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Facile Acylation of Sterically Hindered Alcohols through Ketene Intermediates

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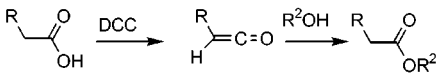
ABSTRACT

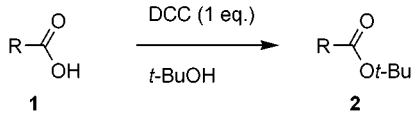


Carboxylic acids possessing strongly electron withdrawing substituents in the α-position in the presence of DCC acylate sterically hindered and chemically sensitive alcohols. The pattern of reactivity, the deuteration experiments, and the formation of a product derived from a [4 + 2] cycloaddition reaction corroborate the existence of ketene intermediates in the reaction.

Acylation of tertiary alcohols is a persistent synthetic problem in organic synthesis.[1] Common acylating agents such as acyl chlorides, even if used in a large excess, in many cases provide only moderate yields of tertiary esters[2] because the steric hindrance at the sp^2 carbon atom of the carbonyl group greatly reduces the rate of acylation. In these cases, ketenes could provide a viable alternative to the commonly used acylating agents. Because the sp carbon of ketenes is relatively exposed to nucleophilic attacks, ketenes could serve as efficient acylating agents for sterically hindered substrates, provided a mild and efficient method of ketene generation is elaborated.[3]

Here we would like to report the highly efficient acylation of sterically hindered alcohols including tertiary alcohols using diethylphosphonoacetic and cognate carboxylic acids with DCC and preliminary studies toward the investigation of the mechanism of the acylation reaction. The reaction is specific for carboxylic acids of type **1a**−**d** possessing strongly electron withdrawing groups such as COOR, P(O)-$(OEt)_2$, CN, or RSO_2 at the α-position to the carboxylic group. The reaction proceeds with equimolar quantities of reagents in essentially neutral conditions at room temperature and takes several minutes to complete. Even sterically hindered and chemically sensitive alcohols can be acylated in excellent yield.

The esterification of *tert*-butyl alcohol was chosen as a model reaction for comparing the reactivity of various carboxylic acids (eq 1). The results are summarized in Table



1 **2** (1)

1. All the reactions were performed in dichloromethane with 1 equiv of DCC except entries **c** and **d** where a dichloromethane−acetonitrile mixture was used because of solubility considerations.

Table 1. Preparation of *tert*-Butyl Esters with DCC

	R	yield (%)
a	$(EtO)_2P(O)CH_2$	100 (isolated)
b	EtO_2CCH_2	100 (isolated)
c	$NCCH_2$	75 (isolated)
d	p-CH_3-$C_6H_4SO_2CH_2$	100 (isolated)
e	Me	0 (^{1}H NMR of crude)
f	$C_6H_5CH_2$	0 (^{1}H NMR of crude)
g	$(C_6H_5)_2CH$	0 (^{1}H NMR of crude)
h	$BrCH_2$	0 (^{1}H NMR of crude)
i	$EtO_2CCH(Me)$	60 (isolated)

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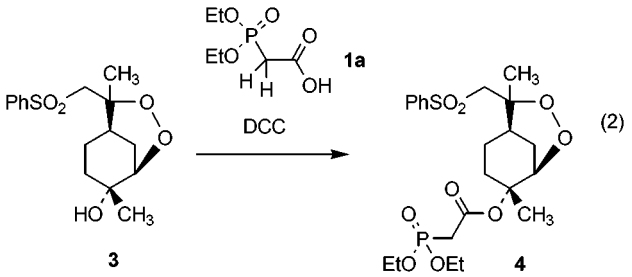
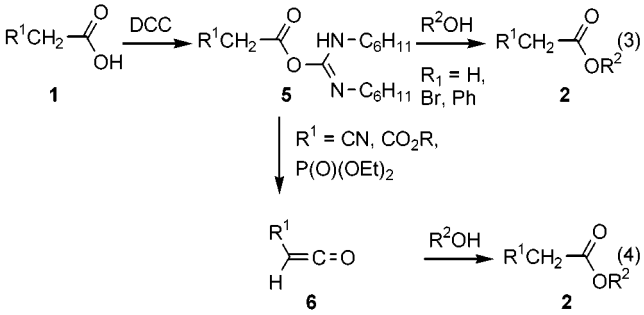
In contrast to acids **1a**−**d**, carboxylic acids **1e**−**h** lacking electron-withdrawing groups failed to give measurable amounts of the corresponding *tert*-butyl esters under these conditions. Similarly, competition studies involving the acylation of *tert*-butyl alcohol with a 1:1 mixture of diethylphosphonoacetic acid and acetic, bromoacetic, or diphenylacetic acids and 1 equiv of DCC provided exclusively the esterification product **2a** derived from the diethylphosphonoacetic acid (**1a**).

