A New Reagent for Activating Carboxy Groups; Preparation and Reactions of Phenyl *N*-Phenylphosphoramidochloridate

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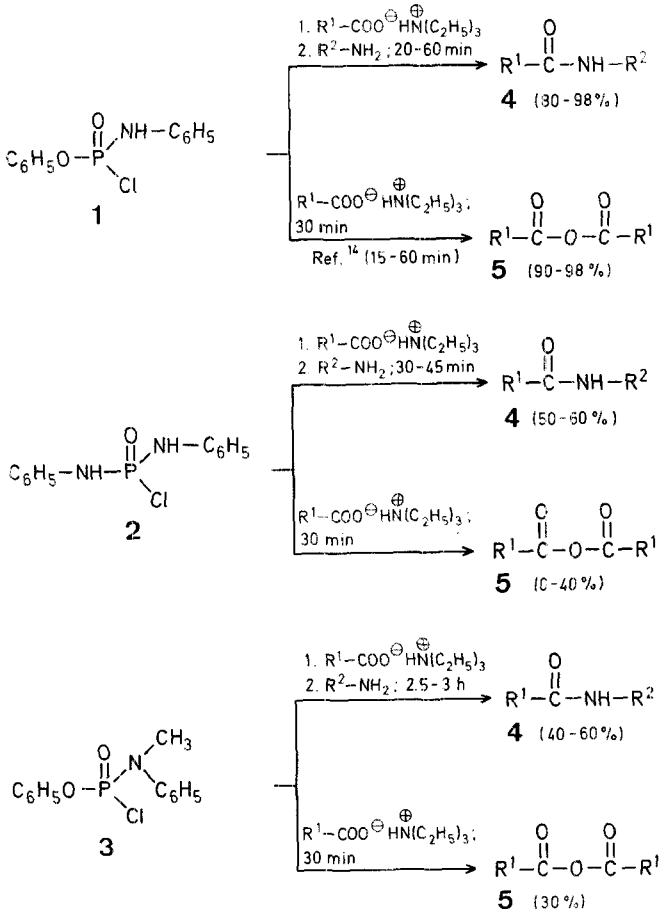
The most frequently used reagents for the one-pot or two-step conversion of carboxylic acids into carboxamides have recently been reviewed[1-4]. Carbodiimides[5] (in particular, dicyclohexylcarbodiimide) are frequently used as condensing agents in the synthesis of carboxamides from carboxylic acids and amines. However, the formation of *N*-acylureas and carboxylic anhydrides, occurring as side reactions, may render the isolation of the desired carboxamides difficult. The synthesis of carboxamides from amines (e.g. anilines) and acyl carbonates[6] such as acyl ethyl carbonates or acyl *t*-butyl carbonates affords the carboxamides (e.g., carboxanilides) only in moderate yields, even after a 12 h reaction time. *N*-Acyl derivatives of imidazole such as *N,N'*-carbonyldiimidazole[7] are highly reactive acylating agents but their use involves the formation of reactive intermediates which may undergo side reactions (sensitivity to moisture); using *N,N'*-carbonyldiimidazole, carboxamides cannot be obtained in a one-step reaction at room temperature.

Other frequently used methods for the conversion of carboxylic acids into carboxamides require either transformation of the acid into the acyl chloride in a first reaction step (this two-step sequence may lead to racemization in the case of amino acid derivatives, and it affords only poor yields in the case of α-chlorophenylacetanilides) or the use of phosphorus-containing reagents such as diethyl phosphorocyanidate[8] and diethyl phosphorobromidate[9]. With the phosphorocyanidate, phenylacetanilide was obtained in 83% yield (100 min reaction time) and with the phosphorobromidate in 88% yield (120 min) but with lower efficiency. *N,N'*-(Chlorophosphinylidene)-bis[2-oxotetrahydro-1,3-oxazole] (*N,N*-bis[2-oxo-3-oxazolidinyl]-phosphorodiamidic chloride)[10] is an efficient reagent for the one-step synthesis of carboxamides, in particular, carboxanilides. Other procedures have not found general application because of low yields, formation of by-products, high reaction temperatures, or long reaction times.

