

Efficient Method for the Esterification of Carboxylic Acids with Alcohols Using Di-2-thienyl Carbonate Promoted by DMAP and Iodine

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Reaction of carboxylic acids with alcohols by using an equimolar amount of di-2-thienyl carbonate (2-DTC) in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) followed by addition of an equimolar amount of iodine proceeded smoothly to afford the corresponding esters and 2(5*H*)-thiophenone in good to high yields.

Esterification of carboxylic acids with alcohols is one of the most important and fundamental reactions in synthetic organic chemistry. Several useful esterification methods of using nearly equimolar amounts of carboxylic acids and alcohols were reported to have been employed widely in the synthesis of natural or unnatural molecules having carboxylic ester moieties; namely, the use of DCC,¹ 2,4,6-trichlorobenzoyl chloride,² di(2-pyridyl) carbonate (DPC),³ *O,O'*-di(2-pyridyl) thiocarbonate (DPTC),⁴ 2-Me-6-NO₂-benzoic anhydride (MNBA),⁵ 4-(trifluoromethyl) benzoic anhydride,⁶ 4-nitrobenzoic anhydride/Sc(OTf)₃,⁷ etc.⁸

In our previous communication, a new esterification method that used di-2-thienyl carbonate (2-DTC)⁹ and nearly equimolar amounts of carboxylic acids and alcohols in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) was reported. This method, however, was not fully convenient on the account that it needed a relatively long reaction time and failed to work well when cinnamic acid, aromatic acids, or hindered carboxylic acid were used. Therefore, it was desired to develop more effective methods of 2-DTC-mediated esterification reaction using various carboxylic acids.

As described in our previous communication,⁹ the reaction proceeds via two-step reactions: namely, formations of thienyl ester **1** and of the corresponding carboxylate by the reaction of alcohol and **1**. Since the latter is the rate determining step, acceleration of the acylation step of alcohol with thienyl ester **1** was essential. Then, the chemical behavior of halogenation of thienyl ester **1** was first studied because 2-oxythiophene moiety of the thienyl ester **1** was thought to behave as a nucleophile under oxidative conditions. Since thienyl ester **1** was halogenated readily, the reaction time and the yield of esterification was expected to be improved so long as suitable halogenating reagents were chosen. Then, esterification of the thienyl esters derived from carboxylic acids and 2-DTC with alcohols by using several halogenating reagents was studied. In this communication, a new method for the 2-DTC-mediated esterification using DMAP and iodine is described.

In the first place, reaction of 2-thienyl 3-phenylpropionate **1** with 3-phenyl-1-propanol was tried by using various halogenating reagents (Table 1). When *N*-haloimides such as *N*-bromosuccinimide, *N*-iodosuccinimide, *N*-chlorosuccinimide, and *N*-bromophthalimide were used (Entries 3–6), the desired ester **2** was obtained in low yields and mostly 5-halogenated 2-thienyl

Table 1. Effect of halogenating reagents

Entry	Activator	Solvent	Time/h	Yield/%
1	none	CH ₂ Cl ₂	22	N.D.
2	DMAP ^a	CH ₂ Cl ₂	4	93
3	NBS	CH ₂ Cl ₂	2	23
4	NIS	CH ₂ Cl ₂	48	40
5	NCS	CH ₂ Cl ₂	48	22
6	NBP ^b	CH ₂ Cl ₂	4	36
7	I ₂	CH ₂ Cl ₂	1	83
8	Br ₂	CH ₂ Cl ₂	2	94
9	CuI	CH ₃ CN	22	N.R.

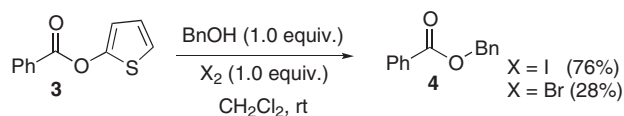
^a 0.1 equiv. of DMAP was used. ^b *N*-bromophthalimide.

