A Convenient Synthesis of Amides with 2-Halo-2,3-dihydro-1,3,4,2-oxadiazaphospholes as New Condensing Agents

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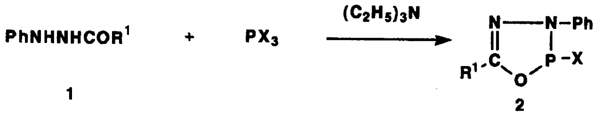
Synopsis. Various amides, including some with bulky substituents, are prepared in good yields from free carboxylic acids and amines under mild conditions by a one-step method using new condensing agents 2-halo-2,3-dihydro-1,3,4,2-oxadiazaphospholes, especially 5-methyl-2-chloro-3-phenyl-2,3-dihydro-1,3,4,2-oxadiazaphosphole.

The synthesis of amide from free carboxylic acid and amine is one of the most important reactions in organic synthesis, and quite a number of methods have been investigated. Among them, various organophosphorus compounds have been recently used as coupling reagents. For example, phosphorus-containing reagents such as triphenylphosphine-2,2′-dipyridyl disulfide,[1] diphenyl phosphoroazidate,[2] diaryl and triaryl phosphite-pyridine system,[3] diethyl phosphorocyanidate,[4] diethyl phosphorobromidate,[5] *O*-succinimido-*O*′, *O*″-diphenyl phosphate,[6] *N*,*N*′-bis(2-oxo-3-oxazolidinyl) phosphorodiamidic chloride,[7] *N*-acylphosphoramidite,[8] phenyl *N*-phenylphosphoramidochloridate,[9] and 1,2-benzisoxazol-3-yl diphenyl phosphate[10] have been used successfully as coupling reagents for this reaction.

In the course of the study of the synthesis of polyamides by using organophosphorus reagents, we found that 2-halodihydrooxadiazaphospholes (**2**) were convenient for the synthesis of amides. These new condensing agents have the advantages of simple preparation, very good solubility in many solvents, and long stability at room temperature.

In this note we wish to report that amides can be easily obtained from free carboxylic acids and amines by a one-step method using 2-halo-2,3-dihydro-1,3,4,2-oxadiazaphospholes (**2a**—**f**), especially 2-chloro and 2-bromo derivatives, in pyridine at room temperature. The coupling reagents **2a**—**f** were conveniently prepared in moderate yields from *N*-acyl-*N*′-phenylhydrazines (**1**) and phosphorous trihalides in benzene in the presence of triethylamine by a modification of the procedure described in Ref. 11 as shown in Scheme 1.



Scheme 1.

In Table 1 are summarized the results of the preparation of various 2-halodihydrooxadiazaphospholes **2a**—**f**. Reagents **2a**—**f** are pale yellow liquids. Compounds **2a**, **2b**, **2d**, and **2f** have not been reported previously. Therefore, they were characterized by IR, MS, and ^{1}H NMR spectroscopies. The IR spectra showed C=N bond absorption band at 1630 cm^{-1}, P–O–C at 960 cm^{-1}, and P–X (X=Cl or Br) at 450 cm^{-1}. The MS spectra showed $M^+ + 2$ isotope peaks of about one third intensity of the molecular ion peaks in chloro compounds **2a**, **2c**, and **2e**, while, $M^+ + 2$ peaks in bromo compounds **2b**, **2d**, and **2f** were almost equal in intensity to the molecular ion peaks (see Experimental).

The syntheses of amides by using 2-halodihydrooxadiazaphospholes **2a**—**f** were performed under the following standard conditions: Compound **2** (2.5 mmol) was added to equimolar amounts of carboxylic acid and amine in pyridine (5 ml) cooled in an ice-water bath, and after 5 min, the ice-water bath was removed and the mixture was stirred at room temperature for 4 h. The results obtained from various free carboxylic acids and amines using the reagents **2a**—**f** are given in Table 2. It seems that the halogen on phosphorus atom and the electron-donating alkyl group at 5-position of the reagent **2** little influenced the yield of the benzanilide. However, the yield of the benzanilide was affected by tertiary amines (Table 3). Among the tertiary amines examined, triethylamine yielded little benzanilide, but pyridine and 3-methylpyridine were very effective for the condensation reaction. These results indicate that the basicity of the tertiary amine is more influential than its steric effect on the yield of the benzanilide. Sterically hindered carboxylic acids, such as isobutyric acid, gave also the anilide in good yield. Furthermore, the reaction was not influenced by the chain length of the carboxylic acids.

