Pergamon

Tetrahedron Vol. 51, No. 35, pp. 9551-9558, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00595-1

Synthesis of New Phosphorus 2,4,5-Imidazolidinetriones

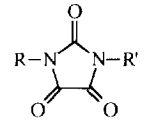
Françoise Plénat*, Murielle Cassagne, Henri Jean Cristau

Laboratoire de Chimie Organique E.N.S.C.M. (URA 458 du CNRS),
8 rue de l'Ecole Normale, 34053 Montpellier Cedex 1, France

Abstract Phosphorus 2,4,5-imidazolidinetriones are obtained in two different ways : the synthesis of dithiophosphate and phosphonium salt derivatives involves the reaction between a common N-chloromethyl heterocycle and corresponding phosphorus partners, while the preparation of phosphonate and phosphine oxide imidazolidinetriones is done by two multi-step synthesis starting from different phosphorus phthalimides.

Numerous 2,4,5-imidazolidinetriones are known for their herbicide[1a], plant growth regulator[1b,1c], and in a minor part, fungicide properties[1d]. As early as 1959, 1-alkyl 3-aryl parabanic acids, and for instance the very simple structure **I**, were found particularly effective as pre-emergent herbicides[1a].

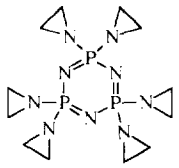
I : R = CH_3, R' = C_6H_5
II : R = CH_3, R' = $C(O)O$*iso*C_4H_9
III : R = CH_3, R' = $C(O)NHC_3H_7$



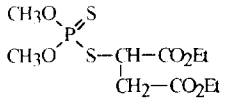
During the following years, more elaborated structures, such as **II** and **III**, were prepared and used as plant growth regulators[1b,1c].

As part of our interest in the emergence of new chemicals in the field of agropharmaceutical manufacturing[2], we chose to associate in the same structure the previous kind of heterocyle with a phosphorus group, which

could serve both as a carrier (as in the case of the phosphazenic derivative Apholate) and as an active part of the molecule (like the dithiophosphate function in Malathion)



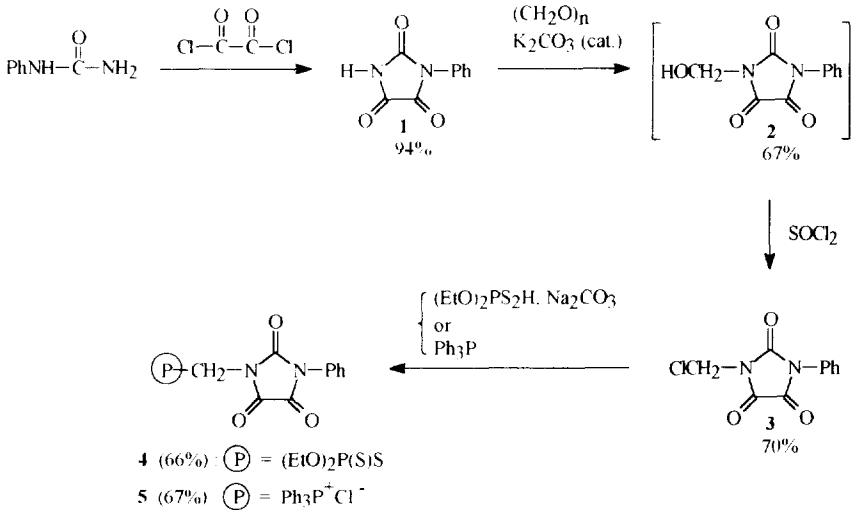
Apholate



Malathion

In order to obtain a series of new 2,4,5-imidazolidinetriones (**4**,**5**,**12** and **13**), we planned to first synthesize the unknown chlorinated precursor **3**, and to react it with the various phosphorus partners chosen : O,O-diethyl dithiophosphate, triphenylphosphine, triethyl phosphite and ethyl diphenylphosphinite.

