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DI-2-PYRIDYL CARBONATE: A NEW EFFICIENT COUPLING AGENT FOR THE DIRECT ESTERIFICATION OF CARBOXYLIC ACIDS[1]

Sunggak Kim*, Jae In Lee, and Young Kwan Ko
Department of Chemistry
Korea Advanced Institute of Science and Technology, Seoul 131, Korea

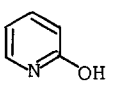
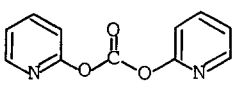
Summary: Reaction of carboxylic acids with equimolar amounts of di-2-pyridyl carbonate and alcohols or thiols in the presence of 4-dimethylaminopyridine as a catalyst in methylene chloride at room temperature affords the corresponding esters in high yields under mild conditions.

The esterification of carboxylic acids is an important reaction which is frequently used in organic synthesis. Among many useful and reliable esterification methods available in the literature,[2] the use of coupling agents is the most efficient and the most convenient. N,N'-Carbonyldiimidazole,[3] N,N'-dicyclohexylcarbodiimide/4-dimethylaminopyridine (DMAP),[4] and 2-halopyridinium salts[5] have been widely used as coupling agents for a number of cases. Recently, reactive carbonates such as N,N'-disuccinimidyl carbonate,[6] diphthalimido carbonate,[7] and 1,1'-(carbonyldioxy)dibenzotriazole[8] have been utilized for the preparation of the corresponding active esters.[9]

We now wish to report the use of a new coupling agent, di-2-pyridyl carbonate (2-DPC),[10] for the direct esterification of carboxylic acids into the corresponding esters in high yields under mild conditions (eq. 1).[11]

2-DPC was conveniently prepared in 90% yield by the reaction of phosgene with 2 equiv of 2-hydroxypyridine in the presence of 2 equiv of triethylamine in methylene chloride-toluene at 0 °C for 1 h (eq. 2). 2-DPC was stable crystalline compound and showed no sign of decomposition when kept under nitrogen at room temperature for one month.

$$\mathrm{RCOOH} + \underset{\mathrm{X=O\ or\ S}}{\mathrm{R'XH}} + \text{2-DPC} \xrightarrow{\text{cat. DMAP}} \mathrm{RCOXR'} + \text{2-PyOH} \qquad (1)$$

$$\mathrm{COCl_2} + \underset{\text{2-PyOH}}{\text{  }} \xrightarrow{\mathrm{Et_3N}} \underset{\text{2-DPC}}{\text{  }} \qquad (2)$$

Esterification of caprylic acid with equimolar amounts of benzyl alcohol and 2-DPC in the absence of a base or in the presence of a base like pyridine or triethylamine in methylene chloride did not proceed to an observable extent, even after stirring at room temperature for 17 h. However, we have found that the use of 2-DPC and a catalytic amount of DMAP[12] is exceedingly effective in the esterification of carboxylic acids. The reaction proceeded rapidly and smoothly in methylene chloride at room temperature and the procedure is operationally very simple. Furthermore, it is noteworthy that a byproduct, water-soluble 2-hydroxypyridine, can be completely removed from the reaction mixture by the usual aqueous workup or it can be recovered in high yields (80-90%) by precipitating 2-hydroxypyridine from the reaction mixture with the addition of petroleum ether or diethyl ether.

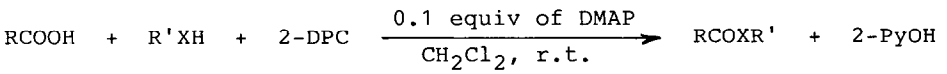
The following procedure is representative. To a solution of caprylic acid (289 mg, 2.0 mmol), benzyl alcohol (220 mg, 2.0 mmol), and DMAP (23 mg, 0.2 mmol) in methylene chloride (5 ml) at room temperature was added 2-DPC (435 mg, 2.0 mmol). The reaction mixture was stirred at room temperature for 2 h and evaporated to dryness under reduced pressure. The residue was treated with petroleum ether (20 ml) and filtered to yield 2-hydroxypyridine (340 mg, 89%). The filtrate was washed with 0.5M HCl solution (10 ml), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was distilled to afford benzyl caprylate (441 mg) in 94% yield.