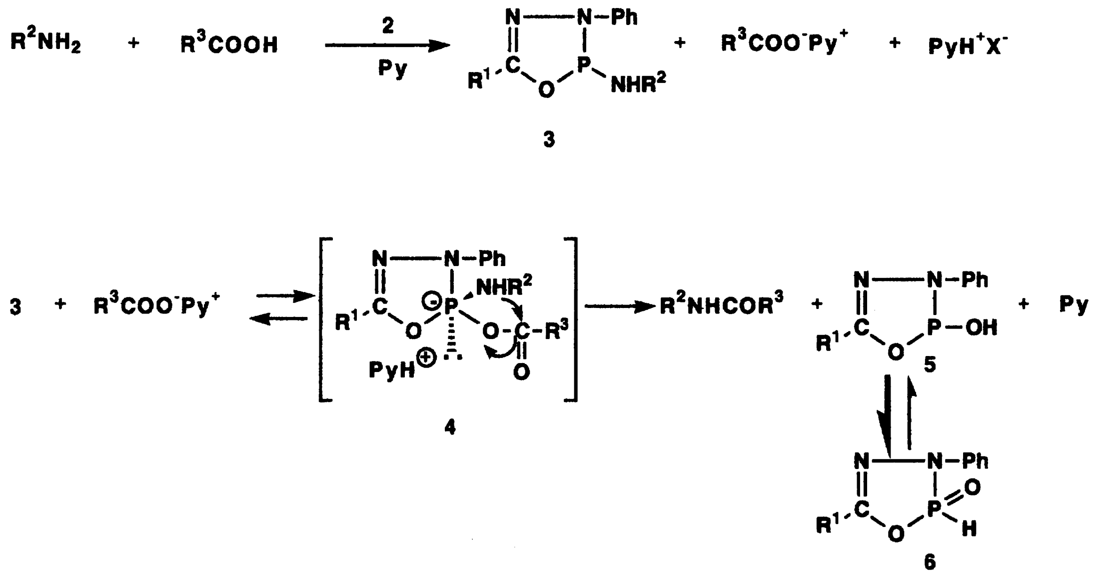
A probable reaction mechanism in this one-step method is shown in Scheme 2. As described above, it seems possible that pyridine participates in the reaction in addition to its roles as a solvent and an acid acceptor.

From the investigation of tracing by thin-layer chromatography (TLC) on this one-step condensation reaction of benzoic acid with aniline using **2c** at 40°C, it was seen that phosphorodiamidite derivative **3** was first formed, and then converted gradually into benzanilide within 4 h. Compound **3** ($R^1=CH_3$, $R^2=C_6H_5$) was confirmed by an authentic sample prepared independently from the reaction of two moles of aniline with one mole of **2c** in ether. Therefore, it seems that the reaction proceeds via the activation of amine, and subsequently, carboxylic acid coordinates to compound **3** to form a pentacoordinate intermediate **4** proposed by Aharoni et al.[12] in the presence of pyridine. Then, the

