O,O'-Di(2-pyridyl) Thiocarbonate as an Efficient Reagent for the Preparation of Carboxylic Esters from Highly Hindered Alcohols

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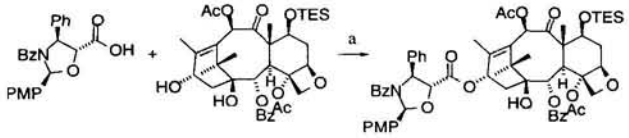
Various carboxylic esters were obtained in high yields from free carboxylic acids and several alcohols including bulky ones by using *O,O'*-di(2-pyridyl) thiocarbonate and a catalytic amount of DMAP.

Recently, the total synthesis of Taxol was completed by achieving the dehydration condensation reaction between a side-chain, a protected phenylisoserine, and 7-TES baccatin III by using *O,O'*-di(2-pyridyl) thiocarbonate (DPTC) (Scheme 1).[1]

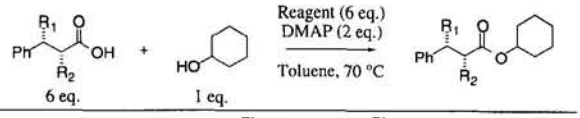


a) DPTC (6.0 eq.), DMAP (2.0 eq.), toluene, 73 °C, 95% based on 93% conversion.

Scheme 1. Synthesis of protected taxol by coupling reaction.

Concerning the above dehydration condensation reaction, a combined reagent DPTC-DMAP proved to be quite effective compared with the conventional combination to use DCC with DMAP,[2] *N*-alkyl-2-halopyridinium salts with trialkylamines,[3] di(2-pyridyl) carbonate (DPC) with DMAP,[4] *etc.* In model studies, dehydration condensation between Taxol side-chains and cyclohexanol using DPTC-DMAP also gave the corresponding esters in high yields in every case (Table 1). This outcome prompted us to study on applicability of this carboxylic ester-forming reaction, and we would like here to report several results of this reagent system.

Table 1. Yields of the cyclohexyl esters of side-chains

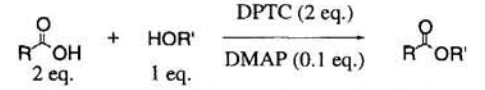


Reagent	BzHN, Ph, OBn	Ph, BzN, PMP	Ph, BzN, PMP	Ph, BzN, PMP
DPTC	**quant.**	**quant.**	**quant.**	**72%**
DPC	quant.	96%	82%	60%
DCC	60% [a]	55%	42%	51%

[a]At room temperature.

In the first place, the condensation reaction between equimolar amounts of 3-phenylpropionic acid (**1**) and cyclohexanol (**5**) in toluene using DPTC (1 eq.) and DMAP (0.1 eq.) was tried, and the corresponding ester was obtained in 83% yield. After screening several reaction conditions, it was found that the desired ester was obtained in almost quantitative yield when amounts of the carboxylic acid and DPTC were increased to 2 mol equivalents (Table 2, Entry 1, 96%).

Table 2. Esterification using DPTC and DMAP



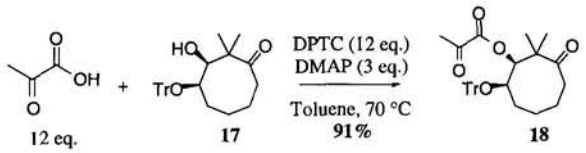
Entry	Carboxylic Acid		Alcohol		Solvent	Temp.	Yield/%
1	Ph, OH	**1**	HO	**5**	Toluene	r.t.	96 (98)[f]
2		**1**	HO	**6**	PhCl	reflux	91
3		**1**	HO	**7**	PhCl	reflux	85
4	Ph, OH	**2**	HO	**6**	PhCl	reflux	85
5		**2**	HO	**7**	Toluene	r.t.	86
6		**2**	Ph, HO, Ph	**8**	Toluene	r.t.	99
7		**2**	Ph, HO	**9**	Toluene	r.t.	95[b] (91)[f,g]
8		**2**	HO	**10**	Toluene	r.t.	94[c]
9		**2**	HO	**11**	Toluene	r.t.	95[d]
10		**2**	HO	**12**	Toluene	r.t.	93[e] (89)[f,h]
11		**2**	HO	**13**	Toluene	r.t.	95 (97)[f]
12		**2**	HO	**14**	PhCl	reflux	quant.
13		**2**	HO, Ph	**15**	PhCl	reflux	84
14	Ph, OH, Ph	**3**	Ph, HO, Ph	**8**	Toluene	r.t.	79
15[a]	$(EtO)_2P$, OH (**4**)		OTBS, HO (**16**)		Toluene	70 °C	91[d]