We report here that carboxamides **(4)** can be easily obtained from carboxylic acids and primary amines by a one-step method using phenyl *N*-phenylphosphoramidochloridate **(1)** as condensing agent. A summary of results and a comparison with the results obtained by similar methods is given in Scheme **A** and in Tables 1 and 3. Scheme **A** includes the analogous synthesis of carboxylic anhydrides **(5)** from carboxylic acids using reagent **1** and the related reagents **2** and **3** (see also Table 2).



Scheme A

Reagent **1** is a colorless solid. It is conveniently prepared from phenyl phosphorodichloridate and aniline by a modification of the procedure described in Ref.[11]. Reagent **2**, *N,N'*-diphenylphosphorodiamidic chloride, is prepared by the known method[12] and reagent **3**, phenyl *N*-methyl-*N*-phenyl-

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Table 1. Carboxamides (4) from Carboxylic Acids and Amines using Reagents 1, 2, or 3

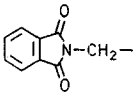
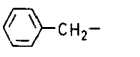
R^1	R^2	Reagent	Reaction time [h]	Yield [%]	m.p. [°C] [Lit. m.p. °C]
		1	0.5	91	162–163° (163°)[15]
		2	0.5	42	
		3	3.5	61	
		1	0.5	96	228–230° (230.5–231.5°)[16]
		2	1.0	60	
		3	2.5	43	
		1	1.0	93	144–146° (145–146°)[10]
		3	3.5	50	

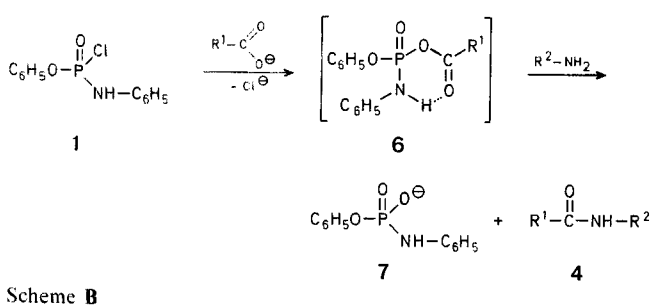
Table 2. Synthesis of Bis[*N*-phthaloylglycine] Anhydride using Reagents 1, 2, and 3

Reagent	Method or Reference	Reaction time [h]	Yield [%]
1	[14]	0.5	98
2	this report	0.5	40
3	this report	0.5	31

phosphoramidochloridate, is prepared from phenyl phosphorodichloridate and *N*-methylaniline in benzene.

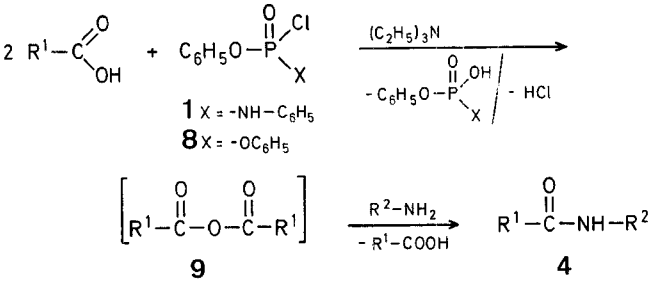
Reagent 1 has previously been used for the preparation of a carboxanilide; the reaction was carried out with 2 equivalents of carboxylic acid in boiling toluene[13]. In two attempts to reproduce this synthesis, we obtained only low yields of benzanilide and *N*-phthaloylglycine anilide under the conditions of Ref.[13]. Better yields of these products could be obtained by the present Method A which is performed in dichloromethane at room temperature and in which purification of the carboxamides 4 is easier. The amides 4 thus prepared from carboxylic acids, 2 equivalents of triethylamine, 1 equivalent of amine, and 1 equivalent of reagent 1 and isolated by filtration or evaporation of solvent and washing with water are almost pure and show sharp melting points which are very close to those of the purified compounds 4. Reagent 1 can be easily regenerated by treatment with phosphorus(V) chloride of the phenyl hydrogen *N*-phenylphosphoroamidate 7 produced in the reaction[14].

