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A NEW CONVENIENT METHOD FOR THE ESTERIFICATION OF CARBOXYLIC ACIDS

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Abstract : Reaction of carboxylic acids with equimolar amounts of alkyl chloroformate and triethylamine in the presence of a catalytic amount of 4-dimethylaminopyridine affords the corresponding esters in high yields without the formation of the symmetrical anhydride in most carboxylic acids.

The esterification of carboxylic acids is an important and well-established reaction which is frequently used in the synthesis and manipulation of many natural products and considerable progress has been made in the development of various mild esterification methods.[1]

We wish to report a new convenient method for the direct, high-yield conversion of carboxylic acids via the intermediacy of the mixed carboxylic-carbonic anhydrides into the corresponding esters in high yields under mild conditions.

It is known that mixed carboxylic-carbonic anhydrides are reasonably stable compounds which can be isolated in pure form and the thermal decomposition of the carboxylic-carbonic anhydride usually yields two types of products: the ester (eq. 1) and the symmetrical anhydride and the carbonate (eq. 2).[2] Contrary to the stability of the carboxylic-carbonic anhydrides toward tertiary amines, facile conversion of the mixed anhydrides of α-keto acids in the presence of triethylamine into α-keto esters has been recently reported (eq. 3).[3]

$$\mathrm{RCOOH + ClCOOR'} \xrightarrow{\mathrm{Et_3N}} \mathrm{RCOOCOOR'} \begin{array}{ll} \nearrow \mathrm{RCOOR' + CO_2} & (1) \\ \searrow \mathrm{(RCO)_2O + (R'O)_2CO} & (2) \\ \qquad\qquad \mathrm{+\ CO_2} & \end{array}$$

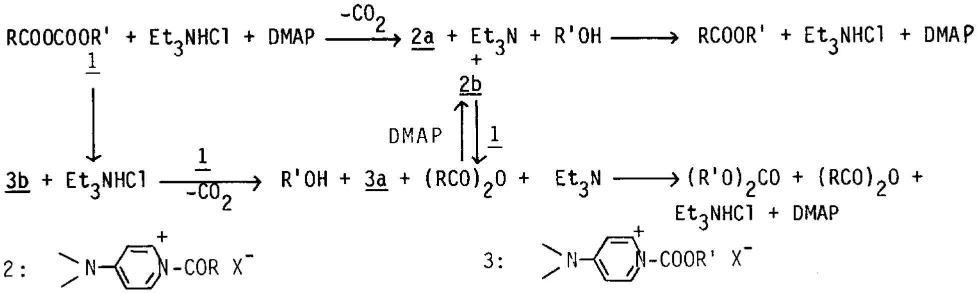
$$\mathrm{RCOCOOH + ClCOOR'} \xrightarrow{\mathrm{Et_3N}} \mathrm{RCOCOOCOOR'} \longrightarrow \mathrm{RCOCOOR' + CO_2} \qquad (3)$$

$$\mathrm{RCOOH + ClCOOR' + Et_3N} \xrightarrow[\mathrm{DMAP}]{\mathrm{cat.}} \mathrm{RCOOR' + CO_2} \qquad (4)$$

We have found that the addition of a catalytic amount of 4-dimethylaminopyridine (DMAP)[4] is exceedingly effective in the conversion of the mixed carboxylic-carbonic anhydride, generated from equimolar amounts of carboxylic acid, alkyl chloroformate, and triethylamine, into the corresponding ester in high yields (eq. 4).[5] The reaction proceeds rapidly and smoothly in methylene chloride at 0°C. The procedure is operationally simple as being illustrated by a typical example.

To a solution of caprylic acid (435 mg, 3.0 mmol), ethyl chloroformate (326 mg, 3.0 mmol), and triethylamine (330 mg, 3.3 mmol) in methylene chloride (10 ml) at 0°C was added DMAP (36 mg, 0.3 mmol). The resulting solution was stirred at 0°C for 30 min, diluted with methylene chloride (30 ml), and washed with saturated NH_4Cl. The aqueous layer was extracted with methylene chloride and the combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was distilled to afford ethyl caprylate (495 mg) in 95% yield.

