Tetrahedron. Vol. 31, pp. 3031 to 3034. Pergamon Press 1975. Printed in Great Britain

STUDIES ON REACTIONS OF THE *N*-PHOSPHONIUM SALTS OF PYRIDINES—XV

DIRECT CARBONYLATION OF AMINES WITH CARBON DIOXIDE BY A HYDROLYSIS-DEHYDRATION REACTION WITH PHOSPHORUS COMPOUNDS

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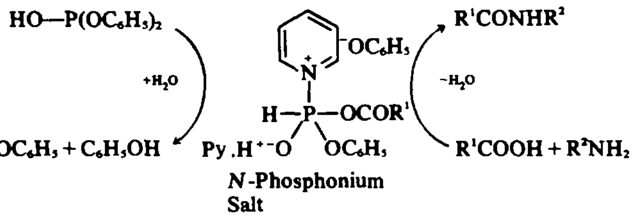
(*Received in Japan 2 February 1975; Received in the UK for publication 19 May 1975*)

Abstract—Carbon dioxide reacts with amines in the presence of phosphorus compounds and tertiary amines to give the corresponding ureas in high yield, and carbon disulfide gave thioureas. The presence of tertiary amines such as pyridine or imidazole facilitated the reactions. Aryl esters of phosphorous, phosphonous, phosphinous and phosphonic acids were effective, whereas their corresponding alkyl esters were ineffective. Various molar ratios of phosphite : tertiary amine : amine (aniline), produced variations in yield showing that the reaction proceeds via a carbamoyloxy and a thiocarbamoylthioxy *N*-phosphonium salt of the tertiary amine.

In our previous papers,[1-3] we have demonstrated a hydrolysis-dehydration reaction for coupling between carboxylic acids and amines promoted by phosphorus compounds, such as phosphites, phosphonites, phosphinites, and phosphonates. The reaction with diphenyl phosphite in pyridine, for example, was proposed to proceed via an *N*-phosphonium salt of pyridine as follows:

$$R^1COOH + R^2NH_2 + HO{-}P(OC_6H_5)_2 \xrightarrow{Py} R^1CONHR^2 + C_6H_5OH + (HO)_2{-}P{-}OC_6H_5 \qquad (1)$$



Considering that the reactions of carbonic acids are similar to those of carboxylic acids, we have introduced gaseous carbon dioxide in place of carboxylic acids in the above reaction (1), and obtained the corresponding ureas in high yields, as shown in our previous paper.[4] Similarly, carbon disulfide reacted with amines to give thioureas.[4]

$$CO_2 + 2NH_2R + HO{-}P(OC_6H_5)_2 \xrightarrow{Py} RNHCONHR + C_6H_5OH + (HO)_2{-}P{-}OC_6H_5. \qquad (2)$$

In this paper, we describe the detailed results of the reactions of carbon dioxide and carbon disulfide with amines in the presence of phosphites and other phosphorus compounds which have been found to promote amidation of carboxylic acids by the hydrolysis-dehydration as mentioned above.

RESULTS AND DISCUSSION

When carbon dioxide was passed at 40°C for 4 h through a pyridine solution of diphenyl phosphite (1 mole, twice theoretical amount) and aniline (1 mole) in a cylindrical flask fitted with a bubbling glass filter (see Fig 1), N,N′-diphenylurea was obtained in 85% yield based on aniline along with phenol (see eqn 2). The urea was also prepared in 93% yield in *N,N*-dimethylformamide (DMF) by using imidazole in lieu of pyridine. Similarly, carbon disulfide gave *N,N*′-diphenylthiourea in a theoretical yield with aniline at 40°C for 4 hr in pyridine in the presence of diphenyl phosphite.

Results of preparation of several symmetrical ureas by

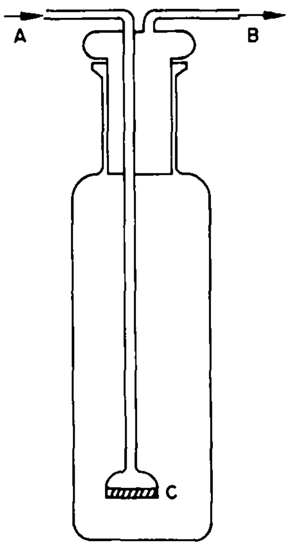


Fig. 1. Reaction vessel: A, inlet; B, outlet; C, a bubbling glass filter.

using diphenyl phosphite in pyridine are given in Table 1. Primary aromatic amines with the lower basicity than pyridine, such as aniline and o-toluidine, gave ureas in higher yields than more basic aliphatic amines, such as isopropylamine and cyclohexylamine. Secondary amines failed to give ureas; diphenylamine (90%) was recovered from the reaction mixture, and *N*-methylaniline and diethylamine gave oily products, which showed no C=O stretching characteristic of ureas in the IR spectra.

