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ARTICLE TYPE

Phosphorus Oxychloride as an Efficient Coupling Reagent for the Synthesis of Ester, Amide and Peptide under Mild Conditions

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A mild method is described for the conversion of carboxylic acids into esters, amides, as well as peptides without racemization through carboxyl activation by the reagent combination of $POCl_3$ and DMAP. Long chain alcohols could be converted to the corresponding ester in good yields. ^{31}P NMR spectrum was used to detect phosphorus-containing intermediates in ongoing reactions directly, and a possible mechanism has been proposed based on these results.

Esters and amides, particularly peptides, have been widely used as chemicals and pharmaceuticals.[1] Activation of the carboxylic groups is required before the reaction can occur. A large number of methods are available for activation of carboxylic acids, including pre-activation of the carboxyl group with dicyclohexylcarbodiimide (DCC),[2] Yamaguchi acid chloride,[3] thionyl chloride,[4] dimethylsulfamoyl chloride,[5] mixed anhydride,[6] triphenylphosphine,[7] 1-tosylimidazole,[8] O-alkylisoureas,[9] imidazole carbamates and ureas,[10] iodosodilactone,[11] T3P,[12] other organocatalyst[13] and coupling agent.[14] Unfortunately, two major disadvantages of most activating reagents invented to date are that they generate substantial amounts of undesired by-products and the potential loss of chiral integrity at the carboxyl residue undergoing activation. Moreover, the preparation of these coupling reagents is often very difficult and requires harsh conditions. Therefore, improved methods for the synthesis of ester and amide bonds, particularly peptide couplings are in great demand.

As one of the most common and diversely used industrial chemicals, phosphorus oxychloride ($POCl_3$) is widely used as a dehydrating agent in the laboratory, a liquid phosphorus source in diffusion processes in the semiconductor industry, and an important material in the manufacture of herbicides, insecticides, plasticizers, oil additives, and flame retardants. $POCl_3$ has been used for amide syntehsis in recent years.[15] However, these methods still suffered from some drawbacks such as high temperature, long reaction time, and often moderate yields. Herein, we wish to report that the combination of $POCl_3$ and DMAP efficiently mediate the esterification and amidation of carboxylic acid under mild conditions. The method provides an efficient method for the activation of carboxylic acid.

We began our study by examining the reaction of 3-phenylpropanoic acid (**1a**) with phenylmethanol (**2a**). To our satisfaction, when a mixture of **1a** (0.50 mmol), **2a** (0.60 mmol), Et_3N (1.2 mmol) and a catalytic amount of DMAP (0.15 mmol) in CH_2Cl_2 (3.0 mL) at room temperature with $POCl_3$ (0.50 mmol) for 2 h, benzyl 3-phenylpropanoate (**3a**) was obtained in a 96% yield. Many solvents (THF, toluene, dichloroethane, and acetonitrile) are effective, obtaining **3a** in all cases more than 90% yields. Inorganic bases such as K_3PO_4, K_2CO_3 and Na_2CO_3 were less effective, giving **3a** in 60-70% yields. Organic bases such as N-methylmorpholine and pyridine also gave high yields. This is likely due to the greater solubility of these bases in organic solvents, leading to the rapid formation of the mixed carboxylic-phosphoric anhydride. However, no product **3a** was observed in the absence of base. Without DMAP, the reaction was very sluggish and gave **3a** in a 32% yield for 12 h.

With the optimized conditions in hand, a variety of alcohols, phenols and carboxylic acids were examined (Table 1). The desired esters were obtained in good to excellent yields regardless of primary alcohols (**3a-3d**) or secondary alcohol (**3e-3f**, **3q**) with **1a**. Sterically hindered secondary alcohol L-menthol also performed well and yielded the corresponding optically pure ester product **3f** with retention of configuration around the alkoxy carbon. Furthermore, phenol and 1-naphthol also proceeded smoothly, affording the corresponding products in good yields (**3g**, **3h**). On the other hand, both aliphatic and aromatic carboxylic acids reacted with phenylmethanol to give products **3k-3n** in good to excellent yields. Moreover, the reactions are completely compatible with the presence of double and triple bonds, both terminal and internal, and no products of addition over these multiple bonds were observed (**3b**, **3c**, **and 3q**). Additionally, α, β-unsaturated carboxylic acid and heterocyclic substituted carboxylic acid were also successfully employed in the reaction with phenylmethanol under the standard conditions (**3i**, **3k**). *tert*-Butyl alcohol was also examined. Unfortunately, only trace amounts of desired ester bond-forming products were detected.

