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Efficient method for the direct preparation of amides from carboxylic acids using tosyl chloride under solvent-free conditions

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Abstract—A simple, clean and highly efficient solvent-free procedure for the preparation of primary, secondary, tertiary and aromatic amides is described from the direct reaction of carboxylic acids and silica-supported ammonium salts, triethylamine (TEA) and tosyl chloride (TsCl) as condensing agent. The reaction proceeds rapidly in high yields at room temperature.

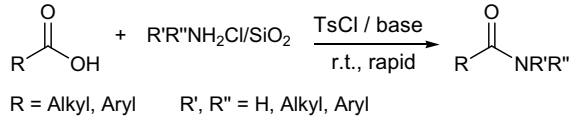
1. Introduction

The amide functional group is important in organic and biological chemistry. Amides are important as pharmaceuticals[1] as well as agrochemicals.[2] The preparation of amides from their corresponding carboxylic acids is an important and well-known transformation in organic synthesis.[3,4] In general, the formation of carboxamides from carboxylic acids requires activation of the carboxyl group. Carboxylic acid activation can be achieved either by conversion into more reactive functional groups such as acyl halide, anhydride, acyl azide or by in situ activation by coupling reagents such as *N*,*N*-dicyclohexylcarbodiimide (DCC),[5] $TiCl_4$,[6] activated phosphate,[7] $Sn[N(TMS)_2]_2$,[8] *N*-halosuccinimide/Ph_3P,[9] Cl_3CCN/Ph_3P,[10] $ArB(OH)_2$,[11] Lawesson's reagent,[12] Boc-Odhbt (*tert*-butyl-3-(3,4-dihydrobenzotriazin-4-one)yl carbonate),[13] $(R_2N)_2Mg$,[14] SO_2ClF,[15] chlorosulfonyl isocyanate[16] and 2-mercaptopyridine-1-oxide based uronium salts.[17]

The application of solvent-free reactions in organic chemistry has been explored extensively within the last decade. Solvent-free conditions often lead to a remarkable decrease in reaction time, increased yields, easier work up matching with green chemistry protocols, and may enhance the regio- and stereoselectivity of reactions.[18] More recently, there have been several reports that describe the preparation of secondary and tertiary amides under solvent-free conditions.[19–21] However, to the best of our knowledge, there is no report of the direct synthesis of all types of amides including primary, secondary, tertiary and aromatic, from carboxylic acids by this means.

Along with our previous work on the direct preparation of amides[22d] and in extension of our previous studies on the application of solvent-free techniques in organic synthesis,[22a–h] we describe here the first procedure for the direct synthesis of primary, secondary, tertiary and aromatic amides by direct reaction of carboxylic acids with ammonium salts of various amines in the presence of TsCl under solvent-free conditions (Scheme 1).

Tosyl chloride was chosen because previously it has been applied as a very efficient condensing agent for the



Scheme 1.

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synthesis of anhydrides,[23a] esters[23b] and amides.[23b] However, this coupling reagent has been used before, for the synthesis of amides in solution, although its application was restricted to the synthesis of non-primary amides and in long reaction times.[23b]

The use of ammonium salts instead of amines has several advantages including (i) ammonium salts of gaseous or volatile amines such as ammonia, methylamine and dimethylamine, etc. can be easily used; (ii) amines are hazardous compounds and their use as ammonium salts can decrease environmental pollution from a green chemistry point of view and (iii) amines are powerful nucleophiles, liable to react with TsCl, thus their direct use can lead to side products.

Firstly, we examined the synthesis of benzamide as a model reaction thus, to a well ground mixture of benzoic acid (1 mmol), ammonium chloride (2 mmol) and tosyl chloride (1 mmol) was added triethylamine (4 mmol), however no reaction was achieved even after a prolonged reaction time. Heating the reaction mixture even up to 100 °C had little effect. To obtain optimized reaction conditions, the effect of different ammonia sources on the reaction progress was studied. Several ammonium salts such as ammonium acetate, ammonium chloride, ammonium sulfate, ammonium carbonate and NH_4Cl/SiO_2 were used for this purpose. The results showed that NH_4Cl/SiO_2 is the most suitable source for in situ generation of ammonia. Using NH_4Cl/SiO_2, the reaction proceeded rapidly, at room temperature. In another study, the effect of various bases was investigated, such as 4-dimethylaminopyridine (DMAP), tributylamine, 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), 1,5-diazabicyclo [4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO), K_2CO_3 and MgO. In general, the liquid bases were more efficient than solid bases but among the liquid bases TEA was the most efficient. The results for amidation of various carboxylic acids are summarized in Table 1.

