Pyridine-3-carboxylic Anhydride (3-PCA): A Versatile, Practical, and Inexpensive Reagent for Condensation Reaction between Carboxylic Acids and Alcohols

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A synthesis of carboxylic esters from various carboxylic acids and alcohols is successfully carried out by using a condensation reagent, pyridine-3-carboxylic anhydride (3-PCA). This reaction materialized synthesis of various carboxylic esters to be carried out under mild conditions by simple experimental procedure.

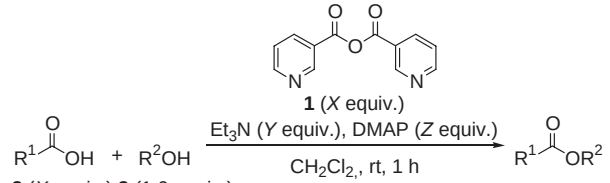
The condensation reaction between a carboxylic acid and an alcohol is considered one of the most important reactions in organic synthesis. Although various esterification methods have been developed to date,[1–10] most of them require strong acids or bases, high reaction temperature, troublesome procedure, or high cost. Therefore, it was strongly desired to find more convenient and effective esterification reaction that proceeds under simple and mild conditions.

Benzoic acid derivatives have been known as effective condensation reagent for synthesizing carboxylic esters under mild condition, whereas an excess amount of a base such as triethylamine is generally required in order to enhance the nucleophilicity of carboxylic acids. Thus, it was needed to develop a new and effective reagent that allows the reaction to proceed smoothly just by mixing carboxylic acids and alcohols. Then, pyridine-3-carboxylic anhydride was chosen with the expectation that it would be reactive because of the electron-withdrawing nature of pyridine ring.[11] In addition, this condensation reaction is assumed to proceed without using any base since the basicity is already inherent in the condensing reagent, and further, the hydrophilic pyridine-3-carboxylic acid formed via this reaction would readily be removed by a simple aqueous workup. We would like to report herein a convenient condensation reaction using pyridine-3-carboxylic anhydride (3-PCA) that is readily prepared quantitatively from inexpensive pyridine-3-carboxylic acid (nicotinic acid).[12,13]

In the first place, a condensation reaction of 3-phenylpropanoic acid with 3-phenylpropan-1-ol was examined in dichloromethane at room temperature in the coexistence of triethylamine, 3-PCA, and DMAP (Table 1). When 1.3 molar amounts of the dehydrating reagent and 2.6 molar amounts of triethylamine were used, the reaction proceeded smoothly within 1 h under the above conditions, and the desired ester, 3-phenylpropyl 3-phenylpropanoate, was afforded in 97% yield (Entry 1). Next, the reactions were further examined in order to reduce the amounts of the reagents, namely carboxylic acid, triethylamine, and the dehydrating reagent. It was then observed that the corresponding ester was formed in high yield even when the amounts of carboxylic acid, dehydrating reagent and trietylamine were all reduced to 1.1 equivalents (Entries 2–4). It is noteworthy that the desired carboxylic ester was obtained in high yield also in the absence of triethylamine (Entry 5). This clearly indicates that the pyridine moiety of 3-PCA worked as the base to capture pyridine-3-carboxylic acid formed in situ. In addition, it was found that the reaction proceeded smoothly even when 2 mol % of DMAP was used (Entries 6 and 7). Interestingly, the desired ester was obtained in 49% yield also in the absence of a base (Entry 8).

In the next place, effect of solvents was examined (Table 2). It was revealed then that the reaction proceeded not only in a non-polar solvent such as CH_2Cl_2 or toluene but also in a polar solvent such as THF, Et_2O, DMF, or MeCN and afford the desired ester **4** in excellent yields (Entries 1–6).

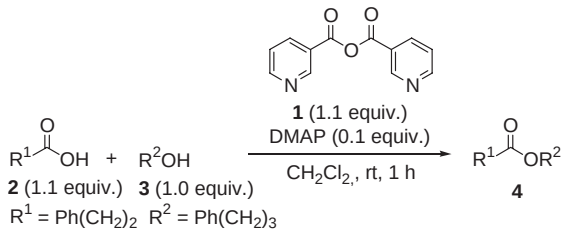
Table 1. Synthesis of carboxylic esters using 3-PCA



Entry	*X*	*Y*	*Z*	Yield[a]/%
1	1.3	2.6	0.1	97
2	1.2	2.4	0.1	96
3	1.1	2.2	0.1	96
4	1.1	1.1	0.1	96
5	1.1	0	0.1	97
6	1.1	0	0.05	96
7	1.1	0	0.02	96
8[b]	1.1	0	0	49

[a]Isolated yield. [b]The reaction mixture was stirred for 24 h.

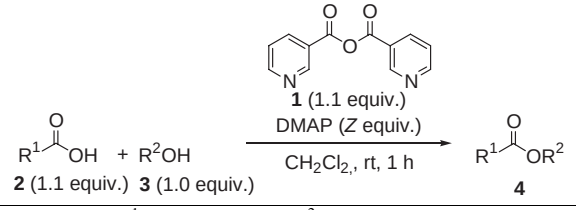
Table 2. Effect of solvents



Entry	Solvent	Yield[a]/%
1	CH_2Cl_2	97
2	Toluene	91
3	Et_2O	93
4	DMF	95
5	THF	94
6	MeCN	96

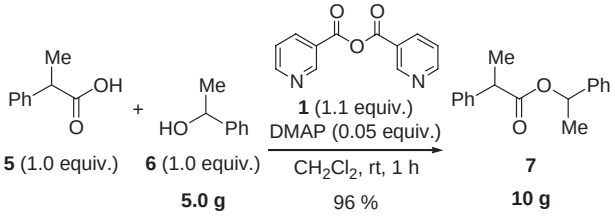
[a]Isolated yield.