It is worth noting that long chain aliphatic acids and long chain alcohols could be converted to the corresponding ester (**3o**, **3p**), although it is less reactive than others.[16] Finally, relatively hindered alcohol was efficiently esterification with our method in a 76% yield (**3q**). Although several methods have been described for the esterification of these steroidal structures, normally using strong basic or acidic media and high temperatures, our procedure proceeds under milder conditions and contribute a precise control over the individual reactivity of functional groups within a complex molecular architecture, which constitutes an important objective in the synthesis of complex natural products.

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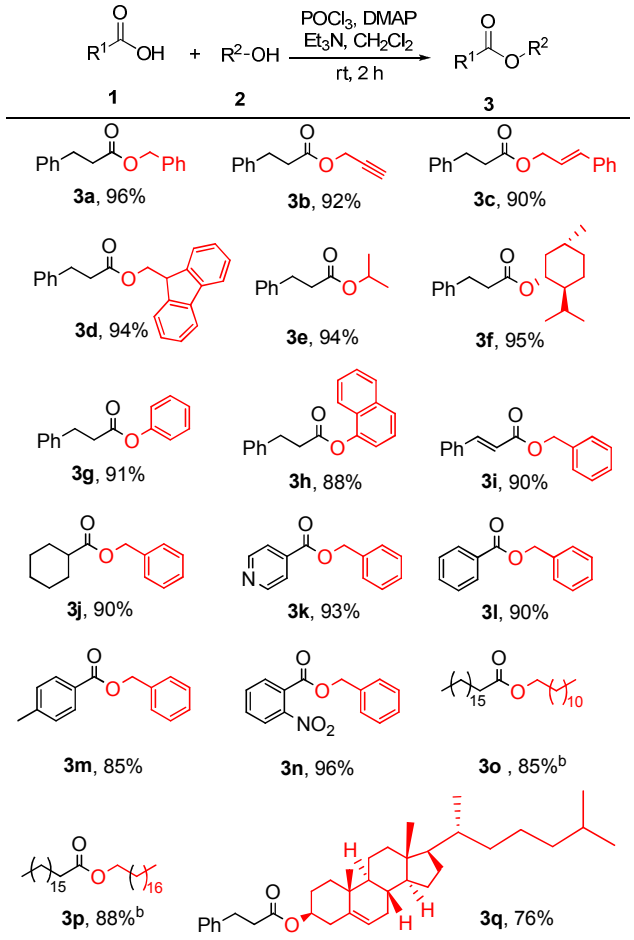
Table 1. Esterification Promoted by $POCl_3$ and DMAP.[a]