To investigate the generality and versatility of this method, the reaction was extended to various structurally diverse carboxylic acids. As is clear from Table 1, the reactions proceeded rapidly and cleanly at room temperature, and the carboxamides were obtained in good to excellent yields. In the case of aromatic carboxylic acids, the presence of electron-releasing groups on the aromatic ring improved the reaction yields. No Michael addition side products were observed when crotonic acid and cinnamic acid (Table 1, entries 10 and 26) were used. The reactions of dicarboxylic acids such as malonic and terephthalic acids (Table 1, entries 27 and 28) with 2 equiv of ammonium salts afforded the bis-carboxamides as the sole products. The reaction of the salt of *tert*-butylamine with benzoic acid provided *N*-*tert*-butyl benzamide in good yield (75%). When the amidation reaction was carried out with (*R*)-(−)-mandelic acid, the corresponding enantiomerically pure primary amide was isolated (Table 1, entry 16).

Table 1. Direct preparation of amides from carboxylic acids and silica-supported ammonium salts using TsCl and TEA under solvent-free conditions

Entry	Acid	R_2NH_2Cl/SiO_2[a]	Product	Yield[b] (%)	Mp, °C (lit.)
1	$CH_3(CH_2)_4CO_2H$	NH_4Cl	$CH_3(CH_2)_4CONH_2$	90	100–102 (101)[24]
2	$PhCO_2H$	NH_4Cl	$PhCONH_2$	83	127–129 (129.1)[24]
3	$PhCH_2CO_2H$	NH_4Cl	$PhCH_2CONH_2$	90	154–156 (157)[24]
4	*p*-$O_2NC_6H_4CO_2H$	NH_4Cl	*p*-$O_2NC_6H_4CONH_2$	75	200–202 (201.5)[24]
5	*m*-$O_2NC_6H_4CO_2H$	NH_4Cl	*m*-$O_2NC_6H_4CONH_2$	80	137–139 (141)[24]
6	(Boc)$NHCH_2CO_2H$	NH_4Cl	(Boc)$NHCH_2CONH_2$	85	84–86 (87)[25]
7	*p*-$MeOC_6H_4OCH_2CO_2H$	NH_4Cl	*p*-$MeOC_6H_4OCH_2CONH_2$	90	114–116 (114–116)[26]
8	$PhOCH_2CO_2H$	NH_4Cl	$PhOCH_2CONH_2$	90	99–101 (101.5)[24]
9	Nicotinic acid	NH_4Cl	Nicotinamide	75	127–129 (129)[24]
10	$PhCH{=}CHCO_2H$	NH_4Cl	$PhCH{=}CHCONH_2$	80	147–149 (148.5)[24]
11	$PhCONHCH_2CO_2H$	NH_4Cl	$PhCONHCH_2CONH_2$	90	139–141 (141)[24]
12	*p*-$MeC_6H_4CO_2H$	NH_4Cl	*p*-$MeC_6H_4CONH_2$	85	157–159 (160)[24]
13	*m*-$MeC_6H_4CO_2H$	NH_4Cl	*m*-$MeC_6H_4CONH_2$	80	93–95 (95)[24]
14	*p*-$BrC_6H_4CO_2H$	NH_4Cl	*p*-$BrC_6H_4CONH_2$	80	188–189 (189.5)[24]
15	*m*-$BrC_6H_4CO_2H$	NH_4Cl	*m*-$BrC_6H_4CONH_2$	77	154–155 (155.3)[24]
16	(*R*)-(−)-$PhCH(OH)CO_2H$	NH_4Cl	(*R*)-(−)-$PhCH(OH)CONH_2$	75[c]	122–123 (123–124)[17]
17	$PhCO_2H$	$MeNH_3Cl$	PhCONHMe	82	75–77 (76–78)[27]
18	$PhCO_2H$	Me_2NH_2Cl	$PhCONMe_2$	77	43–45 (41–45)[27]
19	$PhCO_2H$	$PhNH_3Cl$	PhCONHPh	85	161–163 (163)[24]
20	Nicotinic acid	$MeNH_3Cl$	*N*-Methyl nicotinamide	75	104–106 (102–108)[27]
21	Nicotinic acid	Et_2NH_2Cl	*N*,*N*-Diethyl nicotinamide	70	25–27 (24–26)[24]
22	*p*-$O_2NC_6H_4CO_2H$	$PhNH_3Cl$	*p*-$O_2NC_6H_4CONHPh$	78	214–216 (216)[24]
23	*m*-$MeC_6H_4CO_2H$	Et_2NH_2Cl	*m*-$MeC_6H_4CONEt_2$	76	110–112 (111)[27]
24	*p*-$EtOC_6H_4CO_2H$	$PhNH_3Cl$	*p*-$EtOC_6H_4CONHPh$	83	168–170 (170)[28]
25	$PhCO_2H$	Me_3CNH_3Cl	$PhCONHCMe_3$	75	134–135 (135.1)[15]
26	$MeCH{=}CHCO_2H$	$PhNH_3Cl$	$MeCH{=}CHCONHPh$	80	113–115 (114)[16]
27	$HO_2CCH_2CO_2H$	$PhNH_3Cl$	$PhNHCOCH_2CONHPh$	75	222–224 (223–225)[24]
28	*p*-$HO_2CC_6H_4CO_2H$	Et_2NH_2Cl	*p*-$Et_2NCOC_6H_4CONEt_2$	77	126–127 (127)[24]

