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Acylation through Ketene Intermediates

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Carboxylic acids possessing a strong electron-withdrawing group in the α-position undergo facile dehydration upon reaction with carbodiimides to form the corresponding substituted ketenes that can react in situ with alcohols providing esters in a high yield. The ketene formed by the treatment of ethyl 2-methylmalonate with DCC was trapped in situ by a [4+2] cycloaddition with a second DCC molecule. The chemoselectivity of the acylation through the ketene intermediates was found to be substantially different from that of conventional acylation reagents showing a very low sensitivity toward the steric bulk of alcohols. A comparison of the sensitivity of the acylation to the steric bulk of alcohols supports the presence of a pseudopericyclic pathway for the nucleophilic addition of alcohols to ketenes derived from ethyl malonic and diethylphosphonoacetic acid.

Introduction

Acylation of alcohols with carboxylic acids or their derivatives is one of the most fundamental reactions in organic chemistry. Depending on the type of a carboxylic acid derivative, the nature of the alcohol, and the experimental conditions, a wide variety of reaction mechanisms are possible. Providing high yields with unhindered alcohols, the acylation reaction is sensitive to steric factors. In these cases there is a substantial drop in the reaction rate that often results in low yields of esterification product, especially when side reactions are possible. Likewise, acylation of tertiary alcohols is a persistent problem in organic synthesis. Standard acylation procedures in many cases fail to provide adequate yields[1] especially in cases when chemically sensitive or polyfunctional substrates are used. Commonly used acylation catalysts such as 4-(dimethylamino)pyridine substantially increase the reaction rates and in the cases of simple substrates can provide high yields.[2] The resultant acylation species are, however, highly reactive to a large variety of functional groups such as the widespread primary or secondary amides.[3] This is particularly undesired in the acylation of polyfunctional substrates such as peptides. Methods for the efficient acylation of sterically hindered alcohols without additional nucleophilic functional groups were recently developed using Lewis acid catalysis.[4]

During our synthetic studies toward anticancer antibiotic leinamycin, we discovered a highly efficient acylation of the tertiary hydroxy functionality under very mild conditions using a mixture of diethylphosphonoacetic acid and dicyclohexylcarbodiimide (DCC). This esterification, however, failed to give even traces of the corresponding tertiary esters when acetic acid was used under identical conditions. Formation of tertiary esters by the commonly used carboxylic acid−DCC system contradicted the literature data[2e] as well as our experience, and consequently prompted us to investigate the reasons for the specificity of the reaction as well as its scope and limitations.

Results and Discussion

Our primary objective involved the investigation of the synthetic utility of the reaction. At first, the model acylation of *tert*-butyl alcohol was examined. Acylation of *tert*-butyl alcohol with the diethylphosphonoacetic acid (**1**)/DCC system (Scheme 1) afforded the corresponding *tert*-butyl ester **2** in excellent yield. In contrast, conventional carboxylic acids such as acetic, bromoacetic, phenylacetic, and diphenylacetic acids failed to provide even traces of their 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 in all cases the *tert*-butyl diethylphosphonoacetate **2** without any visible traces of other tertiary esters, as judged by the ^{1}H NMR spectrum of the reaction mixture.

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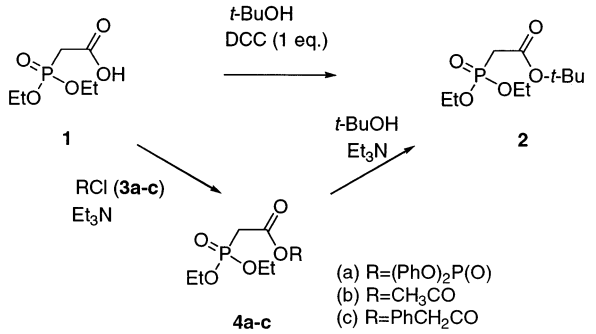
SCHEME 1



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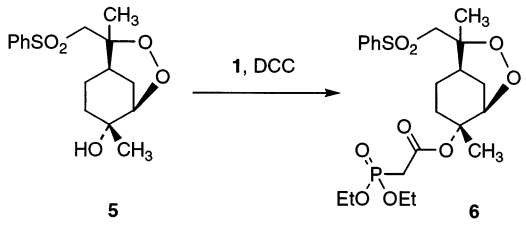
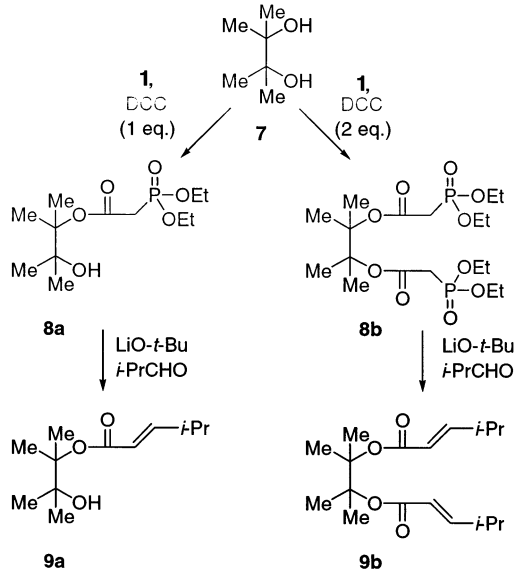


We also observed an identical specificity of the acylation using a mixed anhydride approach[5] for the activation of diethylphosphonoacetic acid (Scheme 1). Acylation of *tert*-butyl alcohol by a 1:1 mixture of diethylphosphonoacetic acid and diphenylphosphoryl chloride (**3a**) in the presence of 2 equiv of triethylamine proceed through the stage of the mixed anhydride **4a** and produced *tert*-butyl ester **2**. The extremely high reactivity of diethylphosphonoacetic acid allowed the use of regular acyl chlorides such as phenyl acetyl chloride as coupling reagents for the same esterification. The reaction with phenyl acetyl chloride produced exclusively the ester **2** without any observable traces of *tert*-butyl acetate or phenylacetate in the ^{1}H NMR of the reaction mixture.