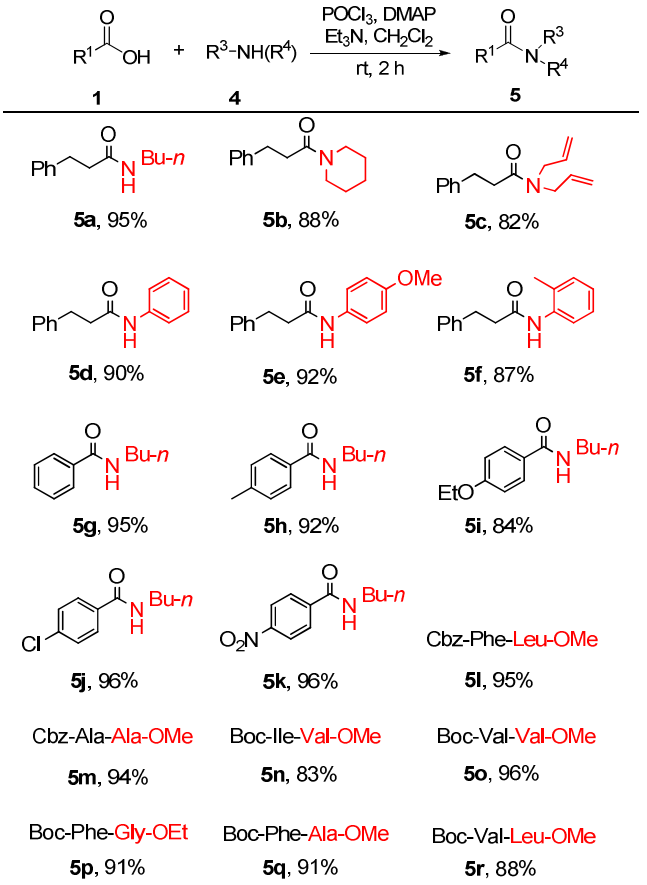


[a] Reaction conditions: acid (0.5 mmol), alcohols or phenol (0.6 mmol), Et_3N (1.2 mmol), $POCl_3$ (0.5 mmol), DMAP (0.15 mmol), solvent (3 mL), rt, 2 h. Isolated yields. [b] 8 h.

After the successful construction of an ester bond, we next turned to change the nucleophile to amines, which are generally thought to be easier to acylate than alcohol. To our satisfaction, various aliphatic or aromatic primary amines and secondary amines effectively reacted with 3-phenylpropanoic acid (**1a**) to provide the desired amides **5a-f** in good to excellent yields (Table 2). Terminal alkene group was tolerated under the present condition (**5c**). Besides, hindered amines also worked well to give corresponding products **5b** and **5c**. Then, aromatic acids with different functional groups were studied and afforded desired amide products **5j-k** in high to excellent yields with butylamine.

Success in the construction of amides inspired us to explore the applications of the present catalysis system in peptide coupling reactions. Accordingly, *N*-Cbz-phenylalanine was treated with methyl ester of leucine in the presence of Et_3N as a base and a catalytic amount of DMAP. $POCl_3$ was added to the above solution, and the reaction mixture was stirred at room temperature for 2 h. To our immense satisfaction, the product formed was found to be the expected dipeptide **5l** in a 95% yield, and its specific rotation was in good agreement with the reported value [**5l**; $[\alpha]_D^{20}$ = -24.7 (*c*=3.1, MeOH) (lit.[17] $[\alpha]_D^{20}$ = -24.7 (*c*=3.1, MeOH))]. The diastereomeric purity was further verified by HPLC analysis of **5l** and a diastereomeric mixture of ($_{D, L}$)- and ($_{L, L}$)-**5l** [prepared by coupling Leu-OMe with racemic Cbz-phe], which clearly showed **5l** to be free from any ($_{D, L}$) isomer, thereby indicating the nonracemizing nature of the above coupling protocol. A variety of amino acid combinations were similarly subjected to dipeptide formation affording the products **5l-r** in good yields and high diastereomeric purity.

Table 2. Amidation and Peptide Coupling Promoted by $POCl_3$ and DMAP.[a]



[a] Reaction conditions: acid or *N*-Protected amino acid (0.5 mmol), amine or methyl ester amino acid (0.6 mmol), Et_3N (1.2 mmol), $POCl_3$ (0.5 mmol), DMAP (0.15 mmol), solvent (3 mL), rt, 2 h. Isolated yields.

A possible mechanism is proposed as shown in Scheme 1. $POCl_3$ is initially activated by DMAP to form the phosphorylpyridinium intermediate **6**[18] that then undergo the addition of the Cbz-Phe to give the mixed anhydride **7**. Once the mixed anhydride is formed, it reacts rapidly with DMAP to form acylpyridinium intermediate **8**, which activates the amino acid carbonyl toward nucleophilic attack. At last, the activated species **8** is attacked by Leu-OMe to give the product **5l**, DMAP and $PO_2Cl_2^-$.