[a] $R_2NH_2Cl:SiO_2$ (4 mmol:1 g).
[b] Pure isolated yields.
[c] $[\alpha]_D^{20}$ −72 (*c* 1.6, acetone); lit.[29] $[\alpha]_D^{20}$ −73 (*c* 1.6, acetone).

Table 2. Effect of various solvents on the amidation reaction of benzoic acid

Entry	Solvent	*t* (min)	Yield[a] (%)
1	MeCN	60	40
2	CH_2Cl_2	60	20
3	Et_2O	60	10
4	DMF	60	5
5	EtOAc	60	2
6	Me_2CO	60	5

[a] Isolated yields.

In another study, the reaction was examined in several solvents to compare the reaction times and yields in both solution and solvent-free conditions. Therefore, to a solution of benzoic acid (1 mmol), ammonium chloride (2 mmol) and tosyl chloride (1 mmol) in different solvents (10 ml) was added triethylamine (4 mmol). Lower yields were obtained and longer reaction times were needed in all cases. The results are depicted in Table 2.

We suggest that initially a tosyl carboxylate is formed which then reacts with amine generated from the reaction of ammonium salt and TEA, providing the carboxamide. To explore the formation of acid tosylates during the reaction, a mixture of benzoic acid, tosyl chloride and silica gel were reacted with TEA. TLC monitoring indicated the formation of tosyl benzoate as identified with an authentic sample.[23b] Moreover, no benzoic anhydride was observed.

In summary, this present procedure provides an efficiently clean and a very simple methodology for the direct preparation of amides from carboxylic acids at room temperature, using silica-supported ammonium salts as very cheap and safe amine sources, with good yields under solvent-free conditions. This method can be easily applied to volatile or gaseous amines and can be applied for the preparation of all sorts of amides.

2. Silica gel-supported ammonium salts

Silica gel (5.0 g, Merck Kieselgel 60, particle size 0.063–0.200 mm, 70–230 mesh) was mixed with a solution of the ammonium salt (20 mmol), in water (5.0 mL). Evaporation of water under reduced pressure gave a dry white powder, which was used as the amine source.

3. General procedure

In a test tube, filled with a well ground mixture of carboxylic acid (1 mmol) silica-supported ammonium salt (2 equiv) and TsCl (1 equiv) was added 0.4 g of triethylamine and mixed by a spatula. After 1 min, the reaction mixture was added to 50 mL ethyl acetate, filtered and the filtrate was washed with 0.02 N solution of HCl (2×50 mL). The aqueous layer was extracted twice with ethyl acetate (25 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated. The crude product was purified by column chromatography on silica gel using *n*-hexane–ethyl acetate (1:1) to obtain a pure product.

