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Report

Phosphorus Trichloride-Mediated and Microwave-Assisted Synthesis of a Small Collection of Amides Bearing Strong Electron-Withdrawing Group Substituted Anilines

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The amide bond is a fundamental linkage tool in organic synthesis and, especially, in medicinal chemistry, because of its metabolic stability and its propensity for establishing intermolecular hydrogen bonds with biological targets.

A plethora of reactants and synthetic procedures for the formation of the amide bond are known. Among these, we have placed our attention on phosphorus trichloride (PCl_3) as a dehydrating agent in the condensation of electron-withdrawing group (EWG) containing aniline derivatives with carboxylic acids. The presence of strong EWGs on the aniline ring reduces the nucleophilic behavior of nitrogen atom, rendering some classical condensation methods, for example activated ester strategies, scarcely efficient. The use of PCl_3 as condensing agent can be a good solution to overcome this poor reactivity. Usually, PCl_3-based procedures entail high temperature heating for, at least, 1−3 h using inert high-boiling solvents, such as toluene, xylene, and chlorobenzene.[1] The necessity of speeding up this condensation process and increasing the throughput led us to envisage the advantages of microwave (MW) irradiation: the more efficient "in core" heating, the possibility of using lower boiling point solvents under pressure in sealed vessels and the easy adaptation to automated sequential synthesis.

With the aim of fixing the optimal reaction conditions, such as heating times and the amount of PCl_3, first condensation trials were performed using 4-trifluoromethylaniline and benzoic acid as reactants with various solvents (Scheme 1 and Table 1). In chlorobenzene (PhCl), the best MW-absorbing solvent among the aforementioned ones,[2] the expected amide **1** was obtained in very high yield by a ten-minute irradiation using 1 equiv of PCl_3 (entry 2). The compound was isolated in high purity by quick and simple liquid/liquid extraction using saturated sodium bicarbonate and ethyl acetate. Other solvents were investigated following the above-described reaction conditions. Toluene (entry 4) led to moderate yield, but a silica gel cartridge was necessary to eliminate some impurities. Moreover, toluene is not a good MW-absorbing solvent. Dimethylformamide (DMF) and dimethylsulfoxide (DMSO), entries 6 and 7, respectively, yielded complex reaction mixtures. Although THF gave satisfactory results (entry 5), the presence of a not-UV visible side-product required a more accurate purification step. The proposed structure of this byproduct **2** might have arisen from the opening of the THF ring by the reaction of PCl_3 at high temperature (Figure 1).[3] Acetonitrile (entry 8) was shown to be the best substitute of chlorobenzene, having better MW-absorbing efficiency and lower boiling point, thus facilitating

Table 1. Set-up of Condensation Conditions for the Preparation of **1**

entry	solvent	equiv of PCl_3	time (min)	yield[a]
1	PhCl	1.5	10	99%
2	PhCl	1.0	10	99%
3	PhCl	0.5	10	97%
4	toluene	1.0	10	65%[b]
5	THF	1.0	10	85%[b]
6	DMF	1.0	10	mixture
7	DMSO	1.0	10	decomp.
8	CH_3CN	1.0	10	99%
9	PhCl	1.0	5	99%
10	CH_3CN	1.0	5	99%

[a] Isolated yield. Purification by liquid/liquid extraction. UPLC-MS and ^1H NMR purity not lower than 95%. [b] Purification by silica gel cartridge.

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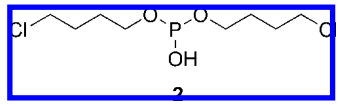
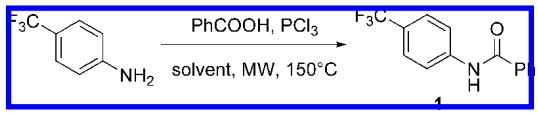


2

Figure 1. Side-product **2**.

