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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Version of record first published: 21 Nov 2007.

To cite this article: Françoise Plénat , Murielle Cassagne & Henri Jean Cristau (1996): Synthesis of new carbamoyl dithiophosphates, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:4, 783-791

To link to this article: http://dx.doi.org/10.1080/00397919608086754

SYNTHETIC COMMUNICATIONS, 26(4), 783-791 (1996)

SYNTHESIS OF NEW CARBAMOYL DITHIOPHOSPHATES

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Abstract : The synthesis of new organophosphorus compounds containing a carbamoyl unit is performed by nucleophilic addition or cycloaddition on substituted acetylisocyanates.

Oxalylchloride and N-unsubstituted amides are well known to react smoothly to form acylisocyanates[1] which are important intermediates in agropharmaceutical drugs manufacturing[2]. As part of our interest in the emergence of new chemicals in this field, we have been interested in the synthesis of various compounds containing together a carbamoyl moiety and a dithiophosphoryl function which could serve both as active ingredients and as carriers : oxadiazines **4**, carbamoylphosphonate **7** and acylsemicarbazide **8** (Scheme 1). Indeed, numerous oxadiazines[3], some carbamoylphosphonates[4], as well as acylsemicarbazides[5] have already shown biological activity (insecticides or herbicides). Also dithiophosphates[6] **9**, as malathion (R^1), azinphos (R^2) and phosalone (R^3), are well known for their insecticidal properties (Scheme 2).

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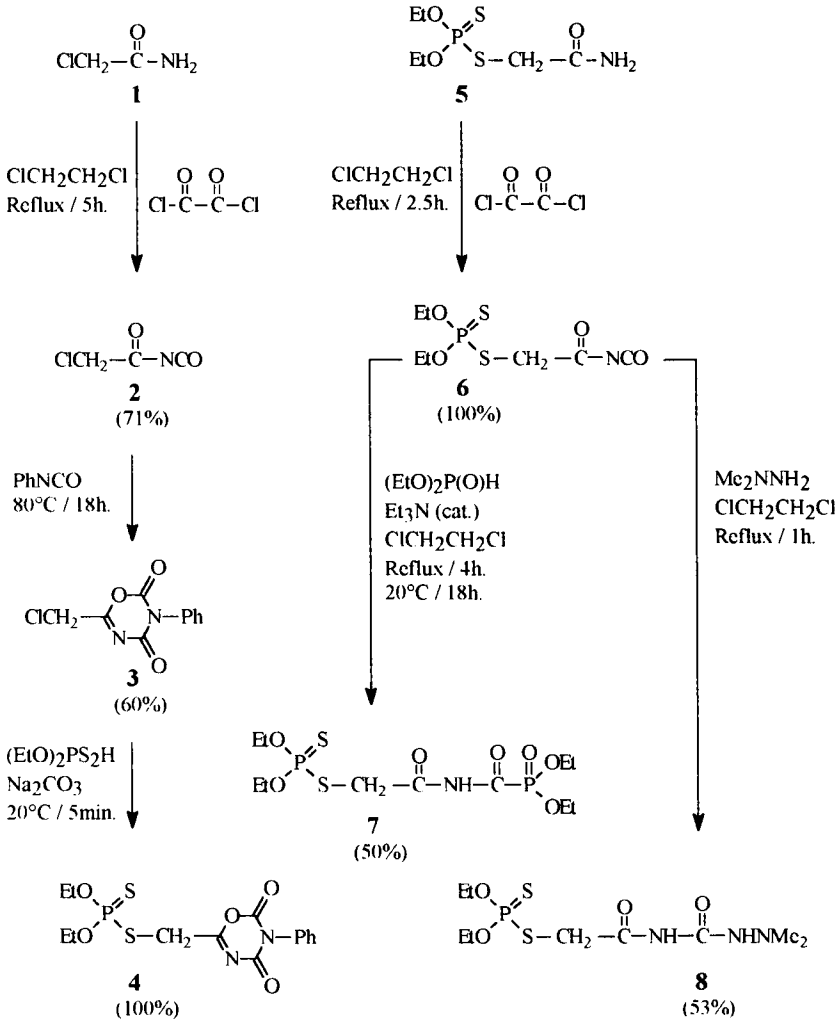
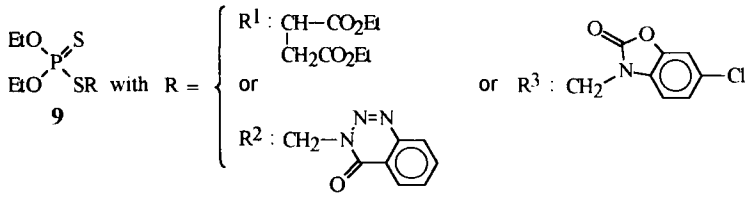
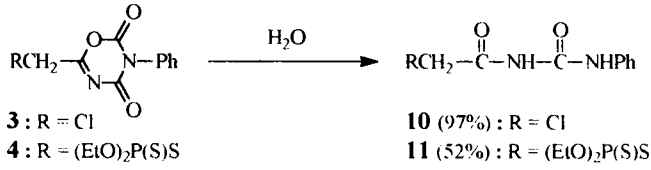


