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Direct formation of esters and amides from carboxylic acids using diethyl chlorophosphate in pyridine

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ABSTRACT

An efficient method involving pyridine activation of the carboxylate–phosphate anhydride pathway is described resulting in a direct synthesis of esters from carboxylic acids and alcohols, as well as in the formation of useful amide and peptide derivatives. The reaction proceeds with retention of configuration with both chiral secondary alcohols and α-amino acid derivatives. Ester and amide products can be isolated directly in high yield due to the water soluble nature of the side products.

1. Introduction

Esterification reactions of carboxylic acids with alcohols are one of the most important and commonly employed reactions in organic synthesis.[1,2] Esterification processes are used in the industrial scale synthesis of a variety of end-products, including monomers, polymers, and plasticizers. In addition, applications to lower volume, high-value fine chemicals such as pharmaceuticals, pheromones, and fragrances are prominent, and often require milder and more stringent coupling protocols to achieve the desired chemo- and stereoselectivity. Situations that proceed with a high degree of stereocontrol, such as in the Mitsunobu[3] esterification process, are especially sought. In addition, mild methods that achieve carboxylic acid activation can also be employed for amide or peptide bond forming reactions. While many reagents have been introduced to achieve these purposes (DCC, DEAD, DIAD, etc.), such reagents produce unwanted hydrated side products that complicate work-up.

The mixed-anhydride method for carboxylic group activation is also well known, typically involving activation with a reactive acid chloride such as the Yamaguchi reagent.[4] Mixed carboxylate–phosphate anhydrides have also been employed in acylation reactions, although the process does not appear to be well known and is rarely applied. In particular, the reactive reagent phenyl dichlorophosphate has been exploited in both ester[5] and thioester[6] bond forming processes. The use of less reactive, more selective monochloro-disubstituted phosphates has also been reported, mainly in the synthesis of macrocyclic lactones, through activation of the corresponding *seco*-acid derivatives via the mixed carboxylic–phosphoric anhydride in the presence of base.[7] This method has continued to escape attention[7a] despite the availability of the required reagents and the selective mixed-anhydride formation in the presence of free hydroxyl groups.

We have been interested in the development of novel carboxylic acid activating agents and conditions for controlled esterification over a number of years,[8] and were attracted to a recent publication[9] describing an activated derivative of the mild phosphorylating agent diethyl chlorophosphate **1**.

This method, outlined in Scheme 1, involves the formation of an activated 6-oxo-6*H*-pyridazin-1-yl phosphorylating agent **4** from the reaction of **1** with **3**. This reagent reacts with the carboxylic acid to form the mixed anhydride **2**, subsequently proceeding to give the ester **5** upon addition of the desired alcohol derivative.

The requirement of the activated intermediate **4** in this chemistry drew our attention and appeared reminiscent of some of the lactonization difficulties encountered with the use of the Yamaguchi macrolactonization method. In problematic cases, Yonemitsu and co-workers[10] reported that the use of excess DMAP and mild heating, so as not to promote symmetrical carboxylic anhydride formation, was highly effective in promoting the mixed-anhydride pathway. Hence we hypothesized that reagent **3** may not be required, and that a pyridine base should allow formation of the mixed anhydride **2** directly from **1** and the carboxylic acid. Herein, we report on the successful activation of this pathway using only pyridine under Yonemitsu conditions[10] allowing for a simple and a direct synthesis of a range of esters and amides.

2. Results and discussion

To begin with, we studied the model reaction of 4-nitrobenzoic acid with the lipophilic alcohol *n*-dodecanol employing 1 equiv of diethyl chlorophosphate **1**. While no reaction occurred in dichloromethane at room temperature in the presence of triethylamine, a

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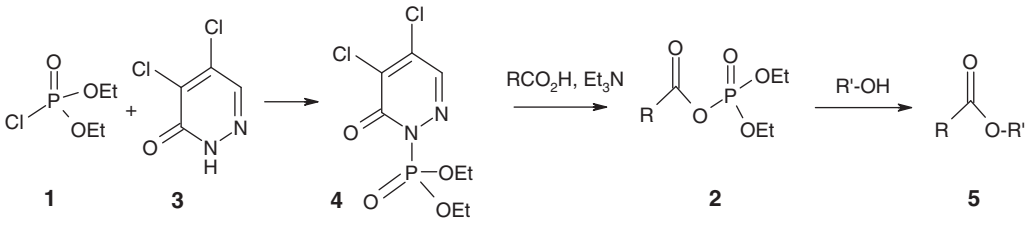
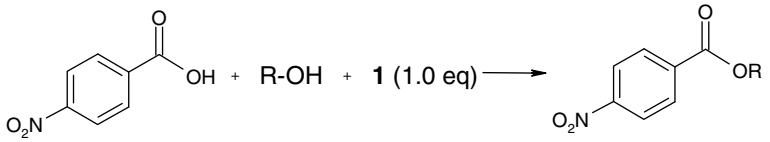


Scheme 1.