The base-catalyzed condensation between N-phenylimidazolidinetrione **1**[3] and paraformaldehyde (Scheme 1) in aqueous solution allowed us to obtain the expected N-hydroxymethyl derivative **2** in a 67% yield but as a mixture of **2** and **1**. However, the instability of **2** made its isolation very difficult. For instance, an attempted recrystallization of impure N-hydroxymethyl N'-phenylimidazolidinetrione in ethanol induced an important decomposition of **2** into **1** (the molar proportions were then nearly inverted from 73/27 to 14/86). Moreover, the use of column chromatography as a method of purification failed, whatever the eluent or support (silica gel, alumina) used, because the Rf value is the same for the two compounds.

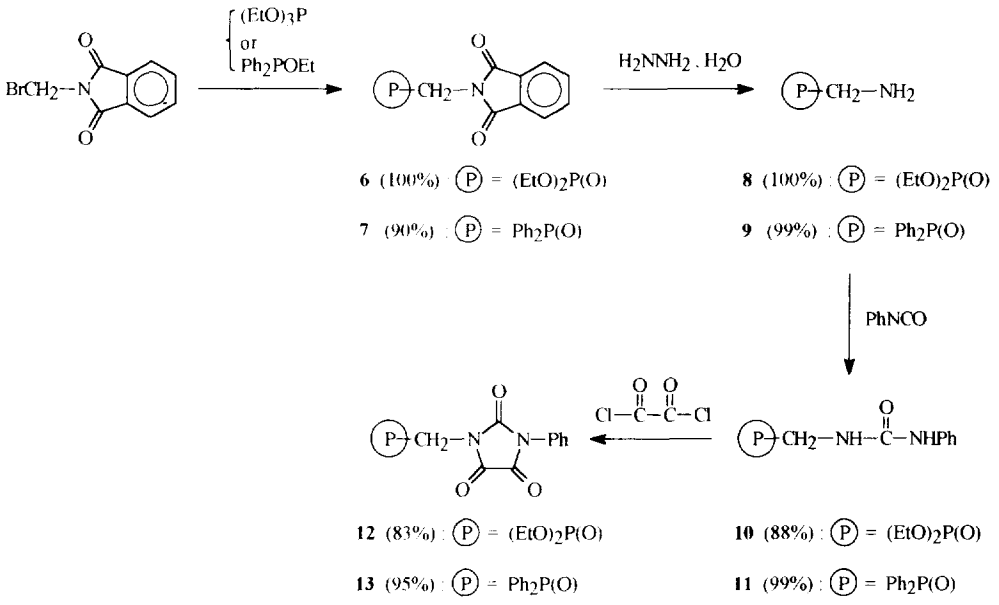


Scheme 1 Synthesis of phosphorus 2,4,5-imidazolidinetriones using the N-chloromethyl precursor **3**.

For this reason, the next step of chlorination, using a large excess of thionyl chloride, was realized starting directly from a mixture of **2** and **1**. The chlorinated precursor **3** was then easily isolated by column chromatography (silica gel, dichloromethane) in 70% overall yield, because under these conditions, the final product has a much higher Rf value than the starting material.

The reaction of **3** with the sodium O,O-diethyl dithiophosphate, prepared *in situ*, or with triphenylphosphine, provided respectively the expected dithiophosphate **4** and the phosphonium salt **5** with correct yields.

In contrast, Michaelis-Arbuzov reactions involving N-chloromethyl N'-phenylimidazolidinetrione **3** and triethyl phosphite or ethyl diphenylphosphinite did not give the corresponding phosphonate **12** and phosphine oxide **13**, although the total amount of phosphorus starting materials was consumed producing, however, complex mixtures of compounds. Therefore, we used a quite different synthetic strategy (Scheme 2), in which the cyclization by oxalyl chloride was realized in the last step of the synthesis whereas it was previously in the first step.



Scheme 2 : Synthesis of 2,4,5-imidazolidinetrione derivatives starting from phosphorus phthalimides.

The Michaelis-Arbuzov reactions already described on N-bromomethylphthalimide were reproduced to prepare the intermediate compounds **6**[4] and **7**[5]. The amine functions were then deprotected in a classic and direct way, using monohydrated hydrazine, although another method was previously reported in the literature[5]

for the synthesis of **9** (acid hydrolysis of **7** followed by a treatment with sodium carbonate). In this last case, the melting point of the solid obtained after the work-up of the reaction was lower than the one given in the literature (88°C instead of 103°C). However, the ^{1}H and ^{31}P NMR spectra agreeing with the expected structure, the compound **9** was used without further purification.