The synthetic utility of the reaction for the acylation of highly sterically hindered and chemically sensitive alcohols is evident from the acylation of peroxide alcohol **5**, known as a key compound in the synthesis of highly potent antimalarial derivatives.[6] The reported acylation of the alcohol **5** (Scheme 2) involved a very large excess of acetyl chloride and 4-(dimethylamino)pyridine and provided a low yield of the ester.[7] In contrast, treatment of the peroxide alcohol **5** with diethylphosphonoacetic acid/DCC provided the corresponding ester **6** in high yield (92%) under very mild conditions.

Acylation with diethylphosphonoacetic acid can be considered as an indirect method for the preparation of a wide variety of esters of sterically hindered and chemically sensitive alcohols that cannot be prepared directly. The diethylphosphonoacetyl group can be converted into other functionalities using the Wittig−Horner−Emmonds olefination that is known to proceed under mild conditions.[8] For example, the acid sensitive pinacol **7** was successfully acylated or diacylated with the same diethylphosphonic acid/DCC system (Scheme 3). The subsequent olefination with isobutyraldehyde and a mixture of lithium perchlorate/DBU was done in one pot without purification of the diesters **8a,b** to give diesters **9a,b** in low yield. We found that lithium *tert*-butoxide is the more convenient reagent for the olefination step and provides substantially better yields of esters **9a**,**b**.

SCHEME 3



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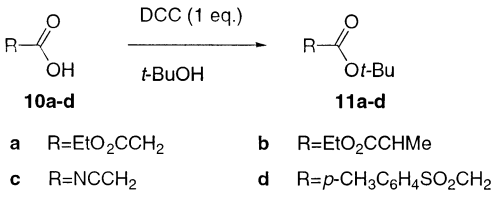

To the best of our knowledge, such a dramatic disparity between esterification reactions of diethylphosphonoacetic and other carboxylic acids has not been reported previously.[9] Because the most obvious reason for the unusual high reactivity of diethylphosphonoacetic acid is the relatively high acidity of the α-methylene group, we tested several analogous carboxylic acids substituted with electron-withdrawing groups in the model reaction with *tert*-butyl alcohol and DCC (Scheme 4).[10] Representative results are summarized in Table 1. All reactions were performed in dichloromethane with 1 equiv of DCC except entries **c** and **d** where dichloromethane−acetonitrile mixtures were used due to solubility considerations. Reactions of acids **10a**−**d** in pure acetonitrile produced results practically identical to those of reactions in dichloromethane. Reactions with diisopropylcarbodiimide proceed in a similar fashion, but a chromatographic purification step is necessary.

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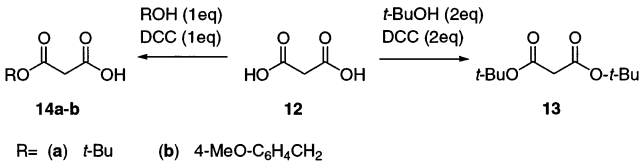
TABLE 1. Preparation of *tert*-Butyl Esters with DCC

acid	R	isolated yield, (%)
1	$(EtO)_2P(O)CH_2$	100
10a	$EtOC(O)CH_2$	100
10b	EtOC(O)CH(Me)	87
10c	$NCCH_2$	75
10d	p-CH_3−$C_6H_4SO_2CH_2$	100

SCHEME 5



The acylation of carboxylic acids of type **10a**−**d** possessing strong electron-withdrawing groups such as COOR, $P(O)(OEt)_2$, CN, or RSO_2 proceeded in a highly efficient manner providing the corresponding *tert*-butyl esters of type **11a**−**d**. The reaction proceeded with equimolar quantities of reagents in essentially neutral conditions at room temperature. At room temperature the reactions are completed in several minutes even at high dilution (0.01 M) and provide good to quantitative yields. If necessary, the acylation reaction can be conducted at temperatures as low as −40 °C although naturally larger reaction times are necessary.

Mono and Diesterification of Malonic Acid. Diesterification of malonic acid with 2 equiv of *tert*-butyl alcohol and carbodiimide proceeded readily, giving di-*tert*-butyl malonate (**13**) in excellent yield (Scheme 5). Surprisingly, to the best of our knowledge, this straightforward way of preparation of this important synthetic reagent has not been reported previously.

Monoesterification of ethyl malonate with *tert*-butyl alcohol could provide an efficient method for the preparation of nonsymmetric dialkylmalonates that are useful synthons in synthetic organic chemistry.[11] However, whereas ethyl malonate and some other monoalkyl malonates are available through selective hydrolysis of the corresponding commercially available dialkylmalonates,[12] the synthesis of other monoalkyl malonates is complicated. The most general existing method involves reaction of alcohols with Meldrum acid that provides a moderate yield of monoesters.[13]

We have found that a variety of monosubstituted malonic derivatives could be prepared by a simple reaction of malonic acid with equimolar amounts of DCC and the alcohol in acetonitrile (Scheme 5). The reaction produces monosubstituted malonates of type **14a**,**b** in good yields without the necessity of chromatographic workup making the reaction suitable for large-scale syntheses.

