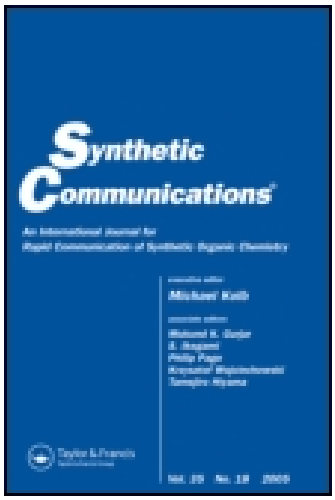

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One-Pot Preparation of Esters from Carboxylic Acids Using the PPh_3-CCl_3CN System

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ABSTRACT

A convenient one-pot process for preparing various esters from carboxylic acids using the Ph_3P-CCl_3CN has been developed. Racemic α-tocopherol, clofibrate and flavoxate were prepared in high yields using this method.

Key Words: Ester; Acyl chloride; Carboxylic acid; Trichloronitrile.

Acyl halides are very useful preparative intermediates for preparing other substances such as amides and esters.[1] Although many coupling reagents for preparing esters directly from carboxylic acids have been

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developed,[2] the method for the preparation of esters through acyl chlorides is still demanded. The traditional methods to prepare acyl chlorides from carboxylic acids used thionyl chloride,[3] phosphorous chlorides,[1] or oxalyl chloride.[4] However, the methods cannot be employed for acid-sensitive molecules due to their strong acidic conditions. When acid-free conditions are required, acyl chlorides can be obtained by treatment of carboxylic acids with an adduct of triphenylphosphine with carbon tetrachloride,[5] cyanuric chloride,[6] tetramethyl-α-chloroenamine,[7] or hexachloroacetone.[8] However, the methods have their own disadvantages such as long reaction times, or using toxic materials to prepare. We have recently reported work on the preparation of acyl chlorides using triphenylphosphine and trichloroacetonitrile.[9] The efficiency of the process prompted us to apply the reaction to preparation of a variety of esters.

First, the reaction was examined with various alcohols. The results are summarized in Table 1. Treatment of benzoic acid with Ph_3P and CCl_3CN in CH_3CN at room temperature, followed by cyclododecanol in the presence of 4-(dimethylamino)pyridine (DMAP) at reflux resulted in the formation of the corresponding ester in 93% yield (Entry 1). The yield of ester decreased as the amount of DMAP decreased (Entries 2–3). Use of zinc as a promoter gave a poor yield of ester (Entry 4).[10] Compared with acyclic alcohols, the reaction proceeded efficiently with cyclic secondary alcohols affording excellent yields of the corresponding esters (Entries 5 and 6). A primary alcohol afforded a high yield of the

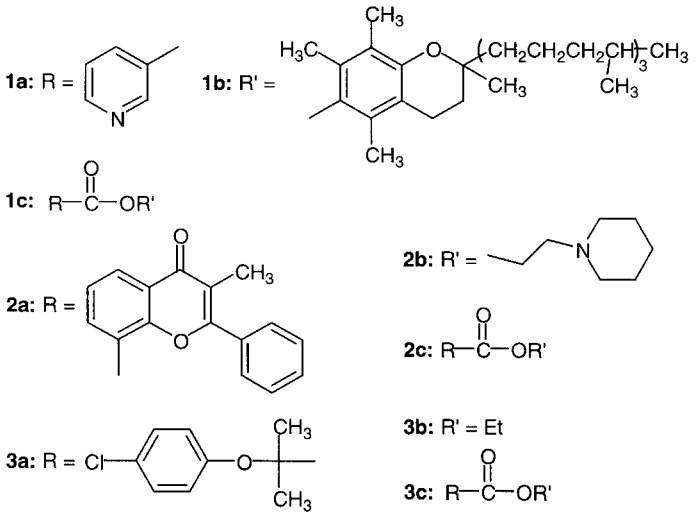
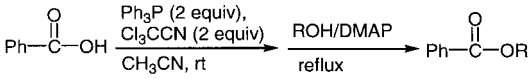


Table 1. Synthesis of esters from benzoic acid using the PPh_3-CCl_3CN system.