Table 1. Symmetrical ureas from carbon dioxide and amines by using diphenyl phosphite in pyridine[a]

Amine	Yield(%) of ureas[b]
Aniline	85
o-Toluidine	74
Isopropylamine	23
Cyclohexylamine	27
N-Methylaniline	0
Diphenylamine	0
Diethylamine	0

[a] $HO{-}P(OC_6H_5)_2$ = Amine = 50 mmoles in 40 ml of pyridine; temperature = 40°C; time = 4 h

[b] Based on the amine used.

Unsatisfactory results with aliphatic amines may be due to a retardation of forming a carbamoyloxy *N*-phosponium salt 1 owing to the predominant production of pyridine-insoluble and unreactive ammonium salts, because of their higher basicity than pyridine. No reaction with secondary amines may be accounted for by steric hindrance around the nitrogen atom, as in an unsuccessful direct carbonylation of diphenylamine with phosgene.[5]

The presence of tertiary amines facilitated the reaction of carbon dioxide with an amine (aniline) (Table 2). The yield of the urea was affected by both the basicity of the tertiary amines and their steric hindrance around the nitrogen atom. The steric hindrance may be more influential on the reaction in pyridine derivatives (pK_a values in the range of 5·0–7·0), as reflected by unsatisfactory results in α-picoline, 2,4-lutidine and (remarkably) in 2,6-lutidine. Different from unfavorable results in amidation of carboxylic acids,[2,3] triethylamine with high basicity gave a favorable result in spite of having large steric hindrance. On the contrary, the reaction with carbon disulfide was not affected so significantly by the basicity and the steric hindrance as that with carbon dioxide. The smaller effect in the reaction with carbon disulfide may be due to the higher reactivity of carbon disulfide towards an amine (aniline) compared with carbon dioxide.

Table 2. N,N'-Diphenyl-urea and thiourea from carbon dioxide and disulfide with aniline in various tertiary amines

		Yield(%)[a]	
Tertiary amine	pK_a	The urea[b]	The thiourea[c]
Imidazole	7·12	93	80
γ-Picoline	6·02	88	84
β-Picoline	5·52	84	76
Pyridine	5·23	85	65(100)[d]
2,4-Lutidine	6·99	74	—
α-Picoline	5·97	60	74
2,6-Lutidine	6·99	32	75
Triethylamine	10·87	70	75
None	—	4[e]	12[e]

[a] Based on aniline used

[b] $HO{-}P(OC_6H_5)_2$ = aniline = 50 mmoles in 40 ml of tertiary amines; imidazole = 100 mmoles in 40 ml of DMF; temperature = 40°C; time = 4 h

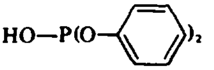
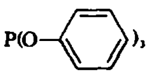
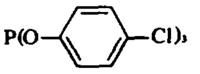
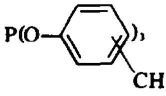
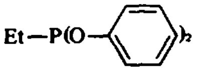
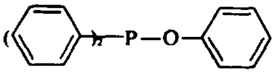
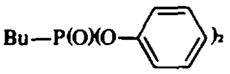
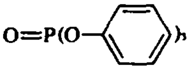
[c] $HO{-}P(OC_6H_5)_2$ = aniline = 50 mmoles, CS_2 = 100 mmoles in 40 ml of DMF containing tertiary amines (100 mmoles); temperature = 40°C; time = 4 h

[d] The yield obtained in 40 ml of pyridine

[e] The reaction was carried out in 40 ml of DMF.

The reaction producing urea was favoured also by the presence of phosphorus compounds other than diphenyl phosphite (Tables 3). As in the coupling between carboxylic acids and amines by the hydrolysis-dehydration,[2,3] triaryl phosphites, diphenyl ethylphospho-

Table 3. N,N'-Diphenylurea from carbon dioxide and aniline by using various phosphorus compounds[a]

Phosphorus compound		Yield(%)[b]
		94
$HO{-}P(OEt)_2$		0
		68
		87
	*o*-	21
	m-	50
	p-	40
$P(OBu)_3$		0
		90
$Et{-}P(OEt)_2$		0
		71
		15
$Et{-}P(O)(OEt)_2$		0
		0
$O{=}P(OEt)_3$		0

[a] Phosphorus compounds = aniline = 50 mmoles in 40 ml of DMF containing imidazole (100 mmoles); temperature = 40°C; time = 4 h

[b] Based on aniline used.

nite, phenyl diphenylphosphinite and diphenyl n-butylphosphonate were effective also for the reaction of carbon dioxide and amines. On the other hand, their alkyl esters failed to give the urea. Both triphenyl and triethyl phosphates failed to promote the reaction.

