Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 20 Aug 2006.

SYNTHETIC COMMUNICATIONS, 28(15), 2761-2768 (1998)

PREPARATION OF ESTERS AND AMIDES FROM CARBOXYLIC ACIDS BY ACTIVATION WITH DIALKYL PHOSPHITE - CARBON TETRACHLORIDE MIXTURE

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Abstract: A simple one pot phase transfer catalytic method is described for the synthesis of carboxylic amides and esters from carboxylic acids and amines or alcohols, respectively. For the activation of the carboxylic acids "in situ" generated phosphoric acid diester chlorides were applied.

During studies directed towards acylation reactions under phase transfer catalytic (PTC) circumstances, a method has been published on the synthesis of carboxylic acid esters and amides, respectively, by activation of the free acids with equivalent amount of sulfonic acid chlorides[1]. As continuation of this work now we disclose our PTC experiments with "in situ" generated phosphoric ester chlorides[2] for this activation.

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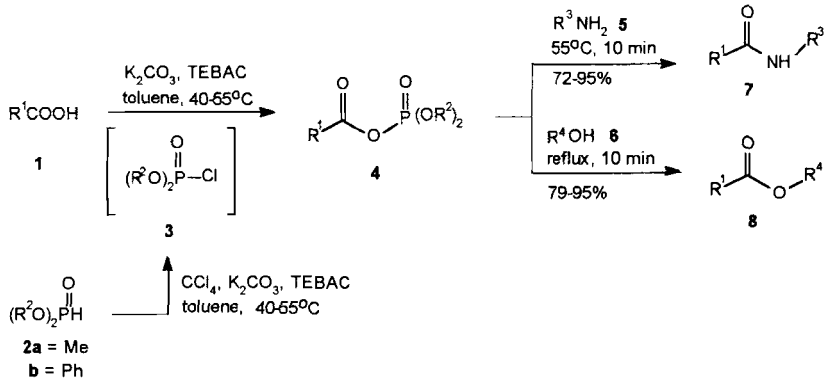
To our best knowledge, this is the first systematic study to get amides and esters by using this method.[3]

For the activation of the carboxylic acids **1** by formation of mixed anhydride **4** a mixture of dialkyl-, or diphenyl phosphite **2** and carbon tetrachloride was applied in a lipophilic solvent, mostly in toluene in the presence of solid potassium carbonate and a lipophilic quaternary salt (phase transfer catalyst, like benzyltriethylammonium chloride, TEBAC) at 40-55°C. The treatment of the "in situ" generated mixed anhydride with amines and alcohols at the same temperature resulted in the formation of carboxamides **7** and esters **8**, respectively, in a one pot process (Scheme 1).

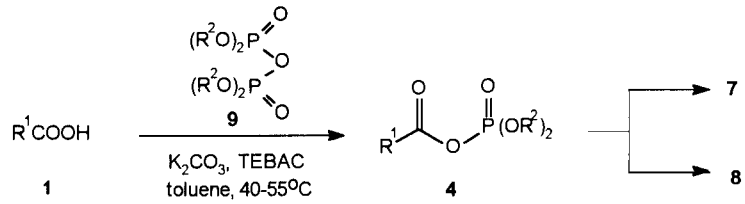


Scheme 1

The rate of the formation for **4** is much faster from dimethyl and diphenyl phosphite (**1a**, **b**) than from diethyl and dibenzyl phosphite, so application of **1a** or **1b** seemed to be more suitable for our purposes.

Monitoring the reactions by GC and ^{31}P-NMR we could detect the formation of tetraalkyl pyrophosphate **9**, beside the mixed anhydride **4**. The

pyrophosphate **9** formed in the "activation period" from the reaction of phosphate anion with **3** never contaminated the final products, as it was consumed in the reaction of the carboxylate ion with **9** furnishing also mixed anhydride **4** (Scheme 2).



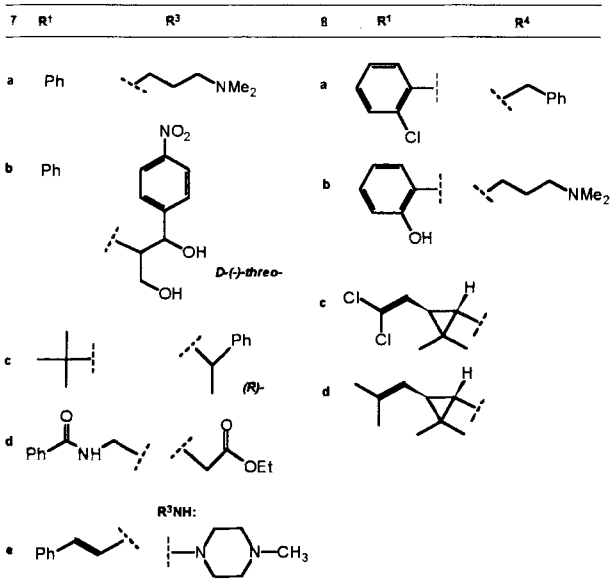
Scheme 2

It has to be noted that the activation process exerted by **9** (Scheme 2) consumes two moles of phosphite **2** in contrast to the one mole required in the activation by **3** (Scheme 1). The ratio of the two types of activation processes determines the excess of the phosphite (0-0.3 equivalent) to be applied in producing **7** or **8**.