The free amines **8** and **9** gave then a very exothermic reaction with phenyl isocyanate affording corresponding ureas **10** and **11** in better yields than those obtained using phosphorus acylisocyanates and phenylamine as substrates[6]. This proved the quality of the unrecrystallized amine **9** previously isolated. It should be noticed that the melting point measured for compound **11** was much higher than the one already reported (216°C instead of 175°C).

In the final step, the well-known cyclization method of ureas by oxalyl chloride[7] was applied to the previous compounds, and these reactions allowed us to isolate the target compounds **12** and **13** in excellent overall yields.

It must be pointed out that this last strategy could be advantageously applied to all kinds of phosphorus urea since aminomethylphosphorus compounds would be readily accessible.
Biological tests of the new imidazolidinetriones are in progress.

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) NMR spectra were taken on a BRUKER Ac 200 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 points were determined on a METTLER FP5 apparatus.

Phenylimidazolidinetrione **1**[3], phosphonates **6**[4] and **8**[4], and phosphine oxide **7**[5], were prepared according to the procedure described in the literature and used without further purifications, as melting points and spectroscopic data were in agreement with the expected structures.

N-Hydroxymethyl N'-phenylimidazolidinetrione (2)

A mixture of phenylimidazolidinetrione **1** (4 g, 21 mmol), paraformaldehyde (0.70 g, 25.4 mmol) and potassium carbonate (60 mg, 0.4 mmol) is heated at 70°C for 1 h. in water (200 mL). After cooling, the solution is filtered affording a mixture (3.6 g) of the N-hydroxymethyl derivative **2** and the starting material **1** in 73/27 molar proportions (on the basis of ^{1}H NMR).

^{1}H-NMR (DMSO-d_6) of the mixture : 5 (d, 1.46H, $^2J_{HH}$ = 7, CH_2 from **2**); 6.8 (t, 0.73H, $^2J_{HH}$ = 7, OH from **2**); 7.2 to 7.7 (m, 5H, Ph from **1** and **2**); 12.2 (s, 0.27H, NH from **1**).

Yield : 67%.

N-Chloromethyl N'-phenylimidazolidinetrione (3)

The reaction is carried out under dry nitrogen. Thionyl chloride (14.3 g, 120 mmol) is added to a suspension of the previous mixture (3.5 g, 13.7 mmol of N-hydoxymethyl derivative **2**) in anhydrous carbon tetrachloride (20 mL). After cooling, the starting material **2** (mixed with **1**) is eliminated by filtration. After removal of the solvent, the N-chloromethyl N'-phenylimidazolidinetrione **3** is purified by column chromatography (silica gel, dichloromethane).

Yield : 70% (2.3 g, 9.6 mmol). Colourless crystals. Mp $_{(EtOH)}$ = 128°C.

^{1}H-NMR (acetone-d_6) : 5.6 (s, 2H, CH_2Cl); 7.4 (m, 5H, Ph). ^{13}C-NMR (acetone-d_6) : 46.31 (s, CH_2Cl); 127.48 (s, *ortho*); 129.94 (s, *para*); 130.10 (s, *méta*); 131.48 (s, *ipso*); 152.41 (s, NC(O)N); 156.31 et 156.57 (2s, C(O)C(O)). GC/MS : m/e (%) : 240 ($[M+2, {}^{37}Cl]^+$, 9); 238 ($[M]^+$,27); 203 (3.6); 119 ($[M-PhNCO]^+$, 100); 91 (23.5). IR (KBr) (cm^{-1}) : 690; 700; 755; 1190; 1295; 1400; 1440; 1500; 1730; 1780.

Anal. Calcd. for : C, 50.33; H, 2.96; N, 11.74; Found : C, 50.1; H, 2.9; N, 11.3.

