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A Mild and Efficient Procedure for the Preparation of Acid Chlorides from Carboxylic Acids

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Abstract: Various carboxylic acids are converted into the corresponding acid chlorides by treatment with trichloroacetonitrile and triphenylphosphine in methylene chloride at room temperature. Aryl acids show higher reactivity than alkyl acids under the conditions.

Acid chlorides are of importance as intermediates to prepare many other functional groups in organic synthesis, especially in the preparation of amide bonds. Although many coupling reagents for the formation of amide bonds directly from carboxylic acids and amines have been reported,[1] there are still demands of using acid chlorides in case of poor activity of amines.[2]

The common reagents such as thionyl chloride,[3] phosphorus chlorides,[4] and oxalyl chloride[5] which are used generally for the preparation of acid chlorides from carboxylic acids can not be applied to acid-sensitive substrates due to the generation of strong acidic conditions during the reaction. The adduct of triphenylphosphine and carbon tetrachloride,[6] cyanuric chloride,[7] or tetramethyl-α-chloroenamine[8] provides acid-free conditions for the transformation of carboxylic acids into acid chlorides. However, the use of the combination of triphenylphosphine and carbon tetrachloride, or cyanuric chloride requires relatively long reaction time at room temperature. Tetramethyl-α-chloroenamine has its own disadvantage: the use of phosgene in the preparation.[9] Recently, it has been reported that the combination of hexachloroacetone and triphenylphosphine which is used for the conversion of alcohols to chlorides[10] is applicable for the transformation of carboxylic acids into acid chlorides.[2]

We considered that the reaction of trichloroacetonitrile (TCA) with triphenylphosphine readily generates triarylphosphonium chloride, which can react with carboxylic acids to produce acid chlorides, triphenylphosphine oxide, and dichloroacetonitrile. Herein, we wish to report that a mild and efficient procedure for the conversion of carboxylic acids into acid chlorides.

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We chose benzoic acid and cyclohexylamine as model compounds. When benzoic acid was treated with TCA (1.2 equiv.) and triphenylphosphine (1.2 equiv.) in CH_2Cl_2 at room temperature for 1 h and the then forming benzoyl chloride was converted into the amide by treatment with cyclohexylamine (1 equiv.) in the presence of Et_3N (3 equiv.), the desired amide in 45% yield along with the unreacted benzoic acid was obtained (Table 1, entry 1). However, when the amount of TCA (2.0 equiv.) and triphenylphosphine (2.0 equiv.) was increased, benzoic acid was transformed to benzoyl chloride completely in 40 min to offer 97% isolated yield of the corresponding amide after treatment with cyclohexylamine (entry 2). The reaction can be carried out even at 0°C without affecting the yield of the amide (entry 3). To compare the reactivity of TCA/Ph_3P combination with CCl_4/Ph_3P combination, we performed the same reaction as entry 2 except the use of CCl_4 instead of TCA. The reaction did not proceed at all under the conditions (entry 4). It shows that TCA/Ph_3P system is much more reactive than CCl_4/Ph_3P system. The conversion of carboxylic acids to acid chlorides is quite satisfactory in various common solvents used in organic synthesis such as toluene, acetonitrile, or ethyl acetate but the use of diethyl ether makes the yield of the amide decrease (entries 5-9). Various amine-derived amides could be prepared from benzoic acid. The primary and secondary alkyl amines offered the amides in high isolated yield (entries 10-13). The aryl amines also gave the amide in high yield (entry 14).

Table 1. Formation of Benzoyl Chloride and Reaction with Various Amines (1 equiv.) at Room Temperature.

Entry	CCl_3CN (equiv.)	Ph_3P (equiv.)	Solvent	Time (min)[a]	Amine	Yield of Amide (%)
1	1.2	1.2	CH_2Cl_2	60	Cyclohexyl	45
2	2.0	2.0	CH_2Cl_2	40	Cyclohexyl	97
3[b]	2.0	2.0	CH_2Cl_2	40	Cyclohexyl	95
4[c]	2.0	2.0	CH_2Cl_2	40	Cyclohexyl	0
5	2.0	2.0	toluene	40	Cyclohexyl	92
6	2.0	2.0	THF	40	Cyclohexyl	94
7	2.0	2.0	CH_3CN	40	Cyclohexyl	99
8	2.0	2.0	EtOAc	40	Cyclohexyl	89
9	2.0	2.0	Et_2O	40	Cyclohexyl	77
10	2.0	2.0	CH_2Cl_2	60	Octadecyl	91
11	2.0	2.0	CH_2Cl_2	60	Benzhydryl	97
12	2.0	2.0	CH_2Cl_2	60	Adamantan	91
13	2.0	2.0	CH_2Cl_2	60	Diethyl	98
14	2.0	2.0	CH_2Cl_2	60	Aniline	89

[a]The time required for the disappearance of benzoic acid on TLC. [b]At 0°C. [c]CCl_4 was used instead of CCl_3CN.

