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Mild one-pot conversion of carboxylic acids to amides or esters with Ph_3P/trichloroisocyanuric acid

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Abstract—The reaction of trichloroisocyanuric acid (TCICA) and triphenylphosphine in the presence of a carboxylic acid results in the in situ formation of the corresponding acid chloride under mild conditions. Subsequent addition of amines or alcohols, in the presence of a tertiary amine affords the corresponding amides, or esters, in good to excellent yields. The methodology was applied to the synthesis of a dipeptide.

The activation of carboxylic acids and their subsequent conversion to esters or amides is a key transformation in organic synthesis. In spite of the host of protocols developed to that end, invariably there is a commitment between functional group compatibility and the cost of the reagents employed to activate the carboxylic acid. This scenario is particularly critical for substrates bearing acid-sensitive functional groups. Thus a mild, cost-effective alternative for acylations would find ample application.

Acid chlorides are valuable intermediates in organic synthesis and are generally prepared by the reaction of carboxylic acids with reagents such as thionyl chloride, PCl_3, PCl_5, and oxalyl chloride, among others.[1] However, such protocols cannot be applied to acid-sensitive compounds due to the vigorous conditions required and the formation of strong acids (HCl) during the process.

It is known that the treatment of alcohols with the chlorine or bromine triphenylphosphine adduct leads to the formation of the corresponding halides in good to high yield.[2] Recently, Hiegel et al. showed that Ph_3P treated with trichloroisocyanuric acid (TCICA) in warm or refluxing anhydrous CH_3CN can convert alcohols to the respective halides, 1,3-diketones to β-chloro-α,β-insaturated ketones, an acid to an ester and a primary amide to a nitrile group.[3] Jang et al. developed an alternative method for obtention of the respective acid chlorides from carboxylic acids by combination of Ph_3P and CCl_3CN. Subsequent addition of primary amines resulted in the obtention of secondary amides in high yield.[4]

In the course of our studies, we have found that carboxylic acids can be converted to the respective acid chlorides under very mild conditions by simply mixing Ph_3P and TCICA in CH_2Cl_2 at 0 °C. Subsequent addition of amines or alcohols, in the presence of a tertiary amine, affords the corresponding amides or esters in a one-pot procedure.

Our initial experiments used a ratio of 1:1:0.3 of the RCOOH–Ph_3P–TCICA. However, under these conditions the reactions were slow and afforded poor yields. Significant improvement was observed when using ratio 1:1:1. Accordingly, the carboxylic acid was added to a mixture of Ph_3P and TCICA in DCM at 0 °C, and the resulting suspension was allowed to warm to rt. After 45 min, triethylamine and the amine or alcohol of interest were added, and the reaction mixture was stirred for an additional 1–2 h.

In order to illustrate the scope of this method, some amides and esters were prepared as shown in Table 1.[5]

An important example that demonstrates the efficiency of this method was the synthesis of the (*Z*)-*N*,*N*-diethyl-2-methyl-2-butenamide (entry 2). This amide

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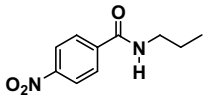
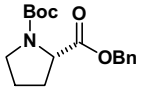
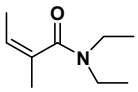
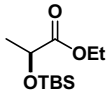
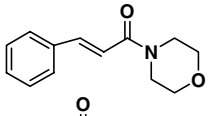
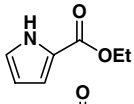
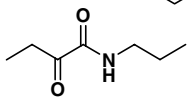
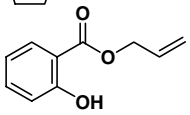
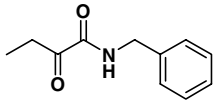
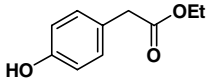
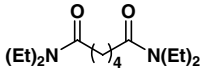
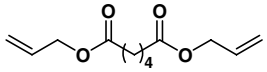
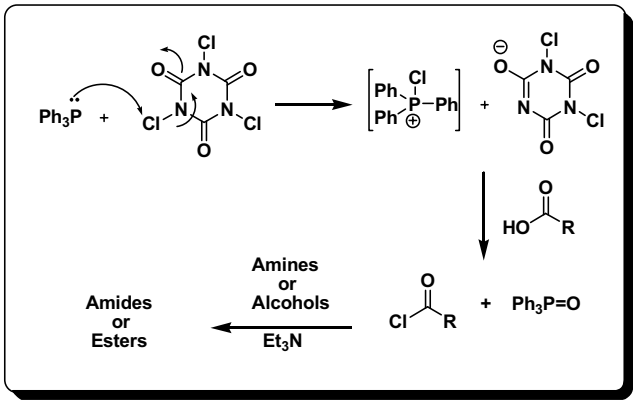
Table 1. Conversion of carboxylic acids to amines and esters by TCICA/Ph_3P

Entry	Amide	Yield (%)	Entry	Ester	Yield (%)
1		96[a]	7		96[d]
2		95[b]	8		95[d]
3		85[b]	9		53[d]
4		92[a]	10		90[d]
5		50[b]	11		30[d]
6		85[c]	12		65[e]

[a] *n*-Propylamine (6.0 equiv) was used.
[b] Triethylamine (3.0 equiv) and corresponding amine (1.0 equiv).
[c] Triethylamine (3.0 equiv) and corresponding amine (2.0 equiv).
[d] Corresponding alcohol (1.0 equiv) and triethylamine (3.0 equiv).
[e] Corresponding alcohol (2.0 equiv) and triethylamine (3.0 equiv).