O,O-diethyl (phenylimidazolidinetrionyl)methyldithiophosphate (4)

N-chloromethyl N'-phenylimidazolidinetrione **3** (0.28 g, 1.17 mmol) is added to O,O-diethyl dithiophosphate (0.23 g, 1.25 mmol) and sodium carbonate (0.13 g, 1.25 mmol) in acetone (20 mL). The mixture is refluxed for 4 h. After cooling, the sodium chloride and sodium hydrogenocarbonate formed during the reaction are filtered off. The dithiophosphate **4** obtained after concentration of the filtrate is purified by column chromatography (silica gel, ether/hexane : 1/1).

Yield : 66% (0.30 g, 0.77 mmol). Colourless crystals. Mp = 68°C.

^{1}H-NMR ($CDCl_3$) : 1.35 (t, 6H, $^3J_{HH}$ = 7, CH_3); 4.2 (m, 4H, CH_2O); 5.05 (d, 2H, $^3J_{PH}$ = 13.8, CH_2S); 7.4 (m, 5H, Ph). ^{13}C-NMR ($CDCl_3$) : 15.73 (d, $^3J_{PC}$ = 8.2, CH_3), 40.08 (d, $^2J_{PC}$ = 4, CH_2S); 64.77 (d, $^2J_{PC}$ = 6.3, CH_2O); 125.56 (s, *ortho*); 129.18 (s, *para*), 129.39 (s, *méta*), 129.46 (s, *ipso*), 151.02 (s, NC(O)N), 154.83 et 154.46 (2s, C(O)C(O)). ^{31}P-NMR ($CDCl_3$) : 89.2. Mass spectrum (EI) : 388 ($[M]^+$,27); 343 (10); 204 (6); 185 (13); 154 (33); 121 (100); 93 (22). IR (KBr) (cm^{-1}) : 650; 750; 940; 965; 1005; 1190; 1275; 1390; 1420; 1735; 1750.

Anal. Calcd. for : C, 43.29; H, 4.41; N, 7.21; Found : C, 43.4; H, 4.5; N, 7.3.

[(Phenylimidazolidinetrionyl)methyl]triphenylphosphonium chloride (5)

Equimolar amounts of N-chloromethyl N'-phenylimidazolidinetrione **3** (0.45 g, 1.9 mmol) and triphenylphosphine (0.50 g, 1.9 mmol) are refluxed for 120 h in acetonitrile (10 mL). After cooling, the solution is precipitated in ether (200 mL) giving the phosphonium salt **5**.

Yield : 67% (0.65 g, 1.3 mmol). Colourless crystals. Mp $_{(MeOH\ AcOEt)}$ = 249°C.

^{1}H-NMR (DMSO-d_6) : 6.1 (d, 2H, $^2J_{PH}$ = 5.2, CH_2P); 7.2 à 7.7 (m, 5H, N-Ph); 7.7 à 8.2 (m, 15H, P-Ph). ^{13}C-NMR (DMSO-d_6) : 34.32 (d, $^1J_{PC}$ = 60.3, CH_2P), 116.17 (d, $^1J_{PC}$ = 85.4, *ipso* P-Ph); 126.34 (s, *ortho* NPh); 128.92 (s, *para* N-Ph); 129.19 (s, *meta* NPh); 129.96 (d, $^2J_{PC}$ = 13, *ortho* P-Ph); 130.09 (s, *ipso* NPh); 134.62 (d, $^3J_{PC}$ = 10.7, *méta* P-Ph); 135.41 (d, $^4J_{PC}$ = 2.7, *para* P-Ph); 152.04 (s, NC(O)N); 155.52 et 156.42 (2s, C(O)C(O)). ^{31}P-NMR (DMSO-d_6) : 18.7. Mass spectrum (FAB$^+$) : 465 ([M]$^+$,100); 411 (2); 389 (3); 350 (7); 318 (22); 262 (14); 201 (3); 183 (13); 93 (12). IR (KBr) (cm^{-1}) : 680; 735; 860; 1030; 1105; 1380; 1430; 1490; 1735.

Anal. Calcd. for : C, 67.19; H, 4.43; N, 5.60; Found : C, 66.9; H, 4.5; N, 5.5.

