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Ester Synthesis with Dicyclohexylcarbodiimide Improved by Acid Catalysts

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When dicyclohexylcarbodiimide is used as condensing agent in ester synthesis, the yield of ester is often unsatisfactory due to formation of *N*-acylurea derivatives as by-product. This side reaction has been found to be suppressed when the esterification is performed in pyridine in the presence of a catalytic amount of a strong acid. Esters of primary and secondary alcohols as well as of phenols can be made in almost quantitative yield by this method.

During recent years, carbodiimides, and especially dicyclohexylcarbodiimide (DCC), have attracted increasing attention as condensing agents in ester synthesis.[1,2] Esters of carboxylic acids with primary and secondary alcohols, as well as with phenols, have been obtained by this method.[3] However, the yield of ester is usually decreased by the simultaneous formation of a *N*-acylurea derivative (*4*) as by-product.[4,5]

$$R^1-COOH + R^2-OH + R^3-N=C=N-R^4 \rightarrow$$

$$R^1-COO-R^2 + R^3-NH-CO-\underset{\displaystyle CO-R^1}{\overset{|}{N}}-R^4 \qquad 4$$

This by-product may also cause problems in the work-up procedure and contaminate the desired ester. Numerous attempts have been made to increase the yield of ester by searching reaction conditions so as to avoid the formation of the by-product. It has been found that the use of pyridine as solvent promotes the formation of ester[1,6], but usually considerable quantities of *N*-acylurea cannot be avoided.

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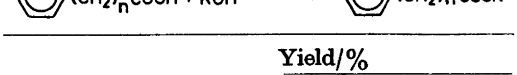
It has now been found that addition of a catalytic amount of a strong acid to the pyridine solution considerably increases the yield of ester and decreases the formation of the *N*-acylurea compound. Table 1 shows that condensation of carboxylic acids with phenols and primary and secondary alcohols in pyridine with DCC in the presence of a catalytic amount of *p*-toluenesulfonic acid (pTSA) gives excellent yields of ester, whereas reactions without the acid catalyst give a poorer result, due to the formation of the corresponding *N*-acylurea derivative.

The unsatisfactory yield of benzoate ester obtained when the reaction is carried out in the absence of an acid catalyst is in agreement with earlier results of esterifications using DCC as condensing agent. Methyl benzoate has been prepared in a 60 % yield using a large excess of methanol,[4] and phenyl benzoate has been

Table 1. Reaction of a carboxylic acid, a hydroxyl compound, and DCC (molar ratio 1.0: 1.1: 1.2) in pyridine.



n	R	Yield/% With pTSA	Yield/% Without pTSA
0	Hexyl	95	40
0	i-Propyl	98	5
0	*t*-Butyl	8	0
0	Phenyl	96	20
2	Butyl	96	66
2	i-Propyl	99	58
2	*t*-Butyl	17	3
2	Phenyl	93	39

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obtained in a 12 % yield from equimolar amounts of reactants.[7]

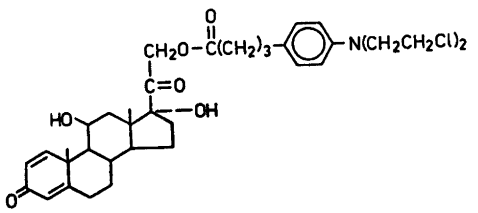
When tertiary alcohols are employed, the yield of ester is relatively poor, even when pTSA is added to the reaction mixture. However, the promoting effect of the acid catalyst on the formation of ester is evident also in this case.

Using phenols and primary and secondary alcohols, high yields of ester are obtained without an excess of one reactant. This indicates that, compared to other esterification procedures, the present method is especially useful in the synthesis of esters of expensive starting materials, where the use of a large excess of one reactant is highly uneconomical.

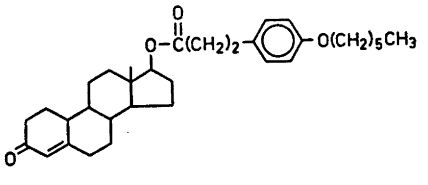
Steroid alcohols esterified with valuable carboxylic acids are one type of ester which might preferably be synthesized by this method. This class of esters is of great pharmaceutical interest, *e.g.* as anti-cancer agents [8,9] and as long-acting hormonal agents.[10] Two steroid esters of long-chain carboxylic acids have now been prepared in pyridine using DCC as condensing agent. The catalytic effect of pTSA on the reactions is evident from the yields given in Table 2.

Catalytic effects were also obtained with other strong acids such as hydrochloric, sulfuric, nitric, perchloric and methanesulfonic acid. However, these effects were not evaluated quantitatively.

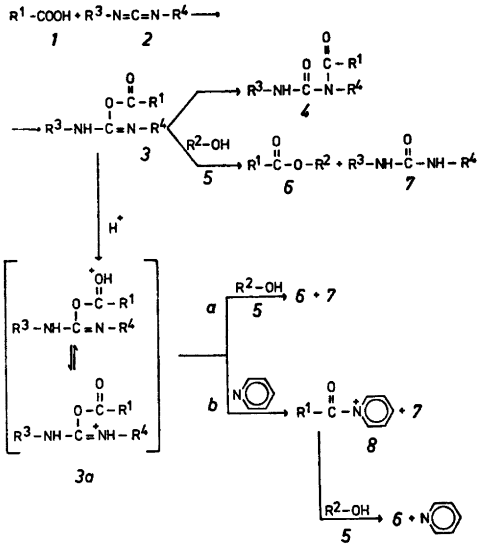
Table 2. Yield of steroid esters of long-chain carboxylic acids.



