanged and epimerization (entries 1 and 2; table-2) does not occur under the reaction conditions. This protocol has strengthened the utility of acid chlorides in amide formation which allows application in peptide synthesis. We have also investigated the possibility that zinc could function catalytically, or at least, in less than stoichiometric amounts. However, high yields of amides can only be achieved using 1 eq. of zinc. A control experiment reacting acid chloride with amine in toluene, without zinc does not yield the desired amide.

In conclusion, we have demonstrated a very simple and general method for amide preparation. The present method is applicable to a variety of alkyl, aryl, heterocycles, carbohydrates and amino acids. Another advantage of the present method is that the zinc can be reused. This is remarkable and makes the method economically valuable.

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#### **References :**

1. Okato, K. *J. Appl.* **1984**, *217*, 97.
2. a) Dasilva Termistoteles, D. *J. Appl.* **1983**, *509*, 442. b) *The Agrochemicals Hand Book* 2nd Ed., Royal Society of Chemistry, **1987**.
3. a) Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley, New York, **1991**, p. 327 & 403 b) Wolman, Y. "Protection of the Amino Group," in *The Chemistry of the Amino Group*, S. Patai, Ed., Wiley-Interscience, New York, **1968**, Vol. 4 pp. 669-682.
4. See, for example: Lai, C.K.; Buckanin, R.S.; Chen, S.J.; Zimmerman, D.F.; Sher, F.T. and Berchtold, G.A. *J. Org. Chem.*, **1982**, *47*, 2364.
5. Mu Cullock, B.; Halpern, J.; Thempson, M.R.; Landir, C.R. *Organo metallica*. **1990**, *9*, 1392.
6. a) Woodward, R.B. and 48 Co. Workers. *J. Am. Chem. Soc.*, **1981**, *103*, 3210. b) Scribner, R.M. *Tetrahedron Lett.*, **1976**, *17*, 3853. and references cited therein.
7. Yadav, J.S.; Reddy, G.S.; Srinivas, D. and Himabindu, K. *Synth. Commun.* (In press).
8. Yadav, J.S.; Reddy, G.S.; Reddy, M.M.; Meshram, H.M. *Tetrahedron Lett.*, (In press).
9. Yadav, J.S.; Reddy, G.S.; Reddy, M.M.; Meshram, H.M. *Synth. Commun.*, (In press).