Table 3. Synthesis of various carboxylic esters with 3-PCA



Entry	R^1	R^2	Z	Yield[a]/%
1	$Ph(CH_2)_2$	$Ph(CH_2)_3$	0.02	97
2	$Ph(CH_2)_2$	$PhCH(CH_3)$	0.02	95
3	$Ph(CH_2)_2$	$PhCH_2$	0.02	96
4	$Ph(CH_2)_2$	Ph	0.02	91
5	$Ph(CH_2)_2$	*c*-C_6H_{11}	0.10	89
6	$Ph(CH_2)_2$	$Ph(CH_2)_2CH(CH_3)$	0.05	94
7	$Ph(CH_2)_2$	$CH_2{=}CHCH_2$	0.02	93
8	*c*-C_6H_{11}	$Ph(CH_2)_3$	0.05	90
9	*c*-C_6H_{11}	$PhCH(CH_3)$	0.05	85
10	$PhCH(CH_3)$	$Ph(CH_2)_3$	0.05	97
11	$PhCH(CH_3)$	$PhCH(CH_3)$	0.05	95

[a]Isolated yield.



Scheme 1. Large-scale synthesis of α-phenylethyl 2-phenylpropanoate with 3-PCA.

The results obtained by using various carboxylic acids and alcohols were summarized in Table 3.[14] When nearly equimolar amounts of primary or secondary alcohols were used, the condensation reaction of 3-phenylpropanoic acid with respective alcohols afforded the corresponding esters in high yields (Entries 1–7). The desired esters were also obtained in good yields when hindered α,α-disubstituted carboxylic acids were used (Entries 8–11).

This method is applicable also to gram-scale synthesis in which the desired ester **7** was given in 96% yield by using 3-PCA and catalytic amount of DMAP (Scheme 1). Importantly, by-products, pyridine-3-carboxylic acid and 1-phenylethyl pyridine-3-carboxylate that were produced from 3-PCA and **6**, were easily removed by aqueous workup.[15,16]

It is noted that a convenient and effective method for the synthesis of various carboxylic esters from carboxylic acids and alcohols is established. The reaction of various alcohols and carboxylic acids with 3-PCA and a catalytic amount of DMAP gave the corresponding esters in high to excellent yields. Thus, pyridine-3-carboxylic anhydride is one of the most efficient and convenient reagents for the condensation reaction between various carboxylic acids and alcohols. Further study on the usefulness of the present dehydrating reagent is now in progress.

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12 3-PCA was prepared from pyridine-3-carboxylic acid. A solution of pyridine-3-carboxylic acid (1.00 g, 8.12 mmol) and diisopropylethylamine (1.41 mL, 8.12 mol) in THF (18 mL) was stirred for 10 min at 0 °C. To the reaction mixture, a solution of triphosgene (402 mg, 1.35 mmol) in THF (2 mL) was added at 0 °C, then stirred for 1 h. The reaction mixture was additionally stirred for 1 h at room temperature. After filtration of the reaction mixture to remove diisopropylethylammonium chloride formed, the filtrate was condensed under reduced pressure. After EtOAc was added to the residue, the mixture was washed with water. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate. The solvent was evaporated to afford 898 mg (97%) of pyridine-3-carboxylic anhydride as a white solid. mp 121–123 °C. IR (neat, cm^{-1}) 1797, 1723. ^1H NMR (400 MHz, Acetone-d_6) δ 7.66 (ddd, 2H, $J = 0.8$, 4.8, 8.0 Hz), 8.55 (ddd, 2H, $J = 1.8$, 1.8, 8.0 Hz), 8.92 (dd, 2H, $J = 1.8$, 4.8 Hz), 9.34 (dd, 2H, $J = 0.8$, 1.8 Hz). ^{13}C NMR (100 MHz, Acetone-d_6) δ 124.2, 125.0, 138.1, 151.6, 155.3, 161.2. Anal: calcd for $C_{12}H_8N_2O_3$: C, 63.16; H, 3.53; N, 12.28%. Found: C, 62.94; H, 3.49; N, 12.21%.
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15 After the reaction of α-phenylethyl alcohol (5.00 g) with 2-phenylpropanoic acid (6.76 g) in dichloromethane (100 mL) at room temperature in the presence of 3-PCA (10.23 g) and DMAP (250 mg) according to the typical procedure,[13] it was quenched with saturated aqueous sodium hydrogencarbonate. The mixture was extracted with *tert*-butyl methyl ether. The organic layer was washed with saturated aqueous sodium hydrogencarbonate (2 times), 1 M hydrogenchloride (3 times), brine, dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 10/1) to afford α-phenylethyl 2-phenylpropanoate (9.96 g, 96%) as colorless oil.
16 After aqueous workup, these by-products were not observed in a crude mixture by ^1H NMR. It indicates that 1-phenylethyl pyridine-3-carboxylate is transferred to aqueous layer by acidic workup.

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