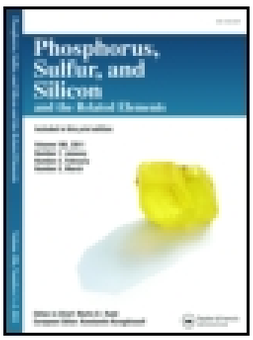

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# A simple and convenient protocol for the synthesis of seven- and eight-membered phosphorus heterocycles

Ananda Kumar Kanduluru* and Suresh Reddy Cirandur

Department of Chemistry, Sri Venkateswara University, Tirupati, India

**ABSTRACT**

A simple procedure for the synthesis of eight-membered 6-(2-chloroethyl)/bis(2-chloroethyl)-amino-12-oxo-dibenzo[d,g][1,3,2]dioxaphosphocin 6-oxides (**3a–b**) and seven-membered 6-(2-chloroethyl)/bis-(2-chloroethyl)aminodibenzo[d,f][1,3,2]dioxaphosphepin 6-oxides (**5a–b**) from cyclocondensation of equimolar ratios of 2,2′-dihydroxybenzophenone (**1**) and 2,2′-dihydroxybiphenol (**4**), respectively with 2-chloroethylphosphonicdichloride (**2a**) and bis(2-chloroethyl)phosphoramidic dichloride (**2b**) in dry toluene in the presence of triethylamine at 45–50 °C is described. All synthesized compounds possessed significant growth inhibition for their antibacteria against 'Bacillus subtilis' and 'Klebsiella pneumonia' and antifungi activity on "Curvularia lunata" and "Aspergillus niger."

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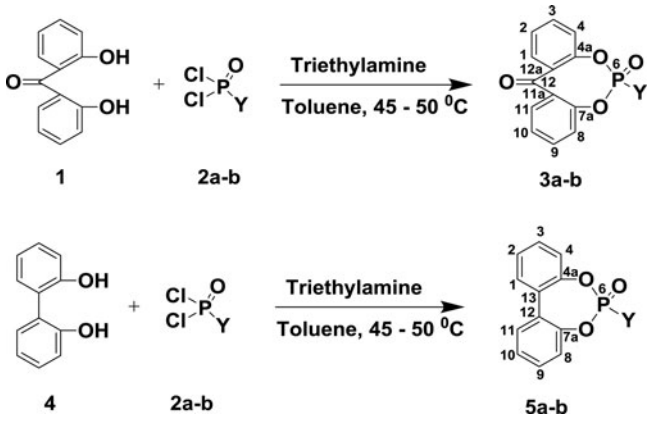
Phosphorus heterocycles; benzodioxaphosphocin oxides; benzodioxaphosphepin oxides; antibacterial; antifungal activities

**GRAPHICAL ABSTRACT**




## Introduction

Organophosphorus compounds (OP) are important class of components with a variety of applications in biology, agriculture and chemistry.[1–6] However, phosphonates and phosphoramidates are organic compounds containing C-$PO(OR)_2$ and $R_2N$-$PO(OR)_2$ groups (R = alkyl, aryl or H), which exhibits multifaceted applications in modern organic and medicinal chemistry.[2,3,8] In particular, alkyl and aryl phosphonates are increasingly used in medicine to treat disorders associated with bone formation and calcium metabolism such as osteoporosis, and also serve as carriers for radionuclides in bone cancer treatments.[8] More importantly, the introduction of an amine group in the molecule increases the metal binding abilities of the corresponding phosphonates.[6,8] In continuation of our efforts for the synthesis of bioactive dioxaphosphocin and dioxaphosphepin oxides,[9–12] herein we report a corresponding eight- and seven-membered phosphorus heterocyclic compounds and their preliminary biological results.