[a]Four tenths eq. of DMAP were used. [b]Diastereomeric ratio: 83/17. [c]Diastereomeric ratio: 64/36. [d]Diastereomeric ratio was not determined. [e]Diastereomeric ratio: 53/47. [f]The reaction was carried out in Et_2O using 1.1 eq. of the carboxylic acid and 1.1 eq. of DPTC. [g]Diastereomeric ratio: 86/14. [h]Diastereomeric ratio: 54/46.

Further, the corresponding esters were obtained in high yields even in cases of using bulky alcohols **7-13** (Entries 5-11 and 14) under similar reaction conditions. The desired ester was obtained in 91% yield when condensation reaction between carboxylic acid **1** and 2,4-dimethyl-3-pentanol (**6**) was carried out in refluxing chlorobenzene (Entry 2) while the yield decreased to 38% at room temperature probably because of low reactivity of the alcohol. The esterification reactions of carboxylic acid **1** with 3,3-

dimethyl-2-butanol (**7**) and 2-phenylpropionic acid (**2**) with 2,4-dimethyl-3-pentanol (**6**) in refluxing chlorobenzene also gave the corresponding esters in 85% yields, respectively (Entries 3 and 4). It is noteworthy that the condensation reaction gave the desired esters in high yields even in the cases of using 1-adamantanol (**14**) and 2-methyl-1-phenyl-2-propanol (**15**) having tertiary hydroxyl groups (Entry 12, quant.; Entry 13, 84%). As shown in Entry 15, dehydration condensation between 2-diethoxyphosphorylpropionic acid (**4**) possessing a phosphonate group and a functionalized alcohol **16** afforded the corresponding ester in 91% yield in toluene at relatively high temperature (70 °C) by using DPTC and a catalytic amount of DMAP.

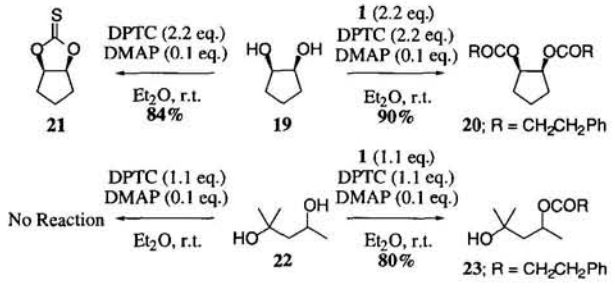
According to the present method, acylation of the hydroxyl group of bulky 8-membered ring compound **17** with pyruvic acid gave the corresponding ester **18** in quite high yield as shown in Scheme 2 whereas the ester **18** was not obtained at all when the combination of DCC with DMAP was employed as a coupling reagent although the reaction conditions were similar.



Scheme 2. Esterification of pyruvic acid with a bulky alcohol.

In order to improve the efficiency of this condensation reaction, the use of nearly equimolar amounts of carboxylic acids, alcohols and DPTC was examined. The reaction between carboxylic acid **1** (1.1 eq.) and alcohol **5** (1.0 eq.) was tried in the presence of DPTC (1.1 eq.) and DMAP (0.1 eq.) under several reaction conditions. At last, the reaction turned out to proceed smoothly to give the desired ester in the highest yield when diethyl ether was used as a solvent (Table 2, Entry 1, 98%). Under the same reaction conditions, the corresponding esters were also obtained from nearly equimolar amounts of carboxylic acid **2** and alcohols **9**, **12** and **13** in 91%, 89% and 97% yields, respectively (Entries 7, 10, 11).

