Highly Efficient Method for the Synthesis of Carboxamides from Carboxylic Acids and Amines Using Benzenesulfonic Anhydride (BSA)

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A highly efficient method by using benzenesulfonic anhydride (BSA) in the presence of 4-(dimethylamino)pyridine (DMAP) to synthesize carboxamides from various carboxylic acids and amines including sterically hindered ones is established. This reaction proceeds smoothly to provide the desired product in high yield.

Preparation of carboxamides from carboxylic acids and amines is one of the most fundamental and important steps for the syntheses of various natural and unnatural compounds, and, therefore, various dehydrating methods for it have been reported to date.[1–11]

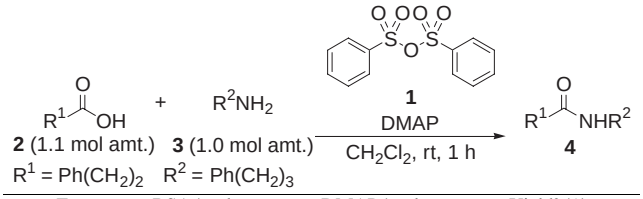
Among them, carboxylic anhydride derivatives such as aromatic carboxylic anhydrides are known to be powerful reagents in the dehydration reaction.[3,7] It was previously reported from our laboratory that an effective method for the synthesis of carboxylic esters or carboxamides using pyridine-3-carboxylic anhydride (3-PCA) in the presence of 4-(dimethylamino)pyridine (DMAP) as the activator.[12] However, it was observed that the yield of carboxylic esters or carboxamides decreased since the yield of by-product increased in the cases of carboxylic acids such as benzoic acid and cinnamic acid due to the factor of steric and leaving-group ability.

On the basis of the above background, we focused on a linker moiety of the carboxylic anhydride, and sulfonic anhydride derivatives such as benzenesulfonic anhydride were chosen. To the best of our knowledge, no general procedures for the preparation of carboxamides from carboxylic acids and amines by using sulfonic anhydrides as a dehydrating agent have been reported. Sulfonic anhydrides are known as good sulfonylation reagents owing to their leaving ability. Thus, the mixed anhydride intermediates are expected to be easily formed at the first step in this condensation reaction.

Herein, we would like to describe a simple and efficient method for the synthesis of carboxamides by using commercially available benzenesulfonic anhydride (BSA) as a dehydrating agent.

In the first place, the reaction of 3-phenylpropionic acid and 3-phenylpropylamine as a model substrate in the presence of DMAP and BSA was examined in CH_2Cl_2 at room temparature (Table 1). As a result, in the case when 1.1 molar amount of BSA with 2.2 molar amount of DMAP were used, the reaction proceeded smoothly within 1 h to provide 3-phenyl-*N*-(3-phenylpropyl)propanamide as the desired carboxamide in 89% yield (Entry 1). Then, the reaction was further investigated about the amount of reagents, namely BSA and DMAP. It was found that the yield of carboxamide decreased to 68% when the amount of DMAP was reduced to 1.2 molar amount (Entry 2). Further, even when the amount of DMAP was increased to 2.4 molar amount,

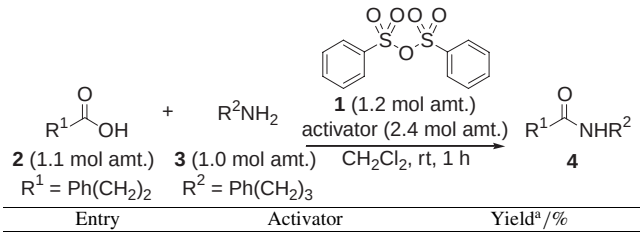
Table 1. Synthesis of carboxamide using DMAP as an activator



Entry	BSA/mol amt.	DMAP/mol amt.	Yield[a]/%
1	1.1	2.2	89
2	1.1	1.2	68
3	1.1	2.4	82
4	1.2	2.4	quant.

[a]Isolated yield.

Table 2. Effect of activators



Entry	Activator	Yield[a]/%
1	DMAP	quant.
2	PPY	87
3	*N*-Methylimidazole	93
4	*N*-Butylimidazole	93
5[b]	HOBt	33
6	*N*-Methylmorpholine	64
7	TEA/cat. DMAP[c]	77

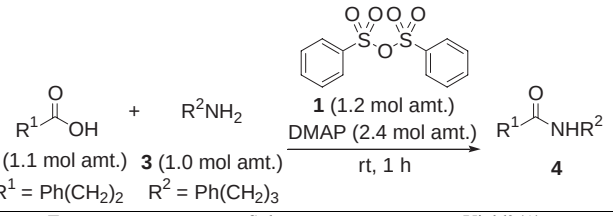
[a]Isolated yield. [b]The reaction was carried out in the presence of *N*-methylmorpholine (2.4 mol amt.). [c]2.4 mol amt. of TEA and 0.1 mol amt. of DMAP were used.

the yield was not improved (Entry 3). On the other hand, the reaction of 1.2 molar amount of BSA with 2.4 molar amount of DMAP gave quantitative yield of the carboxamide.[13]

The effect of activators was further examined (Table 2). Then, 4-(1-pyrrolidinyl)pyridine (PPY) as DMAP derivative was also successfully employed in this reaction and the desired carboxamide was afforded in good yield (Entry 2). It was confirmed that imidazole derivatives such as *N*-methylimidazole and *N*-butylimidazole gave good results similar to the case of using DMAP (Entries 3 and 4). In contrast, the yield decreased markably down to 33% when 1-hydroxybenzotriazole (HOBt) was used (Entry 5). In the case of using excess amount of triethylamine (TEA) and catalytic amount of DMAP the yield decreased to 77% (Entry 7).