Table 1
Direct esterification of acids and alcohols with **1** in pyridine

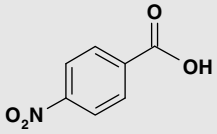
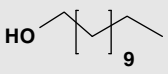
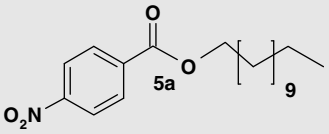
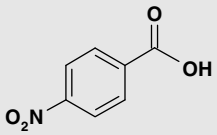
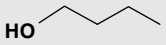
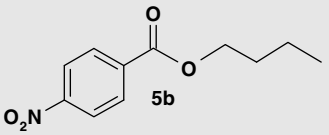
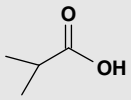
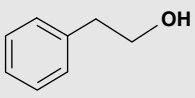
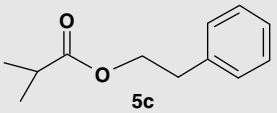
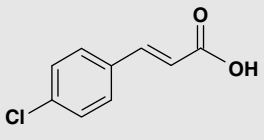
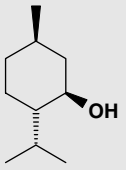
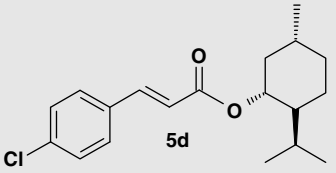
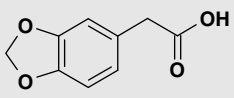
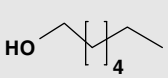
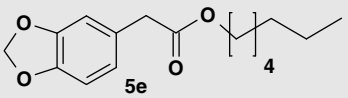


Entry	Base (No. equiv)	Reaction conditions	Isolated yield of **5** (%)
1	Et_3N (2.5 equiv)	CH_2Cl_2, 20 °C, 12 h	0
2	Py (2.5 equiv)	CH_2Cl_2, 20 °C, 6 h	48
3	Py (2.5 equiv)	CH_2Cl_2, 40 °C, 6 h	55
4	Py (neat)	70 °C, 6 h	91

significant turnover was seen with the use of pyridine as a base at room temperature (Table 1, entry 2), and more so upon warming (Table 1, entry 3). Switching to neat pyridine as solvent allowed for complete conversion and isolation of the ester in very high yield (entry 4). Thus neither the more nucleophilic DMAP[10] nor reagent **3**[9] is required to effect efficient esterification using the monochloro phosphate **1**.

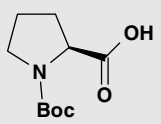
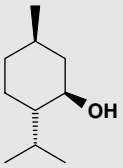
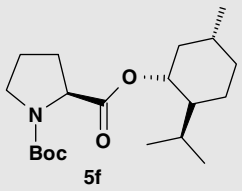
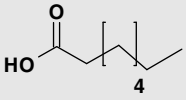
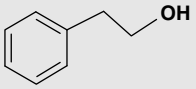
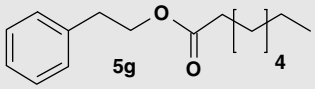
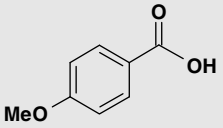
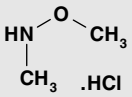
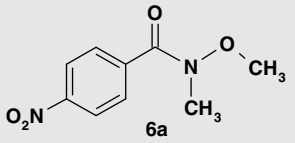
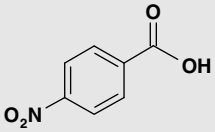
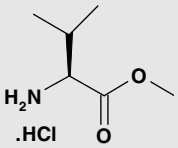
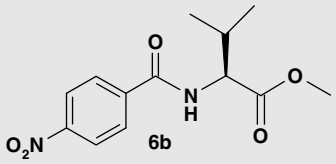
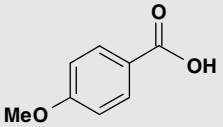
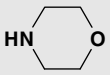
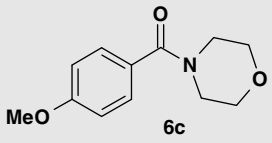
Major advantages of the diethyl chlorophosphate **1** include, first of all, that the reagent can be employed directly in the presence of the alcohol in pyridine. Most likely, the nucleophilic carboxylate anion attacks the activated derivative of **1** to form the mixed anhydride in preference to the alcohol. No diethylphosphate ester was produced from the direct reaction of the alcohol with **1**. Secondly, purification is very straightforward since there are no hydrated

Table 2
Synthesis of various esters and amides

Entry	R–COOH	R–OH/R′–NH_2	Product (**5** or **6**)	Yield of **5** or **6**[a] (%)
1				91
2				88
3				80
4				86
5				79

(*continued on next page*)

Table 2 (*continued*)

Entry	R–COOH	R–OH/R′–NH_2	Product (**5** or **6**)	Yield of **5** or **6**[a] (%)
6				88
7				82
8				79
9				80
10				77

[a] Isolated yield after silica gel column chromatography.

organic side products (such as $DEADH_2$, Ph_3PO, and DCC-urea) to contend with as the phosphate and pyridinium salts formed are water soluble. Simply removing solvents and work-up from aqueous sodium bicarbonate/ethyl acetate yields the ester in relatively high purity (>95% in all cases so far investigated) without chromatographic purification.