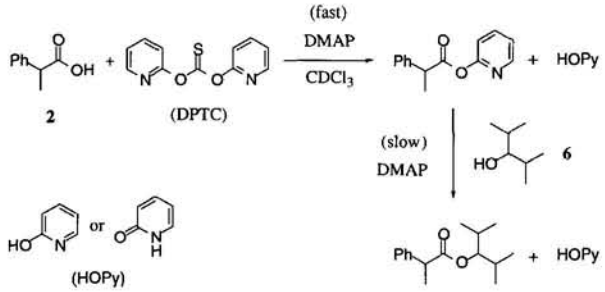
S. Kim *et al.* reported that several 1,2- or 1,3-diols reacted with 1,1'-thiocarbonyldi-2,2'-pyridone, an isomer of DPTC, to afford the corresponding cyclic thionocarbonates in high yields.[5] Then it was generally thought that our procedure would also produce various cyclic thionocarbonates. However, diacylation proceeded exclusively when *cis*-cylopentanediol (**19**) was treated with carboxylic acid **1** (2.2 eq.), DPTC (2.2 eq.) and DMAP (0.1 eq.) affording the corresponding diester **20** in 90% yield without forming the cyclic thionocarbonate **21**, which was obtained in 84% yield in the absence of carboxylic acid **1** (Scheme 3). Further, selective monoacylation of the secondary



Scheme 3. Acylation of diols.

hydroxyl group of 2-methyl-2,4-pentanediol (**22**) was attained by using carboxylic acid **1** (1.1 eq.), DPTC (1.1 eq.) and DMAP (0.1 eq.) under the similar reaction conditions to produce the corresponding monoester **23** in 80% yield instead of the expected cyclic thionocarbonate.

Next, an intermediate of this esterification was studied by taking the reaction between equimolar amounts of 2-phenylpropionic acid (**2**) and 2,4-dimethyl-3-pentanol (**6**) in $CDCl_3$ in the presence of DPTC (1 eq.) and a catalytic amount of DMAP. The reaction sequence was followed by ^1H and ^{13}C NMR, and it was shown that i) both the disappearances of the carboxylic acid and DPTC, and the formation of the 2-pyridyl ester and HOPy (2-hydroxypyridine or 2-pyridone) proceeded rapidly, and ii) the reaction of thus formed pyridyl ester with the alcohol proceeded sluggishly to give the reaction product and HOPy. This observation suggests that the initially formed pyridyl esters of carboxylic acids may be the key intermediates in the above esterification.[6]



Scheme 4. NMR study on reaction system.

A typical experimental procedure was as follows: to a mixture of 2-phenylpropionic acid (**2**) (32.8 mg, 0.218 mmol), diphenylmethanol (**8**) (20.1 mg, 0.109 mmol), and DMAP (1.3 mg, 0.011 mmol) in toluene (0.7 ml) was added DPTC (50.9 mg, 0.219 mmol). After stirring for 1 h at room temperature, the reaction mixture was concentrated and the crude product was purified by preparative thin layer chromatography to afford the corresponding ester (34.1 mg, 99%).

Thus, it is noted that various esters were obtained in high yields by condensation reaction between free carboxylic acids and alcohols including highly hindered ones in the presence of DPTC and a catalytic amount of DMAP.

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References and Notes

1 I. Shiina, H. Iwadare, H. Sakoh, M. Hasegawa, Y. Tani, and T. Mukaiyama, *Chem. Lett.*, **1998**, 1; I. Shiina, K. Saitoh, I. Fréchard-Ortuno, and T. Mukaiyama, *Chem. Lett.*, **1998**, 3.

2 A. M. Kanazawa, J.-N. Denis, and A. E. Greene, *J. Chem. Soc., Chem. Commun.*, **1994**, 2591; A. Commerçon, D. Bezard, F. Bernard, and J. D. Bourzat, *Tetrahedron Lett.*, **33**, 5185 (1992).

3 T. Mukaiyama, *Angew. Chem., Int. Ed. Engl.*, **18**, 707 (1979).

4 a) J. N. Denis and A. E. Greene, *J. Am. Chem. Soc.*, **110**, 5917 (1988); b) S. Kim, J. I. Lee, and Y. K. Ko, *Tetrahedron Lett.*, **25**, 4943 (1984).

5 S. Kim and K. Y. Yi, *J. Org. Chem.*, **51**, 2615 (1986).

6 This is in accordance with Kim's suggestion.[4b] Several esterifications using 2-pyridyl esters were reported: Y. Ueno, T. Tanaka, and E. Imoto, *Bull. Chem. Soc. Jpn.*, **37**, 864 (1964); J. F. Carson, *Synthesis*, **1979**, 24; S. Kim and J. I. Lee, *J. Org. Chem.*, **49**, 1712 (1984); T. Keumi, M. Shimada, T. Morita, and H. Kitajima, *Bull. Chem. Soc. Jpn.*, **63**, 2252 (1990).