## Results and discussion

The synthesis of 6-(2-chloroethyl) and bis-(2-chloroethyl) amino-12-oxo-dibenzo-[*d*,*g*][1,3,2]-dioxaphosphocin 6-oxides (Scheme 3, **3a** and **3b**) was achieved by the cyclocondensation of 2,2′-dihydroxybenzophenone (**1**) with 2-chloroethylphosphonic dichloride (**2a**) and bis-(2-chloroethyl) phosphoramidicdichloride (**2b**), respectively, in equimolar quantities in dry toluene, in the presence of triethylamine. The dichlorides (**2a**, **2b**) were prepared as shown in Schemes 1 and 2 by modified literature procedures. [13,14]

**CONTACT** Ananda Kumar Kanduluru kanduluruak@yahoo.com Department of Chemistry, Sri Venkateswara University, Tirupati 517 502, India.
*Present address: Center for Drug Discovery and Department of Chemistry, Purdue University, West Lafayette, Indiana, USA

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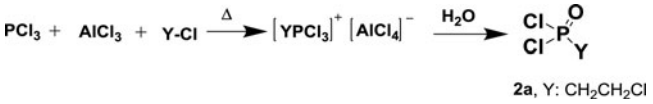
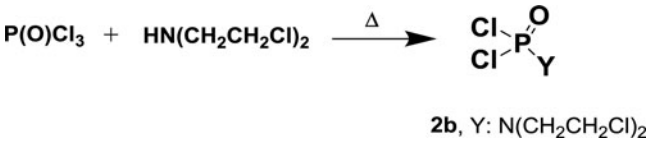


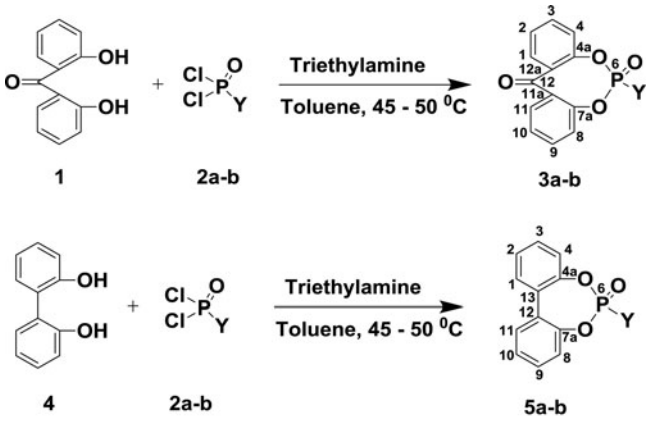

Scheme 1




Scheme 2

The cyclization of compound **1** with 2-chloroethylphosphonic dichloride (**2a**) and bis(2-chloroethyl)phosphoramidic dichloride (**2b**), occurred smoothly in dry toluene in the presence of triethylamine in about 5–6 h at 45–50 °C. The course of the reaction was followed by using TLC analysis (EtOAc-Hex, 1:3) at different time intervals. In the reaction, formation of dibenzodioxaphosphocin 6-oxide heterocyclic system is considered to be a nucleophilic attack by oxygen atom of hydroxy groups of compound **1**, on the phosphorus atom of phosphonicdichlorides and phosphoramidicdichloride. In this condensation, dry toluene was found to be an ideal solvent since the reactants readily dissolved in it in the presence of triethylamine without reacting with it. The use of triethylamine in these reactions is essential as it readily scavenges the liberated hydrogen chloride forming its salt and thereby drives the reaction to completion. Further, work-up of the reaction product is easy by filtration of the insoluble triethylamine hydrochloride salt and removal of solvent from the filtrate and then drying before purification by recrystallization.

Similarly, 6-(2-chloroethyl) and bis-(2-chloroethyl)amino dibenzo[*d,f*][1,3,2]dioxaphosphepin 6-oxides (Scheme 3, **5a** and **5b**) were synthesized from 2,2′-dihydroxybiphenol (**4**) and **2a–b** under these conditions. The 2-chloroethylphosphonic and bis(2-chloroethyl)phosphoramidic dichlorides (**2a** and **2b**) were prepared according to the literature modified procedures with high purity.[13,14] Further, the reported conditions are very convenient, easy handling, simple work-up and purification.[12] The molecular structures of the synthesized compounds were confirmed by IR, $^{1}$H, $^{13}$C, and $^{31}$P NMR spectroscopy and mass spectrometry and elemental analysis.




| Entry | Compound | Y |
|---|---|---|
| 1 | **3a** | -$CH_2CH_2Cl$ |
| 2 | **3b** | -$N(CH_2CH_2Cl)_2$ |
| 3 | **5a** | -$CH_2CH_2Cl$ |
| 4 | **5b** | -$N(CH_2CH_2Cl)_2$ |