We assume that the activation mechanism involves an intermediate mixed anhydride 6 which results from attack from the nucleophilic carboxylate anion on the P-atom with elimination of chloride ion; subsequent nucleophilic attack of the amine on the carbonyl group of 6 followed by cleavage yields the amide 4 and phenyl *N*-phenylphosphoroamidate (7; Scheme B).



Scheme B

The following order of reactivity was observed with reagent 1: carboxylate anion $\lesssim$ aliphatic amines $\gg$ aromatic amines. Based on this order, carboxamides (4) are prepared from amines by different procedures using reagent 1. Method A is the one-step procedure; Method B consists of the reaction of 1 with carboxylate anion and subsequent treatment with the amine. Method B may be used for converting alkanamines into the corresponding carboxamides because with primary aliphatic amines the one-step Method A yields the carboxamides 4 together with the phenyl phosphorodiamidates formed by nucleophilic attack of 1 by the amine. The formation of phosphorodiamidates is precluded in Method C in which the carboxylic acid is first converted into its anhydride 9 by reaction with 0.5 equivalents of reagent 1 or diphenyl phosphorochloridate (8) according to Ref.[14] and the carboxamide 4 formed from the (not isolated) carboxylic anhydride 9 and the amine (Scheme C). The second step of the reaction proceeds with nearly quantitative yield and the carboxylic acid formed in this step can be easily recovered from the reaction medium.



Scheme C

Side reactions are not observed in Method C, the transformation is fast, and the yields are high.

The results obtained in the carboxamide (4) and carboxylic anhydride (5) formation using reagents 2 (Table 1) and 3 (Table 2) show the lower efficiency of these reagents.

Phenyl *N*-Phenylphosphoramidochloridate (1):
A solution of aniline (32.5 ml, 35.5 mmol) in benzene (75 ml) is added dropwise to a stirred solution of phenyl phosphorodichloridate (22.2 ml, 15 mmol) in benzene (175 ml) at room temperature during 30 min, the mixture is heated under reflux for 3 h, and then cooled. The precipitate is isolated by suction, dried, and washed with water (150 ml), to give crude 1; yield: 29 g (72%); m.p. 129–133 °C. For purification, the product is recrystallized from acetonitrile; yield: 23 g (58%); m.p. 129–130 °C (Ref.[11], m.p. 129–133 °C).

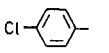
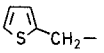
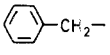
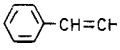
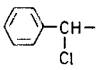
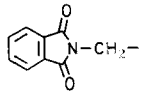
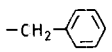
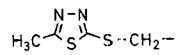
Phenyl *N*-Methyl-*N*-phenylphosphoramidochloridate (3):
A solution of *N*-methylaniline (19 ml, 176 mmol) in benzene (40 ml) is added to a stirred solution of phenyl phosphorodichloridate (11.1 ml, 75 mmol) in benzene (85 ml) at room temperature during 5 min. The mixture is then heated at reflux temperature for 3 h, and allowed to cool. The precipitate is filtered off, the filtrate evaporated in vacuo, and the liquid residue distilled in vacuo to give 3; yield: 13.4 g (64%); b.p. 135–140 °C/0.25 torr.

$C_{13}H_{13}ClNO_2P$	calc.	C 55.43	H 4.65	N 4.97
(281.7)	found	54.41	4.63	4.95

^{1}H-N.M.R. (CCl_4/TMS_{int}): $\delta = 6.90$ (s, 5 H_{arom}); 6.82 (s, 5 H_{arom}); 3.10 ppm (d, 3 H, CH_3).

Carboxamides (4) from Carboxylic Acids and Amines using Reagent 1:
Method A; General Procedure: Phenyl *N*-phenylphosphoramidochloridate (1; 1.34 g, 5 mmol) is added to a solution of the carboxylic acid (5 mmol), triethylamine (1.4 ml, 10 mmol), and the respective amine (5 mmol) in dichloromethane (15 ml) and the mixture is stirred at room temperature for 30–90 min. The solution is washed with water (3 × 10 ml) and the organic layer separated and dried with sodium sul-

Table 3. Carboxamides **4** prepared using Reagent **1** and Comparison with Literature Data