Reaction Mechanism. Conventional mechanisms of acylation of sterically hindered substrates are characterized by the presence of steric hindrance at the transition state, leading to the tetrahedral intermediate that is especially significant in acylation of tertiary alcohols. Facile acylation of tertiary alcohols with carboxylic acids **1** and **10a**−**d** featuring the presence of a strong electron-withdrawing substituent in the α-position suggested that the reaction may proceed through another, completely different type of highly reactive intermediate possessing very low sensitivity toward steric factors. From a purely geometric point of view, ketenes could be possible candidates for the role of these reactive intermediates. Because the sp carbon of ketenes should be relatively exposed to nucleophilic attacks, ketenes could in principle serve as suitable acylating agents for sterically hindered substrates.

The existence of an elimination−addition mechanism of hydrolysis of carboxylic acid derivatives involving the intermediacy of ketenes is well documented.[14] Although the most general method for the generation of ketenes[15] is reaction of acyl chlorides with tertiary amines, various mixed anhydrides (prepared by the reaction of carboxylic acids with dehydrating reagents such as dialkylchlorophosphates) in the presence of tertiary amines generate ketenes.[16] Moreover, some specific, highly stabilized ketenes can be prepared in a direct reaction from carboxylic acids and DCC in the presence of triethylamine although the harsh conditions used in this transformation are radically different from the mild conditions used for the esterification of acids **1** and **10a**−**d**.[17] Because the presence of electron-withdrawing groups is known to substantially facilitate elimination reactions, some carboxylic acid derivatives possessing relatively poor leaving groups can also generate ketenes with the elimination mechanism ranging from E2 to E1cB.[18] Consequently, aminolysis of activated esters including acetoacetyl and malonyl coenzyme A derivatives proceed through a E1cB mechanism.[19] The basic hydrolysis of *p*-nitrophenol esters of diethylphosphonoacetic, cyanoacetic, ethyl malonic, and 2-methyl malonic acids was found to proceed 10^2−10^3 times faster than those of regular carboxylic acids.[20]

Known E1cB reactions tend to proceed in the presence of external bases.[14] However, although *O*-acyl isoureas are relatively weak bases, the suitable geometry of the *O*-acyl urea derivatives of type **17** (Scheme 6) should facilitate an intramolecular proton transfer, thereby

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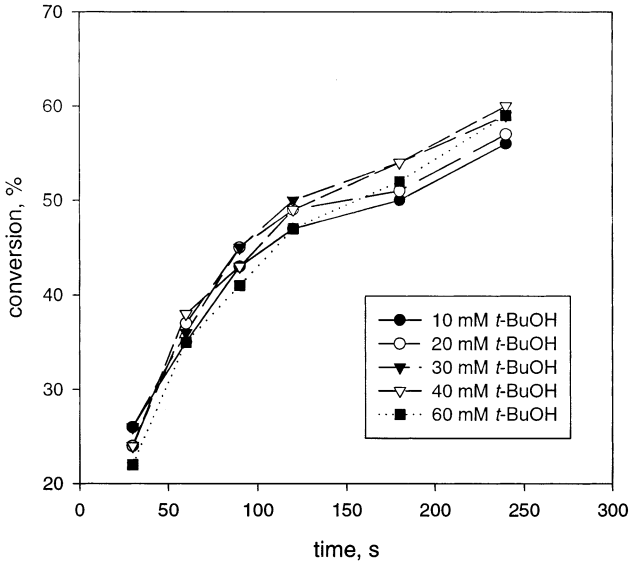


FIGURE 1. Kinetic curve for the esterification of *p*-methoxybenzyl malonate (10 mM) in dichloromethane with *t*-BuOH (10−60 mM) and diisopropylcarbodiimide (10 mM) at 0.4 °C.

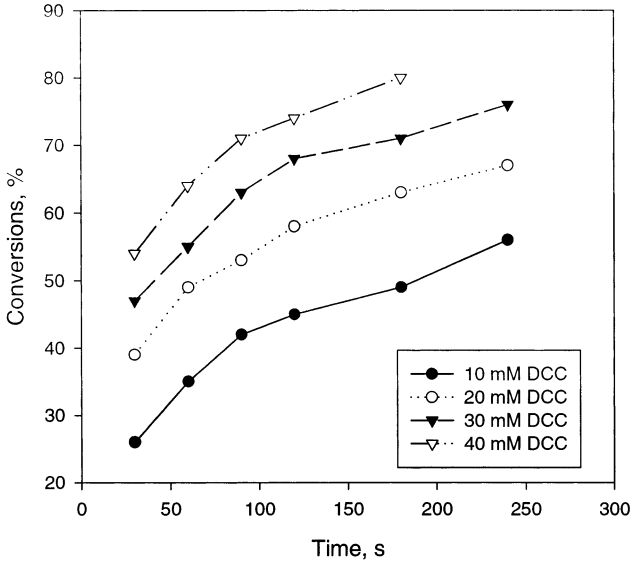
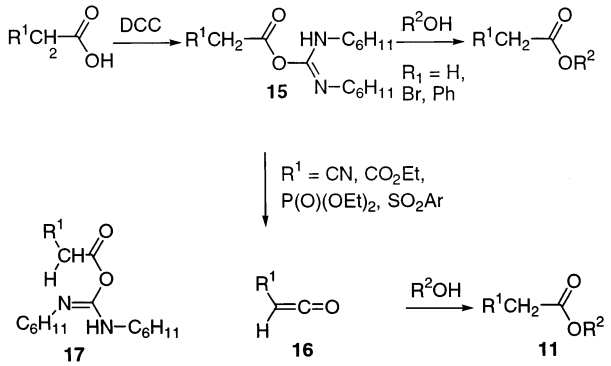


FIGURE 2. Kinetic curve for the esterification of *p*-methoxybenzyl malonate (10 mM) in dichloromethane with *t*-BuOH (10 mM) and diisopropylcarbodiimide (10−40 mM) at 0.4 °C.