Entry	ROH	DMAP (equiv.)	Time (h)	Yield (%)
1	Cyclododecanol	3	1.5	93
2	Cyclododecanol	2	1.5	73
3	Cyclododecanol	1[a]	2.0	81
4	Cyclododecanol	—[b]	2.0	35
5	Cyclohexanol	3	1.5	88
6	(+)-Menthol	3	1.5	92
7	2-Dodecanol	3	1.5	72
8	1-Dodecanol	3	1.5	82
9	*t*-Butanol	3	1.5	26 (70)[c]
10	1-Ethylcyclododecanol	3	3.0	0

[a]Et_3N (3 equiv.) was added.
[b]Zn (1 equiv.) was used instead of DMAP.
[c]Recovered starting material.

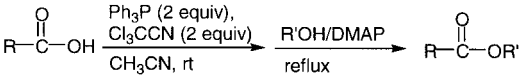
ester than a secondary alcohol (Entries 7 and 8). The method reaches a limit with sterically hindered alcohols such as ^{t}BuOH and 1-ethylcyclododecanol. The reaction gave a poor yield of the ester with ^{t}BuOH (Entry 9), and did not proceed at all with a bulkier tertiary alcohol, 1-ethylcyclododecanol (Entry 10).

The preparation of esters has been performed on a variety of structurally different carboxylic acids to determine the scope and limitations of this method. The results are presented in Table 2. Aromatic carboxylic acids afforded excellent yields while aliphatic acids gave moderate to high yields of the corresponding esters (Entries 1–5).

Next, we applied our method to preparing important medicines such as the hyperkinemic agent, DL-α-tocopherol nicotinate (**1c**),[11] the anticholinergic-spasmolytic agent, flavoxate (**2c**)[12] and the hypolipidemic agent, clofibrate (**3c**).[13] The reaction of nicotinic acid (**1a**) with DL-α-tocopherol (**1b**) under reaction conditions produced the desired ester, DL-α-tocopherol nicotinate (**1c**) in 84% yield (Entry 6). Similarly, flavoxate (**2c**) and clofibrate (**3c**) were prepared in 73% and 78% yields, respectively (Entries 7 and 8).

In conclusion, the Ph_3P/CCl_3CN system provides an efficient one-pot process for preparing various esters from aromatic and aliphatic

Table 2. Synthesis of various esters from carboxylic acids using the PPh_3-CCl_3CN system.



Entry	RCO_2H	R′OH	Time (h)	Yield (%)
1	*p*-Nitrobenzoic	Cyclododecanol	1.0	94
2	*p*-^{t}Butylbenzoic	Cyclododecanol	1.0	94
3	Heptanoic	Cyclododecanol	3.5	85
4	6-Bromohexanoic	Cyclododecanol	3.5	62
5	2-Bromoisovaleric	Cyclohexanol	3.5	64
6[a]	**1a**	**1b**	2.0	84
7[a]	**2a**	**2b**	2.0	73
8[b]	**3a**	Ethanol	2.0	78

[a]The reaction was carried out in THF.
[b]The reaction was carried out with 2 equiv. of ethanol in THF.

carboxylic acids. The reaction conditions are mild, and as a result, functionalities such as double bond, nitro, chloro, bromo, ether, and carbonyl groups remain unaffected. Furthermore, the reagents employed are inexpensive and are readily available.

EXPERIMENTAL

Melting points were determined with a Fisher-Jones melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were determined for solutions in $CDCl_3$ with TMS internal reference on a Varian Gemini 300 NMR spectrometer. Thin-layer chromatography (TLC) was performed on 0.25 mm silica gel plates (Merck, Kieselgel 60F-254). Column chromatography was performed on silica gel (Merck, Kieselgel 60, 230–400 mesh). All commercially available reagents were used as received from the suppliers. Solvents were used either as purchased or dried and purified by standard methodology under argon. All yields refer to isolated products.