Scheme 1. Synthesis of Compound **1**



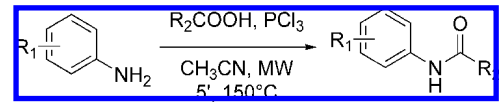
1

its removal and leading to comparable isolated yield and compound purity. The synthetic protocol was then further improved by halving the irradiation time and preserving very high yields (entries 9 and 10). The same results in terms of yield and purity had already been obtained, but through a more time-demanding classical acyl-chloride based reaction.[4]

The optimized protocol (1 equiv of PCl_3, CH_3CN, 150 °C, 5 min) was used to synthesize a small collection of amides starting from commercially available EWG-substituted aniline derivatives and carboxylic acids. Because of the very short reaction times, a quicker workup procedure, adaptable to a parallel approach, was necessary. Good purities were obtained through solid-phase extraction (SPE) technique,[5] choosing basic alumina as stationary phase. The support was able to trap acidic components, such as excess of carboxylic acid and byproduct coming from the dehydrating agent. Isolated yields were also good, even if slightly lower than the results obtained by classical liquid/liquid extraction (entry 1 in Table 2 versus entry 10 in Table 1). This slight decrease was negligible compared to the time-saving advantage given by this workup procedure. The prepared amide collection is summarized in Table 2. Aromatic, aliphatic, and heteroaromatic carboxylic acids and aniline derivatives bearing strong EWGs, for example, nitro and trifluoromethyl moiety, afforded the expected amide compounds in high yield and purity. The presence of very strong EWGs, such as two nitro groups as in entries 37−40, required longer reaction times, up to 15 min, for the complete conversion of the starting materials. The synthetic procedure was not so efficacious with amino-pyridinyl reactants. The conversion was incomplete and the products were recovered only in low-moderate yields after purification through silica cartridge (Scheme 2).

The possibility of using PCl_3 as dehydrating agent was briefly evaluated also with anilines not bearing strong EWGs. Four reactants were chosen as test compounds: aniline, 4-methoxy aniline, 4-chloro aniline, and 2,6-dichloro aniline. This last compound was chosen as an example of sterically hindered starting material (Scheme 3 and Table 3). The application of standard protocol led to a mixture of two derivatives, that are the desired amide and the overcondensation product, respectively, **a** and **b** in Scheme 3.[6] As expected, the greater the nucleophility of nitrogen atom, the higher the amount of the byproduct **b**, namely OMe > H > Cl > diCl (entries 1−4). With the aim of avoiding the formation of the overcondensation products and obtaining only the amide derivatives in good yields, the reaction temperature was lowered to 100−120 °C, while the other parameters were unchanged (entries 5−8).

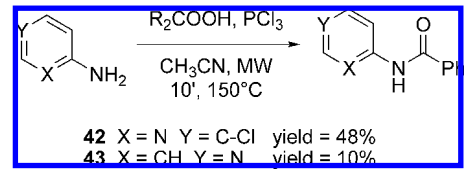
Table 2. Synthesis of Amide Collection



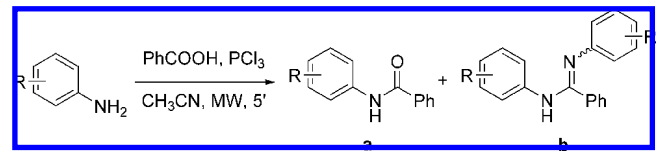
entry	R_1	R_2	yield[a]	amide
1	4-CF_3	Ph	96%	**1**
2	4-CF_3	4-F-Ph	96%	**3**
3	4-CF_3	3-NO_2-Ph	97%	**4**
4	4-CF_3	3,4-diMe-Ph	96%	**5**
5	4-CF_3	4-OMe-Ph	94%	**6**
6	4-CF_3	2-Me-Ph	95%	**7**
7	4-CF_3	4-NO_2-Ph	94%	**8**
8	4-CF_3	Bn	97%	**9**
9	4-CF_3	*n*-propyl	86%	**10**
10	4-CF_3	cyclopentyl	88%	**11**
11	4-CF_3	2-thienyl	95%	**12**
12	4-CF_3	2-pyridinyl	96%	**13**
13	4-NO_2	Ph	85%	**14**
14	4-NO_2	4-F-Ph	85%	**15**
15	4-NO_2	3,4-diMe-Ph	87%	**16**
16	4-NO_2	4-OMe-Ph	88%	**17**
17	4-NO_2	2-Me-Ph	91%	**18**
18	4-NO_2	4-NO_2-Ph	84%	**19**
19	4-NO_2	Bn	95%	**20**
20	4-NO_2	*n*-propyl	89%	**21**
21	4-NO_2	cyclopentyl	91%	**22**
22	4-NO_2	2-thienyl	88%	**23**
23	2-F-5-CF_3	Ph	96%	**24**
24	2-F-5-CF_3	3-NO_2-Ph	93%	**25**
25	2-F-5-CF_3	3,4-diMe-Ph	96%	**26**
26	2-F-5-CF_3	4-OMe-Ph	95%	**27**
27	2-F-5-CF_3	4-NO_2-Ph	97%	**28**
28	2-F-5-CF_3	Bn	99%	**29**
29	2-F-5-CF_3	4-F-PhCH_2−	90%	**30**
30	2-F-5-CF_3	3-NO_2−PhCH_2−	94%	**31**
31	2-F-5-CF_3	4-OMe-PhCH_2−	96%	**32**
32	2-F-5-CF_3	2-Me-PhCH_2−	89%	**33**
33	2-F-5-CF_3	*n*-propyl	96%	**34**
34	2-F-5-CF_3	cyclopentyl	95%	**35**
35	2-F-5-CF_3	2-thienyl	99%	**36**
36	2-F-5-CF_3	2-pyridinyl	94%	**37**
37	2,4-diNO_2	Ph	89%[b]	**38**
38	2,4-diNO_2	3,4-diMe-Ph	92%[b]	**39**
39	2,4-diNO_2	Bn	91%[b]	**40**
40	2,4-diNO_2	*n*-propyl	94%[b]	**41**