**Scheme 3.** Synthesis of dioxaphosphocin and dioxaphosphepin-6-oxides.

In order to confirm the reaction through characteristic functional groups in the molecules, the infrared spectra were used, and confirmed the phosphoryl (P = O) group in the given structures (**3a–b and 5a–b**) based on absorption bands for P = O stretching frequencies in the region 1290–1312 cm$^{-1}$. The appearance of P = O absorption in the normal region indicates that the phosphoryl group is not involved in hydrogen bonding in these compounds.[11,14] The carbonyl groups in **3a** and **3b** showed absorption bands at 1627 and 1636 cm$^{-1}$ respectively, in a relatively low region than normal due to the effect of two aromatic phenyl rings attached to it.[11,16] Proton ($^{1}$H) NMR showed two distinct multiplets for compounds **3a** and **5a** in the regions $\delta$ 2.03–2.64 (P-$CH_2$) and $\delta$ 3.33–3.94 (-$CH_2$Cl) for aliphatic methylene groups attached to phosphorus, whereas, bis(2-chloroethyl)amino group compounds **3b** and **5b**, proton signals observed in the regions $\delta$ 3.18–3.45 ($N(CH_2)_2$) and $\delta$ 3.53–3.60 ((-$CH_2$Cl)$_2$). The aromatic protons appeared in the expected regions, $\delta$ 6.80–8.10.[11,14] The $^{31}$P resonance signals were within the region from 42.7 to 12.3 ppm.[15–16] The EI mass spectra of compounds **3b** and **5b** are recorded and interpreted in support of the structures proposed based on their synthesis.[9–11]

## Biological activity

The synthesized compounds (**3a–b, 5a–b**) were screened for their antibacterial activity against the growth inhibition of *Bacillus subtilis* (gram + ve) and *Klebsiella pneumoniae* (gram-ve) at concentrations 500 and 1000 ppm[17] and all these compounds exhibited promising activity against both the organisms. The results are presented in Table S1 (Supplemental Materials). Penicillin and Tetracycline were tested as standard reference compounds to compare the activity of these compounds. The antifungal activity was also tested for the compounds (**3a–b, 5a–b**) against the growth inhibition of *Curvularia lunata* (Pink disease) and *Aspergillus niger* (dry root rot of sun flower and citrus) with two different concentrations (500 and 1000 ppm).[18] Griseofulvin was used as reference compound to compare the activity of the synthesized compounds. Most of the compounds showed moderate antifungal activity against the growth of both the fungi.

## Experimental procedures

**General Information**: The melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. The infrared spectra were recorded as KBr pellets on Perkin Elmer 1000 unit. $^{1}$H, $^{13}$C, and $^{31}$P-NMR spectra were recorded on a Varian AMX 400 MHz NMR instrument operating at 400 MHz for $^{1}$H, 100.56 MHz for $^{13}$C and 161.7 MHz for $^{31}$P. All the compounds were dissolved in chloroform-d and chemical shifts were referenced to tetramethylsilane (TMS) ($^{1}$H, $^{13}$C) and 85% $H_3PO_4$ ($^{31}$P). Microanalysis data were obtained from Central Drug Research Institute, Lucknow, India. Toluene

procured from S.D. Fine Chem. Ltd., Boisar, India, was dried over anhydrous calcium chloride followed by sodium wire and distilled before use. The other solvents were obtained from S.D. Fine Chem. Ltd., Boisar, India and Qualigens Fine Chemicals, Mumbai, India and were used after purifying by the established procedures. [19]

Phosphorus oxychloride was procured from Ubichem Ltd., England, whereas, Phosphorus trichloride was procured from Spectrochem, Mumbai, India and used without further purification. Triethylamine obtained from S.D.Fine Chem. Ltd., Boisar, India was dried over potassium hydroxide pellets and distilled. 2,2′-Dihydroxybenzophenone and 2,2′-dihydroxybiphenol were purchased from Sigma-Aldrich Chemical Company, Inc. USA and used without further purification.

