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DIRECT ROOM TEMPERATURE ESTERIFICATION OF CARBOXYLIC ACIDS[1]

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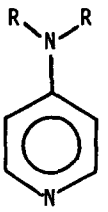
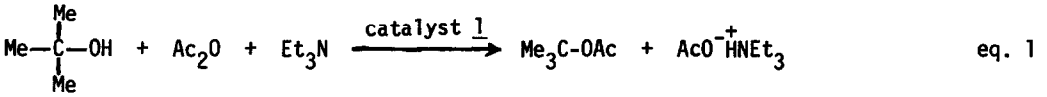
We wish to report a mild one pot esterification method, which allows the conversion of a carboxylic acid at room temperature and under essentially neutral conditions into an ester. The method is applicable to N-protected amino acids and to formation of tert butyl esters.

Mild esterification procedures are of considerable interest in the synthesis and manipulation of many natural products. While a number of such methods are known,[2] most require either the presence of strong acids, the isolation of intermediate acyl derivatives or the application of heat.

A useful catalytic acylation of alcohols, including tertiary alcohols,[3] consists of reaction of the alcohol with an acid anhydride or acid chloride in the presence of an equivalent amount of triethylamine and an amino pyridine, e.g., 1, as a catalyst (0.05-0.1 equiv) as shown in eq. 1. Among the catalysts studied, 2 and 3 appear to be the most effective.[4]



1, R:Me
2, R:$(CH_2)_4$
3, R:$C(NMe_2)_2$



eq. 1

While this represents an excellent method for acylation of alcohols, it is less adequate for the esterification of carboxylic acids because of the necessity of preformation of the anhydride, the requirements of an equivalent amount of base (triethylamine) and finally in the case of valuable starting material because half of the RCO_2H moiety is wasted in the reaction (e.g., AcOH in eq. 1).

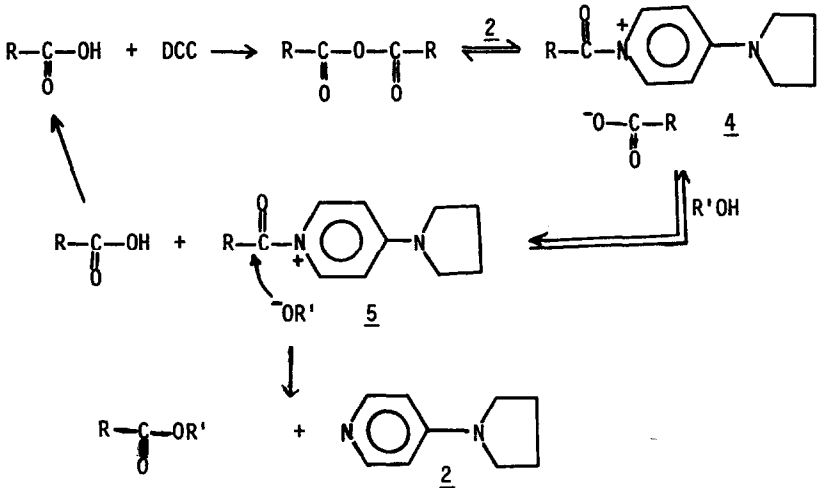
We have solved the above problems by incorporation of a carbodiimide (DCC) into the reaction. The presence of one equivalent of DCC permits one to start with one equivalent of a carboxylic acid, which can be completely converted to ester as shown by eq. 2.

$$R{-}CO_2H + R'{-}OH + DCC \xrightarrow{\text{catalyst } \underline{2}} R{-}\underset{\underset{O}{\|}}{C}{-}O{-}R' + (C_6H_{11}{-}NH)_2C{=}O \qquad \text{eq. 2}$$

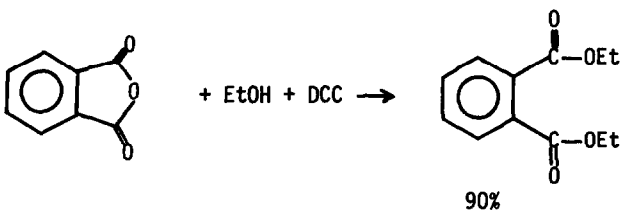
Several examples are shown in Table I. The reaction proceeds at 25°, the urea is filtered, the solution evaporated and the product crystallized. The yields of isolated pure ester are generally high. Hindered carboxylic acids like pivalic or mesitoic acid work well with unhindered alcohols. N-protected amino acids can likewise be esterified at room temperature. The method is applicable to the formation of benzyl or t-butyl esters important as protecting groups.

The reaction is based on a requirement for both DCC and aminopyridine catalyst. Thus, in the absence of 2, phenyl benzoate is formed in 10% instead of 94% yield, whereas in the absence of DCC no reaction occurs. Apparently, the carboxylic acid is converted by DCC to anhydride, which forms an acylpyridinium species 4 with the catalyst.[4] This is followed by equilibration of 4 with the alcohol to produce ion pair 5 (see Scheme 1). Nucleophilic attack by $R'O^-$ on the acyl group of 5 generates the ester and catalyst 2. The carboxylic acid is recycled by DCC while the catalyst is reused in the formation of 4.

Scheme 1



If an acid anhydride is to be esterified by this method, only half of an equivalent is required since the acid is recycled. This is demonstrated by the conversion of phthalic anhydride into the diester in 90% yield, while in the absence of DCC, triethylamine is required and only the half ester is formed.



90%

Further studies to apply these concepts are underway.

Typical Procedure: A solution of carboxylic acid (0.010 mol), N,N-dicyclohexylcarbodiimide (0.011 mole), the alcohol (0.011 mol) and 4-pyrrolidinopyridine (0.001 mol) in ether or dichloromethane (25-50 ml) was allowed to stand at room temperature until esterification was complete. The N,N-dicyclohexyl urea was filtered and the filtrate washed with water (3x50 ml), 5% acetic acid solution (3x50 ml) and again with water (3x50 ml), dried ($MgSO_4$) and the solvent evaporated in vacuuo to give the ester (see Table).

TABLE 1

DIRECT ESTERIFICATION OF RCO_2H WITH R'OH WITH DCC AND CATALYST 2 AT 25° IN ETHER OR CH_2Cl_2

RCO_2H	R'OH	TIME HR	% YIELD OF ESTER[a]
benzoic	EtOH	0.5	90
benzoic	PhOH	6	94
acetic	tBuOH	3	90
p-Br phenylacetic	EtOH	12	96
diphenylacetic	EtOH	12	96
mesitoic	p-NO_2 phenol	12	90
isobutyric	t-BuOH	24	65
N-benzoyl ala	$PhCH_2OH$	2	80
N-CBZ ala-DL	o-nitrobenzyl alcohol	2	78
L-N-CBZ-phenyl ala	p-nitrophenol	1	71

[a]Isolated pure material (recrystallized or distilled).

Acknowledgment

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References and Notes

1. Synthetic Methods 12. For Part 11 see A. Hassner and J.A. Soderquist, J. Organometal. Chem. in press (1978).
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