3-phenylpropionate was formed. On the other hand, the desired ester **2** was obtained in good or high yields when iodine or bromine was the activator (Entries 7, 8). In the case of using copper iodide, however, the desired ester was not detected although affinities of copper to sulfur seemed to contribute considerably to the promotion of this reaction (Entry 9).

Next, esterification of 2-thienyl benzoate **3** with benzyl alcohol was examined by using iodine or bromine as an activator (Scheme 1). The corresponding ester **4** was obtained in good yield when iodine was used. In the case of bromine, however, the yield was low and 5-brominated 2-thienyl benzoate was formed as a main product. This result indicated that the iodine worked more effectively than the bromine in the present esterification.

Esterification of carboxylic acids with alcohols was then tried by using 2-DTC. The reaction generally proceeded rapidly by adding an equimolar amount of iodine in the presence of a catalytic amount of DMAP in CH₂Cl₂ and the corresponding esters were obtained in high yields. Further, it is noteworthy that the above reaction proceeded quite smoothly in CH₃CN. The amount of DMAP was reduced to 1/2 which was effective enough for the first step of the formation of thienyl ester **1** and the reaction of the second step of the synthesis of ester **2** proceeded rapidly.¹⁰

Esterification of 3-phenylpropionic acid with various alco-



Scheme 1. Esterification of benzyl alcohol with 2-thienyl benzoate.

Table 2. Esterification using various alcohols

$\text{Ph-CH}_2\text{-CH}_2\text{-COOH} \xrightarrow[\text{DMAP (0.05 equiv.)}]{\text{2-DTC (1.0 equiv.)}} \xrightarrow[\text{I}_2 \text{ (1.05 equiv.)}]{\text{R'OH (1.2 equiv.)}} \text{Ph-CH}_2\text{-CH}_2\text{-COOR'}$ (1.0 equiv.) CH_3CN, rt			
Entry	R'OH	Time () ^a /h	Yield () ^a /%
1	Rh(CH ₂) ₃ OH	0.5 (6)	94 (94)
2	CH ₃ (CH ₂) ₃ OH	0.5 (8)	86 (91)
3	BnOH	0.5 (4)	89 (96)
4	Ph(CH ₂) ₂ CH(OH)CH ₃	0.5 (8)	90 (82)
5	c-C ₆ H ₁₁ OH	1 (11)	88 (81)

^a Values in parentheses are those obtained previously in CH₂Cl₂ in the presence of 0.1 equiv. of DMAP.⁹

Table 3. Esterification using various carboxylic acids and alcohols

$\text{R}-\text{C}(=\text{O})\text{OH} \xrightarrow[\text{DMAP (0.05 equiv.)}]{\text{2-DTC (1.0 equiv.)}} \xrightarrow[\text{I}_2 \text{ (1.05 equiv.)}]{\text{R'OH (1.2 equiv.)}} \text{R}-\text{C}(=\text{O})\text{OR'}$ (1.0 equiv.) CH_3CN, rt				
Entry	RCO ₂ H	R'OH	Time () ^a /h	Yield() ^a /%
1	CH ₃ (CH ₂) ₃ COOH	Ph(CH ₂) ₃ OH	0.5	86
2	PhMeCHCOOH	Ph(CH ₂) ₃ OH	2 (6)	93 ^b (79)
3	PhMeCHCOOH	<i>c</i> -C ₆ H ₁₁ OH	2 (11)	81 ^c (83)
4	<i>c</i> -C ₆ H ₁₁ COOH	Ph(CH ₂) ₃ OH	0.5 (11)	91 (87)
5	<i>c</i> -C ₆ H ₁₁ COOH	Ph(CH ₂) ₂ CH(OH)CH ₃	0.5 (48)	93 ^b (69)
6	Me ₃ CCOOH	Ph(CH ₂) ₃ OH	0.5 (22)	91 (N.D.)
7	Me ₃ CCOOH	Ph(CH ₂) ₂ CH(OH)CH ₃	0.5	81
8	(<i>E</i>)-PhCH=CHCOOH	Ph(CH ₂) ₃ OH	0.5 (22)	88 (37)
9	(<i>E</i>)-PhCH=CHCOOH	Ph(CH ₂) ₂ CH(OH)CH ₃	0.5	83
10	PhCOOH	Ph(CH ₂) ₃ OH	6 (22)	89 (33)
11	<i>p</i> -MeOPhCOOH	Ph(CH ₂) ₃ OH	0.5 (22)	87 (3)