### Preparation of 2-chloroethylphosphonic dichloride (2a)

A mixture of phosphorus trichloride (34.4 g, 0.25 mole), anhydrous aluminum chloride (33.4 g, 0.25 mol) and 1,2-dichloroethane (24.8 g, 0.25 mole) was refluxed in a three-necked round bottomed flask with stirring till all the $AlCl_3$ dissolved. After cooling to −5 to 0 °C, 300 mL of methylene chloride was added slowly from a dropping funnel with stirring and then water (45.0 g, 2.5 mol) was added dropwise at −10°C with vigorous stirring. After removal of aluminum salts, the solvent was distilled off and the residual liquid was removed under reduced pressure, (bp 100 °C / 20 mm), to give a colorless liquid (yield, 15.0 g).[13]

### Bis(2-chloroethyl)phosphoramidic dichloride (2b)

Triethylamine (20.2 g, 0.2 mole) in dry toluene (75 mL) was added dropwise to a stirred suspension of bis(2-chloroethyl)amine hydrochloride (17.8 g, 0.1 mole) and phosphorus oxychloride (15.3 g, 0.1 mole) in dry toluene (150 mL) under inert atmosphere in a three-necked round bottomed flask (500 mL), equipped with reflux condenser. After completion of the addition, the reaction mixture warmed to reflux, filtered and the filtrate was subjected to flash evaporation. The residue obtained was purified by vacuum distillation under reduced pressure to yield 19.5 g (75%) of compound **2a**, bp 126–129°C/1.5 mm.[14]

### General procedure for cyclocondensation reactions (3a–b and 5a–b)

A solution of dichloride **2a–b** (0.01 moles) in dry toluene (20 mL) was added over a period of 20 min to a stirred solution of 2,2′-dihydroxybenzophenone, **1** or 2,2′-dihydroxybiphenol, **4** (0.01 moles) and triethylamine (0.02 moles) in dry toluene (50 mL) at 0 °C. After completion of the addition, temperature of the reaction mixture was raised to 45–50 °C and stirred for 5–6 h. The progress of the reaction was monitored by TLC analysis (EtOAc-Hex, 1:3). The precipitated triethylamine hydrochloride was filtered and then filtrate was evaporated in a rotaevaporator under vacuum. The residue obtained was washed with water followed by chilled 2-propanol. Colorless crystals were obtained by recrystallization of the crude product from 2-propanol. The synthetic and analytical data of all the compounds (**3a–b, 5a–b**) provided.

### 6-(2-Chloroethyl)-12-oxo-dibenzo[d,g][1,3,2] dioxaphosphocin 6-oxide (3a)

Yield: 58%. m.p: 152–154 °C. IR data (KBr): 1211 (P = O), [(P)-O-$C_{aromatic}$]: 993 (P-O), 1149 (O-C), 1627 (C = O) $cm^{-1}$. $^1$H NMR ($CDCl_3$): $\delta$ 6.80–7.52 (m, 8H), 2.03–2.23 (m, 2H, $PCH_2$), 3.33–3.50 (m, 2H, $CH_2Cl$). **$^{13}$C NMR ($CDCl_3$)**: $\delta$ 132.6 (C-1&11), 130.2 (C-2&10), 133.9 (C-3&9), 121.9 (C-4&8), 146.6 (*d*, $^2J_{POC}$ = 9.5 Hz, C4a&7a,), 125.7 (C-11a&12a), 199.9 (C-12), 30.5 (*d*, $^1J_{PC}$ = 140.3 Hz, P$\underline{C}H_2$), 36.7 ($\underline{C}H_2Cl$). **$^{31}$P NMR (85% $H_3PO_4$)**: 42.7 ppm. **Anal. Calcd**. for $C_{15}H_{12}O_4PCl$: C 55.84, H 3.75; **Found**: C 55.69, H 3.62

