A mild and efficient procedure for the conversion of aromatic carboxylic esters to secondary amides

Revika Arora, Satya Paul, and Rajive Gupta

Abstract: A mild and efficient procedure has been developed for the conversion of aromatic carboxylic esters to secondary amides using reusable Zn dust with microwave heating in the presence of *N*,*N*-dimethylformamide or conventional heating by stirring in an oil bath using THF as solvent. Zn dust can be reused several times after simple washing with dil. HCl and distilled water.

Key words: aromatic carboxylic esters, aromatic primary amines, secondary amides, Zn dust, microwave activation.

Résumé : On a mis au point une méthode douce et efficace de transformer des esters d'acides carboxyliques aromatiques en amides secondaires en faisant appel à un catalyseur de Zn en poudre réutilisable, avec chauffage microonde en présence de *N*,*N*-diméthylformamide ou par chauffage conventionnel à l'aide d'un bain d'huile en utilisant du THF comme solvant. La poudre de Zn peut être réutilisée plusieurs fois après simple lavage avec de l'acide chlorhydrique dilué et de l'eau distillée.

Mots clés : esters d'acides carboxyliques aromatiques, amines primaires aromatiques, amides secondaires, poudre de Zn, activation par micro-ondes.

[Traduit par la Rédaction]

Introduction

The amide unit (1) is one of the most widely occurring functional groups as it represents a key feature in many biologically important natural and synthetic products. Numerous methods are available for the preparation of amides. These include ammonolysis of carboxylic acids and derivatives, thermal decomposition of ammonium salts of carboxylic acids, partial hydrolysis of cyanides, etc. The reaction of carboxylic acids with ammonia or amines to provide the corresponding amides is not a mild, efficient, and cost-effective method (2) as it requires the use of expensive reagents like DCC (3), Fe^{3+}-K10 montmorillonite clay (4), molecular sieves (5), silicon tetrachloride in pyridine (6), polymer-supported HOBT (7), chlorosulfonyl isocyanate (8), PCl_3 (9), etc. The other derivatives of carboxylic acids, particularly acyl halides, acid anhydrides and esters, are most commonly used. However, limitations are associated with the use of acyl halides and acid anhydrides and thus esters are preferred. Reactions of ammonia or amines with acyl halides are highly exothermic. Acid anhydrides, especially cyclic anhydrides, easily form imides with ammonia and primary amines.

Usually, reactions with esters require strongly basic catalysts and (or) high pressure. Although quite a number of methods are reported for the conversion of esters to amides (10), most of these have serious drawbacks with regard to toxicity of the reagent, particularly those involving tin compounds (10*b*, 10*c*), operational simplicity and efficiency. Thus, in recent times other approaches involving *N*-acylimidazoles (11), *N*-acylbenzotriazoles (12), and indium triiodide (13) have been demonstrated that also are not very simple and cost effective. Thus, there is a need to develop a simple, mild, cost-effective, and environment friendly procedure for the preparation of secondary amides. Some microwave-assisted synthesis of amides in the presence of strong bases has been reported (14–16).

In recent years, metal- or metal-salt-catalyzed reactions (17) are finding considerable attention because metals can be removed by simple filtration and be reused several times only by washing with suitable solvents. Among various metals, Zn dust (18) is attracting great attention because of its easy availability, inexpensiveness, and nontoxic nature. Recently, we have reported the use of reusable Zn powder for the Friedel–Crafts acylation (19), the Fries rearrangement (20), and the Williamson ether synthesis (21), and here we wish to report another successful application of Zn dust for the conversion of aromatic carboxylic esters to secondary amides by treatment with primary amines with microwave heating in the presence of *N*,*N*-dimethylformamide or conventional heating by stirring in an oil bath using THF as a solvent (Scheme 1).

Results and discussion

To demonstrate the applicability of this method, a series of secondary amides were prepared in good to excellent yields by taking various substituted methyl benzoates and aromatic primary amines using Zn dust with both microwave (MW) heating (70%–91%) or stirring in an oil bath at 70 °C using THF as the solvent (70%–84%).