4	R^1	R^2	Method	Reaction time [min]	Yield [%]	m.p. [°C]	I.R. ($CHCl_3$) $\nu_{C=O}$ [cm^{-1}]	Literature data or Molecular formula[b]			
								Method[a]	Yield [%]	m.p. [°C]	Reference
a			A	30	95	162–163°	1670	—	—	163°	15
b			B C	90 45	70 90	149–150°	1665	I II	99 0	149–150° 151–152°	9 8
c			A	20	93	198–199°	1680	—	—	194°	15
d			A	60	94	131–133°	1670	—	—	130–132°	15
e			C	30	90	130–131°	1670	I	94	129–130°	9
f			A	60	97	115–117°	1680	III	90	116–117°	15
g			A	60	94	149–151°	1685	—	—	150°	15
h			A	60	94	117–118°	1655	I IV	88 83	117–118° 118–119°	9 8
i			A	60	93	144–146°	1660	III	97	145–146°	10
j			A	45	90	152–153°	1670	—	—	152°	15
k	t-C_4H_9		A	90	91	127–128°	1680	—	—	128°	15
l			A	30	98	146–147°	1669	V	50	146–147°	17
m			A	30	97	160–161°	1670	V	50	160–161°	17
n			B C	30 45	70 90	127–128°	1655	V	40	127°	18
o			A	60	90	140–142°	1675	$C_{16}H_{14}ClNO_2$ (287.7)			
p			B C	60 60	80 91	87–90°	1738, 1665	$C_{19}H_{20}ClNO_3$ (345.7)			
q			A	30	96	228–230°	1775, 1725, 1670	VI	—	230–231.5°	16
r			B C	60 45	71 90	217–218°	1770, 1725, 1665	VII	92	216–218°	16
s		$-CH_2-COOC_2H_5$	B C	60 60	80 95	190–191°	1770, 1730, 1650	VI	78	189°	13
t			A	30	90	148–149.5°	1680	$C_{11}H_{11}N_3OS_2$ (265.4)			

[a] Method I: Diethylphosphorobromidate.
Method II: Dicyclohexylcarbodiimide.
Method III: *N,N'*-(Chlorophosphinylidene)-bis[2-oxotetrahydro-1,3-oxazole] (*N,N*-Bis[2-oxo-3-oxazolidinyl]-phosphorodiamidic chloride).
Method IV: Diethyl phosphorocyanidate.
Method V: via the acid chloride; yields are based on starting carboxylic acid.
Method VI: Ethyl phosphorodichloridate.
Method VII: Dibenzyl phosphorochloridate.

[b] The microanalyses of compounds **4l–t** were in good agreement with the calculated values: C, ±0.04; H, ±0.03; N, ±0.04.

phate. Evaporation of the solvent gives the solid *carboxamide* **4**; yield: 90–97%. The combined aqueous washings layers are acidified to pH 1 with hydrochloric acid. The precipitated product is isolated by suction and washed with water to give *phenyl hydrogen* N-*phenylphosphoramidate* (**7**); yield: 1.0–1.2 g (80–97%); m.p. 134–136°C (Ref.[14], m.p. 134–135°C).

Method B: General Procedure: Phenyl *N*-phenylphosphoramidochloridate (**1**; 1.34 g, 5 mmol) is added at room temperature to a solu-