### 6-Bis(2-chloroethyl)amino-12-oxo-dibenzo[d,g][1,3,2] dioxaphosphocin 6-oxide (3b)

Yield: 62%. m.p: 128–130 °C. IR data (KBr): 1290 (P = O), [(P)-O-$C_{aromatic}$]: 945 (P-O), 1207 (O-C), 1636 (C = O) $cm^{-1}$. $^1$H NMR ($CDCl_3$): $\delta$ 7.27–8.10 (m, 8H), 3.18–3.29 (m, 4H, $N(CH_2)_2$), 3.53–3.58 (m, 4H, $(CH_2Cl)_2$). **$^{13}$C NMR ($CDCl_3$)**: $\delta$ 133.1 (C-1&11), 132.1 (C-2&10), 134.9 (C-3&9), 124.3 (*d*, $^3J_{POCC}$ = 2.9 Hz, C-4&8), 148.2 (*d*, $^2J_{POC}$ = 8.8 Hz, C4a&7a,), 127.1 (C-11a&12a), 188.1 (C-12), 42.0 ($N(\underline{C}H_2)_2$), 50.4 (*d*, $^3J_{PN\text{-}2C}$ = 2.3 Hz, $(\text{-}\underline{C}H_2Cl)_2$). **$^{31}$P NMR (85% $H_3PO_4$)**: 20.5 ppm. **Anal. Calcd**. for $C_{17}H_{16}NO_4PCl_2$: C 51.02, H 4.03; **Found**: C 50.88, H 3.97. **EI-MS (70 eV), *m/z* (%)**: 399 (1.2, $M^+$.), 366 (1.2), 364 (2.5), 352 (32.5), 350 (100), 288 (13.7), 259 (15), 215 (3.7), 198 (3.7), 168 (12.5), 151 (7.5), 139 (13.7), 124 (21.2), 109 (8.7), 92 (18.7).

### 6-(2-Chloroethyl) dibenzo[d,f][1,3,2]-dioxaphosphepin 6-oxide (5a)

Yield: 62%. m.p: 97–99 °C. IR data (KBr): 1299 (P = O) $cm^{-1}$. $^1$H NMR ($CDCl_3$): $\delta$ 7.26–7.56 (m, 8H), 2.53–2.64 (m, 2H, $PCH_2$), 3.85–3.94 (m, 2H, $CH_2Cl$). **$^{13}$C NMR ($CDCl_3$)**: $\delta$ 130.2 (C-1&11), 126.6 (C-2&10), 130.3 (C-3&9), 121.4 (*d*, $^3J_{POCC}$ = 3.4 Hz, C-4&8), 128.6 (C-12&13), 147.4 (*d*, $^2J_{POC}$ = 9.2 Hz, C4a&7a,), 28.0 (*d*, $^1J_{PC}$ = 131.7 Hz, P$\underline{C}H_2$), 35.7 ($\underline{C}H_2Cl$). **$^{31}$P NMR (85% $H_3PO_4$)**: 25.3 ppm. **Anal. Calcd**. for $C_{14}H_{12}O_3PCl$: C 57.06, H 4.10; **Found**: C 56.92, H 3.99.

### 6-Bis(2-chloroethyl)amino dibenzo[d,f]-[1,3,2]dioxaphosphepin 6-oxide (5b)

Yield: 68%. m.p: 98–100 °C. IR data (KBr): 1312 (P = O) $cm^{-1}$. $^1$H NMR ($CDCl_3$): $\delta$ 7.33–7.57 (m, 8H), 3.36–3.45 (m, 4H, $N(CH_2)_2$), 3.58–3.60 (m, 4H, $(CH_2Cl)_2$). **$^{13}$C NMR ($CDCl_3$)**: $\delta$ 130.0 (C-1&11), 126.5 (C-2&10), 130.1 (C-3&9), 121.6 (*d*, $^3J_{POCC}$ = 4.6 Hz, C-4&8), 127.9 (C-12&13), 148.0 (*d*, $^2J_{POC}$ = 9.1 Hz, C4a&7a,), 41.9 ($N(\underline{C}H_2)_2$), 49.3 (*d*, $^3J_{PN\text{-}2C}$ = 3.4 Hz, $(\text{-}\underline{C}H_2Cl)_2$). **$^{31}$P NMR (85% $H_3PO_4$)**: 12.3 ppm. **Anal. Calcd**. for $C_{16}H_{16}NO_3PCl_2$: C 51.63, H 4.33; **Found**: C 51.48, H 4.26. **EI-MS (70 eV), *m/z* (%)**: 399 (1.2, $M^+$.), 366 (1.2), 364 (2.5), 352 (32.5), 350 (100), 288 (13.7), 259 (15), 215 (3.7), 198 (3.7), 168 (12.5), 151 (7.5), 139 (13.7), 124 (21.2), 109 (8.7), 92 (18.7).

## Conclusion

In conclusion, the biologically active eight- and seven-membered organophosphorus heterocyclic compounds were synthesized successfully via cyclocondensation procedure in high yield. All the synthesized compounds have shown significant activity in their antimicrobial studies.

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