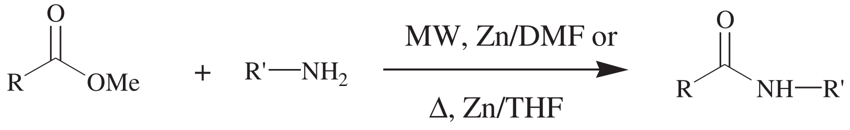
Received 28 March 2005. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 21 September 2005.

R. Arora, S. Paul,[1] and R. Gupta. Department of Chemistry, University of Jammu, Jammu-180 006, India.

[1] Corresponding author (e-mail: paul7@rediffmail.com).

doi: 10.1139/V05-134

Scheme 1.



1 2 3

3a. R = C_6H_5, R' = C_6H_5
3b. R = C_6H_5, R' = 4-$MeOC_6H_4$
3c. R = C_6H_5, R' = 2-$NO_2C_6H_4$
3d. R = C_6H_5, R' = 3-$NO_2C_6H_4$
3e. R = C_6H_5, R' = 4-$NO_2C_6H_4$
3f. R = $CH_2C_6H_5$, R' = C_6H_5
3g. R = $CH_2C_6H_5$, R' = 4-$MeOC_6H_4$
3h. R = $CH_2C_6H_5$, R' = 2-$NO_2C_6H_4$
3i. R = $CH_2C_6H_5$, R' = 3-$NO_2C_6H_4$
3j. R = $CH_2C_6H_5$, R' = 4-$NO_2C_6H_4$
3k. R = 4-ClC_6H_4, R' = C_6H_5
3l. R = 4-ClC_6H_4, R' = 4-$MeOC_6H_4$
3m. R = 4-ClC_6H_4, R' = 2-$NO_2C_6H_4$
3n. R = 4-ClC_6H_4, R' = 3-$NO_2C_6H_4$
3o. R = 4-ClC_6H_4, R' = 4-$NO_2C_6H_4$

Firstly, with MW heating, experimental conditions were carefully monitored to regulate the use of Zn dust, irradiation time, and power level to achieve the optimum conditions. The 1:1 ratio of an ester and amine was the most acceptable one, whereas 0.5 equiv. each of Zn dust and DMF were required to allow the reaction to proceed efficiently. The power level of 640 W was found to be the most acceptable as the low power level gave low yields along with prolonged reaction time, whereas, at a high power level, charring of the reaction mixture was observed. Further, the addition of DMF along with Zn dust in the ratio of 1:1 was very important as without DMF, the reaction did take place, but after 10 s of irradiation, the reaction became violent and charring of the reaction mixture was observed. So the role of DMF is possibly to make the reaction medium homogeneous and absorb some of the extra energy so that the reaction proceeds safely (every reaction was repeated four times to ensure that the reaction proceeds safely). Further, the amount of Zn dust to be used was examined. If a lesser amount of Zn dust was used, the product yield was low and with more amounts, the reaction became violent, which could burn the reaction mixture. The work-up procedure is simple, involving dilution with DMF and filtration followed by the addition of crushed ice.

With conventional heating (stirring in an oil bath), the optimum conditions selected are: for 5 mmol of an ester and amine each, 2.5 mmol of Zn dust, 10 mL of THF as the solvent, and 70 °C as the reaction temperature. When compared with MW heating, the yields of the products using oil-bath heating were lower and also the reaction times were longer (Table 1).

To see whether the formation of amides was catalyzed by commercially available Zn dust, the reaction of methyl benzoate (5 mmol) with aniline (5 mmol) was carried out in the absence of Zn dust with MW heating using DMF (2.5 mmol) or by stirring in an oil bath at 70 °C using THF (10 mL) as the solvent (product **3a**, Table 1). It was found that under conditions similar to those described for Zn dust, no reaction was observed on TLC (2 min under MW irradiation and 16 h in the case of oil-bath heating). Thus, Zn dust catalyzes the conversion of carboxylic esters into secondary amides.

