A New Method for the Esterification of Carboxylic Acids with Various Alcohols by Using Di-2-thienyl Carbonate, a New Coupling Reagent

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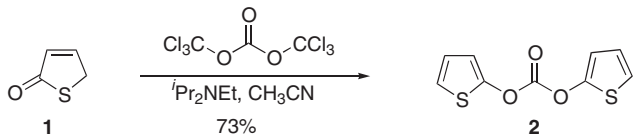
Esterification of carboxylic acids with alcohols by using di-2-thienyl carbonate in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) proceeded smoothly under mild conditions to afford the corresponding esters and 2(5*H*)-thiophenone in good to high yields.

Esterification of carboxylic acids with alcohols is one of the most important and fundamental reactions in synthetic organic chemistry. There have been reported several useful coupling reagents such as *N*,*N*′-dicyclohexylcarbodiimide/DMAP,[1] 2,4,6-trichlorobenzoyl chloride/Et_3N/DMAP,[2] di(2-pyridyl) carbonate/DMAP,[3] *O*,*O*′-di(2-pyridyl) thiocarbonate/DMAP,[4] 2-Me-6-NO_2-benzoic anhydride/DMAP,[5] or 4-(trifluoromethyl)benzoic anhydride/$TiCl_4$/2$AgClO_4$, Me_3SiCl,[6] 4-NO_2-benzoic anhydride/$Sc(OTf)_3$,[7] and several other coupling reagents which activated carboxylic acids in the coexistence of a base or a Lewis acid, respectively.[8]

Esterification that uses these coupling reagents is widely employed in the synthesis of natural or unnatural molecules with carboxylic ester moieties. It is still necessary to develop various type of coupling reagents that effectively afford the desired esters. Therefore, it is important to design and to prepare the active esters that possess a new efficient leaving group. Then, carboxylic acid esters derived from five-membered hetero lactones such as 2(5*H*)-thiophenone were considered useful since the reaction proceeded effectively by utilizing the transformation of 2-oxythiophene to more stable 2(5*H*)-thiophenone. Thus formed 2(5*H*)-thiophenone were no longer involved in further reactions. In this communication, we would like to report on di-2-thienyl carbonate (2-DTC), a new and effective coupling reagent, for the esterification of carboxylic acids with alcohols in the presence of a catalytic amount of DMAP under mild conditions.

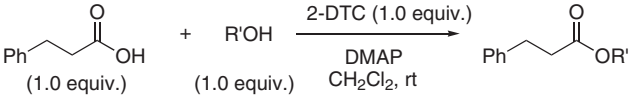
Di-2-thienyl carbonate was prepared easily in good yield by the reaction of triphosgene with 2(5*H*)-thiophenone in the presence of $^iPr_2NEt$ in CH_3CN (Scheme 1).[9]

Esterification of carboxylic acids with alcohols was then tried by using 2-DTC and the reaction proceeded smoothly in the presence of a catalytic amount of DMAP in CH_2Cl_2 to afford the corresponding esters in high yields.[10] Similarly, the desired ester was afforded also in other solvents such as Et_2O, CH_3CN, toluene.



Scheme 1. Synthesis of di-2- thienyl carbonate.

Table 1. Esterification using various alcohols.



Entry	R′OH	Time / h	Yield /%
1	$Ph(CH_2)_3OH$	6	94
2	$CH_3(CH_2)_3OH$	8	91
3	BnOH	4	96
4	$Ph(CH_2)_2CH(OH)CH_3$	8	82[a]
5	*c*-$C_6H_{11}OH$	11	81[a]
6	Ph_2CHOH	8	87
7	PhOH	2	95

[a]1.2 equivalent of alcohol was used.

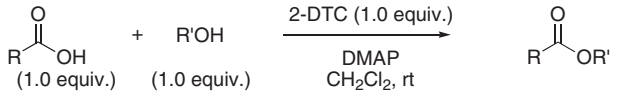
Condensation of 3-phenylpropionic acid with various alcohols afforded the corresponding esters in high yields by using equimolar amounts of primary alcohols (Table 1, Entries 1–3). In the case when secondary alcohols and phenol were used (Entries 4–7), the esters were also obtained in good to high yields.

