Efficient Method for Dehydration Condensation Using Pyridine-3-carboxylic Anhydride (3-PCA): Synthesis of Carboxamides from Nearly Equimolar Amounts of Carboxylic Acids and Amines

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A highly useful method for the preparation of carboxamides from various carboxylic acids and amines is established by using pyridine-3-carboxylic anhydride (3-PCA) in the presence of 4-(dimethylamino)pyridine (DMAP). This reaction proceeds smoothly under mild conditions by simple experimental procedure.

Since amide bond formation is one of the most fundamental and important reactions in synthetic organic chemistry, medicinal chemistry, and so forth, various efficient coupling methods for the synthesis of carboxamides have been reported.[1–11] In the point of process chemistry, however, the further development of mild, efficient, and inexpensive reagents is still desired toward large-scale synthesis.[12]

Recently, a novel condensation reaction between various carboxylic acids and alcohols using pyridine-3-carboxylic anhydride (3-PCA), which can be readily prepared from inexpensive pyridine-3-carboxylic acid (nicotinic acid), was reported from our laboratory.[13] This anhydride is considered one of the most practical and useful reagents because the by-product, pyridine-3-carboxylic acid, can be removed just by biphasic separation. Now, we would like to report on a mild and convenient method using a novel-dehydrating reagent, 3-PCA, for the synthesis of carboxamides from the corresponding carboxylic acids and amines including sterically hindered ones.

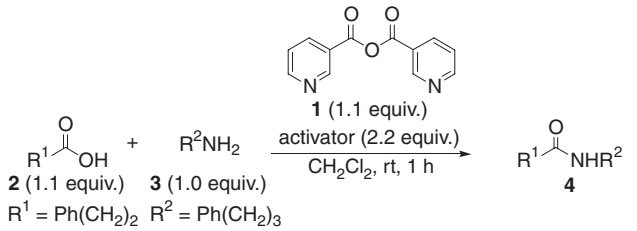
In the first place, a condensation reaction of 3-phenylpropionic acid with 3-phenylpropylamine was examined according to the procedure reported previously for the preparation of carboxylic esters: that is, the reaction was carried out in dichloromethane in the presence of 3-PCA and an activator at room temperature shown in Table 1. When 2.2 molar amounts of DMAP were used, the reaction proceeded smoothly within 1 h to afford the carboxamide, 3-phenyl-*N*-(3-phenylpropyl)propanamide, in 91% yield (Entry 1). Then, the effect of the activators was further examined: in the case of using 4-pyrrolidinopyridine (PPY) as DMAP derivative and benzotriazole derivative such as 1-hydroxybenzotriazole (HOBt), the coupling reactions proceeded smoothly to afford the desired carboxamide in good yield (Entries 2 and 3). Imidazole derivatives such as *N*-methylimidazole or *N*-butylimidazole that are known to be good nucleophilic bases[14] also worked as the activator for this coupling reaction (Entries 4 and 5). On the other hand, the yield decreased to 67% when *N*-methylmorpholine was used (Entry 6).

Next, the amount of DMAP was examined (Table 2). The yield of the desired carboxamide **4** decreased to 79% when a catalytic amount of DMAP was used (Entries 4 and 5). However, it was observed that the carboxamide **4** was obtained in high yields even when the amount of DMAP was reduced to 1.1 equiv. (Entries 1–3).

In the next place, the effect of solvents was examined: it was observed then that the reaction proceeded smoothly in each solvent (Table 3). As shown in Entry 1, CH_2Cl_2 was found to be most suitable solvent. It is also noted that the yield increased when the reaction was carried out at 0 °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 carbox-

Table 1. Effect of activators



Entry	Activator	Yield[a]/%
1	DMAP	91
2	PPY[c]	78
3[b]	HOBt[c]	81
4	*N*-Methylimidazole	79
5	*N*-Butylimidazole	80
6	*N*-Methylmorpholine	67

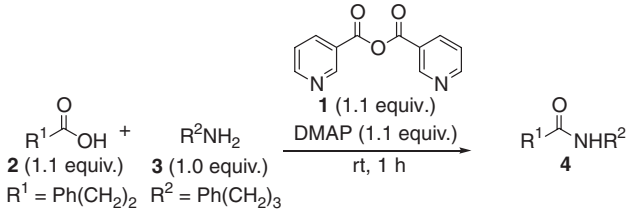
[a]Isolated yield. [b]The reaction was carried out in the presence of *N*-methylmorpholine (2.2 equiv.). [c]PPY = 4-pyrrolidinopyridine, HOBt = 1-hydroxybenzotriazole.