Since the reactions were not carried out under an inert atmosphere and unpurified commercially available zinc dust was used, there may be a possibility of the formation of ZnO, which may catalyze the reaction. To see whether the reaction was catalyzed by Zn or ZnO, we carried out the reaction in the case of product **3a** using 0.5 equiv. of ZnO, instead of Zn dust, under the same conditions as described for the microwave and oil-bath heating experiments. It was found that we were not able to isolate the desired product after the final work-up (10 min under MW irradiation and 16 h using oil-bath heating). This observation clearly indicated that the formation of secondary amides was catalyzed by Zn dust.

The Zn powder can be reused six times after simple washing with diethyl ether and dilute HCl without much loss of activity, thus rendering the process more economical (Table 2).

To check the possibility of specific nonthermal MW effects for the Zn catalyzed conversion of aromatic carboxylic esters to secondary amides, we carried out the reaction of aniline with methyl benzoate (product **3a**, Table 1) using a preheated oil bath at 135 °C (temperature measured at the end of the reaction in the MW oven) for 2 min, keeping all other conditions identical as for the MW experiment. It was found that no reaction took place (TLC), although a yield of 60% was obtained when the reaction time was extended up to 12.5 h. This observation suggests that the effect of MW irradiation is not purely thermal. The results are summarized in Table 3.

Experimental

Melting points were determined on a Buchi melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Bruker DPX-200 NMR spectrometer (200 MHz) in $CDCl_3$, with tetramethylsilane as the internal standard, and IR spectra were recorded using a KBr disc on a FT-Bruker Vector 22 spectrophotometer. The mass spectral data

Table 1. Synthesis of secondary amides from aromatic carboxylic esters and aromatic primary amines in the presence of Zn dust.

	MW[a]		Oil bath[b]		
Product	Time (min)	Yield[c] (%)	Time (h)	Yield[c] (%)	mp/lit. mp (°C)
3a	2	90	16	82	160–162/162 (22)
3b	1	91	12	82	152–154/154 (22)
3c	8	78	26	70	96–98/98 (22)
3d	2	90	11	84	155–157/158 (22)
3e	4	89	18	80	195–197/199 (22)
3f	6	88	15	80	113–115/117 (22)
3g	4	89	12	79	122–124/124 (23)
3h	8	70	30	64	81–84/84 (24)
3i	6	89	20	82	124 to 125[d]
3j	4	78	22	73	183 to 184[d]
3k	1	90	12	81	193–195/195 (22)
3l	1	88	6	80	153 to 154/155 (25)
3m	5	78	20	70	88–90[d]
3n	1	88	7	80	130 to 131[d]
3o	1.25	84	6	80	168 to 169/170 (26)

[a] Reactions were carried out with a pulse of 15 s (5 s cooling time) in the presence of DMF.

[b] Reactions were carried out by stirring in an oil bath at 70 °C.

[c] Isolated yield from three experimental runs.