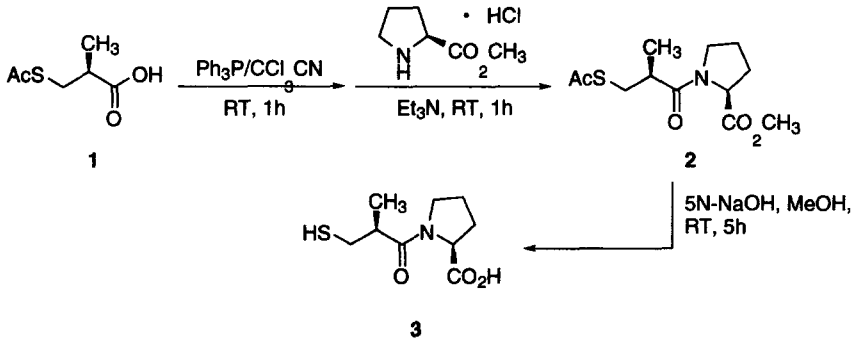
The conversion of various carboxylic acids into acid chlorides has been examined under the conditions. The results are summarized in Table 2. Compared to alkyl carboxylic acids, aryl acids gave higher yields of amides. Acids with electron-donating group offered higher yield among aryl acids.

Table 2. Formation of Various Acid Chlorides and Reaction with Cyclohexyl Amine in CH_2Cl_2 at Room Temperature.

Entry	Acid	CCl_3CN (equiv.)	PPh_3 (equiv.)	Time (h)	Yield of Amide (%)
1	*p*-Bromo benzoic	2	2	2	90
2	*p*-Methoxy benzoic	2	2	2	90
3	*p*-^{t}Butyl benzoic	2	2	1	95
4	*p*-Nitro benzoic	2	2	2	80
5	Acetylsalicylic	2	2	2	70
6	*trans*-Cinnamic	2	2	2	83
7	*n*-Octanoic	4	4	4	80
8	2-Octenoic	2	2	4	79
9	2-Bromoisovaleric	4	4	2	76

[a]The time required for the disappearance of benzoic acid on TLC.

Most interestingly, the reaction can be applicable for the synthesis of (-)-Captopril (**3**), which is being used in the treatment of hypertension.[11] The amide **2** was obtained from (*S*)-(-)-acetyl-β-mercaptoisobutyric acid (**1**) and L-proline methyl ester.HCl in 81% yield under our standard conditions. The hydrolysis of **2** brought out (-)-Captopril (**3**).[12]



In summary, trichloroacetonitrile and triphenylphosphine can be used for the conversion of various acids into the corresponding acid chlorides in high isolated yields at room temperature.

Typical experimental procedure: To a mixture of benzoic acid (122 mg, 1.0 mmol) and trichloroacetonitrile (288 mg, 2.0 mmol) in CH_2Cl_2 (1 mL) under argon was added Ph_3P (524 mg, 2.0 mmol) in CH_2Cl_2 (1 mL) dropwise at room temperature. The reaction mixture was stirred for 40 min (TLC showed the disappearance of benzoic acid). The reaction mixture was then treated with cyclohexylamine (99 mg, 1mmol) followed by triethylamine (0.42 mL, 3mmol). The reaction mixture was allowed to react for 30 min. The mixture was washed with water. The organic layer was dried over anhydrous $MgSO_4$. After filtration, the solvent was removed and the residue was purified with column chromatography on silica gel (hexanes/EtOAc, 2:1) to give *N*-cyclohexylbenzamide (197 mg, 97 %).

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12. For compound **3**: mp 105-106 °C (lit.[11] 103-105 °C); $[\alpha]^{20}_D$ = -129.5 (EtOH, c = 1.3) (lit[11] -129.4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, d, *J* = 6.6 Hz), 1.58 (1H, t, *J* = 8.6 Hz), 2.00-2.20 (3H, m), 2.25-2.35 (1H, m), 2.45-2.55 (1H, m), 2.80-2.95 (2H, m), 3.60-3.67 (2H, m), 4.60-4.62 (1H, m), 11.10 (1H, broad).