SCHEME 6

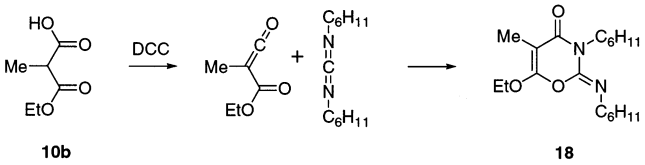


inducing such a concerted or stepwise elimination even in the absence of external bases to give ketenes of type **16**.

We found that the rate of reaction of 4-methoxybenzyl malonate **14b** with *tert*-butyl alcohol in dichloromethane was practically identical at different concentrations of *tert*-butyl alcohol in the 10−60 mM range (Figure 1). At the same time, the reaction rate showed strong dependence on the concentration of diisopropylcarbodiimide in the same 10−60 mM range (Figure 2), thus indicating that the addition of 4-methoxybenzyl malonate to the carbodiimide molecule is most likely to be the rate-limiting step of the reaction. However, the kinetic curve in both cases did not correspond completely to a second-order reaction, most probably because the addition of carboxylic acids to carbodiimides can proceed through acid dimers.[21]

The validity of the ketene pathway was indirectly supported by deuteration experiments.[10] To prove directly the formation of ketene intermediates in these reactions, we attempted trapping experiments in situ using [2+2] cycloaddition reactions typical for ketenes. The reaction

SCHEME 7



of carboxylic acids **10a**−**d** with 1 equiv of DCC was conducted in the presence of a large excess of nucleophilic olefins such as cyclopentadiene or ethyl vinyl ether.[22] In all these reactions, however, we did not succeed in observing even traces of cyclobutanone derivatives in the ^{1}H NMR of the reaction mixture. Most likely, competing reactions such as formation of acyl anhydrides or *N*-acyldicyclohexylurea proceed much faster than the [2+2] cycloaddition.

It is known that [4+2] cycloaddition reactions in acylketenes are in many cases faster than [2+2] ones and, therefore, the former can be used for trapping the ketene intermediates.[23] Particularly, the reaction of acylketenes with carbodiimides is known to produce oxazines.[24] Our attempts to perform the reaction of acylketene precursors **10b**[25] with 2 equiv of DCC resulted in the formation of oxazine **18** in 59% yield (Scheme 7). Similar reactions with carboxylic acids **1** and **10c**,**d** failed to provide the corresponding cycloaddition products.

The preparation of ketenes under mild conditions is of great interest, and several approaches including pho-

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(25) Ethyl malonate **1b** also participates in a similar reaction.

SCHEME 8

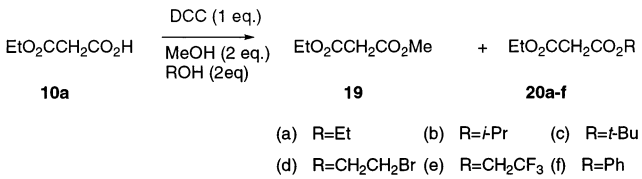

TABLE 2. Relative Rates (to MeOH) for the Acylation of Alcohols with the Ethyl Malonate−DCC System in Dichloromethane and Acetonitrile at 25 °C

product	R	CH_2Cl_2	MeCN
21a	Et	1	1
21b	*i*-Pr	1	0.7
21c	*t*-Bu (**2b**)	0.07	0.07
21d	$BrCH_2CH_2$	0.10	0.7
21e	CF_3CH_2	<0.01	<0.01
21f	Ph	<0.01	<0.01

tolysis reactions, Wolf rearrangement of diazoketones,[26a] insoluble bases,[26b,c] and mixed anhydride methods[26d] have been successfully used. We believe that the proposed methodology provides a simple and efficient method for the in situ preparation of ketenes in neutral conditions.

Examples involving the preparation of esters of tertiary alcohols suggested that the chemoselectivity of ketene intermediates of type **16** in acylation of tertiary alcohols is substantially different from that of conventional acylation reagents. To estimate the scope, limitations, and chemoselectivity of the acylation of alcohols through ketene intermediates, we determined the relative reactivities of different aliphatic alcohols and phenols on the model reaction with ethyl malonate. This model was chosen because of the availability of data on the chemoselectivity of nucleophilic addition to acetylketene.[27]

The relative rates of the reactions were determined by conducting the reaction using a mixture of two alcohols (Scheme 8) followed by ^{1}H NMR analysis of the reaction mixture. To determine the influence of solvents on the relative rates, the acylation experiments were conducted in both dichloromethane and acetonitrile.

As seen from Table 2, the reactivities of methanol, ethanol, and 2-propanol are remarkably similar. Only *tert*-butyl alcohol was found to react approximately 15 times slower than methanol. These relative rates were almost identical in both dichloromethane and acetonitrile. These results are completely different form those reported for conventional acylation reactions[28] that show that the reactivities of primary, secondary, and tertiary alcohols differ by several orders in magnitude. Because data on relative rates of acylation of alcohols are surprisingly scarce, we performed several experiments ourselves. The competitive acylation of similar mixtures of alcohols with phenylacetyl chloride in dichloromethane displayed a relative rate of ca. 0.04 for 2-propanol and a very low rate (<0.01) for *tert*-butyl alcohol. The acylation with the acetic anhydride/(dimethylamino)pyridine system in acetonitrile provided a relative rate of ca. 0.02 for 2-propanol and again a very low rate for *tert*-butyl alcohol. Literature data on nucleophilic addition to ketenes show a substantially smaller difference in the reactions of aliphatic alcohols than conventional acylation reactions with a 2−3 times difference in acylation rates between primary and secondary alcohols.[29] Even so, the esterification of ethyl malonate shows the lowest sensitivity toward steric hindrance.