Both phosphorus compounds and tertiary amines were found to be stoichiometrically involved in the reactions of carbon dioxide and carbon disulfide with aniline. Figure 2 shows the variation of the yield of the urea and thiourea based on aniline with the employed amount of diphenyl phosphite, indicating an increase of the yield of *N,N'*-diphenylurea and *N,N'*-diphenylthiourea to a limiting value of about 1·0 in the molar ratio of diphenyl phosphite to aniline.

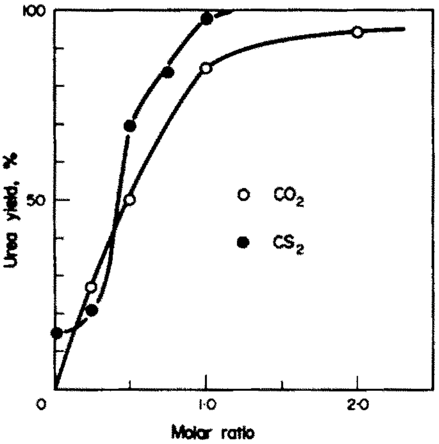


Fig. 2. Variation of the yield of N,N'-diphenyl-urea (○) and -thiourea (●) with the molar ratio of diphenyl phosphite to aniline: aniline = 50 mmoles, CS_2 = 100 mmoles in 40 ml of pyridine.

A similar dependence of the yield on the amount of a tertiary amine (imidazole) was observed in these reactions (Fig. 3).

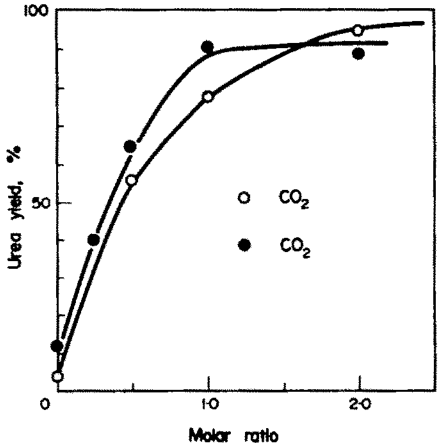


Fig. 3. Variation of the yield of N,N'-diphenyl-urea (○) and -thiourea (●) with the molar ratio of imidazole to diphenyl phosphite: aniline = diphenyl phosphite = 50 mmoles, CS_2 = 100 mmoles in 40 ml of DMF.

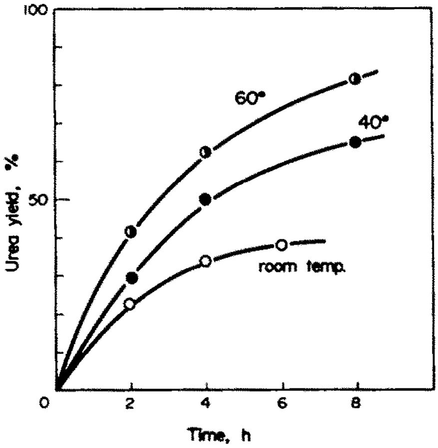
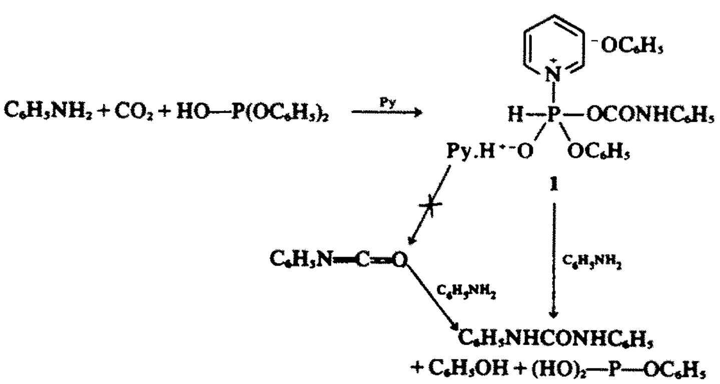


Fig. 4. Effect of reaction conditions upon the urea formation: aniline = 50 mmoles, diphenyl phosphite = 25 mmoles in 40 ml of pyridine.

The effect of the reaction conditions upon the yield of the urea in the reaction with aniline (2 moles) by using diphenyl phosphite (1 mole) in pyridine (Fig 4, Table 4). Better results were obtained at higher reaction temperatures, and the yield was nearly theoretical according to eqn (2), despite the decrease of the concentration of carbon dioxide in the reaction mixture at high temperatures. In addition, a higher concentration of reactants in the mixture resulted in higher rate of producing the urea (Table 4). These results suggest that an initial reaction of carbon dioxide, phosphite and aniline, which probably forms 1, is rapid. So a rate-determining step is an aminolysis of 1 with amine into the urea.