Yield with pTSA 85 % and without pTSA 74 %.



Yield with pTSA 87 % and without pTSA 50 %.



Scheme 1.

The role of the acid catalyst is not clear but is tentatively explained as follows (Scheme 1): In the uncatalyzed reaction, intermediate *3*, which is initially formed from carboxylic acid *1* and carbodiimide *2*, may either rearrange, by a cyclic electronic displacement, to the stable *N*-acylurea *4* or be attacked by alcohol *5* to give the desired ester *6* and the urea derivative *7*.

In the presence of an acid catalyst intermediate *3* is transformed to its protonated form *3a* which is less prone to rearrange to *4*. Ester *6* is then formed from *3a* either directly by attack of alcohol *5* (path *a*), or *via* an *N*-acylpyridinium ion *8* (path *b*). Acylpyridinium ions as intermediates are known from the literature.[11,12]

Path *b* has some resemblance to the mechanism proposed by Fritz and Schenk for the acid catalyzed acetylation of alcohols in pyridine.[13] Also in that case it was found advantageous to use a combination of pyridine and a strong acid.

It is, of course, conceivable that acetylpyridinium intermediates are formed also in the non-catalyzed reaction. However, since the *O*-acylisourea *3* is a poorer electrophile than its protonated analogue *3a*, the rate of attack by pyridine would be expected to be much slower in this case.

EXPERIMENTAL

Reactions according to Table 1. Benzoic acid (12.2 g, 0.10 mol), 1-hexanol (11.2 g, 0.11 mol) and pTSA (0.900 g) were dissolved in pyridine (90 ml). After addition of DCC (24.8 g, 0.12 mol), the solution was stirred at room temperature for 24 h. Acetic acid (10 ml) was added, and the mixture was kept overnight at 4 °C and then filtered. The crystals were washed with cold pyridine, and chloroform (100 ml) and ice (100 g) were added to the filtrate. The mixture was acidified with 5 M HCl, the phases separated and the organic phase washed with water, aqueous $NaHCO_3$ and water, dried and evaporated to give hexyl benzoate (95 % yield), b.p. 99–100 °C/13 Pa (lit.[10] 101 °C/13 Pa).

The other reactions illustrated in Table 1 were performed in an analogous way. The physical data of the products agreed with literature data.

Reactions according to Table 2. 11α,17,21-Trihydroxypregna-1,4-diene-3,20-dione (prednisolone, 7.20 g, 0.020 mol) and 4-[4-(*N*,*N*-bis(2-chloroethyl)amino)phenyl]butyric acid (chlorambucil, 7.00 g, 0.023 mol) were dissolved in dry pyridine (60 ml). pTSA (0.200 g) was added and the mixture was stirred for 15 min. To the homogeneous solution DCC (5.77 g, 0.028 mol) was added and stirring was continued for 24 h at room temperature. Acetic acid (2 ml) was added and the reaction mixture was kept overnight at 4 °C. The mixture was filtered and the crystals were washed with cold pyridine. A mixture of ethyl acetate (100 ml), ether (100 ml), and ice (100 g) was added to the filtrate and 5 M HCl was then slowly added to the stirred solution until pH reached 2.5. The organic phase was washed with water, 0.5 M aqueous K_2CO_3, and water. After evaporation of the solvent and recrystallization from isopropanol cream-coloured crystals of 21-[4-(4-(*N*,*N*-bis(2-chloroethyl)amino)phenyl)butanoyloxy]-11α, 17-dihydroxypregna-1,4-diene-3,20-dione (prednimustine), m.p. 165–166 °C, were obtained in an 85 % yield.

The structure was confirmed by comparison with a sample prepared by another route [8] and by physical data such as NMR, IR, and analysis for Cl and N. The significant signals of the NMR spectrum (60 MHz, $CDCl_3$) are the following: δ 0.95 (s, 3H, H-18), 1.44 (s, 3H, H-19), 3.67 (s, 8H, $-CH_2CH_2Cl$), 4.50 (broad signal, 1H, H-11), 5.00 (s, 2H, $-COCH_2OCO-$), 6.03 (d, 1H, H-4, $J_{4,2}=2$ Hz), 6.30 (dd, 1H, H-2, $J_{2,1}=10$ Hz, $J_{2,4}=2$ Hz), 6.69 and 7.12 (doublets, 2H each, aromatic H, $J=8$ Hz), 7.33 (d, 1H, H-1, $J_{1,2}=10$ Hz).

A mixture of 17β-hydroxyestr-4-en-3-one (5.48 g, 0.020 mol) and 3-(4-hexyloxyphenyl)-propionic acid (5.75 g, 0.023 mol) was dissolved in dry pyridine (60 ml). After addition of pTSA (0.200 g) and DCC (5.77 g, 0.028 mol), the solution was stirred for 72 h at room temperature, acetic acid (2 ml) was added, and the reaction mixture was kept overnight at 4 °C. The same work-up procedure as above gave 17β-[3-(4-hexyloxyphenyl)propanoyloxy]estr-4-en-3-one (m.p. 52–53 °C, pale yellow) in an 87 % yield after recrystallization from methanol/water.

The structure was confirmed by comparison with a sample prepared by another route [10] and by physical data such as NMR, IR, and UV. The significant signals of the NMR spectrum (60 MHz, $CDCl_3$) are the following: δ 0.80 (s, 3H, H-18), 3.93 (t, 2H, $\phi-O-CH_2-$), 4.65 (t, 1H, H-17), 5.85 (s, 1H, H-4) 6.83 and 7.11 (doublets, 2H each, aromatic H, $J=9$ Hz).

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