Highly Efficient Method for the Synthesis of Carboxamides from Carboxylic Acids and Amines Using Pyridine-3-sulfonyl Chloride (3-PSC)

Setsuo Funasaka,[1] Koji Kato,[1] and Teruaki Mukaiyama*[1,2]
[1]*Center for Basic Research, The Kitasato Institute, 6-15-5 (TCI) Toshima, Kita-ku, Tokyo 114-0003*
[2]*Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641*

(Received February 27, 2008; CL-080223; E-mail: mukaiyam@abeam.ocn.ne.jp)

The use of pyridine-3-sulfonyl chloride (3-PSC) in dehydrating condensation was investigated. This novel reagent was successfully employed as a mild dehydrating reagent for preparing various carboxamides in good to excellent yields from the corresponding carboxylic acids and amines.

To prepare carboxamide is one of the most important and fundamental reactions in synthetic chemistry since there exist numerous natural or unnatural bioactive compounds having carboxamide moieties. Thus, mild and efficient condensation methods for synthesizing carboxamides have been developed and widely employed in the syntheses of many natural products to date.[1–11]

In our previous communication, an efficient method for the syntheses of carboxamides by using pyridine-3-carboxylic anhydride (3-PCA) with 4-(dimethylamino)pyridine (DMAP) as the activator was reported.[12a–12c] One of the features in this reaction is that the by-products such as pyridine-3-carboxylic acid and pyridine-3-carboxamide formed are easily removed by aqueous workup. This method, however, has some drawbacks that the yield of carboxamide decreased in the case of carboxylic acid such as benzoic acid or cinnamic acid. The reason of low yield may be due to the steric factor of the substrate, that is, there is not such a steric bulk difference between a phenyl ring and a pyridine ring in the mixed anhydride formed from 3-PCA and benzoic acid in situ.

Then, in order to improve the yield we focused on the linker moiety of carboxylic anhydride, and benzenesulfonic anhydride (BSA) was found to show high reactivity even in the case of benzoic acid or cinnamic acid to provide the corresponding carboxamides in excellent yields.[12d] On the other hand, since by-product such as sulfoxamide derived from the condensing reagent was obtained in some cases this method requires purification by using silica gel column chromatography to remove by-products. Then, as our continuous investigation for the purpose of extending the utility of BSA in the point of the purification pyridine-3-sulfonyl chloride (3-PSC; **1**) was designed. Since this reagent has a basic pyridine moiety, the by-products such as pyridine-3-sulfonic acid and pyridine-3-sulfoxamide formed in the reaction are assumed to be removed by aqueous workup as in the case of 3-PCA.

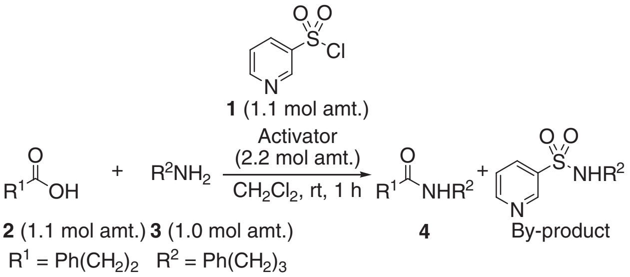
In this communication, we would like to report a convenient synthetic method for carboxamides from the corresponding carboxylic acids and amines by using commercially available 3-PSC as a dehydrating reagent.

In the first place, the reaction of 3-phenylpropionic acid (**2**) and 3-phenylpropylamine (**3**) as a model substrate in the presence of 3-PSC with DMAP was examined in CH_2Cl_2 under the conditions similar to those applied to 3-PCA or BSA. The reaction was found to proceed smoothly within 1 h to provide the desired carboxamide in 99% yield (Table 1, Entry 1), and the by-products such as pyridine-3-sulfonic acid and pyridine-3-sulfoxamide formed in this reaction were found to be easily removed by aqueous workup.[13] Further, the effect of activators was investigated. As the result, in the cases where a DMAP derivative such as 4-(1-pyrrolidinyl)pyridine (PPY) and an imidazole derivative such as *N*-methylimidazole or *N*-butylimidazole were used the carboxamides were obtained in high yield respectively (Entries 2–4). Among them, DMAP was found to give the best result (Entry 1).

The effect of solvent was further examined as shown in Table 2. The results obtained by using CH_2Cl_2 or MeCN were also excellent (Entries 1 and 2). On the other hand, in the case of using DMF, THF, or toluene, the carboxamide was obtained in moderate yields (Entries 3–5).