Experimental results by using various carboxylic acids are listed in Table 2. The corresponding esters were obtained in good to high yields by using equimolar amounts of primary carboxylic acids (Entries 1–2) or a 3-pyridine propionic acid possessing a basic part in the molecule (Entry 3). The corresponding esters were obtained in good yields even when α,α-disubstituted carboxylic acids and secondary alcohols were used (Entries 5, 7 and 9).

In order to study the mechanism of this reaction, isolation of thienyl ester **4**,[11] an active ester intermediate, was tried by treating carboxylic acid **3** with 2-DTC in the presence of DMAP (10 mol%). The reaction completed immediately to afford the desired thienyl ester **4** in high yield along with the evolution of carbon dioxide while nothing was obtained in the absence of base. In regard to reaction time with other bases such as Et_3N or DBU, it became longer i.e. 10 and 4 h, respectively. Actually, the corresponding ester **5** was not detected when acylation of 1-phenylpropanol with isolated thienyl ester **4** was tried in the absence of bases. In the presence of DMAP (10 mol%), on the other hand, the above reaction proceeded smoothly within 4 hours to afford the corresponding ester **5** in high yield while the yield was 20% even after 22 hours if Et_3N was used instead of DMAP. These concludes that a catalytic amount of DMAP was quite effective in the above two steps in forming thienyl ester **4** and the acylated product of alcohol. The acylpyridinium salts are thus key intermediates in the above steps.

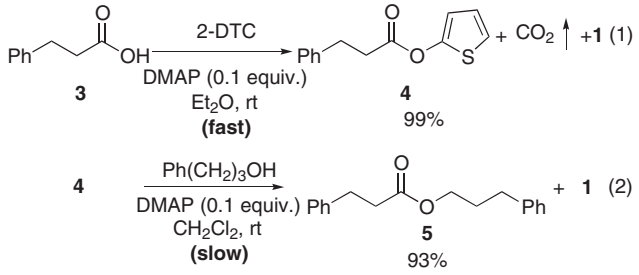
It is noted that various esters could be obtained in good to high yields by the coupling reaction between free carboxylic acids and alcohols including hindered ones with the use of 2-

Table 2. Esterification using various carboxylic acids.



Entry	RCO_2H	R′OH	Time /h	Yield /%
1	$PhCH_2CH_2COOH$	$Ph(CH_2)_3OH$	6	94
2	$CH_3(CH_2)_3COOH$	$Ph(CH_2)_3OH$	8	91[a]
3	*m*-$PyCH_2CH_2COOH$[b]	$Ph(CH_2)_3OH$	6	84
4	PhMeCHCOOH	$Ph(CH_2)_3OH$	6	79
5	PhMeCHCOOH	*c*-$C_6H_{11}OH$	11	83
6	*c*-$C_6H_{11}COOH$	$Ph(CH_2)_3OH$	11	87
7	*c*-$C_6H_{11}COOH$	Ph_2CHOH	22	90[a]
8	$Ph_2CHCOOH$	$Ph(CH_2)_3OH$	11	95[a]
9	$Ph_2CHCOOH$	$Ph(CH_2)_2CH(OH)CH_3$	22	86[a]

[a]1.2 equivalent of alcohol was used. [b]3-pyridinepropionic acid.



Scheme 2. Esterification of 3-phenylpropanol with 3-phenylpropionic acid using di-2- thienyl carbonate.

DTC in the presence of a catalytic amount of DMAP.

References and Notes

1 B. Neises and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, **17**, 522 (1978); A. Hssner and V. Alexanian, *Tetrahedron Lett.*, **1978**, 4475.

2 J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **52**, 1989 (1979).

3 S. Kim, J. I. Lee, and Y. K. Ko, *Tetrahedron Lett.*, **25**, 4943 (1984).

4 K. Saitoh, I. Shiina, and T. Mukaiyama, *Chem. Lett.*, **1998**, 679.

5 I. Shiina, R. Ibuka, and M. Kubota, *Chem. Lett.*, **2002**, 286; I. Shiina, M. Kubota, and R. Ibuka, *Tetrahedron Lett.*, **43**, 7535 (2002).

6 I. Shiina, S. Miyoshi, M. Miyashita, and T. Mukaiyama, *Chem. Lett.*, **1994**, 515; I. Shiina and T. Mukaiyama, *Chem. Lett.*, **1994**, 677; I. Shiina, *Tetrahedron*, **60**, 1587 (2004).