The difference in reactivity induced by electronic effects was much more substantial than steric effects. Reaction with 2-bromoethanol proceeds substantially slower than with methanol, but the chemoselectivity strongly depends on the solvent. Trifluoroethanol possessing an extremely low nucleophilicity predictably showed a very low reaction rate in comparison to methanol. Phenol also showed a much lower reaction rate in comparison to aliphatic alcohols.[30] Both esters **20a**,**f** can nevertheless be prepared by the reaction of ethyl malonate with these alcohols and DCC although yields are only moderate.

Qualitatively, the obtained data on the chemoselectivities in nucleophilic addition corresponded to those reported by Birney for acetylketene using a pyrolysis technique at 400 °C.[27] The most important differences are the relative rates of 2-propanol (ca. 1 for ethyl malonate vs 0.33 for acetylketene) and of trifluoroethanol (<0.02 for ethyl malonate vs 0.16 for acetylketenes). These differences can be expected by taking into account the large differences in experimental conditions.

Mechanism of Nucleophilic Addition of Alcohols to Ketenes of Type 16. The most commonly accepted models for the mechanism of noncatalyzed nucleophilic addition of water and alcohols to ketenes are a stepwise addition with the formation of intermediate zwitterions of type **21**[31] (Scheme 9) and an energetically favorable concerted termolecular mechanism with a six-membered transition state of type **22** (Scheme 9).[32] The presence of strong electron-withdrawing groups (like in ketenes of type **16**) should substantially stabilize the zwitterionic transition state,[33] making the stepwise mechanism preferable over the concerted termolecular mechanism. At the same time, there is strong experimental and theoretical evidence that acylketenes are capable of an unusually

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(30) In similar competition experiments with *tert*-butyl alcohol the relative rates of trifluoroethanol and phenol were also less that 0.02.

(31) For a review on addition reactions of ketenes see: (a) Seikali, H. R.; Tidwell, T. T. *Tetrahedron* **1986**, *42*, 2587−2613. (b) Qiao, G. G.; Andraos, J.; Wentrup, C. *J. Am. Chem. Soc.* **1996**, *118*, 5634−5638. (c) Visser, P.; Zuhse, R.; Wong, M. W.; Wentrup, C. *J. Am. Chem. Soc.* **1996**, *118*, 12598−12602. (d) Wagner, B. D.; Arnold, B. R.; Brown, G. W.; Lusztyk, J. *J. Am. Chem. Soc.* **1998**, *120*, 1827−1834. (e) de Lucas, N. C.; Netto-Ferreira, J. C.; Andraos, J.; Lusztyk, J.; Wagner, B. D.; Scaiano, J. C. *Tetrahedron Lett.* **1997**, *38*, 5147−5150.

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SCHEME 9

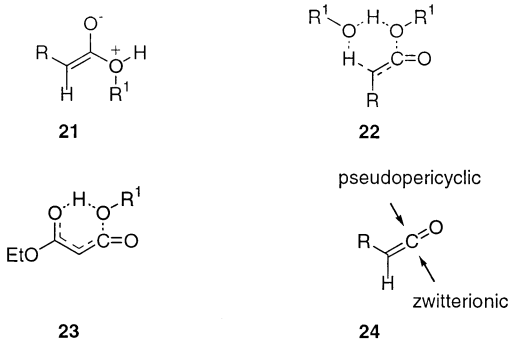

TABLE 3. Relative Rates (to MeOH) for the Acylation of Aliphatic Alcohols with the Carboxylic Acids 1, 10a−c−DCC System in Acetonitrile at 25 °C

	carboxylic acid			
alcohol	**10a**	**10c**	**10b**	**1**
EtOH	1	1	1	1
i-PrOH	0.7	0.4	0.7	0.7
t-BuOH	0.07	0.01	0.13	0.07

high reactivity[34] in nucleophilic additions with alcohols reacting through a concerted bimolecular (pseudopericyclic) mechanism.[35] The pseudopericyclic mechanism involving the transition state of type **23** can explain the high reactivity of ketenes obtained from malonates **10a**,**b**.

The pseudopericyclic transition state **23** is characterized by a cis nucleophilic attack on the LUMO, as shown on **24**. In contrast, for the zwitterionic transition state of type **21** the direction of nucleophilic attack is determined by steric factors[36] that favor trans attack, at least for monosubstituted ketenes. Because of this difference, transitions states of type **21** and **23** must display different steric demands to attacking nucleophiles. The degree of such a difference could be estimated by a comparison of the relative rates of esterification of primary, secondary, and tertiary alcohols. The relative rates of esterification of carboxylic acids **1** and **10a−c** in a series EtOH−*i*-PrOH−*t*-BuOH are shown in Table 3.

Despite a known very sizable difference in reactivity of mono- and disubstituted ketenes,[37] the presence of an additional methyl substituent in malonate **10b** has almost no effect on the relative rates of esterification, suggesting that the direction of the nucleophilic attack is indeed opposite to that of the methyl substituent. This is in good agreement with the pseudopericyclic transition state of type **23** but not with that of **21**.