Table 4. ^{1}H-N.M.R. (TMS_{int}) Data[a] of Compounds **4l–t**

4	Solvent	δ [ppm]
l	$CDCl_3$	8.50 (s, 1H, NH); 7.48 (m, $10H_{arom}$); 5.50 (s, 1H, CH)
m	$CDCl_3$	8.25 (s, 1H, NH); 7.4 (m, $5H_{arom}$); 5.40 (s, 1H, CH)
n	$CDCl_3$	7.60 (s, $5H_{arom}$); 6.60 (s, 1H, NH); 5.31 (s, 1H, CH); 2.4–0.99 (m, 11H, CH_2)
o	$CDCl_3$	8.51 (s, 1H, NH); 7.7 (m, $4H_{arom}$); 6.33 (s, $5H_{arom}$); 5.50 (s, 1H, CH); 2.51 (s, 3H, CH_3)
p	$CDCl_3$	7.85–6.9 (m, 11H, NH_{arom}); 5.45 (d, 1H, CH); 5.34 (s, 1H, CH); 5.25–4.75 [m, 1H, $CH(CH_3)_2$]; 1.20 (d, 3H, CH_3); 1.05 (d, 3H, CH_3)
q	DMSO-d_6	7.4 (m, $9H_{arom}$); 4.32 (s, 2H, CH_2); 3.00 (s, 1H, NH)
r	DMSO-d_6	7.68 (s, $4H_{arom}$); 7.10 (s, $5H_{arom}$); 4.2 (m, 4H, CH_2); 3.00 (s_{br}, 1H, NH)
s	DMSO-d_6	8.40 (s_{br}, 1H, NH); 7.70 (s, $4H_{arom}$); 4.0 (m, 6H, CH_2); 1.20 (t, 3H, CH_3)
t	DMSO-d_6	10.00 (s, 1H, NH); 7.2 (m, $5H_{arom}$); 4.20 (s, 2H, CH_2); 2.65 (s, 3H, CH_3)

[a] The spectra were recorded on a Varian EM 360 A spectrometer.

tion of the carboxylic acid (5 mmol) and triethylamine (0.7 ml, 5 mmol) in dichloromethane (10 ml). The suspension is stirred for 5 min; then, a solution of the amine (5 mmol) and triethylamine (0.7 ml, 5 mmol) in dichloromethane (5 ml) is added dropwise during 20 min at room temperature, and the mixture is stirred for 60 min. The solvent is evaporated in vacuo, the solid residue isolated by suction, washed with water, and recrystallized from isopropanol/water to give pure **4**.

Method C; Typical Procedure:

Phthaloylglycine Benzylamide: Diphenyl phosphorochloridate (**8**; 0.51 ml, 2.5 mmol) is added to a solution of *N*-phthaloylglycine (1 g, 5 mmol) and triethylamine (0.7 ml, 5 mmol) in dichloromethane (10 ml) and the mixture is stirred at room temperature for 15 min. Triethylamine (0.35 ml, 2.5 mmol) and then benzylamine (0.25 ml, 2.5 mmol) are added. The resulting solution is stirred at room temperature for 60 min. Evaporation of the solvent gives a crude product which is successively washed with 1 normal sodium hydroxide (5 ml), 1 normal hydrochloric acid (5 ml), and then water to give the pure product; yield: 1.32 g (90%); m.p. 216–217 °C. The product may be recrystallized from ethanol; m.p. 217–218 °C (Ref.[16], m.p. 216–218 °C).

Carboxamides (4) from Carboxylic Acids and Amines using Reagents 2 or 3; General Procedure:

N,N'-Diphenylphosphorodiamidic chloride (**2**; 1.32 g, 5 mmol) or phenyl *N*-methyl-*N*-phenylphosphoramidochloridate (**3**; 1.4 g, 5 mmol) is added to a solution of the carboxylic acid (5 mmol), triethylamine (1.4 ml, 10 mmol) and the amine (5 mmol) in dichloromethane (15 ml) and the mixture is stirred at room temperature for 0.5–3.5 h). Work-up is the same as in Method A.

Carboxylic Anhydrides (5) from Carboxylic Acids using Reagents 2 or 3; Typical Procedure:

Bis[N-Phthaloylglycine] Anhydride: N,N'-Diphenylphosphorodiamidic chloride (**2**; 1.32 g, 5 mmol) or phenyl *N*-methyl-*N*-phenylphosphoramidochloridate (**3**; 1.4 g, 5 mmol) is added to a solution of *N*-phthaloylglycine (2.05 g, 10 mmol) and *N*-ethylpiperidine (1.4 ml, 10 mmol) in dichloromethane (10 ml) and the mixture is stirred at room temperature for 30 min. The resultant precipitate is isolated by suction and the colorless product washed with cold water (10 ml) and dried to give bis[*N*-phthaloylglycine] anhydride; yield: 0.4 g (40%) or 0.3 g (30%), respectively; m.p. 239–240 °C (Ref.[14], 239–240 °C).

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