From the initial results, we developed a generally effective procedure and work-up protocol employing a 1 to 1 ratio of carboxylic acid and alcohol and 1.05 equiv of **1** reacting in neat pyridine at 70 °C for 3 h.

The overall scope of this acylation method is presented in Table 2. Yields reported are for the chromatographically purified products. Under these conditions, a range of aromatic, α,β-unsaturated, and aliphatic carboxylic acids could readily be condensed with alcohols, entries 1–7 (Table 2).[11a] For example, L-menthol readily reacted with the phosphate-activated cinnamic acid derivative giving the methyl cinnamate ester in good yield and with complete retention of stereochemistry (Table 2, entry 4). In addition, N-protected α-amino acids (Table 2, entry 6) could also be coupled with alcohols including L-menthol, yielding a single diastereomeric product. These results confirm that the reaction proceeds without loss of optical integrity on both the part of the chiral secondary alcohol and α-amino carboxylic acid stereogenic centers. The successful participation of 2-phenylethanol (Table 2, entries 3 and 7) in the reaction provided 2-phenylethylesters in good yield without styrene formation, again indicating that no activation of the alcohol occurs.

The reaction of the same diethyl phosphate-activated carboxylic acid anhydrides with amines could also be carried out effectively, however, requiring a small change to the procedure. The overall reaction was not successful when done in the presence of the amine as diethylphosphoramide side products were obtained, no doubt due to the higher nucleophilicity of the amine. Simple sequential addition of the amine to the activated acid completely suppressed phosphoramide formation, and resulted in high yields of the desired condensed amide products.[11b] This protocol proved to be general, and we were able to obtain synthetically useful Weinreb amide derivatives, as well as the amide adducts from both primary and secondary amines, including chiral α-amino acid derivatives (Table 1, entries 8–10).

3. Conclusion

In conclusion, we describe the synthesis of a range of esters and amides from the pyridine mediated formation of mixed carboxylate–phosphate anhydride intermediates. The reaction takes place selectively in the presence of an alcohol and sequentially in the presence of amines allowing access to useful ester, amide, and peptide analogs. All side products are water soluble allowing for the straightforward isolation of high purity products. Work in our laboratories continues with the exploration of the reactivity of the lesser reactive chlorophosphates with a view to expanding their chemical utility.

Acknowledgments

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11. (a) Typical procedure for the synthesis of L-menthol-4-chloro cinnamate **5d**: To a mixture of 4-chlorocinnamic acid (0.365 g, 2.00 mmol) and L-menthol (0.312 g, 2.00 mmol) in pyridine (3.00 mL) was added diethyl chlorophosphate (0.320 mL, 2.10 mmol) slowly at rt in an atmosphere of argon, and the reaction mixture was stirred at rt for about 30 min. The heterogenous mixture was heated at 70 °C under argon atmosphere for 3 h, during which the reaction mixture became homogenous. Pyridine was removed in vacuo, and the residue partitioned between ethyl acetate (15.0 mL) and saturated sodium bicarbonate (5.00 mL). After stirring well (10 min), the organic layer was separated, dried over anhyd Na_2SO_4 and the solvent evaporated in vacuo to yield the crude product. In all cases, crude products were >95% pure by ^1H NMR. Purification of **5d** over silica gel (5% ethyl acetate in hexane) afforded 0.552 g, 86% yield of pure product **5d**.[12]
    (b) Typical procedure for the synthesis of L-*N*-(4-nitro-benzoyl)-Val-OMe **6b**: To a mixture of 4-nitrobenzoic acid (0.334 g, 2.00 mmol) in pyridine (3.00 mL) was added slowly diethyl chlorophosphate (0.320 mL, 2.10 mmol) at rt in an atmosphere of argon, and the reaction mixture was stirred at rt for about 45 min. To this was then added L-valine methylester hydrochloride (0.335 g, 2.00 mmol) in one lot, and the reaction mixture was heated to 70 °C under argon atmosphere for 5 h. After completion of the reaction, pyridine was removed in vacuo and the residue partitioned between ethyl acetate (15.0 mL) and saturated sodium bicarbonate solution (5.00 mL) and stirred well for about 10 min. The organic layer was separated, dried over anhyd Na_2SO_4, and the solvent was evaporated in vacuo yielding the crude product. Purification of **6b** over silica gel (5% ethyl acetate in hexane) afforded 0.448 g, 80% yield of pure product **6b**.[13]
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