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References and notes

1. Negwer, M.; Scharnow, H.-G. *Organic-Chemical Drugs and their Synonyms*, 8th ed.; Wiley-VCH, 2001, 4254.
2. Milne, G. W. A. *CRC Handbook of Pesticides*; CRC Press, ISBN 0849324475, 1995.
3. (a) March, J. In *Advanced Organic Chemistry*, 5th ed.; John Wiley and Sons: New York, 2001; pp 508–510; (b) *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 6; pp 381–417.
4. Brown, W. *Idrugs* **1999**, *2*, 1059–1068.
5. Sheehan, J. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067–1068.
6. Wilson, J. D.; Hobbs, C. F.; Wengaten, H. *J. Org. Chem.* **1970**, *15*, 1542–1545.
7. Yasuhara, T.; Nagaka, Y.; Tomioka, K. *J. Chem. Soc. Perkin Trans. 1* **2000**, 2901–2902.
8. Burnell-Curty, C.; Roskamp, E. J. *Tetrahedron Lett.* **1993**, *34*, 5193–5196.
9. Froyen, P. *Synth. Commun.* **1995**, *25*, 959–968.
10. Jang, D. O.; Park, D. J.; Kim, J. *Tetrahedron Lett.* **1999**, *40*, 5323–5326.
11. Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196–4199.
12. Thorsen, J. D.; Andersen, T. P.; Pedersen, U.; Yde, B.; Laweson, S. *Tetrahedron* **1985**, *41*, 5633–5636.
13. Basel, Y.; Hassner, A. *Tetrahedron Lett.* **2002**, *43*, 2529–2533.
14. Sanchez, R.; Vest, G.; Depres, L. *Synth. Commun.* **1989**, *19*, 2909–2913.
15. Olah, G. A.; Narang, S. C.; Luna, A. G. *Synthesis* **1980**, *8*, 661–662.
16. Keshavamurthy, K. S.; Vankar, Y. D.; Dhar, D. N. *Synthesis* **1982**, 506–508.
17. Bailen, M. A.; Chinchilla, R.; Dodsworth, D. J.; Najera, C. *Tetrahedron Lett.* **2000**, *41*, 9809–9813.
18. (a) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025–1074; (b) Tanaka, K. *Solvent-free Organic Synthesis*; Wiely-VCH, GmbH and KGaA: Weinheim, 2004.
19. Baldwin, B. W.; Hirose, T.; Wang, Z. H. *Chem. Commun.* **1996**, 2669–2670.
20. Varma, R. S.; Naicker, K. P. *Tetrahedron Lett.* **1999**, *40*, 6177–6180.
21. Perreux, L.; Loupy, A.; Volatron, F. *Tetrahedron* **2002**, *58*, 2155–2162.
22. (a) Khalafi-Nezhad, A.; Zarea, A.; Soltani Rad, M. N.; Mokhtari, B.; Parhami, A. *Synthesis* **2005**, 419–424; (b) Khalafi-Nezhad, A.; Mokhtari, B. *Tetrahedron Lett.* **2004**, *45*, 6737–6739; (c) Khalafi-Nezhad, A.; Soltani Rad, M. N.; Khoshnood, A. *Synthesis* **2004**, 583–589; (d) Khalafi-Nezhad, A.; Mokhtari, B.; Soltani Rad, M. N. *Tetrahedron Lett.* **2003**, *40*, 7325–7328; (e) Khalafi-Nezhad, A.; Soltani Rad, M. N.; Hakimelahi, G. H. *Helv. Chim. Acta* **2003**, *86*, 2396–2403; (f) Khalafi-Nezhad, A.; Hashemi, A. *Iran. J. Chem. Chem. Eng.* **2001**, *20*, 9–12; (g) Khalafi-Nezhad, A.; Fareghi Alamdari, R.; Zekri, N. *Tetrahedron*

2000, *56*, 7503–7506; (h) Khalafi-Nezhad, A.; Hashemi, A. *J. Chem. Res.* **1999**, *12*, 720–721.
23. (a) Kazemi, F.; Sharghi, H.; Naseri, M. A. *Synthesis* **2004**, 205–207; (b) Jaszay, Z. M.; Petnehazy, I.; Tock, L. *Synthesis* **1989**, 745–747.
24. CRC, Handbook of Tables for Organic Compounds Identification, 54th and 80th.
25. Chen, S. T.; Wu, S. H.; Wang, K. T. *Synthesis* **1989**, 37–38.
26. This product is available from Maybridge PLC: Trevillett, Tintagel, Cornwall, England. PL34 0HW. CAS# 30893-64-2.
27. http://www.acros.be.
28. Shreiner, R. L.; Fuson, R. C.; Curtin, D. Y.; Morrill, T. C. In *The Systematic Identification of Organic Compounds*; John Wiely and Sons, 1980.
29. *Dictionary of Organic Compounds*; Chapman and Hall: New York, 1982.