Scheme 1



Scheme 2

Various 2,4-dioxo 2,4-H 1,3,5-oxadiazines can be formed by [4+2]-cyclization between acylisocyanates and isocyanates[7]. We applied this method to the synthesis of the precursor heterocycle **3**. This compound was obtained with 60% yield starting from the chloroacetylisocyanate **2**; however, it is very sensitive to hydrolysis, and should be stored under nitrogen. Then, it was condensed with the sodium O,O-diethyl dithiophosphate formed *in situ*. A ^{31}P and ^{1}H-NMR study of this reaction shows that it gives quantitatively the expected oxadiazine **4** [$^{4}J_{PH}$ = 16 Hz (P-S-CH_2)]. However, this compound is difficult to isolate in pure form because it undergoes rapid decomposition. The main decomposition products of **3** and **4** are the corresponding acylureas **10** and **11** (Scheme 3) resulting from the hydrolysis of the heterocyclic unit.



Scheme 3

The same lability has already been observed in some other cases of oxadiazines[7]

In the synthesis of the carbamoylphosphonate **7**, which could be expected to be more stable, we used triethylamine as a catalyst in the condensation between phosphorus acylisocyanate **6** and diethylphosphite, by analogy with a previously described reaction of this type[8]. The analytical data for the final oil (^{31}P and ^{1}H-NMR and Mass spectra) show that the target molecule **7** is effectively formed in about 50% yield. But, here too, when it is removed from anhydrous conditions, it undergoes a slow decomposition to give a very complex mixture of products. For this reason, we have been unable to isolate compound **7** in a pure state, even by column chromatography. In this case, the instability probably results from the C(O)-P linkage, as the acylsemicarbazide **8** was successfully isolated in a 53% yield, without any decomposition, after condensation between acylisocyanate **6** and N,N-dimethylhydrazine. Mass spectrum and C,H,N-analysis are in good agreement with the expected structure. In view of the splitting on several signals in ^{31}P, ^{13}C and ^{1}H-NMR, the compound **8** does exist in solution as an equilibrium between two tautomeric forms. A complete coalescence at all these signals is observed in NMR spectra at 70°C. The compound **8** shows a wide activity spectrum in first insecticide screening, while nearly no activity has been detected during fongicide and herbicide tests.

Conclusion

Starting from oxalylchloride, the easily prepared acylisocyanate derivatives **2** and **6** can be successfully used in the synthesis of three new dithiophosphates containing a carbamoyl unit. In spite of the problems of instability encountered in the case of the oxadiazine **4** and the carbamoylphosphonate **7**, which makes the biological tests not very practicable in these two cases, the described synthetic strategies must be relevant for modified structures in the same chemical families.