[d] Spectral data of some compounds. **3i**: IR (ν_{max} in cm^{-1}, KBr): 3344 (NH), 1706 (C=O). ^1H NMR ($CDCl_3$) δ: 3.90 (s, 2H, CH_2), 6.90–8.30 (m, 9H, H_{arom}), 10.20 (bs, 1H, NH). *m/z* (%): 256 (0.2), 211 (8.3), 166 (1.7), 132 (4.6), 123 (8.1), 92 (100), 65 (70.9). **3j**: IR (ν_{max} in cm^{-1}, KBr): 3340 (NH), 1700 (C=O). ^1H NMR ($CDCl_3$) δ: 3.82 (s, 2H, CH_2), 6.92–8.20 (m, 9H, H_{arom}), 10.25 (bs, 1H, NH). *m/z* (%): 256 (0.4), 211 (7.2), 166 (1.3), 132 (4.2), 123 (8.3), 92 (98), 65 (68.2). **3m**: IR (ν_{max} in cm^{-1}, KBr): 3342 (NH), 1701 (C=O). ^1H NMR ($CDCl_3$) δ: 6.80–8.20 (m, 8H, H_{arom}), 10.10 (bs, 1H, NH). *m/z* (%): 279 (1.4), 156 (72.7), 139 (100), 111 (42), 92 (32.5), 65 (34.7). **3n**: IR (ν_{max} in cm^{-1}, KBr): 3340 (NH), 1702 (C=O). ^1H NMR ($CDCl_3$) δ: 6.90–8.10 (m, 8H, H_{arom}), 10.00 (bs, 1H, NH). *m/z* (%): 279 (1.3), 156 (70.2), 139 (99), 111 (44), 92 (36), 65 (32.1).

Table 2. Reuse studies of Zn dust for the synthesis of secondary amides.

	MW		Oil bath	
No. of uses	Time[a] (min)	Yield[b] (%)	Time[a] (h)	Yield[b] (%)
1	2	90	16	82
2	2.5	89	16.5	80
3	3	85	18	78
4	4.5	82	19	75
5	5	78	21.5	72
6	6	72	22	64

[a] Time at which maximum yield was obtained.

[b] Isolated yield from three experimental runs.

Table 3. Comparison of microwave activation (MW) and thermal heating (Δ) in the case of aniline (5 mmol) and methyl benzoate (5 mmol) using Zn dust (2.5 mmol) and DMF (2.5 mmol) (power = 640 W).

Method	Time (min)	Temp. (°C)[a]	Yield (%)[b]
MW	2	133–135	90
Δ	2	135	No reaction
Δ	12.5[c]	135	60

[a] The final temperature was measured by immersing the glass thermometer into the reaction mixture at the end of exposure during the MW experiment and was approximate temperature range.

[b] Isolated yield from three experimental runs.

[c] Time reported in hours.

was obtained on a JEOL JMS-D 300 spectrometer. The reactions were monitored by TLC. For the microwave irradiation experiments described in the following, a conventional (unmodified) household microwave oven equipped with a turntable was used (LG Little Chef MS 194 W operating at 2450 MHz having a maximum output of 800 W).

General procedure for the synthesis of secondary amides in the presence of Zn dust

Microwave heating approach

To a mixture of the aromatic carboxylic ester (5 mmol), the appropriate aromatic amine (5 mmol), and Zn dust (2.5 mmol) in a 50 mL borosil beaker, DMF (2.5 mmol) was added. The reaction mixture was mixed thoroughly with a glass rod (10 s) and then irradiated in a microwave oven for an appropriate time (Table 1) at 640 W. After cooling, DMF (5 mL) was added and the reaction mixture was filtered. To the filtrate, ice-cold water (100 mL) was added and the product extracted with ethyl acetate (3 × 15 mL). The combined extracts were washed with water and dried over anhydrous sodium sulfate. The product was obtained after the removal of the solvent under reduced pressure followed by crystallization from EtOAc – petroleum ether or by passing through a column of neutral alumina and elution with petroleum ether.

Oil-bath heating approach

To a mixture of the aromatic carboxylic ester (5 mmol), the appropriate aromatic amine (5 mmol), and Zn dust

(2.5 mmol) in a round-bottomed flask (50 mL), THF (10 mL) was added. The round-bottomed flask was fitted with a reflux condenser and the reaction mixture was stirred at 70 °C in an oil bath for an appropriate time (Table 1). After completion (monitored by TLC), the reaction mixture was cooled and filtered. The THF was removed under reduced pressure and the product was obtained by the same procedure as described for the MW experiment.

The structures of the products were confirmed by ^{1}H NMR, IR, mass spectral data, and by comparison with authentic samples.