Several examples of carboxamides obtained by using 3-PSC as a dehydrating reagent are listed in Table 3.[14] In most cases, the reactions of 3-phenylpropionic acid proceeded smoothly at room temperature within 1 h to form the corresponding carboxamides in good to high yields even when hindered amine such as *tert*-butylamine was used (Entry 6). Even in the cases of hindered α,α-disubstituted carboxylic acids such as diphenylacetic acid, the desired products were afforded in high yields (Entries 7 and 8). It was noteworthy that this protocol is applicable to the carboxylic acids such as benzoic acid, cinnamic acid, and

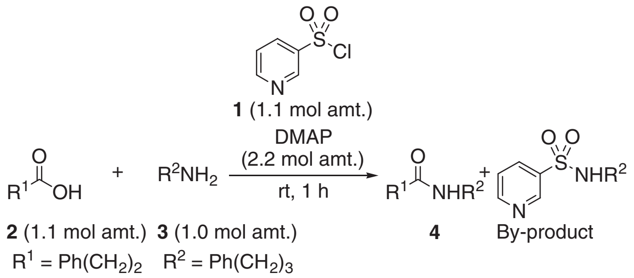
Table 1. Effect of activators



Entry	Activator	Isolated yield/%	
		4	By-product
1	DMAP	99	1
2	PPY[b]	96	1
3	*N*-Methylimidazole	97	2
4	*N*-Butylimidazole	96	2
5[a]	HOBt[b]	78	14
6	*N*-Methylmorpholine	66	9

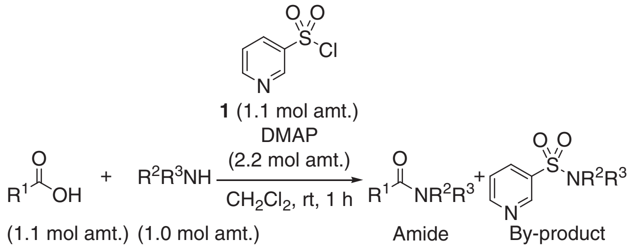
[a]The reaction was carried out in the presence of *N*-methylmorpholine (2.2 mol amt.). [b]PPY = 4-(1-pyrrolidinyl)pyridine, HOBt = 1-hydroxybenzotriazole.

Table 2. Effect of solvents



Entry	Solvent	Isolated yield/%	
		4	By-product
1	CH_2Cl_2	99	1
2	MeCN	96	1
3	DMF	84	0
4	THF	68	21
5	Toluene	72	9

Table 3. Synthesis of various carboxamides with 3-PSC



Entry	Carboxylic acid	Amine	Isolated yield/%	
			Amide	By-product
1	$Ph(CH_2)_2CO_2H$	$Ph(CH_2)_3NH_2$	99	1
2	$Ph(CH_2)_2CO_2H$	$Ph(CH_2)NHCH_3$	97	0
3	$Ph(CH_2)_2CO_2H$	$PhCH(NH_2)CH_3$	98	0
4	$Ph(CH_2)_2CO_2H$	$PhNH_2$	98	0
5	$Ph(CH_2)_2CO_2H$	Piperidine	88	0
6	$Ph(CH_2)_2CO_2H$	*t*-$BuNH_2$	87	0
7	Ph_2CHCO_2H	$PhCH(NH_2)CH_3$	96	3
8	Ph_2CHCO_2H	Piperidine	91	0
9	$PhCO_2H$	$PhCH(NH_2)CH_3$	93	1
10	$PhCO_2H$	Piperidine	89	0
11	(*E*)-PhCH=CHCO$_2$H	$PhCH(NH_2)CH_3$	94	0
12	(*E*)-PhCH=CHCO$_2$H	Piperidine	89	0
13	2-PyCOOH	$PhCH(NH_2)CH_3$	93	1
14	2-PyCOOH	Piperidine	82	1

picolinic acid to provide the corresponding carboxamides in high yields because in the case of condensation reaction of above carboxylic acids such as benzoic acid using 3-PCA the desired product was obtained in a poor yield (Entries 9–14).

Thus, this effective dehydrating reagent, 3-PSC was employed conveniently for the preparation of various carboxamides from nearly equimolar amounts of free carboxylic acids and amines including sterically hindered substrates in good to high yields under mild conditions. It is noted that effective workup procedure is one of the advantages in the present protocol because the desired carboxamides are easily obtained in an almost pure form by simple aqueous workup.

