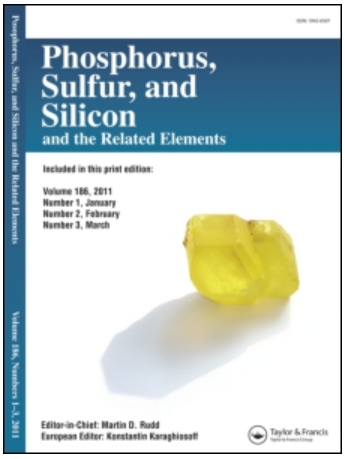

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PREPARATION AND CYCLIZATION OF PHOSPHONYL CHLOROVINYLALDEHYDE

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PREPARATION AND CYCLIZATION OF PHOSPHONYL CHLOROVINYLALDEHYDE

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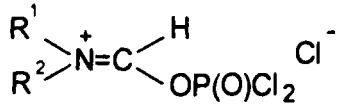
β-Phosphonyl-β-chlorovinylaldehyde was synthesized through chloroformylation of the Vilsmeier reagent with acetylphosphonate, and reacted with hydrazine, oxyammonia, formamidine, and guanidine to give the corresponding phosphonyl heterocyclic compounds.

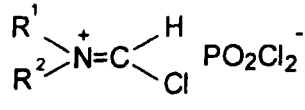
Keywords: Chloroformylation; β-phosphonyl-β-chlorovinylaldehyde; Vilsmeier reagent; cyclization; phosphonyl heterocyclic compounds

INTRODUCTION

The Vilsmeier reagent, $HCONR^1R^2/POCl_3$, has found extensive application in the synthesis of aldehyde derivatives and formamidines[1]. The reagent is an equilibrium mixture of two iminium salts, the more reactive being the beta-phosphoryliminium chloride (A) rather than the beta-chloroiminium phosphate (B)[2].



(A)



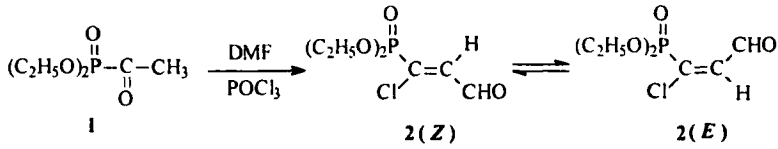
(B)

* Correspondence Author.

In the literature, we found little application of the Vilsmeier reagent in the synthesis of organophosphorus compounds,[3–7] and no application in the synthesis of phosphonyl heterocyclic compounds. Furthermore, although some synthetic approaches to phosphonyl heterocyclic compounds have been reported,[8–12] there is still much active research in this area, owing to their potential biological activity. This promoted us to investigate the applicability of the Vilsmeier reagent ($DMF/POCl_3$) for preparation and cyclization of phosphonyl chlorovinylaldehyde

RESULTS AND DISCUSSION

Recently we have discovered a practical and general method for the synthesis of β-phosphonyl-β-chlorovinylaldehyde **2** using the general procedure of chloroformylation.[13–15] The action of $DMF\text{-}POCl_3$ on acetylphosphonate **1** at 30°C led stereospecificly to (*Z*)-β-phosphonyl-β-chlorovinylaldehyde **2** (54.6% yield). A little of *Z*-isomer could converted to *E*-isomer, the ratio of *Z/E* is 93/7 when pure *Z* isomer was refluxed in ethyl acetate for about 10 h, while most of E-isomer could be converted to Z-isomer under the same condition, and the ratio of *Z/E* is almost the same as the former. The equilibration of the geometrical isomers ($Z \rightleftharpoons E$) takes place in each case, and the ratio of *Z/E* (93/7) is almost the same. Pure *Z* and *E* isomers were separated by TLC, and their configuration was deduced from the coupling constant between the phosphorus nucleus and the vinylic proton.[16,17] The coupling constant of the *E* isomer is far larger than that of the *Z* isomer. ^{31}P NMR spectroscopy shows that the *E* isomer is found at a higher field than the *Z* isomer, and the difference is approximately ~2.5 ppm (Scheme 1).