To further study the reaction mechanism, we decided to use ^{31}P NMR spectrum analysis, which has been successfully employed in studying a number of phosphorus-containing reactions.[19] The formation of **5l** was monitored by ^{31}P NMR spectroscopy as shown in Figure 1. The initial ^{31}P NMR spectrum

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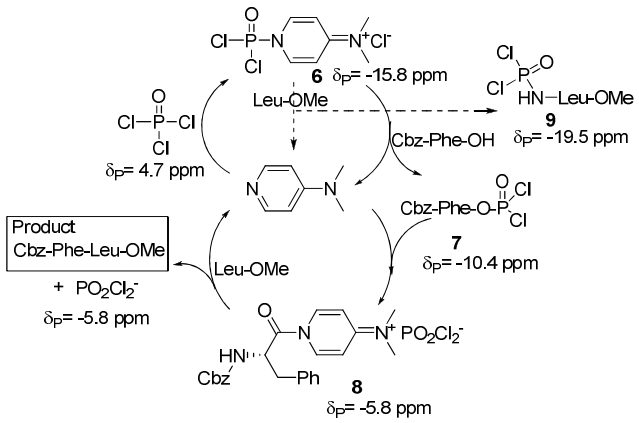
studies indicated Et_3N was used as base only, which prompted the use of excess DMAP instead of Et_3N, reducing the sets of ^{31}P NMR spectrum peaks. The starting $POCl_3$ in CH_2Cl_2 showed signal in the ^{31}P NMR spectrum at $\delta = 4.7$ ppm. After DMAP (2.4 eq.) was added to the solution of $POCl_3$, the peak of $POCl_3$ was decreasing while a new peak at -15.8 ppm corresponding to intermediate **6** emerged (A in Figure 1). When Cbz-Phe (**1k**) was added to the mixture, two sets of new signals appear at –5.8 and –10.4 ppm (B in Figure 1), which indicated the forming of the mixed phosphoric-carboxylic anhydride **7**[19b,20] that subsequent react with DMAP to give the more reactive intermediate **8**. Although no spectroscopic data for intermediate **8** are available, $PO_2Cl_2^-$ (–5.8 ppm） has been previously studied by ^{31}P NMR,[21] showing chemical shifts at –7.5 ppm in MeCN, similar to that observed for our proposed intermediate. However, addition of Leu-OMe resulted in a peak (–10.4 ppm) rapidly decrease (C in Figure 1), meanwhile the peak at –5.8 ppm was gradually increased, indicating the existence of the intermediate **7** again. In addition, a new peak at –19.5 ppm was assigned as the by-product **9**, which was proved by mix of acetylpyridinium intermediate **6** with Leu-OMe.



Scheme 1. Possible reaction mechanism

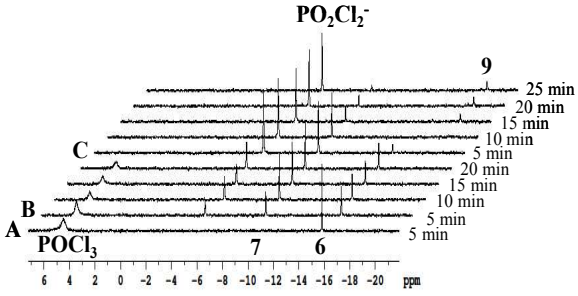


Figure 1. ^{31}P NMR spectra for the synthesis of **5l**.

A: $POCl_3$ (1.0 mmol), DMAP (2.4 mmol), CH_2Cl_2 (1 mL).
B: Cbz-Phe(1.5 mmol) in CH_2Cl_2 (2 mL) was added to A.
C: Leu-OMe(1.5 mmol) in CH_2Cl_2 (2 mL) was added to B.

In summary, we have developed a mild, safe, and economic one-pot protocol for the conversion of carboxylic acids into esters, amides, as well as peptides without racemization through carboxyl activation by the reagent combination of $POCl_3$ and DMAP. The method eliminates some commonly encountered problems, such as separation of product from reagent derived coproducts, racemization, poor recovery of product, high cost, instability of the reagent, etc. The "*in situ*" activation of the carboxylic acid makes our method an excellent alternative to the known acylation procedures, useful for the synthesis of peptides, particularly complex natural products. The suggested possible mechanism is supported by the ^{31}P NMR spectrum analyses.

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Notes and references

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