In the next place, the effect of solvents was examined (Table 3). The results obtained by the reactions in CH_2Cl_2, MeCN, and DMF were also excellent (Entries 1, 3, and 4). Whereas, in the case of using THF or toluene, the yield of de-

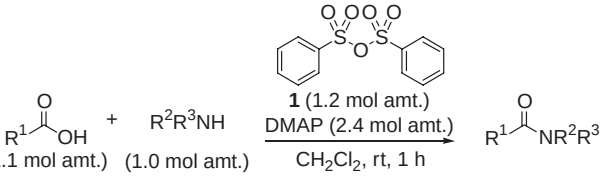
Table 3. Effect of solvents



Entry	Solvent	Yield[a]/%
1	CH_2Cl_2	quant.
2[b]	CH_2Cl_2	99
3	MeCN	99
4	DMF	96
5	THF	75
6	Toluene	66

[a]Isolated yield. [b]The reaction was carried out at −78 °C.

Table 4. Synthesis of various carboxamides with BSA



Entry	Carboxylic acid	Amine	Yield[a]/%
1	$Ph(CH_2)_2CO_2H$	$Ph(CH_2)_3NH_2$	quant.
2	$Ph(CH_2)_2CO_2H$	$PhCH_2NHCH_3$	94
3	$Ph(CH_2)_2CO_2H$	$PhCH(NH_2)CH_3$	99
4	$Ph(CH_2)_2CO_2H$	$PhCH_2NH_2$	94
5	$Ph(CH_2)_2CO_2H$	$PhNH_2$	97
6	$Ph(CH_2)_2CO_2H$	Piperidine	quant.
7	$Ph(CH_2)_2CO_2H$	*t*-$BuNH_2$	92
8	*c*-$C_6H_{11}CO_2H$	$Ph(CH_2)_3NH_2$	97
9	*c*-$C_6H_{11}CO_2H$	$PhCH(NH_2)CH_3$	96
10	*c*-$C_6H_{11}CO_2H$	Piperidine	92
11	Ph_2CHCO_2H	$PhCH(NH_2)CH_3$	quant.
12	Ph_2CHCO_2H	$Ph(CH_2)_3NH_2$	quant.
13	Ph_2CHCO_2H	Piperidine	95
14	$PhCO_2H$	$Ph(CH_2)_3NH_2$	97
15	$PhCO_2H$	$PhCH(NH_2)CH_3$	95
16	$PhCO_2H$	Piperidine	96
17	$PhCO_2H$	$PhNH_2$	97
18	(*E*)-$PhCH{=}CHCO_2H$	$Ph(CH_2)_3NH_2$	quant.
19	(*E*)-$PhCH{=}CHCO_2H$	$PhCH(NH_2)CH_3$	quant.
20	(*E*)-$PhCH{=}CHCO_2H$	Piperidine	quant.
21	2-PyCOOH	$Ph(CH_2)_3NH_2$	quant.
22	2-PyCOOH	$PhCH(NH_2)CH_3$	quant.
23	2-PyCOOH	Piperidine	quant.

[a]Isolated yield.

sired carboxamide decreased (Entries 5 and 6). In addition, it was observed that the desired product was obtained quantitatively even when the reaction was carried out at −78 °C (Entry 2).

The results obtained by using various carboxylic acids and amines under the optimized conditions are summarized in Table 4. The reactions of 3-phenylpropionic acid with respective amines proceeded smoothly to afford the corresponding carboxamides in high to excellent yields even when primary or secondary amines including sterically hindered one such as *tert*-butylamine were used (Entries 1–7). In most cases examined, no sulfoxamides were detected as by-products. It was then confirmed that the desired carboxamides were also obtained in high yields when hindered α,α-disubstituted carboxylic acids such as cyclohexanecarboxylic acid and diphenylacetic acid were used (Entries 8–13). It was noteworthy that this reaction was applicable also to α,β-unsaturated carboxylic acids such as cinnamic acid and aromatic carboxylic acids such as benzoic and 2-pyridinecarboxylic acids (Entries 14–23) because in the case of condensation reaction between amine and carboxylic acid such as benzoic acid using 3-PCA as a dehydrating agent pyridine-3-carboxamide as a by-product derived from 3-PCA was mainly formed and the yield of desired product decreased markably.[12c]

Thus, an effective method for the synthesis of various carboxamides from nearly equimolar amounts of carboxylic acids and amines by using BSA and DMAP is successfully developed. Since this reaction was carried out under mild conditions by simple experimental procedure and the desired corresponding carboxamides were easily prepared in high to excellent yields, it is noted that the benzenesulfonic anhydride is an efficient and convenient reagent for the condensation reaction between various carboxylic acids and amines including sterically hindered ones.

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13 Typical experimental procedure for the preparation of 3-phenyl-*N*-(3-phenylpropyl)propanamide is shown in the following: To a stirred solution of 3-phenylpropionic acid (49.6 mg, 0.33 mmol) in CH_2Cl_2 (1.5 mL) were successively added benzenesulfonic anhydride (107.5 mg, 0.36 mmol) and DMAP (88.1 mg, 0.72 mmol) at room temperature. After having been stirred for 10 min, a solution of 3-phenylpropylamine (40.6 mg, 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 hydrogencarbonate. The mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous sodium hydrogencarbonate, brine, dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by preparative TLC (hexane/EtOAc = 1/9) to afford 3-phenyl-*N*-(3-phenylpropyl)propanamide (79.8 mg, quant.) as a white solid.

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