Experimental

Mass spectra were recorded on a JEOL JMS-DX 300 spectrometer with ionizing energy of 70eV. ^{1}H (200 MHz), ^{13}C (50.3 MHz) and ^{31}P (80.1 MHz) spectra were taken on a BRUKER Ac 200 spectrometer with tetramethylsilane or phosphoric acid (85%) as reference (the chemical shift values are given in ppm and the coupling constants are measured in Hertz). IR spectra were recorded on a PERKIN-ELMER 377. Melting point were determined on a METTLER FP5 apparatus.

Compounds **2**[1a], **5**[9] and **6**[10] were prepared as described in the literature : amide **5** was used after recrystallization (m.p. = 59°C from CCl_4) and chloroacetyl-isocyanate **2** was used after distillation (bp_{20mmHg} = 55°C), whereas compound **6** was used without further purification.

Preparation of 6-chloromethyl 3-phenyl 2,4-dioxo 2,4-H 1,3,5-oxadiazine 3 : The reaction is conducted under dry nitrogen. A mixture of chloroacetylisocyanate **2** (6.9 g, 58 mmol) and phenylisocyanate (6.9 g, 58 mmol) is warmed and kept at 80°C for 18 hours. The unreacted isocyanates are evaporated under reduced pressure (0.5 mmHg) to afford pure product **3** as a solid stored under nitrogen. The yield is 60% (8.4 g, 35 mmol); ^{1}H-NMR (acetone-d_6) δ : 4.6 (s, 2H, CH_2Cl), 7.5 (m, 5H, aromatic hydrogens); Mass Spectrum m/z (relative intensity) : 119 (100, $[M\text{-}PhNCO]^{+\cdot}$), 91 (52), 77 (5).

Hydrolysis : A sample of **3** (0.36 g, 1.5 mmol) is dissolved in acetone (5 mL) and treated with a large excess of water (0.55 mL, 20 eq.). After one hour at room temperature, the solution is dried over anhydrous sodium sulfate and evaporated.

The purification of the residue by column chromatography (silica gel, ether) gives the N-chloroacetyl N'-phenylurea **10** in 97% yield (0.32 g, 1.45 mmol); m.p. 161°C (lit[11] 161-162°C); ^{1}H-NMR (acetone-d_6) δ : 4.4 (s, 2H, CH_2Cl), 7.1 (t, 1H, J = 7.2, *para* aromatic hydrogen), 7.35 (~t, 2H, J ≅ 8, *meta* aromatic hydrogens), 7.6 (d, 2H, J = 8, *ortho* aromatic hydrogens), 9.8 (s, 1H, NH), 10.3 (s, 1H, NH).

Preparation of O,O-diethyl [3-phenyl 6-(2,4-dioxo 2,4-H 1,3,5-oxadiazinyl)] methyl dithiophosphate 4 : The reaction, conducted under dry nitrogen, is followed by ^{31}P and ^{1}H-NMR spectroscopy. Compound **3** (76 mg, 0.32 mmol) dissolved in anhydrous acetone-d_6 (3 mL) is added to a mixture of equivalent amounts of O,O-diethyl dithiophosphate (60 mg, 0.32 mmol) and anhydrous disodium carbonate (34 mg, 0.32 mmol) in the same solvent (1 mL). After 5 mn, NMR spectra of this solution is recorded : ^{1}H-NMR (acetone-d_6) δ : 1.35 (t, 6H, J = 7, CH_3), 4.1 (d, 2H, J = 16, CH_2S), 4.25 (m, 4H, CH_2O), 7.2 to 7.8 (m, 5H, aromatic hydrogens); ^{31}P-NMR (acetone-d_6) δ : 89.1.

Hydrolysis : On the above reaction, realized on a larger scale (3.2 mmol of each starting material) and in undeuterated acetone, the solution obtained after 5 mn is filtrated to eliminate the resulting sodium chloride and sodium hydrogenocarbonate; then the filtrate is immediately treated with a large excess of water (2 mL, 40 eq.). After 10 mn at room temperature, the solution is dried over anhydrous sodium sulfate, filtrated and evaporated. The O,O-diethyl phenylaminocarbamoylcarbonylmethyl dithiophosphate **11** is obtained after purification by column chromatography (silica gel, ether) in 52% yield (0.61 g, 1.7 mmol); m.p. 85°C (lit[12] 84-86°C); ^{1}H-NMR ($CDCl_3$) δ : 1.35 (t, 6H, J = 7, CH_3), 3.8 (d, 2H, J = 16.5, CH_2S), 4.25 (m, 4H, CH_2O), 7.1 (t, 1H, J = 7.2, *para* aromatic hydrogen), 7.35 (~t, 2H, J ≅ 8, *meta* aromatic hydrogens), 7.6 (d, 2H,