The esterification of cyanoacetic acid **10c** shows substantially different relative rates (0.4 for 2-propanol, 0.01 for *tert*-butyl alcohol) than **10a** and **10b**. This is in contrast to the smaller steric size of ketenes derived from cyanoacetic acid in comparison to that of ethyl malonate. Because of the linear geometry of the cyano group, the pseudopericyclic transition state of type **23** should be highly strained (if even possible) for the intermediate cyanoketene, making the stepwise pathway through the intermediacy of a zwitterion of type **21** preferred. The existence of two different mechanisms can adequately explain the different relative rates of esterification as well as the lower yield of ester **11c**.

Despite the substantial difference in steric and electronic properties, the esterification of diethylphosphonoacetic acid (**1**) and ethyl malonate (**10a**) showed remarkably similar relative rates of esterification (Table 3). Taking into account that these relative rates of esterification are highly unusual and characteristic, it would be reasonable to suggest that there is a high possibility of similar (i.e., pseudopericyclic) mechanisms for nucleophilic addition to ketenes derived from carboxylic acids **10a** and **1**. Future quantum mechanical studies could provide further evidence for this suggestion.

Conclusions

Carboxylic acids possessing a strong electron-withdrawing group in the α-position upon treatment with carbodiimide produce ketenes. The resulting ketenes were found to be highly efficient acylating agents capable of forming esters with sterically hindered substrates that fail to react using conventional acylation methods. Studies of the relative rates of acylation of different aliphatic alcohols are consistent with a reaction pathway involving the concerted six-membered transition state in the nucleophilic addition to ketenes derived from malonic and diethylphosphonoacetic acids.

Experimental Section

General Information. Unless otherwise stated, all reagents used are commercially available. Solvents for reactions were purified by standard procedures. The ^{1}H spectra were acquired by 300 and 400 MHz instruments in $CDCl_3$ using the residual solvent peaks for calibration. IR spectra were recorded on a FT-IR spectrometer in thin films. Flash chromatography was performed on Merck Si 60 silica gel (230−400 mesh) using ethyl acetate−40-60 petroleum ether mixtures as the eluent. Reactions were monitored by analytical TLC, which was performed on Merck silica gel 60 F_{254} covered aluminum sheets.

General Procedure for Preparation of Esters. To a mixture of 1 mL of a 1 M solution of a carboxylic acid in dry dichloromethane (or acetonitrile for acids **10c−d**) and *tert*-butyl alcohol (1.25 mmol) was added under stirring at 25 °C 1.1 mL of a 1 M solution of DCC. The reaction mixture was stirred for 15 min, filtered through a sintered glass, evaporated, and purified using short-path distillation in a Kugelrohr apparatus or flash chromatography. The products of esterification (**2, 11a−d**) were positively identified by their 300 MHz ^{1}H NMR using literature data for comparison. No traces of the *tert*-butyl esters of acetic, bromoacetic, diphenylacetic, and phenylacetic acids were obtained in the reaction under these reaction conditions (negative identification by ^{1}H NMR of the reaction mixture before workup including doping experiments with commercial samples of these *tert*-butyl esters). Compounds **2** and **11a**,**c** were found to be identical to authentic commercial samples, and the identity of compounds **11b**,**d** was

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established by comparison with the NMR and IR spectra reported in the literature.

Preparation of *tert*-Butyl Diethylphosphonoacete (2) through the Mixed Anhydrides Method. To the solution of diethylphosphonoacetic acid (196 mg, 1 mmol) and *tert*-butyl alcohol (74 mg, 1 mmol) in dichloromethane (5 mL) at 0 °C was added diphenylchlorophosphate **3a** (292 mg, 1 mmol) and triethylamine (202 mg, 2 mmol). The reaction mixture was stirred for 20 min and dissolved in ethyl acetate (30 mL), and the solution was washed with 5% HCl water solution, saturated $NaHCO_3$ solution, and brine, dried, and evaporated to give ester **2** as the only reaction product (160 mg, 0.63 mmol, 63%)

The same reaction was performed with acetyl **3b** and phenyl acetyl chloride **3c** instead of **3a**, providing the title product with 60 and 61% yields correspondingly. No traces of *tert*-butyl phenyl acetate impurities were found in 300 MHz ^{1}H NMR of the product.

4,8-Dimethyl-4-[(phenylsulfonyl)methyl]-2,3-dioxabicyclo[3.3.1]non-8-yl 2-(Diethoxyphosphoryl) Acetate (6). To a solution of alcohol **5** (55 mg, 0.17 mmol) in dichloromethane (0.5 mL) were added diethylphosphonoacetic acid (0.19 mL of a 1 M solution in dichloromethane, 0.19 mmol) and DCC (0.19 mL of a 1 M solution in dichloromethane, 0.19 mmol). The reaction mixture was stirred for 15 min, filtered through a sintered glass, and evaporated. The residue was purified by flash chromatography (50−70% ethyl acetate−40-60 petroleum ether) to give the title compound (80 mg, 0.16 mmol, 92%). ^{1}H NMR (300 MHz): 1.23 (t, 6H, J = 7.1 Hz), 1.59 (s, 3H), 1.81 (s, 3H), 1.91−2.14 (m, 7H), 2.91 (d, 2H, J = 21.6 Hz), 3.03, 3.33 (2 × d, 2H; J = 4.1 Hz), 4.16 (app quintet, 4H, J = 7 Hz), 4.39 (br d, 1H, J = 3.6 Hz), 7.58 (dt, 2H, J = 1.5, 6.9 Hz), 7.67 (dt, 1H, J = 1.2, 8.1 Hz), 7.92 (br d, 2H, J = 7.5 Hz). Anal. Calcd for $C_{21}H_{31}O_9PS$: C, 52.37; H, 6.59. Found: C, 51.96; H, 6.61.