[a] Isolated yield. Purification by basic alumina SPE cartridge. UPLC-MS and ^1H NMR purity not lower than 95%. [b] Reaction time: 15 min.

Scheme 2. Condensation of Amino-pyridinyl Reactants



Scheme 3. Condensation of Anilines Not Bearing Strong EWGs



a **b**

In conclusion, a simple, quick and versatile method for the preparation of amide compounds from EWG-substituted aniline derivatives was described. PCl_3-mediated condensation may be considered an alternative synthetic route in the formation of various aniline amides, both bearing electron

Table 3. Variation of Reaction Temperature

entry	R	*T* (°C)	**a/b** ratio [a]	yield[b]	amide
1	H	150	75:25		
2	4-OMe	150	60:40		
3	4-Cl	150	85:15		
4	2,6-diCl	150	83:17		
5	H	100	only **a**	86%	**44**
6	4-OMe	100	only **a**	88%	**45**
7	4-Cl	100	only **a**	90%	**46**
8	2,6-diCl	120	only **a**	92%	**47**

[a] Determined by UPLC at 254 nm. [b] Isolated yield. Purification by basic alumina SPE cartridge. UPLC-MS and ^{1}H NMR purity not lower than 95%.

withdrawing and also electron releasing groups. The main advantages of the described protocol were the short reaction times because of the use of microwave irradiation and the easiness of workup. Liquid/liquid extraction is a prompt workup method for classical batch synthesis, whereas the use of basic alumina SPE may be indicated for the parallel purification.

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Supporting Information Available. Experimental procedures and spectroscopic data for prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) See for example: (a) Singh, H.; Singh, A. K.; Sharma, S.; Iyer, R. N.; Srivastava, O. P. *J. Med. Chem.* **1977**, *20*, 826. (b) Vaillancourt, V. A.; Cudahy, M. M.; Staley, S. A.; Brideau, R. J.; Conrad, S. J.; Knechtel, M. L.; Oien, N. L.; Wieber, J. L.; Yagi, Y.; Wathen, M. W. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2079. (c) Waisser, K.; Bures, O.; Holy, P.; Kunes, J.; Oswald, R.; Jiraskova, L.; Pour, M.; Klimesova, V.; Kubicova, L.; Kaustova, J. *Arch. Pharm. Pharm. Med. Chem.* **2003**, *1*, 53.

(2) (a) Hayes, B. L. *Microwave synthesis: Chemistry at the speed of light*; CEM publishing: Mattews, NC, 2002. (b) Kappe, C. O.; Stadler, A. *Microwaves in organic and medicinal chemistry*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2005.

(3) Analytical data of the proposed structure **2** (colorless oil): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (m, 4H), 3.58 (m, 4H), 1.87 (m, 8H). MS/ESI$^+$ *m/z* calcd for $C_8H_{17}Cl_2O_3P$ 262.03, found 263.05 (MH^+).

(4) Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449.

(5) For the uses and the advantages of SPE see for example: (a) Nilsson, U. J. *J. Chromatogr. A* **2000**, *855*, 305. (b) Simpson, N. J. K. *Solid-phase extraction: principles, techniques and applications*; Marcel Dekker: New York, NY, 2000.

(6) MS/ESI$^+$ *m/z* of the overcondensation products **b**: R = H, *m/z* 273.1 (MH^+); R = 4-OMe, *m/z* 333.2 (MH^+); R = 4-Cl, *m/z* 341.2 (MH^+); R = 2,6-diCl, *m/z* 409.0 (MH^+).

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