O,O-diethyl (phenylaminocarbamoylmethyl)phosphonate (10)

The reaction is carried out under dry nitrogen. Phenyl isocyanate (0.43 g, 3.6 mmol) is added to a suspension of O,O-diethyl (aminomethyl)phosphonate **8** (0.57 g, 3.4 mmol) in anhydrous dichloromethane (15 mL). The mixture is refluxed for 1 h. After removal of the solvent, the phosphonate **10** is purified by column chromatography (silica gel, ethyl acetate/methanol : 9/1).

Yield : 88% (0.85 g, 3 mmol). Colourless crystals. Mp = 75°C (lit [6] 78-79°C).

^{1}H-NMR ($CDCl_3$) : 1.35 (t, 6H, $^3J_{HH}$ = 7, CH_3); 3.8 (dd, 2H, $^3J_{HH}$ = 5.9, $^2J_{PH}$ = 10.6, CH_2P); 4.2 (m, 4H, CH_2O); 6.6 (t, 1H, $^3J_{HH}$ = 5.9, $CH_2\underline{NH}$); 7 (t, 1H, $^3J_{HH}$ = 7.6, *para*); 7.25 (t, 2H, $^3J_{HH}$ = 7.6, *méta*); 7.4 (d, 2H, $^3J_{HH}$ = 7.6, *ortho*); 8.4 (s, 1H, $\underline{NH}$-Ph). ^{31}P-NMR ($CDCl_3$) : 24.9.

O,O-diethyl (phenylimidazolidinetrionyl)methylphosphonate (12)

The reaction is carried out under dry nitrogen. Oxalyl chloride (9.1 g, 72 mmol) is added to a suspension of O,O-diethyl (phenylaminocarbamoylmethyl)phosphonate **10** (17.1 g, 60 mmol) in anhydrous ether (140 mL). The mixture is refluxed for 3 h. After cooling, the phosphonate **12** is isolated by filtration.

Yield : 83% (17.0 g, 50 mmol). Colourless crystals. Mp $_{(EtOH)}$ = 120°C.

^{1}H-NMR ($CDCl_3$) : 1.35 (t, 6H, $^3J_{HH}$ = 7, CH_3); 4 à 4.4 (m, 6H, CH_2O et CH_2P); 7.3 (m, 5H, Ph). ^{13}C-NMR ($CDCl_3$) : 16.18 (d, $^3J_{PC}$ = 6.2, CH_3), 34.26 (d, $^1J_{PC}$ = 156.5, CH_2P); 63.17 (d, $^2J_{PC}$ = 6, CH_2O); 125.56 (s, *ortho*); 129.03 (s, *para*); 129.30 (s, *meta*); 129.64 (s, *ipso*); 151.69 (s, NC(O)N); 155.04 (s, C(O)C(O)). ^{31}P-NMR ($CDCl_3$) : 17.7. GC/MS : m/e (%) : 340 ([M]$^+$,23); 312 (7); 295 (2); 204 (9); 137

(16); 119 (100); 91 (20). IR (KBr) (cm^{-1}) : 740; 750; 790; 980; 1020; 1040; 1190; 1255; 1395; 1415; 1500; 1720; 1750.

Anal. Calcd. for : C, 49.42; H, 5.04; N, 8.23; Found : C, 49.6; H, 5.0; N, 8.3.

Diphenyl(aminomethyl)phosphine oxide (9)

Monohydrated hydrazine (0.9 g, 18.3 mmol) is added to a solution of diphenyl(N-phthalimido methyl)phosphine oxide 7 (6 g, 16.6 mmol) in ethanol (60 mL). The mixture is stirred for 18 h at 20°C, and refluxed for 5 h. After cooling, the phthalhydrazide formed during the reaction is eliminated by filtration. The filtrate is concentrated affording the phosphine oxide **9**

Yield : 99% (3.80 g, 16.4 mmol). Colourless crystals. Mp = 88°C (lit.[5] 103°C).

^{1}H-NMR ($CDCl_3$) : 1.6 (s, 2H, NH_2); 3.5 (d, 2H, $^2J_{PH}$ = 4.2, CH_2P); 7.3 à 7.9 (m, 10H, Ph). ^{31}P-NMR ($CDCl_3$) : 31.1

Diphenyl(phenylaminocarbamoylmethyl)phosphine oxide (11)

The reaction is carried out under dry nitrogen. Phenyl isocyanate (2 g, 17.4 mmol) is added to a suspension of diphenyl(aminomethyl)phosphine oxide **9** (3.8 g, 16.6 mmol) in anhydrous dichloromethane (35 mL). The mixture is refluxed for 1 h. After cooling, the urea **11** is isolated by filtration.