Conclusion

In conclusion, we have developed an efficient procedure for the synthesis of secondary amides using Zn dust with MW heating in the presence of DMF or by stirring in an oil bath using THF as a solvent. The salient features of our method is that it is simple, rapid, economic, general, and environment friendly, and Zn dust can be reused several times without much loss of activity. This method could be a very efficient alternative to other existing methods.

Acknowledgements

The authors thank the Jammu and Kashmir State Council, the Department of Science and Technology, and the Jammu and Kashmir Government for providing financial assistance and awarding a project fellowship to Revika Arora.

References

1. W.-C. Chou, C.-W. Tan, S.-F. Chen, and H. Ku. J. Org. Chem. **63**, 10 015 (1998).
2. (*a*) J. March. *In* Advanced organic chemistry. 4th ed. John Wiley and Sons, New York. 1992. pp. 417–425; (*b*) A. Vogel. *In* Textbook of practical organic chemistry. Longman Scientific and Technical and Wiley, New York. 1989. pp. 708–710; (*c*) G.V.M. Sharma, T. Shekharam, and V. Upender. Tetrahedron, **46**, 5665 (1990).
3. S.-T. Chen, S.-H. Wu, and K.-T. Wang. Synthesis, 37 (1989).
4. K.V.N.S. Sriniwas and B. Das. J. Org. Chem. **68**, 1165 (2003).
5. J. Cossy and C. Pale-Grosdemange. Tetrahedron Lett. **30**, 2771 (1989).
6. T.-H. Chan and L.T.L. Wong. J. Org. Chem. **34**, 2766 (1969).
7. K. Dendrinos, J. Jeong, W. Huang, and A.G. Kalivretenos. Chem. Commun. 499 (1998).
8. K.S. Keshavamurthy, Y.D. Vankar, and D.N. Dhar. Synthesis, 506 (1982).
9. H.W. Grimmel, A. Guenther, and J.F. Morgan. J. Am. Chem. Soc. **68**, 539 (1946).
10. (*a*) H. Yazawa, K. Tanaka, and K. Kariyone. Tetrahedron Lett. **15**, 3995 (1974); (*b*) W.-B. Wang and E.J. Roskamp. J. Org. Chem. **57**, 6101 (1992); (*c*) W.-B. Wang, J.A. Restituyo, and E.J. Roskamp. Tetrahedron Lett. **34**, 7217 (1993).
11. (*a*) G.M. Strunz and H. Finlay. Tetrahedron, **50**, 11 113 (1994); (*b*) N. Raju, K. Ramalingam, and D.P. Nowotnik. Tetrahedron, **48**, 10 233 (1992).
12. A.R. Katritzky, H.-Y. He, and K. Suzuki. J. Org. Chem. **65**, 8210 (2000), and refs. cited therein.
13. B.C. Ranu and P. Dutta. Synth. Commun. **33**, 297 (2003).
14. R.S. Varma and K.P. Naicker. Tetrahedron Lett. **40**, 6177 (1999).
15. F.-Z. Zradni, J. Hamelin, and A. Derdour. Synth. Commun. **32**, 3525 (2002).
16. L. Perreux, A. Loupy, and M. Delmotte. Tetrahedron, **59**, 2185 (2003).
17 (*a*) J.K. Shorrock, J.H. Clark, K. Wilson, and J. Chisem. Org. Process Res. Dev. **5**, 249 (2001); (*b*) C. Baleizao, A. Corma, H. Garcia, and A. Leyva. Chem. Commun. 606 (2003); (*c*) E.B. Mobofu, J.H. Clark, and D.J. Macquarrie. Green Chem. **3**, 23 (2001).
18. (*a*) S.D. Burke and R.L. Danheiser. Handbook of reagents for organic syntheis: Oxidizing and reducing agents. John Wiley and Sons, Chichester. 1999. pp. 504–510; (*b*) M.S.R. Murty, B. Jyothirmai, P.R. Krishna, and J.S. Jadav. Synth. Commun. **33**, 2483 (2003); (*c*) J.S. Yadav, B.V.S. Reddy, G. Kondaji, R.S. Rao, and S.P. Kumar. Tetrahedron Lett. **43**, 8133 (2002); (*d*) Y. Ogawa, A. Saiga, M. Mori, T. Shibata, and K. Takegi. J. Org. Chem. **65**, 1031 (2000).
19. S. Paul, P. Nanda, R. Gupta, and A. Loupy. Synthesis, 2877 (2003).
20. S. Paul and M. Gupta. Synthesis, 1789 (2004).
21. S. Paul and M. Gupta. Tetrahedron Lett. **45**, 8825 (2004).
22. N.K. Vishnoi. *In* Advanced practical organic chemistry. 2nd ed. 1996. Vikas Publishing House Pvt. Ltd., New Delhi.
23. V. Joshi, S.S. Jalisatgi, and M.I. Hari. Indian J. Chem. Sect. B, **25B**, 83 (1986).
24. T. Jan, D. Floner, and C. Moinet. Electrochim. Acta, **42**, 2075 (1997).
25. A.F.M. Fahmy, G. Hosni, and H. Abdel Fadeel. Indian J. Chem. Sect. B, **14B**, 871 (1976).
26. A.F.M. Fahmy, N.F. Aly, and M.H. Arief. Indian J. Chem. Sect. B, **16B**, 697 (1978).