To demonstrate the synthetic utility of the method, we performed the acylation of the highly sterically hindered and chemically sensitive peroxide alcohol **3** known as a key compound in the synthesis of highly potent antimalarial derivatives.[4] The reported acylation of the alcohol **3** proceeds with a very big excess of acetyl chloride and provides a low yield of the ester.[5] In contrast, treatment of the alcohol **3** with diethylphosphonoacetic acid/DCC provides the ester **4** in a high yield (92%) under very mild conditions (eq 2).

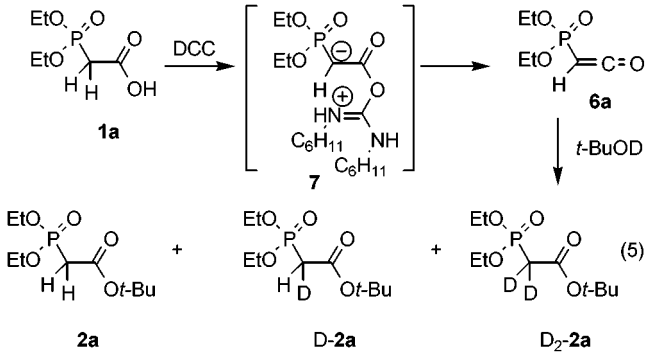


The very high reactivity of acids of type **1a**−**d** coupled with the very low reactivity of "regular" carboxylic acids of type **1e**−**h** under identical reaction conditions can be rationalized through the intermediacy of a highly electrophilic species with relatively low steric demand, e.g., the formation of the corresponding ketene. In contrast to "regular" carboxylic acids such as **1e**−**h** that acylate alcohols through acid−DCC adducts of type **5**,[6] the presence of a strongly electron withdrawing group in the α-position to the carboxyl can enable an elimination pathway through an E1cB mechanism to give the corresponding ketenes of type **6** (eq 4).



The formation of ketene intermediates through an E1cB mechanism has been well established in reactions of hydrolysis or aminolysis of activated esters including acetoacetyl and malonyl coenzyme A derivatives.[7] Furthermore, it has been reported that some specific, highly stabilized ketenes can be prepared in a direct reaction from carboxylic acids and DCC in the presence of triethylamine, although under relatively harsh conditions.[8] The reaction of carboxylic acids with various dehydrating reagents such as dialkylchlorophosphates in the presence of triethylamine is also known to provide ketenes.[9] The preparation of ketenes under mild conditions is highly important, and several approaches including photolysis reactions, Wolff rearrangement of diazoketones,[10a] the use of insoluble bases,[10b,c] and mixed anhydride methods[10d] have been tried. We believe that the proposed approach provides a simple and efficient alternative to these methods.