The results as described above led to consider that the reaction of carbon dioxide with amines proceeded through a mechanism of the hydrolysis-dehydration similar to those of the amidation of carboxylic acids with amines. The reaction with carbon dioxide by using diphenyl phosphite in pyridine, for example, may be represented in the following way (Scheme 1). As



Scheme 1.

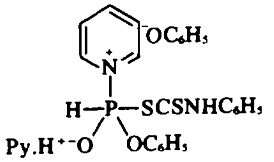
Table 4. Effect of the concentration of reactants upon the urea formation[a]

$HO{-}P(OC_6H_5)_2$ mmole	$C_6H_5NH_2$ mmole	N,N'-Diphenylurea Yield, g
12	24	1·0
24	48	2·5
48	96	4·9

[a] The reaction was carried out at 40°C for 4 h in 40 ml of pyridine.

previously proposed,[4] a carbamoyloxy *N*-phosphonium salt of pyridine **1** is formed initially in the reaction of diphenyl phosphite, carbon dioxide and an amine (aniline) in pyridine, involving release of a phenolate anion from phosphite. **1** is converted into the corresponding urea, monophenyl phosphite and phenol by aminolysis with the amine. Another possible pathway for forming the urea through the isocyanate from **1** can be ruled out by the fact that exclusive yield of the urea and no urethane was obtained in the reaction in the presence of both phenol and aniline in a separate experiment.

As with carbon dioxide, the reaction with carbon disulfide may be proceed via a thiocarbamoylthioxy *N*-phosphonium salt **2** like **1** followed by aminolysis.



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In a similar fashion, the reactions using triaryl phosphites, diphenyl ethylphosphonite, phenyl diphenylphosphinite and diphenyl n-butylphosphonate may proceed via the corresponding carbamoyloxy and thiocarbamoylthioxy *N*-phosphonium salts like **1** and **2** given by the hydrolysis-dehydration followed by aminolysis (eqns 3–6).

EXPERIMENTAL

Ureas from carbon dioxide and amines in the presence of diphenyl phosphite. Gaseous carbon dioxide was passed at 40°C for 4 h into a mixture of diphenyl phosphite (50 mmoles) and aniline (50 mmoles) in 40 ml of pyridine in the cylindrical flask (see Fig. 1). The resulting mixture was evaporated under reduced pressure to a syrup. On treatment of the syrup with 20 ml of 50% aqueous ethanol, N,N'-diphenylurea was obtained in 85% yield. The reaction was also carried out in 40 ml of various tertiary amines or in 40 ml of DMF containing imidazole (100 mmoles). Various phosphorus compounds (50 mmoles) were tested in the reaction with aniline (50 mmoles) in the presence of imidazole in 40 ml of DMF. The reaction with aniline (50 mmoles) was carried out by varying the amounts of diphenyl phosphite (0 ~ 100 mmoles) in 40 ml of pyridine and of imidazole (0 ~ 100 mmoles) in 40 ml of DMF containing diphenyl phosphite (50 mmoles). The reactions under various temperatures and times were conducted using diphenyl phosphite (25 mmoles) and aniline (50 mmoles) in 40 ml of pyridine.

Similarly, several symmetrical ureas were obtained by the reaction of amines (50 mmoles) and diphenyl phosphite (50 mmoles) in 40 ml of pyridine.

N,N'-*Diphenylthiourea from carbon disulfide, aniline and diphenyl phosphite.* A mixture of carbon disulfide (100 mmoles), aniline (50 mmoles) and diphenyl phosphite (50 mmoles) was heated at 40°C for 4 h in 40 ml of pyridine or in 40 ml of DMF containing various tertiary amines (100 mmoles). The reaction of carbon disulfide (100 mmoles) and aniline (50 mmoles) was also carried out in 40 ml of pyridine by varying the amount of diphenyl phosphite (0 ~ 100 mmoles). The thiourea thus produced was obtained by working up as above.

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$$P(OAr)_3 + 2NH_2R + CO_2 \xrightarrow{\text{Imidazole}} RNHCONHR + ArOH + HO{-}P(OAr)_2 \qquad (3)$$

$$C_2H_5{-}P(OC_6H_5)_2 + 2NH_2R + CO_2 \xrightarrow{\text{Imidazole}} RNHCONHR + C_6H_5OH + C_2H_5{-}P(OH)(OC_6H_5) \qquad (4)$$

$$(C_6H_5)_2{-}P{-}OC_6H_5 + 2NH_2R + CO_2 \xrightarrow{\text{Imidazole}} RNHCONHR + C_6H_5OH + (C_6H_5)_2{-}P{-}OH \qquad (5)$$

$$C_4H_9{-}P(O)(OC_6H_5)_2 + 2NH_2R + CO_2 \xrightarrow{\text{Imidazole}} RNHCONHR + C_6H_5OH + C_4H_9{-}P(O)(OH)(OC_6H_5). \qquad (6)$$