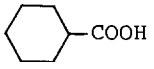
Table I includes some experimental results and illustrates the efficiency, the mildness, the applicability, and the scope of this method. Most aliphatic carboxylic acids, upon treatment with equimolar amounts of the alcohol and 2-DPC in the presence of 0.1 equiv of DMAP, yielded the corresponding esters in high yields without the formation of byproducts such as the symmetrical anhydrides and 2-pyridyl esters. However, when esterification of caprylic acid with benzyl alcohol was stopped in 10 min, we were able to isolate a small amount of 2-pyridyl caprylate, indicating the participation of 2-pyridyl ester as one of the possible intermediates.

This method reaches a limit with aromatic acids and relatively hindered carboxylic acids. For example, reaction of benzoic acid with equimolar amounts of ethanol and 2-DPC in the presence of 0.1 equiv of DMAP gave a 51:38 mixture of ethyl benzoate and 2-pyridyl benzoate in 0.5 h, whereas the reaction using pivalic acid and benzyl alcohol gave a 28:56 mixture of benzyl pivalate and 2-pyridyl pivalate along with a small amount of pivalic anhydride (<8%) under the same reaction conditions. Unlike the observation in the direct esterification using alkyl chloroformate and DMAP as a catalyst,[13] the product composition was not significantly altered by the increment of the amount of DMAP or prolonged stirring.

This method can be successfully applied for the preparation of thiol esters. The reaction was carried out under the almost same reaction conditions used in the preparation of carboxylic esters. Using this method, several thiol esters were obtained in high yields as shown in Table I.

Table I. Esterification of Carboxylic Acids



RCOOH	R'XH	Time, h	Yield, %[a] RCOXR'
$CH_3(CH_2)_6COOH$	$C_6H_5CH_2OH$	0.2	84(8)
	$C_6H_5CH_2OH$	2	94
	CCl_3CH_2OH	0.5	91
$C_6H_5CH_2COOH$	CH_3OH	1	89
	$(CH_3)_2CHOH$	3	90
$(CH_3)_2CHCOOH$	C_6H_5OH	1	92
	CCl_3CH_2OH	0.5	86
$(C_6H_5)_2CHCOOH$	CH_3OH	1	95
	$C_6H_5CH_2OH$	1	90
$C_6H_5CH=CHCOOH$	CH_3OH	2	93
	$CH_2=CHCH_2OH$	2	86
C_6H_5COOH	C_2H_5OH	0.5	51(38)
	C_2H_5OH	24	68(23)
	C_2H_5OH	24	80(20)[b]
$(CH_3)_3CCOOH$	$C_6H_5CH_2OH$	0.5	28(56)[c]
	$C_6H_5CH_2OH$	24	42(45)[c]
$CH_3(CH_2)_6COOH$	C_6H_5SH	6	84
$C_6H_5CH_2COOH$	n-C_4H_9SH	1	82
	n-C_4H_9SH	1	89
	$(CH_3)_2CHSH$	12	82
$C_6H_5CH=CHCOOH$	C_6H_5SH	6	95
C_6H_5COOH	n-C_4H_9SH	12	88

[a] The yields refer to isolated products. The numbers in parentheses indicate isolated yields of the corresponding 2-pyridyl esters. [b] The reaction was carried out with 0.5 equiv of DMAP and the product composition was determined by NMR analysis. [c] A small amount of pivalic anhydride (<8%) was also isolated.

In conclusion, this method appears to offer several advantages over previously known methods for the esterification of carboxylic acids with respects to a direct high-yield synthesis, the mildness, the rapidity, the simple workup of this procedure, and the stability of 2-DPC and should, therefore, find many useful applications in organic synthesis.[14]

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References and Notes

1. Part of this work was presented at the Second Japan-Korea Joint Seminar on Organic Chemistry, Kyoto, Japan, May 28, 1984.
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9. Esterification of caprylic acid with benzyl alcohol in the presence of 0.1 equiv of DMAP in methylene chloride using N,N'-disuccinimidyl carbonate, diphthalimido carbonate, and 1,1'-(carbonyldioxy)dibenzotriazole as coupling agents yielded the corresponding active esters as major products along with small amounts (<5%) of benzyl caprylate at r.t. in 12 h.
10. mp 84-86 °C; NMR($CDCl_3$) δ 7.10-7.46 (m, 2H), 7.64-8.00 (m, 1H), 8.36-8.52 (m, 1H); IR(KBr) 1770 cm^{-1}. Calcd. for $C_{11}H_8O_3N_2$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.03; H, 3.45; N, 13.15.
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14. Further studies on the synthetic utility of 2-DPC and related compounds are in progress and will be published elsewhere.

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