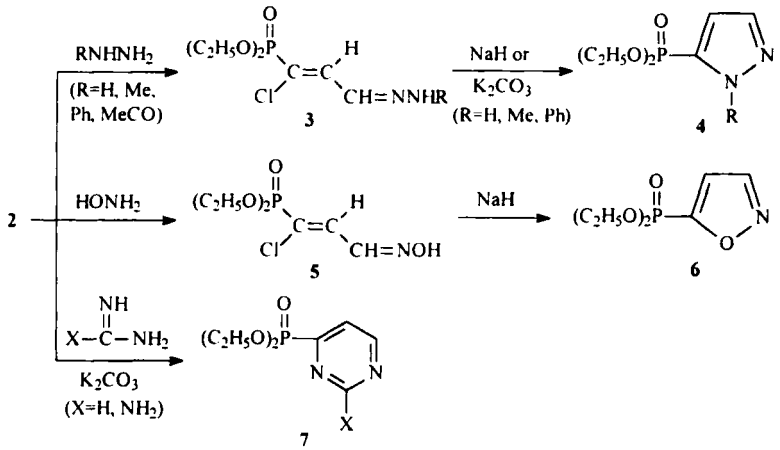


1 **2(*Z*)** **2(*E*)**

SCHEME 1

β-Phosphonyl-β-chlorovinylaldehyde **2** is a novel type of a versatile intermediate compound for the synthesis of phosphonyl compounds and

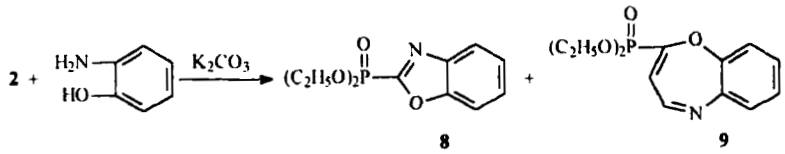
phosphonyl heterocyclic compounds. The reaction of β-phosphonyl-β-chlorovinylaldehyde **2** with hydrazine, oxyammonia, formamidine, and guanidine, gave phosphonyl pyrazoles **4**, phosphonyl isoxazole **6**, phosphonyl pyrimidines **7** respectively in presence of NaH or K_2CO_3. Hydrazones **3** (R = Me, Ph) and oxime **5** could be separated or detected by GCD in absence of NaH or K_2CO_3. The intermediates hydrazones **3** (R = Me, Ph) and oxime **5** in presence of NaH or K_2CO_3 could further produce the corresponding phosphonyl pyrazoles **4**, or phosphonyl isoxazole **6** respectively. Hydrazones **3** (R = MeCO) under the same condition was difficult to yield the corresponding pyrazole 4 because the electron withdrawing effect of the acetyl group reduced the nucleophilicity of nitrogen atom (Scheme 2). These intermediates and phosphonyl heterocyclic compounds were characterized by their ^1H, ^{31}P NMR spectra and MS data.



SCHEME 2

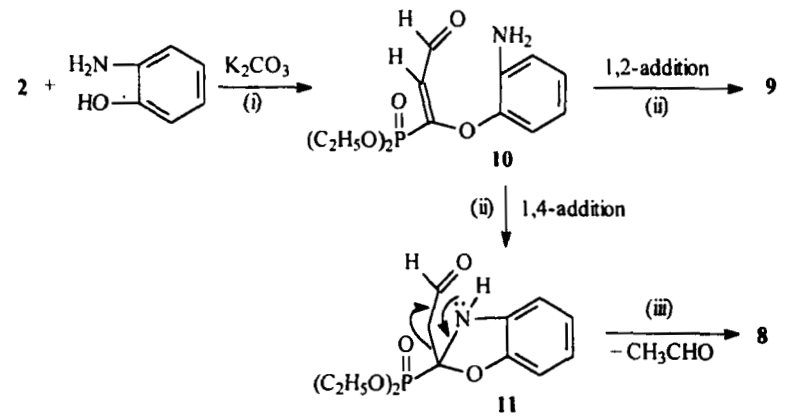
But β-phosphonyl-β-chlorovinylaldehyde **2** reacted with o-aminophenol in presence of K_2CO_3 to give 2-phosphonyl benzoxazole **8** (45.4% yield) in addition to the expected product 2-phosphonyl benzoxepine **9** (15.7% yield) (Scheme 3). Phosphonyl heterocyclic compounds **8** and **9** were characterized by their ^1H, ^{31}P NMR spectra and MS data.