4-Methylpent-2-enoic Acid 2-Hydroxy-1,1,2-trimethylpropyl Ester (9a). To the solution of pinacol (118 mg, 1 mmol) and diethylphosphonoacetic acid (196 mg, 1 mmol) in THF (5 mL) was added a solution of DCC (227 mg, 1.1 mmol) in THF (1.1 mL). The reaction mixture was stirred for 10 min at room temperature, and filtered, the filtrate was cooled to 0 °C, and isobutyraldehyde (144 mg, 2 mmol) and a solution of *t*-BuOLi (prepared by mixing of a solution of *tert*-butyl alcohol (81 mg, 1.1 mmol) in THF (5 mL) with a solution of BuLi in hexanes (0.45 mL of 2.5 M solution)) were subsequently added through a syringe. The reaction mixture was stirred 30 min at 0 °C and evaporated, and the residue was dissolved in ethyl acetate (30 mL). The ethyl acetate solution was washed with saturated $NaHCO_3$ (3 × 20 mL) and brine, dried, and evaporated. The residue was purified by flash chromatography (10% ethyl acetate−40-60 petroleum ether) to give the title compound (0.125 g, 0.58 mmol, 58%). ^{1}H NMR (300 MHz): 1.05 (d, J = 6.8 Hz, 6H), 1.21 (s, 6H), 1.50 (s, 6H), 2.45 (dd of septets, J = 1.5, 6.8, 6.8 Hz, 1H), 3.78 (s, 1H), 5.73 (dd, J = 16.0, 1.5 Hz, 1H), 6.89 (dd, J = 6.8, 16.0 Hz, 1H). IR: 1652, 1715 (br), 2873, 2984, 3447 (br) cm^{-1}. Anal. Calcd for $C_{12}H_{22}O_3$: C, 66.67; H, 11.11. Found: C, 66.92; H, 10.73.

4-Methylpent-2-enoic Acid 1,1,2-Trimethyl-2-[(4-methylpent-2-enoyl)oxy]propyl Ester (9b). To the solution of pinacol (118 mg, 1 mmol) and diethylphosphonoacetic acid (392 mg, 2 mmol) in THF (10 mL) was added a solution of DCC (2.5 mmol) in THF (2.5 mL). The reaction mixture was stirred for 10 min at room temperature and filtered, the filtrate was cooled to 0 °C, and isobutyraldehyde (288 mg, 4 mmol) and a solution of *t*-BuOLi (prepared by mixing of a solution of *tert*-butyl alcohol (185 mg, 2.5 mmol) in THF (10 mL) with a solution of BuLi in hexanes (1 mL of 2.5 M solution)) were subsequently added through a syringe. The reaction mixture was stirred 30 min at 0 °C and evaporated, and the residue was dissolved in ethyl acetate (30 mL). The ethyl acetate solution was washed with satuarted $NaHCO_3$ (3 × 20 mL) and brine, dried, and evaporated. The residue was separated by flash chromatography (10% ethyl acetate−40-60 petroleum ether) to give the title compound (0.160 g, 0.53 mmol, 53%), ^{1}H NMR (300 MHz): 1.05 (d, J = 6.8 Hz, 12H), 1.63 (s, 12H), 2.45 (dd of septets, J = 1.4, 6.6, 6.6 Hz, 2H), 5.70 (dd, J = 15.7, 1.4 Hz, 1H), 6.84 (dd, J = 6.6, 15.7 Hz, 1H). IR: 1653, 1718 (br), 2871, 2930, 2967, 3007 cm^{-1}. Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.67; H, 9.68. Found: C, 70.05; H, 9.42. Further elution provided monoalkylated product **9a** (0.079 g, 0.37 mmol, 37%).

Di-*tert*-butyl Malonate (13). To a solution of malonic acid (1.06 g, 10 mmol) and *tert*-butyl alcohol (1.44 g, 20 mmol) in acetonitrile (30 mL) was added a solution of DCC (4.12 g, 20 mmol) in acetonitrile (20 mL). The reaction mixture was stirred for 20 min, filtered, and evaporated. The residue was bulb-to-bulb distilled in a Kugelrohr apparatus to give title product **13** (1.96 g, 9.1 mmol, 91%); all data are identical to a commercial sample.

***tert*-Butyl Malonate (14a).** To a solution of malonic acid (1.06 g, 10 mmol) and *tert*-butyl alcohol (1.44 g, 20 mmol) in acetonitrile (30 mL) was added a solution of DCC (227 mg, 11 mmol) in acetonitrile (11 mL). The reaction mixture was stirred for 20 min, filtered, and evaporated. The residue was dissolved in ether (50 mL), and the ether layer was extracted with saturated $NaHCO_3$ solution (2 × 20 mL). The water solution was acidified to pH 1 by 10% HCl solution and extracted with ethyl acetate (2 × 35 mL). The ethyl acetate solution was dried and evaporated to give the title product (1.17 g, 7.3 mmol, 73%). Evaporation of the ether solution gave di-*tert*-butyl malonate (0.20 g, 0.9 mmol, 9%).