Table 1. Synthesis of Various 2-Halodihydrooxadiazaphospholes **2**

2			Yield[a)]	Bp	^{1}HNMR
	R^1	X	%	°C (1.5 Torr [b)])	δ, $CDCl_3$
2a	H	Cl	62	100–102	7.10–7.50 (m, 5H), 8.65 (s, 1H)
2b	H	Br	58	113–116	7.13–7.52 (m, 5H), 8.70 (s, 1H)
2c	CH_3	Cl	82	110–111	2.34 (s, 3H), 7.13–7.55 (m, 5H)
2d	CH_3	Br	90	124–126	2.33 (s, 3H), 7.12–7.57 (m, 5H)
2e	C_2H_5	Cl	85	117–118	1.30 (t, 3H, J=7 Hz), 2.75 (q,2H, J=7 Hz), 7.15–7.50 (m, 5H)
2f	C_2H_5	Br	75	128–130	1.33 (t, 3H, J=7 Hz), 2.80 (q, 2H,J=7 Hz), 7.15–7.50 (m, 5H)

a) Isolated yield of once distilled product. b) 1 Torr=133.322 Pa.



Scheme 2.

Table 2. Synthesis of Amides Using 2-Halodihydrooxadiazaphospholes **2**[a)]

2		Amine	Carboxylic acid	Yield[b)]
X	R^1	R^2	R^3	%
Cl	H	C_6H_5	C_6H_5	94
Br	H	C_6H_5	C_6H_5	95
Cl	CH_3	C_6H_5	CH_3	90
Cl	CH_3	C_6H_5	C_6H_5	97
Cl	CH_3	$C_6H_5CH_2$	C_6H_5	85
Cl	CH_3	$C_6H_5CH_2$	$CH_3(CH_2)_7$	82
Cl	CH_3	C_6H_5	$(CH_3)_2CH$	90
Cl	CH_3	$C_6H_5CH_2$	$(CH_3)_2CH$	89
Cl	CH_3	C_6H_{11}	$(CH_3)_2CH$	84
Cl	CH_3	C_6H_{11}	CH_3	90
Cl	CH_3	C_6H_5	$CH_3(CH_2)_7$	94
Br	CH_3	C_6H_5	C_6H_5	92
Cl	C_2H_5	C_6H_5	C_6H_5	96
Br	C_2H_5	C_6H_5	C_6H_5	94

a) Reaction was carried out with 2.5 mmol of each reactants in pyridine (5 ml) for 4 h at room temperature. b) Isolated yields.

Table 3. Effect of Tertiary Amines on the Preparation of Benzanilide Using **2c**

Solvent	pK_a	Benzanilide, Yield[a)]/%
N,*N*-Dimethylaniline	5.07	0
Pyridine	5.25	97
3-Methylpyridine	5.52	90
2-Methylpyridine	5.97	63
4-Methylpyridine	6.03	65
2,6-Dimethylpyridine	6.99	Trace
Triethylamine	10.75	Trace

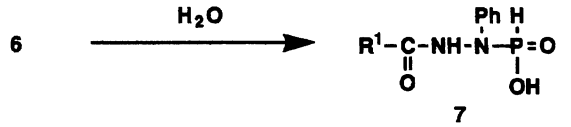
a) Based on benzoic acid used.

lone-pair electrons of the amino group of the intermediate **4** attack the carbonyl carbon to form the amide and 2-hydroxydihydrooxadiazaphosphole (**5**). In this case, pyridine promoted the reaction of **3** with carboxylic acid by behaving as a proton scavenger. Compound **5** may be immediately tautomerized to the more stable phosphorus(V) form, 2-oxo-dihydrooxadiazaphosphole (**6**). Compound **5** (R^1=CH_3) was difficult to isolate because of its instability. However, compound **6** (R^1=CH_3) was obtained as heavy oil and was confirmed by converting into authentic sample **7** (R^1=CH_3) by hydrolysis (Scheme 3).

This tautomeric equilibrium between **5** and **6** also may be favorable for the condensation reaction.

Experimental

All of the reagents and solvents were used after recrystal-



$$6 \xrightarrow{H_2O} R^1\text{-}\underset{\overset{\|}{O}}{C}\text{-NH-}\overset{Ph}{N}\text{-}\overset{H}{\underset{OH}{P}}{=}O \quad \mathbf{7}$$

Scheme 3.

lization or distillation. All boiling points are uncorrected. ^{1}H NMR spectra were recorded on a Hitachi R-600, ^{1}H FT-NMR instrument, with tetramethylsilane (TMS) as an internal standard. IR and mass spectra were recorded on Shimadzu 27G and Hitachi RMU-6 spectrometers, respectively.