J = 8, *ortho* aromatic hydrogens), 9.9 (s, 1H, NH), 10.4 (s, 1H, NH); ^{31}P-NMR ($CDCl_3$) δ : 92.3.

Preparation of (O,O-diethyldithiophosphate S-)acetylcarbamoyl O,O-diethyl phosphonate 7 : The reaction is conducted under dry nitrogen. Diethylphosphite (2.4 g, 17.1 mmol) and triethylamine (3 drops) are added to a solution of **6** (4.6 g, 17.1 mmol) in anhydrous 1,2-dichloroethane (5 mL). The mixture was refluxed for 4 hours, and left at room temperature for 18 hours. After removal of the solvent, a mixture of the reactants and the expected phosphonate **7** is obtained as a thick oil (4 g); ^{1}H-NMR ($CDCl_3$) δ : 1.4 (t, CH_3), 3.6 (d, J = 17.4, CH_2S of precursor **6**), 4 (d, J = 17.1, CH_2S of compound **7**), 4.25 (m, CH_2O), 9.75 (s, NH of compound **7**); ^{31}P-NMR ($CDCl_3$) δ : 92.4 and -4.5 (70%, compound **7**), 89 (15%, precursor **6**), 8 (15%, diethylphosphite); Mass Spectrum m/z (relative intensity) : 407 (100, $[M]^{+\cdot}$), 269 (28), 226 (56), 197 (31), 180 (50), 171 (48), 153 (82), 138 (22), 125 (78), 121 (60), 97 (100).

Preparation of O,O-diethyl (1,1-dimethyl 4-semicarbazidyl) carbonylmethyl dithiophosphate 8 : The reaction is conducted under dry nitrogen. N,N-dimethylhydrazine (1.56 g, 26 mmol) is added to a solution of **6** (7 g, 26 mmol) in anhydrous 1,2-dichloroethane (20 mL) and the mixture is refluxed for one hour. After evaporation of the solvent the residue is purified by column chromatography (silica gel, ethyl acetate) and gives the acylsemicarbazide **8**. The yield is 53% (4.5 g, 13.7 mmol); m.p. 101°C; C,H,N-analysis $C_9H_{20}N_3O_4PS_2$: Calcd. C, 32.82, H, 6.12, N,12.76, Found C, 32.7, H, 6.30, N, 12.80; ^{1}H-NMR (DMSO-d_6, 70°C) δ : 1.35 (t, 6H, J = 7, CH_3C), 2.5 (s, 6H, CH_3N), 3.9 (d, 2H, J = 15.6, CH_2S), 4.1 (m, 4H, CH_2O), 8.6 (s, 1H, NH), 9.9 (s, 1H, NH); ^{13}C-NMR

(DMSO-d_6, 70°C) δ : 15.4 (d, J = 8, CH_3C), 36.3 (s, CH_2S), 46.7 (s, CH_3N), 63.9 (d, J = 6.2, CH_2O), 151.4 (s, NC(O)N), 168.4 (s, CC(O)N); ^{31}P-NMR (DMSO-d_6, 70°C) δ : 92; Mass Spectrum m/z (relative intensity) : 329 (10, $[M]^{+\cdot}$), 227 (17), 171 (25), 153 (22), 125 (24), 97 (38), 86 (100). IR (KBr) : 650, 820, 970, 1005, 1200, 1310, 1505, 1535, 1690, 1720 and 2980 cm^{-1}.

Acknowledgment : We are grateful for the financial support of a part of this work by the *Société Nationale des Poudres et Explosifs* (SNPE).

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(Received in The Netherlands 28 July 1995)