***p*-Methoxybenzyl Malonate (14b).** To a solution of malonic acid (424 mg, 4 mmol) and *p*-methoxybenzyl alcohol (552 mg, 4 mmol) in acetonitrile (24 mL) was added a solution of DCC (9.06 g, 4.4 mmol) in acetonitrile (4.4 mL). The reaction mixture was stirred for 10 min at room temperature, filtered, and evaporated. The residue was dissolved in EtOAc (50 mL), and the organic layer was extracted with saturated $NaHCO_3$ solution (4 × 25 mL). The water solution was immediately acidified by a saturated solution of NaH_2PO_4 (100 mL) and then to pH 3 by a 10% HCl solution and extracted with ethyl acetate (3 × 25 mL). The ethyl acetate solution was dried and evaporated to give the pure title product (0.639 g, 2.8 mmol, 71%); all data are identical to literature.

Kinetic Studies. The kinetic data were measured in the reaction of 4-methoxybenzyl malonate (10 mM in dichloromethane) with *tert*-butyl alcohol (10−60 mM) and DCC (10−40 mM) at 0.4 °C. The reaction was quenched at 30−480 s intervals with 1 mL of methanol. One milliliter samples were filtered and dissolved in $CDCl_3$ followed by the 300 MHz ^{1}H NMR analysis. Conversion was measured by the integration of the peak belonging to *tert*-butyl group of the product (4-methoxybenzyl *tert*-butyl malonate) vs peaks of the methyl group of the quenching product (4-methoxybenzyl methyl malonate).

The individual sample of *p*-methoxybenzyl *tert*-butyl malonate was prepared from *p*-methoxybenzyl malonate (**14b**), *tert*-butyl alcohol, and DCC using the general procedure for the preparation of esters **11a**−**d**. ^{1}H NMR (300 MHz): 1.42 (s, 9H), 3.30 (s, 2H), 3.83 (s, 3H), 5.11 (s, 2H), 6.89 (dd, J = 1.2, 8.7 Hz, 2H), 7.30 (d, J = 1.5 Hz, 8.7 Hz, 2H). IR (film). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.28; H, 7.14. Found: C, 64.40; H, 7.30. The individual sample of known *p*-methoxybenzyl methyl malonate was prepared from *p*-methoxybenzyl malonate **14b**, methanol, and DCC using the general procedure for the preparation of esters **11a**−**d**.

3-Cyclohexyl-2-(cyclohexylimino)-6-ethoxy-5-methyl-2*H*-1,3-oxazin-4(3*H*)-one (18). To a solution of monoethyl 2-methylmalonate (**10a**) in dichloromethane (1 mL of 1M solution) was added a solution of DCC in dichloromethane (2 mL of a 1 M solution). The reaction mixture was stirred for 1 h at room temperature, filtered through a sintered glass, and evaporated. The residue was purified by flash chromatography (40-60 petroleum ether−ethyl acetate 25:1) to give the title

compound (198 mg, 0.59 mmol, 59%). ^{1}H NMR (300 MHz): 1.13 (t of br t, J = 12.9 Hz, 1H), 1.21−1.35 (m, 7H), 1.36 (t, J = 6.9 Hz, 3H), 1.40−1.80 (m, 10H), 1.72 (s, 3H), 2.48 (q of d, J = 12.3, 3.3 Hz, 2H), 3.58 (m, 1H), 4.26 (q, J = 6.9 Hz, 2H), 4.67 (t of t, J = 3.9, 12 Hz, 1H). IR (film, cm^{-1}): 748, 1205, 1344, 1414, 1645, 1674, 1707, 2924. Anal. Calcd for $C_{19}H_{30}N_2O_3$: C, 68.23; H, 9.04; N, 8.38. Found: C, 68.51; H, 9.27; N, 8.35.

General Procedure for the Determination of Relative Rates of Acylation through Ketene Intermediates by Competition. To a solution of the carboxylic acid (1 mmol), methanol (2 mmol), and an alcohol (2 mmol) in dichloromethane or acetonitrile (5 mL) was added a solution of DCC (1 mmol) in dichloromethane or acetonitrile (1 mL). The reaction mixture was stirred for 20 min, a 1 mL sample was filtered, evaporated, dissolved in $CDCl_3$, and filtered again, and the 300 MHz ^{1}H NMR was measured. Relative rates were calculated from the relative ratios of products that were calculated from the integration of ^{1}H NMR peaks of competition products.

All products of competition reactions, except mentioned below, are previously known. References and ^{1}H NMR spectra are provided in the Supporting Information.

Trifluoroethyl Ethyl Malonate (20e). The individual sample was prepared using the general procedure for the preparation of esters **11a**−**d**. ^{1}H NMR (300 MHz): 1.29 (t, J = 7.2 Hz, 3H), 3.49 (s, 2H), 4.22 (q, J = 7.2 Hz, 2H), 4.54 (q, J = 7.8 Hz, 2H). IR: 1742, 1772, 2987 cm^{-1}. Anal. Calcd for $C_7H_9O_4F_3$: C, 39.25; H, 4.21, F, 26.62. Found: C, 39.48; H, 4.32.

Ethyl Isopropyl 2-Methylmalonate. The individual sample was prepared from ethyl 2-methylmalonate, 2-propanol, and DCC using the general procedure for the preparation of esters **11a**−**d**. ^{1}H NMR (300 MHz): 1.22 (d, J = 6.4 Hz, 6H), 1.37 (d, J = 7.3 Hz, 3H), 3.36 (q, J = 7.3 Hz, 1H), 4.15 (br q, 2H), 5.03 (sept., J = 6.4 Hz, 1H). IR: 1732 (br), 2943, 2984 cm^{-1}.

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Supporting Information Available: ^{1}H NMR data and literature references for known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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