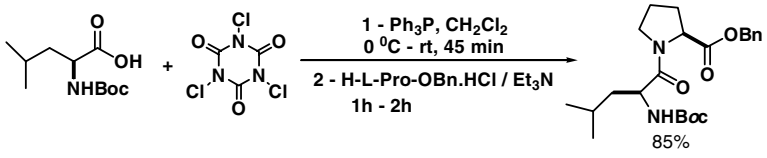
was obtained in 95% yield without isomerization (lit.[6] 49% yield, 12% additional of the (*E*)-isomer when using $SOCl_2$). An inexpensive amine can be used in excess in place of the ad-mixture with Et_3N (entry 1). α-Keto-amides[7] are versatile synthetic intermediates, and could be efficiently prepared by using this method (entries 4 and 5). Some representative esters were also synthesized (entries 7–12). Boc-L-proline gave the benzyl ester in 96% yield (entry 7), no racemization was observed after hydrogenolysis $\{[\alpha]_D^{20}$ −60.1 (*c* 2.0, AcOH) (lit.[9] −60.3)}. The TBS-protected lactate (entry 8) was prepared in good yield, with no detectable racemization $\{[\alpha]_D^{23}$ −28.7 (*c* 1.16, $CHCl_3$) (lit.[10] −28.9)}, leading to the conclusion that the acylation does not involve ketene as intermediate. In some instances however, the protection of functional groups is not required to perform this transformation efficiently (entries 9, 10, and 11), making this protocol even more versatile. Finally, a dicarboxylic acid afforded the corresponding diester (entry 12), as well as the diamide (entry 6), both in good yields.[8]

The mechanism proposed for the generation of the acid chloride is depicted in Scheme 1. Thus, the initial attack at the halogen in TCICA by triphenylphosphine leads to the halogen–phosphonium salt, which then reacts with the carboxylic acid, yielding triphenylphosphine oxide and the corresponding acyl chloride.



Scheme 1. Proposed mechanism.

The demonstrated methodology was applied to the synthesis of the important dipeptide Boc-L-Leu-L-Pro-OBn, a common intermediate in the synthesis of the tamandarin cyclic depsipeptides, important natural products with immunosuppressive, antiviral, and antitumor activity.[11] The ester Boc-L-Pro-OBn (entry 6) after removal of



Scheme 2. Synthesis of the dipeptide Boc-L-Leu-L-Pro-OBn.

the Boc group, by treatment with 4.0 M HCl–EtOAc was coupled in 85% yield using conditions analogous to those previously described. No loss of the stereochemical integrity was observed {$[\alpha]_D^{20}$ −64.5 (*c* 2.0, DCM) (lit.[12] −64.7)} (Scheme 2).[13,14]

In summary, a convenient and practical method for the preparation of amides and esters in good to excellent yields, from readily available, inexpensive starting materials has been described.

Acknowledgments

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13. Typical experimental procedure (**1**): To a solution of triphenylphosphine (1.31 g, 4.99 mmol) and TCICA (1.16 g, 4.99 mmol) in DCM, 30 mL at 0 °C was added (0.500 g, 4.99 mmol) (*Z*)-2-methyl-2-butenoic acid in portion. The solution was stirred for 45 min, diethylamine (0.516 mL, 4.99 mmol) was added dropwise followed by triethylamine (2.00 mL, 14.98 mmol). The ice bath was removed and the solution was stirred for 1 h. The mixture was filtered and the organic layer was washed with water and dried over Na_2SO_4. The solution was then filtered on a short column of silica gel with 10% EtOAc/hexanes and the filtrate was concentrated in vacuo affording **2** in 95% yield.[6] ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.13 (6H, t, J = 7.0 Hz, CH_3); 1.59 (3H, dd, J = 7.0, 1.0 Hz, CH_3), 1.76 (3H, d, J = 2.0 Hz, CH_3); 3.31 (4H, q, J = 7.0 Hz, CH_2); 5.52 (1H, qq, J = 7.0, 1.5 Hz, C*H*).
14. Typical experimental procedure (**2**): To a solution of triphenylphosphine (0.226 g, 0.86 mmol) and TCICA (0.200 g, 0.86 mmol) in DCM, 4.3 mL at 0 °C was added dropwise (0.200 g, 0.86 mmol) Boc-L-Leu in DCM, 4.6 mL. The solution was stirred for 30 min. H-Pro-L-OBn·HCl was added dropwise followed by triethylamine (0.360 mL, 2.58 mmol). The ice bath was removed and the solution was stirred for 2 h. The mixture was filtered and the organic layer was washed with water and dried over Na_2SO_4. The solution was then filtered on a short column of silica gel with 5–10% EtOAc/hexanes and the filtrate was concentrated in vacuo affording dipeptide Boc-L-Leu-L-Pro-OBn in 85% yield.[12] ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.86 (3H, d, J = 6.5 Hz, CH_3); 0.88 (3H, d, J = 6.5, CH_3), 1.45 (9H, s, CH_3); 1.56–2.45 (6H, m, CH_2, C*H*); 3.50–3.68 (2H, m, CH_2); 4.38–4.54 (3H, m, CH_2, C*H*); 5.10 (2H, d, J = 12.3 Hz, CH_2); 5.11 (1H, br, N*H*); 7.24 (5H, m, C*H*).