Preparation of 2-Halo-2,3-dihydro-1,3,4,2-oxadiazaphospholes (2). The typical example is as follows. To a suspension of *N*-acetyl-*N′*-phenylhydrazine (20.0 g, 0.133 mol) in triethylamine (26.9 g, 0.267 mol) and dry benzene (200 ml) was added a solution of phosphorous tribromide (36.0 g, 0.133 mol) in bezene (50 ml) with stirring at 0 to 5°C. After stirring at 5°C for 1 h and at 60°C for 1 h, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residual oil was distilled in vacuo to give a pale yellow liquid (**2d**; 31.0 g, (90%), bp 124°C/1.5 Torr (1 Torr=133.322 Pa)); IR ($CHCl_3$) 2950, 1630, 1590, 1480, 1305, 1236, 1010, 960, 790, 745, and 450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.33 (3H, s, CH_3) and 7.12—7.57 (5H, m, phenyl) ; MS *m/z* (rel intensity %) 260 (M^++2; 30), 258 (M^+; 30), 179(100), 137(58), and 91(45). Other 2-halodihydrooxadiazaphospholes **2** were prepared in a similar manner. Some data of **2** are summarized in Table 1. Mass spectra data [*m/z* (%)] of **2** are as follows: **2a**, 202 (M^++2; 12), 200 (M^+; 39), 165 (100), 137 (26), and 91 (45). **2b**, 246 (M^++2; 17), 244 (M^+; 17), 165 (100), 137 (37), and 91 (22). **2c**, 216 (M^++2; 18), 214 (M^+; 57), 179 (40), 148 (13), 137 (24), 132 (40), and 91 (100). **2e**, 230 (M^++2; 13), 228 (M^+; 42), 193 (43), 162 (38), 137 (30), 106 (66), and 91 (100). **2f**, 274 (M^++2; 39), 272 (M^+; 39), 193 (100), 162 (40), 137 (42), and 91 (44).

Preparation of Amides from Carboxylic Acids and Amines Using 2-Halo-2,3-dihydro-1,3,4,2-oxadiazaphospholes (2). The typical example is as follows. 5-Methyl-2-chloro-3-phenyl-2,3-dihydro-1,3,4,2-oxadiazaphosphole (**2c**; 0.54 g, 2.5 mmol) was added dropwise with stirring at 0°C to a mixture solution of the benzoic acid (0.31 g, 2.5 mmol) and aniline (0.24 g, 2.5 mmol) in pyridine (5 ml). After stirring at 0°C for 5 min, the reaction mixture was stirred at room temperature for 4 h, and then poured into water. The precipitated product was isolated by filtration, washed with 1% hydrochloric acid, aqueous sodium carbonate, and then thoroughly with water to give benzanilide. The yield was 0.48 g (97%). Benzanilide thus obtained showed IR spectrum and melting point identical with those of authentic sample.

5-Methyl-3-phenyl-2-phenylamino-2,3-dihydro-1,3,4,2-oxadiazaphosphole (3). A solution of **2c** (2.15 g, 10 mmol) in 20 ml of ether was added dropwise over a period of 40 min to a stirred solution of aniline (2.0 g, 21.5 mmol) in 10 ml of ether under 10°C. The reaction mixture was stirred overnight at room temperature. The aniline hydrochloride was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dried overnight in vacuo to give 2.1 g (78%) of **3** (R^1=CH_3, R^2=C_6H_5) : Mp 100—102°C; IR (KBr) 3200, 2950, 1630, 1590, 1480, 1325, 1240, 1000, 970, 790, 740, and 670 cm^{-1}; MS *m/z* (rel intensity %) 271 (M^+; 22), 179 (44), 137 (56), and 91 (100).

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