Synthesis of DL-α-tocopherol nicotinate (1c). To a mixture of nicotinic acid (**1a**) (246 mg, 2.0 mmol) and CCl_3CN (0.4 mL, 4.0 mmol) in anhydrous THF (10 mL) under argon was added Ph_3P (1.05 g, 4.0 mmol) at room temperature. The reaction mixture was stirred for 3 h. The

reaction mixture was then treated with DL-α-tocopherol (**1b**) (862 mg, 2.0 mmol) followed by DMAP (733 mg, 6.0 mmol). The reaction mixture was allowed to react for 2 h at 75°C. The reaction mixture was then concentrated under vacuum. The reaction 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 (*n*-hexane:EtOAc, 2:1) to give DL-α-tocopherol nicotinate (**1c**) (900 mg, 84%): M.p. 37–38°C (Lit.[13] 32°C); ^{1}H NMR δ ($CDCl_3$, 300 MHz) δ 0.83–0.88 (m, 15H), 2.02 (s, 3H), 2.06 (s, 3H), 2.12 (s, 3H), 2.63 (t, $J = 6.6$ Hz), 7.48 (dd, $J = 5.1$ Hz, $J = 8.0$ Hz, 1H), 8.49 (d, $J = 8.1$ Hz, 1H), 8.86 (d, $J = 5.1$ Hz, 1H), 9.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.9, 12.1, 13.9, 19.8, 19.9, 21.3, 21.6, 22.7, 24.8, 25.2, 25.2, 28.6, 32.6, 33.0, 33.1, 37.5, 37.7, 37.8, 37.9, 39.7, 41.5, 75.1, 120.2, 123.1, 123.5, 124.4, 125.4, 130.6, 136.8, 144.8, 146.3, 151.4, 152.5, 167.7.

Synthesis of flavoxate (2c). Flavoxate (**2c**) was prepared according to the typical procedure with 3-methylflavone-8-carboxylic acid (**2a**) (560 mg, 2.0 mmol) and 1-(2-hydroxyethyl)piperidine (**2b**) (0.27 mL, 2.0 mmol). The product was purified with column chromatography on silica gel (*n*-hexane:EtOAc, 2:1) to give 572 mg (73%) of flavoxate (**2c**): M.p. 87–88°C (Lit.[12] 85–86°C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.37–1.57 (m, 6H), 2.10 (s, 3H), 2.38 (m, 4H), 2.43 (t, $J = 5.4$ Hz, 2H), 3.55 (t, $J = 5.4$ Hz, 2H), 7.56 (m, 4H), 7.81 (m, 2H), 8.19 (d, $J = 7.8$ Hz, 1H), 8.26 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.9, 25.1, 26.4, 55.5, 57.9, 62.3, 112.2, 114.4, 121.5, 125.4, 128.8, 128.8, 129.0, 129.3, 123.0, 135.3, 158.7, 162.1, 165.4, 176.6.

Synthesis of clofibrate (3c). Clofibrate (**3c**) was prepared according to the typical procedure with clofibric acid (**3a**) (860 mg, 4.0 mmol) and ethanol (0.47 mL, 8.0 mmol). The product was purified with column chromatography on silica gel (*n*-hexane:EtOAc, 2:1) to give 752 mg (78%) of clofibrate (**3c**): b.p. 148–150°C/20 mmHg (Lit.[11] 80–84°C/0.1 mmHg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.34 (t, $J = 7.1$ Hz, 3H), 1.59 (s, 6H), 4.23 (q, $J = 6.6$ Hz, 2H), 6.79 (d, $J = 8.9$ Hz, 2H), 7.19 (d, $J = 8.9$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 24.9, 61.5, 78.7, 115.9, 128.3, 136.6, 155.6, 170.3.

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