The preparation of the esters has been performed on a variety of structurally different acids to determine the scope and limitations of this method. Some experimental results are summarized in Table I. Most aliphatic carboxylic acids, upon treatment with equimolar amounts of alkyl chloroformate and triethylamine in the presence of a catalytic amount of DMAP, yield the corresponding esters in high yields without contamination of the symmetrical acid anhydrides and the carbonates. However, the formation of the symmetrical acid anhydride as a minor product is observed in the esterification of aromatic carboxylic acids. Also, it is found that increment of the amount of DMAP drastically decreases the formation of symmetrical acid anhydride. Thus, applications of 0.1, 0.2 and 0.5 equiv of DMAP to an equimolar mixture of benzoic acid, ethyl chloroformate, and triethylamine yield 33%, 10%, <1% of benzoic anhydride, respectively. Furthermore, this method reaches a limit with sterically hindered carboxylic acids. Pivalic acid, upon treatment with equimolar amounts of benzyl chloroformate and triethylamine in the presence of 0.1 or 0.5 equiv of DMAP, gives approximately a 1:1 mixture of benzyl pivalate and pivalic anhydride, whereas a highly hindered mesitoic acid gives only mesitoic anhydride without the ester formation.[6]



2a : X = Cl, 2b : X = RCOO

3a : X = Cl, 3b : X = RCOO

Scheme I

Table I. Esterification of Carboxylic Acids

$$\mathrm{RCOOH + ClCOOR' + Et_3N \xrightarrow[CH_2Cl_2,\ 0^oC]{cat.\ DMAP} RCOOR'}$$

R	R'	Molar equiv of DMAP	Time, h[a]	Yield, %[b,c] RCOOR'
$CH_3(CH_2)_6$	CH_2CH_3	0.1	0.5	95
	$CH_2C_6H_5$	0.1	0.5	97
	$CH(CH_3)_2$	0.3	0.25	96
	$CH[CH(CH_3)_2]_2$	0.3	1	96
$C_6H_5CH_2$	CH_3	0.1	1	94
	$CH_2C_6H_5$	0.1	1	94
$(CH_3)_2CH$	$CH_2C_6H_5$	0.1	0.25	89
	$CH[CH(CH_3)_2]_2$	0.3	1	93
	CH_2CH_3	0.1	1	91
	$CH_2C_6H_5$	0.2	1	92
$(C_6H_5)_2CH$	CH_2CH_3	0.1	0.25	93
	$CH_2C_6H_5$	0.1	0.25	95
	$CH[CH(CH_3)_2]_2$	0.1	1	98
C_6H_5	CH_2CH_3	0.1	3	56(33)
	CH_2CH_3	0.2	3	82(10)
	CH_2CH_3	0.5	0.5	91(<1)
	$CH(CH_3)_2$	0.5	0.5	85(9)
	$CH(CH_3)_2$	1.0	0.5	96(<1)
P-Cl-C_6H_4	CH_2CH_3	0.5	0.5	89(<1)
$(CH_3)_3C$	$CH_2C_6H_5$	0.1	1	47(52)[d]
2,4,6-$(CH_3)_3$-C_6H_2	$CH_2C_6H_5$	0.1	4	0(81)[e]

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[a] Not optimized. [b] Isolated yields. Satisfactory spectral data (NMR, IR) and physical data (MP, BP) have been obtained for the esters. [c] The numbers in parentheses indicate isolated yields of the symmetrical acid anhydrides. [d] The yield was determined by NMR analysis and dibenzyl carbonate was isolated in 45% yield. [e] Dibenzyl carbonate was also isolated in 76% yield.

Although clear conclusions regarding the reaction mechanism await further study, the esterification proceeds apparently via the intermediacy of the carboxylic-carbonic anhydride.[7] As seen in Scheme I, the mixed anhydride may be converted to an acylpyridinium species (2a) as a major pathway along with an alkoxycarbonylpyridinium species (3b) to some extent in most carboxylic acids. Nucleophilic attack by R'OH on the acyl group of 2a gives the ester and DMAP, which is reused in the formation of 2a. Also, the acid anhydride, which is formed via nucleophilic attack by $RCOO^-$ of 3b on the carboxyl carbonyl group of the mixed anhydride, can be partly converted to 2b by DMAP to raise the yield of the ester, while 3a is converted to the carbonate. In the case of hindered carboxylic acids, presumably the reaction proceeds via the intermediacy of 3b.[8]

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References and Notes

1. For an excellent review, see: E. Haslam, Tetrahedron, 36, 2409 (1980) and references therein.
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6. Application of 0.1, 0.5, and 1 equiv of DMAP did not alter the ratio of the ester and the acid anhydride, yielding only mesitoic anhydride in all cases.
7. When pure mixed anhydride ($CH_3(CH_2)_6COOCOOC_2H_5$) was treated with 0.1 equiv of DMAP in methylene chloride at room temperature for 15 min, only ethyl caprylate was obtained in 91% yield after distillation.
8. Reaction of mesitoic anhydride with 1 equiv of DMAP in methylene chloride at r.t for 2h did not form an acylpyridinium species and the unreacted mesitoic anhydride was recovered in 92% yield.

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