^a Values in parentheses are those obtained previously in CH₂Cl₂ in the presence of 0.1 equiv. of DMAP.⁹

^b Reactions were performed by using 0.1 equiv. of DMAP and 1.1 equiv. of iodine and CH₂Cl₂ as a solvent.

^c Reactions were performed by using 0.1 equiv. of DMAP and 1.5 equiv. of iodine and CH₂Cl₂ as a solvent.

hols proceeded smoothly to afford the corresponding esters in good to high yields by using nearly equimolar amounts of primary alcohols (Table 2, Entries 1–3). Also, the esters were obtained in good to high yields when secondary alcohols were used (Entries 4, 5). It is interesting to note that these reactions completed quickly in the presence of iodine i.e. 30 min–1 h whereas it took much longer i.e. 4–11 h in the absence of iodine.⁹

The results of the esterification using various carboxylic acids are listed in Table 3. The corresponding ester was obtained in good yield by using *n*-valeric acid (Entry 1). Also, the desired products were obtained rapidly in good to high yields even when α,α -disubstituted carboxylic acids and secondary alcohols were used (Entries 3, 5). In the cases of trans-cinnamic acid and aromatic acids or a hindered carboxylic acid such as pivalic acid, the esters were likewise obtained rapidly in good to high yields whereas the former two acids gave the corresponding esters in low yields and the latter one did not form the ester at all under previously reported conditions⁹ (Entries 6–11).

The above procedure consists of two reactions. As described, thienyl ester **1** was formed immediately by treating carboxylic acid with 2-DTC in the presence of DMAP (0.05 equiv.) in CH₃CN whereas the reaction in CH₂Cl₂ needed to use more

molar amount of DMAP (0.1 equiv.)⁹ But, no product was formed when an equimolar amount of iodine was used instead of DMAP under the above conditions (Step 1). The corresponding ester **2** in the previous report⁹ was obtained in 4 h by the acylation of 3-phenyl-1-propanol with isolated thienyl ester **1** in the presence of DMAP. On the other hand, it is noted that the above reaction proceeded within 30 min in the presence of iodine to afford the ester **2** in high yield (Step 2). These results indicate that a catalytic amount of DMAP behaved effectively in the first step and iodine worked efficiently in the second step. The detailed mechanism of the activation of thienyl esters with iodine is now under investigation.

It is noted that a simple and effective method for the synthesis of various esters was established by using nearly equimolar amounts of free carboxylic acids including aromatic and hindered ones, alcohols and 2-DTC in the presence of a catalytic amount of DMAP and an equimolar amount of iodine.

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- A typical experimental procedure was as follows: to a mixture of 3-phenylpropionic acid (26.5 mg, 0.176 mmol) and 2-DTC (40.0 mg, 0.176 mmol) in CH₃CN (0.2 mL) was added DMAP (1.08 mg, 0.0088 mmol). After stirring for 10 min at room temperature, 3-phenyl-1-propanol (28.8 mg, 0.211 mmol) and then iodine (47 mg, 0.185 mmol) was added. The reaction mixture was stirred for 30 min at room temperature and then 10% aqueous sodium thiosulfate was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative thin layer chromatography to afford the corresponding ester (44.3 mg, 94%).