The validity of the ketene pathway was investigated by deuteration experiments. Neither diethylphosphonoacetic acid (**1a**) nor its ester **2a** undergo deuteration in the presence of weak bases such as DCC.[11] In contrast, reaction of **1a** with *tert*-butyl alcohol-*d* and 1 equiv of DCC resulted, as evidenced by ^{1}H and ^{31}P NMR, in the incorporation of deuterium into the α-position of the resultant ester **2a** in full agreement with the ketene mechanism (eq 5).[12]



The ^{31}P NMR of the deuterated ester **2a** strongly evidences in favor of the E1cB mechanism of ketene formation vs a

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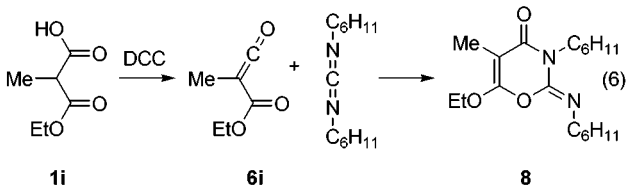
(11) No deuteration product was detected after treatment of **2a** with *t*-BuOD/DCC for 5 h or with *t*-BuOD/triethylamine for 30 min in dichloromethane at room temperature.

possible E2 mechanism. The proton-decoupled ^{31}P NMR of the isolated product shows three singlets assigned to nondeuterated, monodeuterated, and dideuterated molecules at 25.500, 25.518, and 25.536 ppm. The presence of d_2-**2a** products, obtained also by the treatment of unlabeled ester **2a** with *t*-BuOK/*t*-BuOD, is consistent with an E1cB mechanism but not with an E2 mechanism.

To prove directly the formation of ketene intermediates in these reactions, we attempted trapping experiments in situ. The reaction of carboxylic acids **1a**−**d** with DCC was conducted in the presence of a big excess of nucleophilic olefins such as cyclopentadiene or ethyl vinyl ether. In all these reactions, in the ^1H NMR of the reaction mixture we did not observe cyclobutane derivatives typical of a [2 + 2] addition of ketenes to the olefins. However, [4 + 2] cycloaddition reactions of the ketenes take place. For example, the reaction of **1i** (or **1b**) with 2 equiv of DCC resulted in the formation of oxazine **8** in 59% yield (eq 6).



1i **6i** **8**

Formation of the oxazine products is typical for acylketenes and various double and triple C−C and C−N bonds compounds.[13]

While the exact mechanism of the acylation reaction using carboxylic acids of type **1a**−**d** will probably need further investigation, the synthetic utility of the present method for esterification of sterically hindered alcohols is evident. After the acylation, the acylated tertiary esters of type **2a**−**d** can be further transformed into a variety of other acyl derivatives using well-established methodologies based on the high acidity of the α-CH_2 group such as the Wittig−Horner reaction.[14]

In summary, we demonstrated a facile and highly efficient acylation of tertiary alcohols with various carboxylic acids possessing strongly electron withdrawing substituents in the α-position to the carboxyl group in the presence of DCC. Even highly hindered and chemically sensitive alcohols are acylated with excellent yields under neutral conditions at room temperature. The pattern of reactivity, the deuteration experiments, and the formation of a [4 + 2] cycloaddition product strongly suggest that the mechanism of the acylation involves the formation of highly reactive ketene intermediates.

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Supporting Information Available: Experimental procedures and characterization of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) In the ^1H NMR of *d*-**2a** the doublet (J_{PH} = 21.8 Hz) of broad triplets of the PCHD proton is shifted upfield by 0.014 ppm in comparison to the PCH_2 protons of **2a**.

(13) For example, see: (a) Saidi, K.; Shaterian, H.; Aghaei, D. *Heterocycl. Commun.* **2000**, 93−93. (b) Ried, W.; Nenniger, H. *Synthesis* **1990**, 167−170. (c) Yamamoto, Y.; Watanabe, Y.; Ohnishi, S. *Chem. Pharm. Bull.* **1987**, *35*, 1860−1870. (d) Stetter, H.; Kiehs, K. *Chem. Ber.* **1965**, *98*, 2099−2102. (d) *Helv. Chim. Acta* **1982**, *65*, 2230−2241. (e) Barbaro, G.; Battaglia, A.; Giorgianni, P. *J. Org. Chem.* **1987**, *52*, 3289−3296.

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