References and Notes

1 a) S.-Y. Han, Y.-A. Kim, *Tetrahedron* **2004**, *60*, 2447. b) C. A. G. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827.

2 DCC see: a) B. Neises, W. Steglich, *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522. b) A. Hassner, V. Alexanian, *Tetrahedron Lett.* **1978**, *19*, 4475.

3 2,4,6-Trichlorobenzoyl chloride see: J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

4 2,2′-Dipyridyl disulfide/Ph_3P see: a) T. Mukaiyama, R. Matsueda, M. Suzuki, *Tetrahedron Lett.* **1970**, *11*, 1901. b) E. J. Corey, K. C. Nicolaou, *J. Am. Chem. Soc.* **1974**, *96*, 5614.

5 *O,O′*-Di(2-pyridyl)thiocarbonate (DPTC) see: K. Saitoh, I. Shiina, T. Mukaiyama, *Chem. Lett.* **1998**, 679.

6 Di(2-pyridyl)carbonate (DPC) see: S. Kim, J. I. Lee, Y. K. Ko, *Tetrahedron Lett.* **1984**, *25*, 4943.

7 2-Me-6-NO_2-benzoic anhydride (MNBA) see: a) I. Shiina, R. Ibuka, M. Kubota, *Chem. Lett.* **2002**, 286. b) I. Shiina, M. Kubota, R. Ibuka, *Tetrahedron Lett.* **2002**, *43*, 7535. c) I. Shiina, M. Kubota, H. Oshiumi, M. Hashizume, *J. Org. Chem.* **2004**, *69*, 1822. d) I. Shiina, Y. Kawakita, *Tetrahedron* **2004**, *60*, 4729.

8 4-(Trifluoromethyl)benzoic anhydride see: I. Shiina, S. Miyoshi, M. Miyashita, T. Mukaiyama, *Chem. Lett.* **1994**, 515; I. Shiina, T. Mukaiyama, *Chem. Lett.* **1994**, 677; I. Shiina, *Tetrahedron* **2004**, *60*, 1587.

9 4-Nitrobenzoic anhydride/Sc(OTf)$_3$ see: K. Ishihara, M. Kubota, H. Kurihara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4560.

10 Di-2-thienyl carbonate (2-DTC) see: a) Y. Oohashi, K. Fukumoto, T. Mukaiyama, *Chem. Lett.* **2004**, *33*, 968. b) Y. Oohashi, K. Fukumoto, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1508.

11 Another condensation reagents see: K. Saigo, M. Usui, K. Kikuchi, E. Shimada, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1863; H. A. Staab, A. Mannschreck, *Chem. Ber.* **1962**, *95*, 1284; J. D. Meseguer, A. L. P. Coll, J. R. F. Lizarbe, A. Z. Bilbao, *Synthesis* **1980**, 547; K. Wakasugi, A. Iida, T. Misaki, Y. Nishii, Y. Tanabe, *Adv. Synth. Catal.* **2003**, *345*, 1209; I. Shiina, Y. Kawakita, *Tetrahedron Lett.* **2003**, *44*, 1951.

12 Preliminary communications: a) T. Mukaiyama, S. Funasaka, *Chem. Lett.* **2007**, *36*, 326. b) S. Funasaka, T. Mukaiyama, *Chem. Lett.* **2007**, *36*, 658. c) S. Funasaka, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 148. d) S. Funasaka, K. Kato, T. Mukaiyama, *Chem. Lett.* **2007**, *36*, 1456.

13 After aqueous workup these by-products were not included in a crude mixture as observed by ^{1}H NMR. It indicates that by-products, such as pyridine-3-sulfonic acid and pyridine-3-sulfoxamide, are transferred to the aqueous layer by aqueous workup.

14 Typical experimental procedure for the preparation of carboxamides by using 3-PSC (Table 3); To a stirred solution of carboxylic acid (0.33 mmol) in CH_2Cl_2 (1.5 mL) were successively added 3-PSC (0.33 mmol) and DMAP (0.66 mmol) at room temperature. After having been stirred for 10 min, a solution of an amine (0.30 mmol) in CH_2Cl_2 (1.5 mL) was added. After the reaction mixture was stirred for 1 h, it was quenched with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with EtOAc. The organic layer was washed with 5 mol/dm^3 hydrochloric acid (3 times), brine, dried over anhydrous sodium sulfate, and evaporated. The crude product was purified by preparative TLC to afford the corresponding carboxamide.

Published on the web (Advance View) March 29, 2008; doi:10.1246/cl.2008.506