Yield : 99% (5.7 g, 16.3 mmol). Colourless crystals. Mp = 216°C (lit.[6] 175°C).

^{1}H-NMR ($CDCl_3$) : 4.35 (dd, 2H, $^3J_{HH}$ = $^2J_{PH}$ = 5.5, CH_2P); 7 (t, 1H, $^3J_{HH}$ = 5.5, $CH_2\underline{NH}$); 7.1 à 8 (m, 15H, Ph); 9 (s, 1H, $\underline{NH}$-Ph). ^{13}C-NMR ($CDCl_3$) : 39.34 (d, $^1J_{PC}$ = 80.6, CH_2P); 118.16 (s, *ortho* N-Ph); 121.64 (s, *para* N-Ph); 128.67 (s, *meta* N-Ph); 128.94 (d, $^3J_{PC}$ = 11.9, *meta* P-Ph); 129.81 (d, $^1J_{PC}$ = 99.4, *ipso* P-Ph); 130.83 (d, $^2J_{PC}$ = 9.8, *ortho* P-Ph); 132.53 (d, $^4J_{PC}$ = 2.8, *para* P-Ph); 139.92 (s, *ipso* N-Ph); 156.72 (d, $^3J_{PC}$ = 6.5, C(O)). ^{31}P-NMR ($CDCl_3$) : 34.2. Mass spectrum (EI) : 350 ($[M]^+$,2.5); 258 (28); 201 (100); 183 (15); 155 (20); 119 (28); 93 (60); 77 (60).

Anal. Calcd. for : C, 68.55; H, 5.47; N, 8.00; Found : C, 68.4; H, 5.5; N, 8.1.

Diphenyl[(phenylimidazolidinetrionyl)methyl]phosphine oxide (13)

The reaction is carried out under dry nitrogen. Oxalyl chloride (1.17 g, 9.2 mmol) is added to a suspension of diphenyl(phenylaminocarbamoylmethyl)phosphine oxide **11** (2.8 g, 8 mmol) in anhydrous ether (70 mL). The mixture is refluxed for 3 h. After cooling, the phosphine oxide **13** is isolated by filtration.

Yield : 95% (3.07 g, 7.6 mmol). Colourless crystals. Mp $_{(EtOH)}$ = 237°C.

^{1}H-NMR ($CDCl_3$) : 4.6 (d, 2H, $^2J_{PH}$ = 5, CH_2P); 7.1 à 8 (m, 15H, Ph). ^{13}C-NMR ($CDCl_3$) : 39.58 (d, $^1J_{PC}$ = 71.1, CH_2P); 125.54 (s, *ortho* N-Ph); 128.86 (d, $^3J_{PC}$ = 12.2, *meta* P-Ph); 128.98 (s, *para* N-Ph); 129.25 (s, *meta* N-Ph); 129.53 (s, *ipso* N-Ph); 130.28 (d, $^1J_{PC}$ = 75.2, *ipso* P-Ph); 131.27 (d, $^2J_{PC}$ = 10, *ortho* P-Ph); 132.79 (d, $^4J_{PC}$ = 2.9, *para* P-Ph); 151.80 (s, NC(O)N); 154.80 et 155.20 (2s, C(O)C(O)). ^{31}P-

NMR ($CDCl_3$) : 26.4. Mass spectrum (EI) : 404 ($[M]^+$,11); 201 (100); 183 (5); 119 (8); 91 (7); 77 (28). IR (KBr) (cm^{-1}) : 635; 690, 740; 870; 1185, 1195; 1390, 1410; 1435; 1500; 1730; 1750.
Anal. Calcd. for : C, 65.35; H, 4.24; N, 6.93; Found : C, 65.4; H, 4.4; N, 7.0.

We are grateful for the partial funding of this work by the Société Nationale des Poudres et Explosifs (SNPE).

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(*Received in Belgium* 13 *April* 1995; *accepted* 7 *July* 1995)