Table 2. Synthesis of carboxamide using DMAP as an activator

Entry	DMAP/equiv.	Yield[a]/%
1	3.3	75
2	2.2	91
3	1.1	92
4	0.55	84
5	0.05	79

[a]Isolated yield.

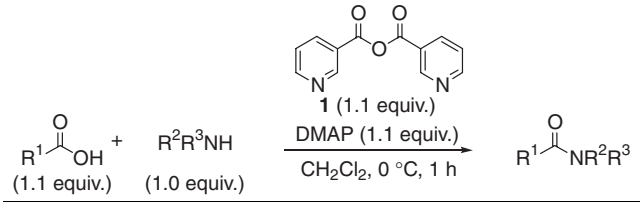
Table 3. Effect of solvents



Entry	Solvent	Yield[a]/%
1	CH_2Cl_2	92
2[b]	CH_2Cl_2	95
3	THF	75
4	Et_2O	85
5	DMF	86
6	Toluene	90
7	MeCN	92

[a]Isolated yield. [b]The reaction was carried out at 0 °C.

Table 4. Synthesis of various carboxamides with 3-PCA



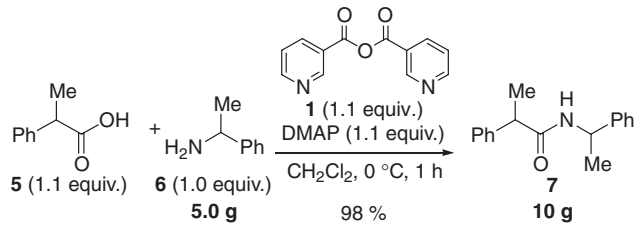
Entry	Carboxylic acid	Amine	Yield[a]/%
1	$Ph(CH_2)_2CO_2H$	$Ph(CH_2)_3NH_2$	95
2	$Ph(CH_2)_2CO_2H$	$PhCH_2NHCH_3$	92
3	$Ph(CH_2)_2CO_2H$	$PhCH(NH_2)CH_3$	98
4	$Ph(CH_2)_2CO_2H$	$PhCH_2NH_2$	94
5	$Ph(CH_2)_2CO_2H$	Ph_2CHNH_2	97
6	$Ph(CH_2)_2CO_2H$	$PhNH_2$	98
7	$Ph(CH_2)_2CO_2H$	Piperidine	88
8	c-$C_6H_{11}CO_2H$	$Ph(CH_2)_3NH_2$	90
9	c-$C_6H_{11}CO_2H$	$PhCH(NH_2)CH_3$	90
10	$PhCH(CH_3)CO_2H$	$Ph(CH_2)_3NH_2$	92
11	$PhCH(CH_3)CO_2H$	$PhCH(NH_2)CH_3$	98

[a]Isolated yield.

amides in good to high yields even when nearly equimolar amounts of primary or secondary amines were used (Entries 1–7).[15] It was then confirmed that the desired carboxamides were also obtained in good yields when hindered α,α-disubstituted carboxylic acids were used (Entries 8–11).

This method is also applicable to the gram-scale synthesis in which the desired carboxamide **7** was obtained in 98% yield by using 3-PCA and DMAP (Scheme 1). It is noteworthy that DMAP and the by-products, pyridine-3-carboxylic acid and 1-phenylethylpyridine-3-carboxamide that were produced from 3-PCA and **6**, were easily removed by aqueous workup.[16]

Thus, a convenient and effective method for the synthesis of various carboxamides from nearly equimolor amounts of carboxylic acids and amines by using 3-PCA and DMAP is successfully developed. Since this reaction was carried out under mild conditions by simple experimental procedure and gave the corresponding carboxamides in good to high yields, it is noted that pyridine-3-carboxylic anhydride is one of the most efficient and convenient reagents for the condensation reaction between various carboxylic acids and amines. Further study on the applicability of the present dehydrating reagent is now in progress.



Scheme 1. Large-scale synthesis of 2-phenyl-*N*-(1-phenylethyl)-propanamide (**7**) with 3-PCA.

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15 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 pyridine-3-carboxylic anhydride (75.4 mg) and DMAP (40.4 mg) at 0 °C. After having been stirred for 10 min, a solution of 3-phenylpropylamine (40.6 mg, 0.30 mmol) in dichloromethane (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, 1 M hydrogen chloride (3 times), 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 (75.9 mg, 95%) as a white solid.
16 After aqueous workup these by-products were not observed in a crude mixture by ^{1}H NMR. It indicates that 1-phenylethyl-pyridine-3-carboxamide is transferred to aqueous layer by acidic workup.

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