Efficient Method for the Esterification of Carboxylic Acids with Alcohols Using Di-2-thienyl Carbonate Promoted by Catalytic Amounts of DMAP and $Hf(OTf)_4$

Yoshiaki Oohashi,[†] Kentarou Fukumoto,[†] and Teruaki Mukaiyama*[†,††]

[†]*Center for Basic Research, The Kitasato Institute, 6-15-5 (TCI) Toshima, Kita-ku, Tokyo 114-0003*

[††]*Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641*

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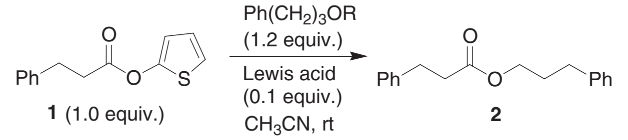
Esterification of carboxylic acids with alcohols including bulky secondary ones by using an equimolar amount of di-2-thienyl carbonate (2-DTC) in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) followed by addition of a catalytic amount of hafnium(IV) trifluoromethanesulfonate ($Hf(OTf)_4$) afforded the corresponding esters in good to high yields.

Preparation of carboxylic esters from nearly equimolar amounts of carboxylic acids and alcohols is one of the most important and fundamental methods in synthetic organic chemistry. Therefore, several useful methods for those esterifications have been developed[1–8] and are widely employed in the synthesis of natural or unnatural molecules that have carboxylic ester moieties.

In our previous communication, a new method for the above esterification was reported by using di-2-thienyl carbonate (2-DTC) in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP).[9] Recently, it was reported from our laboratory that the further addition of an equimolar amount of iodine accelerated this esterification and the yield was improved.[10] But, this reaction did not proceed satisfactorily when a catalytic amount of iodine was used. Also, this method did not afford the corresponding esters in satisfactory yields when the substrates containing an olefinic moiety such as allyl alcohol or hexenoic acid were used. Now, in order to improve the utility of 2-DTC mediated esterification, the above reaction was tried by using several Lewis acids. In this communication, a newly developed 2-DTC-mediated highly efficient ester-forming reaction by using DMAP and $Hf(OTf)_4$[11] is described.

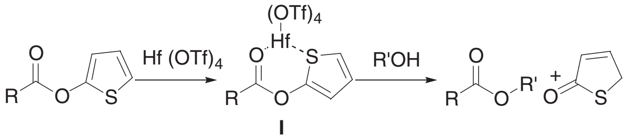
In the first place, effect of various Lewis acid catalysts was screened by taking the reaction of 2-thienyl 3-phenylpropionate **1** with 3-phenyl-1-propyl trimethylsilyl ether as a model (Table 1). In the cases when typical Lewis acids were used (Entries 1–3), none or only a small amount of desired ester **2** was obtained except when $SnCl_4$ was used. Then, reactions in the presence of various Lewis acid catalysts, as metal triflates, were screened. As a consequence, the corresponding ester **2** was obtained in high yields when catalysts such as $Cu(OTf)_2$, $Sc(OTf)_3$, or $Hf(OTf)_4$ were used (Entries 6–8). Next, the reaction of 2-thienyl 3-phenylpropionate **1** with 3-phenyl-1-propanol was examined in the presence of catalytic amounts of various Lewis acids. The desired ester **2** was obtained in high yield only when $Hf(OTf)_4$ was used (Entry 8). It was interesting to note that $Hf(OTf)_4$ worked more effectively than $Sc(OTf)_3$ which was known as a remarkably active Lewis acid catalyst for the acylation of alcohols with acid anhydrides[7] (Entries 7, 8).

Table 1. Esterification of 2-thienyl 3-phenylpropionate by using silyl ether or alcohol using various Lewis acids

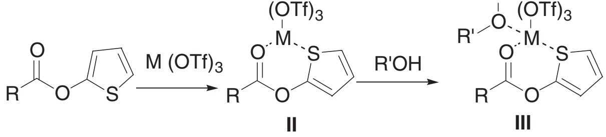


Entry	Lewis acid	R=TMS		R=H	
		Time/h	Yield/%	Time/h	Yield/%
1	BF_3-OEt_2	4	N.R.	4	7
2	$TiCl_4$	4	9	4	17
3	$SnCl_4$	4	82	4	16
4	$HfCl_4$	4	65	4	66
5	$Mg(OTf)_2$	4	24	4	2
6	$Cu(OTf)_2$	0.5	quant.	4	6
7	$Sc(OTf)_3$	4	86	4	29
8	$Hf(OTf)_4$	0.5	quant.	0.5	92
9	$La(OTf)_3$	4	trace	4	N.R.
10	$Gd(OTf)_3$	4	5	4	4
11	$Yb(OTf)_3$	4	7	4	7

These results are explained by considering an initial formation of the active chelate complex **I** by the interaction of $Hf(OTf)_4$ at carbonyl oxygen and sulfur atoms of thienyl ester. The complex **I** subsequently reacted with alcohol to afford the corresponding ester because an alcohol hardly coordinate further to complex **I** that is fully saturated by ligands (Scheme 1). On the other hand, group 3 metal triflates such as $Sc(OTf)_3$ and $Ln(OTf)_3$ are assumed to form chelate complexes **II** which are still not fully occupied by ligands. Then further coordination of alcohol results in the formation of the chelate complexes **III**. They are considered to be deactivated because of decrease in Lewis acidity of metal triflates (Scheme 2). Thus, the reaction of **1** with 3-phenyl-1-propanol using group 3 metal triflates did not proceed effectively (Table 1, Entries 7, 9–11).