The whole amount of **2** has to be consumed in the carboxyl activation process prior to the addition of the amine **5** or alcohol **6** to obtain the amide **7**, or ester **8** final products, otherwise trialkyl phosphate and dialkyl phosphoric amides, respectively, would be formed as by-products. The end of the activation process can be determined by monitoring the consumption of the phosphite ester by TLC, GC or ^{31}P-NMR.

The procedure seems to be generally useful for obtaining esters and amides from carboxylic acids and works even at hindered substrates like pivalic acid, but failed to work in the case of phenyl acetic acid or of

diphenyl acetic acid; here no mixed anhydrides **4** were formed according to the ^{31}P-NMR data. Structure of products **7** and **8** are summarised in Scheme 3.



Scheme 3

Experimental

Melting points were determined by a Büchi capillary melting point apparatus, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer FT-IR 1600 instrument. Optical rotations were measured on a Perkin Elmer 241 polarimeter.

Data regarding the reaction conditions and intermediates are collected in Table 1, whereas those for the final products with the yield are shown in Table 2.

General procedure for the preparation of carboxamides 7:

To a mixture of carboxylic acid **1** (10 mmol), CCl_4 (100 mmol, 10 mL),

Table 1. Reaction conditions and intermediates in the preparation of carboxamides **7a-e** and carboxylic esters **8a-d**

Product	Reagent		Reaction conditions		
		equiv.	Intermediate **4**		
			Time (min)	Temperature (°C)	^{31}P-NMR (δ ppm)
7a	**2a**	1.1	10	55	-5.0
	2b	1.0	10	40	-10.2
7b	**2a**	1.1	10	55	-5.0
7c	**2a**	1.1	10	55	-5.5
	2b	1.0	10	40	-11.0
7d	**2a**	1.3	20	55	-5.3
7e	**2a**	1.1	10	55	-5.3
8a	**2a**	1.1	10	55	-5.7
8b	**2a**	1.2	15	55	-5.1
8c	**2a**	1.0	10	55	-6.1
	2b	1.0	10	40	-11.3
8d	**2a**	1.0	10	55	-6.2

K_2CO_3 (5.52 g, 40 mmol), and TEBAC (0.23 g, 1 mmol) in toluene (30 mL), phosphite **2** (10-13 mmol) in toluene (15 mL) is added and stirred (temperature and reaction time is given in Table 1). Subsequently the amine **5** (10 mmol) is added and stirring is continued for 10 minutes at the given

Table 2. Yield and analytical data for carboxamides **7a-e** and carboxylic esters **8a-d**

Product	Yield (%)	mp (°C) or bp (°C/mbar)	Lit. mp (°C) or Lit. bp (°C/mbar)	IR υ_{CO}(cm^{-1})
7a	84	162-163/0.5	158/0.4[4]	1640, 1541 (neat)
7b	81	171-172[a]	172[5]	1654, 1546 (KBr)
7c	92	118-119[a]	119-120[6]	1638, 1529 (KBr)
7d	72	113-115	113.5-114.5[7]	1671, 1570 (KBr)
7e	95	81-82	81-83[8]	1645, 1590 KBr)
8a	91	130-133/0.6	153-155/1.3[9]	1729 (neat)
8b	79	95-99/0.6	113-116/1.3[10]	1723 (neat)
8c	95	36-37	35-36[1]	1720 (KBr)
8d	94	34-35	35[1]	1720 (KBr)

[a] **7b**, $[\alpha]_D^{25}$ +139° (c=1, EtOH), Lit. $[\alpha]_D^{25}$ +138° (c=1, EtOH)[1]; **7c**, $[\alpha]_D^{25}$ +109° (c=2, $CHCl_3$), Lit. $[\alpha]_D^{25}$ +107° (c=5.3, $CHCl_3$)[6]

temperature. The precipitate is filtered off, and the filtrate is evaporated under reduced pressure. The carboxamide obtained crystallised from EtOH (**7b,c,**), or from benzene/hexane (**7d**), or distilled under reduced pressure (**7a**).

General procedure for the preparation of carboxylic acid esters 8:

To a mixture of carboxylic acid **1** (10 mmol), CCl_4 (100 mmol, 10 mL), K_2CO_3 (5.52 g, 40 mmol), and TEBAC (0.23 g, 1 mmol) in toluene (30 mL), phosphite **2** (10-13 mmol) in toluene (15 mL) is added and stirred

(temperature and reaction time is given in Table 1). Subsequently the alcohol **6** (10 mmol) is added and stirring is continued for 10 minutes at reflux temperature. The mixture is worked up as described above. The esters obtained are distilled under reduced pressure except for **8c** and **8d**, which are purified by column chromatography on silica gel using benzene/acetone (9:1) as eluent.

Acknowledgement. Support from the Hungarian National Research Foundation (OTKA T020921) and the Ministry of Culture and Education (MKM 612/1995) is acknowledged.

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(Received in The Netherlands 29 January 1998)