This article has been cited by:

1. Xiaoya Li, Zhengkai Li, Hang Deng, Xiangge Zhou. 2013. An efficient protocol for the preparation of amides by copper-catalyzed reactions between nitriles and amines in water. *Tetrahedron Letters* **54**:18, 2212-2216. [CrossRef]
2. Subhash Chandra Ghosh, Joyce S. Y. Ngiam, Christina L. L. Chai, Abdul M. Seayad, Tuan Thanh Dang, Anqi Chen. 2012. Iron-Catalyzed Efficient Synthesis of Amides from Aldehydes and Amine Hydrochloride Salts. *Advanced Synthesis & Catalysis* **354**:8, 1407-1412. [CrossRef]
3. P SIRISHA, SUHAS PEDNEKAR, ANANT R KAPDI, MINAL NAIK. 2011. Facile solvent-free one-pot synthesis of pyranobenzopyrans and their derivatives. *Journal of Chemical Sciences* **123**:5, 667-672. [CrossRef]
4. C. Liana Allen, Jonathan M. J. Williams. 2011. Metal-catalysed approaches to amide bond formation. *Chemical Society Reviews* **40**:7, 3405. [CrossRef]
5. M. S. R. Murty, Rayudu Venkateswara Rao, Kesur R. Ram, N. Rami Reddy, J. S. Yadav, B. Sridhar. 2010. Zinc-Mediated Facile and Efficient Chemoselective S -Alkylation of 5-Aryl-1,3,4-oxadiazole-2-thiols in the Absence of Base. *Synthetic Communications* **40**:19, 2914-2921. [CrossRef]
6. M. S. R. Murty, Kesur R. Ram, Rayudu Venkateswara Rao, J. S. Yadav. 2010. Efficient and Novel Synthesis of Benzoxazole Derivatives in the Presence of Zinc Dust Under Solvent-Free Conditions. *Synthetic Communications* **40**:19, 2844-2849. [CrossRef]
7. Dongsik Yang, Mihyun Kwon, Yujin Jang, Heung Bae Jeon. 2010. A convenient and efficient synthesis of C-carbamoyl-1,2,3-triazoles from alkyl bromide by a one-pot sequential addition: conversion of ester to amide using Zr(Ot-Bu)4. *Tetrahedron Letters* **51**:28, 3691-3695. [CrossRef]
8. Revika Arora, Satya Paul, Rajive Gupta. 2006. A Mild and Efficient Procedure for the Conversion of Aromatic Carboxylic Esters to Secondary Amides. *ChemInform* **37**:14. . [CrossRef]