7 K. Ishihara, M. Kubota, H. Kurihara, and H. Yamamoto, *J. Org. Chem.*, **61**, 4560 (1996).

8 K. Saigo, M. Usui, K. Kikuchi, E. Shimada, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **50**, 1863 (1977); H. A. Staab and A. Mannschreck, *Chem. Ber.*, **95**, 1284 (1962); J. D. Meseguer, A. L. P. Coll, J. R. F. Lizarbe, and A. Z. Bilbao, *Synthesis*, **1980**, 547; K. Takeda, A. Akiyama, H. Nakamura, S. Takizawa, Y. Mizuno, H. Takayanagi, and Y. Harigaya, *Synthesis*, **1994**, 1063; K. Wakasugi, A. Nakamura, and Y. Tanabe, *Tetrahedron Lett.*, **42**, 7427 (2001); K. Wakasugi, A. Nakamura, A. Iida, Y. Nishii, N. Nakatani, S. Fukushima, and Y. Tanabe, *Tetrahedron*, **59**, 5337 (2003); K. Wakasugi, A. Iida, T. Misaki, Y. Nishii, and Y. Tanabe, *Adv. Synth. Catal.*, **345**, 1209 (2003); I. Shiina and Y. Kawakita, *Tetrahedron Lett.*, **44**, 1951 (2003); I. Shiina, Y. Fukuda, T. Ishii, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **1998**, 831; I. Shiina, H. Fujisawa, T. Ishii, and Y. Fukuda, *Heterocycles*, **52**, 1105 (2000); L. Gooßen and A. Dohring, *Adv. Synth. Catal.*, **345**, 943 (2003).

9 Di-2-thienyl carbonate was synthesized as follows: After a mixture of 2(5*H*)-thiophenone (100 mg, 1.0 mmol) and $^iPr_2NEt$ (0.174 mL, 1.0 mmol) in CH_3CN (3 mL) had been stirred for 10 minutes at room temperature under argon atmosphere, triphosgene (49.6 mg, 0.167 mmol) in CH_3CN (1 mL) was added at $-50\,^\circ C$, and the reaction mixture was stirred for 2 h at $-50\,^\circ C$. After evaporation of the solvent, the residue was dissolved in ether and filtered. After evaporation of the solvent, the residue was separated by short silica gel column chromatography (eluent : hexane/AcOEt = 12/1) and recrystallized from 2-propanol to afford 2-DTC (82.4 mg, 73%) as a colorless solid. Thus prepared 2-DTC was stable crystalline and showed no sign of decomposition when kept standing under argon at room temperature for one month. ^1H NMR (270 MHz, C_6D_6): δ 6.47 (dd, $J = 3.2$, 1.8 Hz, 2H), 6.35 (dd, $J = 6.0$, 3.2 Hz, 2H), 6.29 (dd, $J = 6.0$, 1.8 Hz, 2H); ^{13}C NMR (67.8 MHz, C_6D_6): δ 152.6, 150.2, 123.8, 118.5, 114.5; MS (EI^+) m/z 226 $[M]^+$; HRMS (EI^+) calcd for $C_9H_6O_3S_2$ $[M]^+$ 225.9758, found m/z 225.9784; mp 53–54 °C.

10 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 CH_2Cl_2 (0.2 mL) was added DMAP (2.2 mg, 0.0176 mmol). After stirring for 10 minutes at room temperature, 3-phenylpropanol (24.1 mg, 0.176 mmol) was added and the mixture was stirred for 6 h at room temperature. After evaporation of the solvent, crude product was purified by preparative thin layer chromatography to afford the corresponding ester (44.6 mg, 94%).

11 2-Thienyl 3-phenylpropionate: ^1H NMR (270 MHz, $CDCl_3$): δ 7.34 − 7.19 (m, 5H), 6.87 (dd, $J = 5.8$, 1.9 Hz, 1H), 6.81 (dd, $J = 5.8$, 3.9 Hz, 1H), 6.65 (dd, $J = 3.9$, 1.9 Hz, 1H), 3.06 (t, $J = 7.4$ Hz, 2H), 2.91 − 2.83 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 169.3, 152.0, 140.0, 128.5, 128.2, 126.4, 123.2, 117.9, 113.2, 35.7, 30.7; HRMS (EI^+) calcd for $C_{13}H_{12}O_2S$ $[M]^+$ 232.0558, found m/z 232.0573.

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