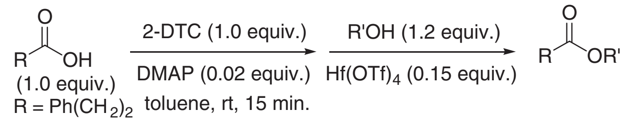


Scheme 1. The active chelate complex **I** derived from 2-thienyl ester and $Hf(OTf)_4$.



Scheme 2. The deactivation of chelate complex **II** by further coordination of alcohol.

Table 2. Esterification of various alcohols in the presence of DMAP and Hf(OTf)$_4$

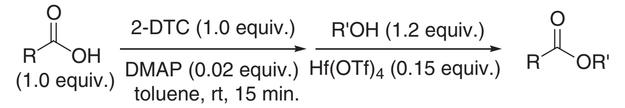


Entry	R′OH	Time ( )^a /h	Yield ( )^a /%
1	Ph(CH$_2$)$_3$OH	0.5 (4)	90 (66)
2	Ph(CH$_2$)$_2$CH(OH)CH$_3$	1 (4)	84 (28)
3	c-C$_6$H$_{11}$OH	2 (4)	85 (9)
4	i-Pr$_2$CHOH	1 (4)	91 (53)
5	t-BuMeCHOH	1 (4)	93 (77)
6	(-)-MenthylOH	1 (4)	90 (16)

[a]Values in parentheses are those obtained in CH$_3$CN by using 0.15 equivalents of I$_2$ instead of Hf(OTf)$_4$.

Next, esterification of carboxylic acids with alcohols using 2-DTC was tried in the presence of catalytic amounts of DMAP and Hf(OTf)$_4$.[12] The esterification of 3-phenylpropionic acid with various alcohols including bulky secondary ones proceeded smoothly to afford the corresponding esters in high yields (Table 2, Entries 1–6). It is noted that the above reactions using a catalytic amount of Hf(OTf)$_4$ proceeded smoothly though the same reactions did not proceed effectively when a catalytic amount of iodine was used.

Table 3. Esterification using various carboxylic acids and alcohols



Entry	RCO$_2$H	R′OH	Time/h	Yield/%
1	Ph(CH$_2$)$_2$COOH	CH$_2$=CHCH$_2$OH	2	59[a]
2	Ph(CH$_2$)$_2$COOH	CH$_2$=CHCH$_2$OH	1	94
3	(E)-EtCH=CHCH$_2$COOH	Ph(CH$_2$)$_3$OH	0.5	76[a]
4	(E)-EtCH=CHCH$_2$COOH	Ph(CH$_2$)$_3$OH	0.5	89
5	c-C$_6$H$_{11}$COOH	Ph(CH$_2$)$_2$CH(OH)CH$_3$	0.5	94
6	c-C$_6$H$_{11}$COOH	c-C$_6$H$_{11}$OH	0.5	86
7	Me$_3$CCOOH	Ph(CH$_2$)$_3$OH	0.5	94[b]
8	Me$_3$CCOOH	Ph(CH$_2$)$_2$CH(OH)CH$_3$	0.5	80[b,c]

[a]Reaction was performed by using 0.05 equivalents of DMAP and 1.05 equivalents of I$_2$ in CH$_3$CN. [b]Synthesis of 2-thienylester was completed within 1 h. [c]DMAP (0.05 equivalents) and Hf(OTf)$_4$ (0.35 equivalents) in toluene (0.2 mL) were used.

Finally, this esterification between various carboxylic acids and alcohols was tried (Table 3). The corresponding ester was obtained in high yield when allyl alcohol was used, whereas the use of 1.05 equivalents of iodine instead of 0.15 equivalents of Hf(OTf)$_4$ gave the desired product in 59% yield along with a by-product formed by the addition of iodine to olefinic bond of the resulted product (Entries 1, 2). Also, the desired ester was obtained in high yield when hexenoic acid was used but the yield of the desired product decreased to 76% when 1.05 equivalents of iodine was used (Entry 3, 4). The corresponding esters were also obtained in good to high yields in the case of using hindered α,α-disubstituted carboxylic acid and pivalic acid (Entries 5–8).

It is noted that an efficient method for the synthesis of various esters by using nearly equimolar amounts of free carboxylic acids, alcohols and 2-DTC in the presence of catalytic amounts of DMAP and Hf(OTf)$_4$ was established.

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[12] 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 toluene (0.4 mL) was added DMAP (0.43 mg, 0.0035 mmol). After stirring for 15 min at room temperature, 3-phenyl-1-propanol (28.8 mg, 0.211 mmol) and then a solution of Hf(OTf)$_4$ (20.5 mg, 0.027 mmol) in CH$_3$CN (0.05 mL) was added. The reaction mixture was stirred for 30 min at room temperature and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with ether, 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 (42.8 mg, 90%) as a colorless oil.

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