A plausible pathway for this reaction (Scheme 3) would consist of three steps: in the first step, nucleophilic substitution of the oxygen atom of



SCHEME 3

o-aminophenol with chlorine atom on β-C of phosphonylchlorovinylaldehyde **2** forms an intermediate **10**; in the second step, the competition reaction of 1,4- and 1,2- additions of the nitrogen atom gives an intermediate **11** and 2-phosphonyl benzoxepine **9** respectively; in the last step, the intermediate **11** with elimination of CH_3CHO leads to 2-phosphonyl benzoxazole **8** (Scheme 4).



SCHEME 4

The reactions of other ketophosphonates with the Vilsmeier reagent and the synthesis of corresponding phosphonyl heterocyclic compounds are under investigation.

EXPERIMENTAL SECTION

^1H and ^{31}P NMR spectra were taken on a BRUKER AC-P200 Spectrometer with $CDCl_3$ as solvent. ^1H chemical shifts are reported in ppm relatives

to internal tetramethylsilane. ^{31}P chemical shifts are reported in ppm relatives to 85 % phosphoric acid (external). Mass spectra were recorded on a Hewlett-Packard 5988 instrument.

General procedure for preparation and cyclization of phosphonyl chlorovinylaldehyde 2

DMF (0.12mol) in 5ml CH_2Cl_2 was added dropwise to $POCl_3$ (0.12mol) in 15ml CH_2Cl_2at 5~10°C under nitrogen atmosphere, then the mixture was stirred at 30°C for 30 minutes. Ketophosphonate **1** (0.02mol) in 5ml CH_2Cl_2 was added dropwise at 15°C. The reaction mixture was stirred at 35°C for 30h. The mixture was poured onto 150g crushed ice, and stirred at room temperature for 3h. The aqueous layer was extracted with dichloromethane (3 × 30 ml). The combined organic layers were washed with 50 ml saturated brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was isolated by column chromatography or preparative chromatography on silica gel using ethyl acetate : petroleum ether (1 : 6 or 3 : 1) as eluent or developing solvent. *E* and *Z* isomers of phosphonylchlorovinylaldehyde **2** could be obtained respectively. $RNHNH_2$ (R = Ph, MeCO), or o-aminophenol (0.5mmol) in CH_2Cl_2 (0.5 ml) was added into compound **2** (0.5mmol) in CH_2Cl_2 (0.5 ml) at 20°C. The reaction mixture was kept at 30°C for 2h and isolated by preparative chromatography (using ethyl acetate : petroleum ether (3 : 1) as developing solvent) to afford hydrazone **3** (R = Ph, MeCO), or phosphonyl heterocyclic compounds **8** and **9**. The reaction mixture of hydrazone **3** (R = Ph)(0.25mmol) in presence of NaH (0.25 mmol) was stirred at 30°C for 2h and isolated by preparative chromatography (using ethyl acetate : petroleum ether (3 : 1) as developing solvent) to afford phosphonyl pyrazole **4**.

Diamine hydrate, methylhydrazine sulfate, oxyammonia hydrochloride, formamidine acetate, or guanidine hydrochloride (0.5mmol) in water (2ml), was added to phosphonylchlorovinylaldehyde **2** (0.5mmol) in CH_2Cl_2 (2ml) at 20°C, then K_2CO_3 (0.5mmol) in water (2ml) was added dropwise. The reaction mixture was kept at 30°C for 2~3h. The aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were washed with 20 ml saturated brine, dried over Na_2SO_4, filtered and concentrated. The residue was isolated by preparative chromatography on silica gel using ethyl acetate : petroleum ether

(3 : 1) as developing solvent to afford corresponding phosphonyl heterocyclic compounds **4** or **7**.

2(*Z*): NMR($CDCl_3$): δ_H 10.12 (d, $^3J_{HH}$ = 6.69Hz, 1H, C<u>H</u>O), 6.91 (dd, $^3J_{HH}$ = 6.69Hz, $^3J_{HP}$ = 13.38 Hz, 1H, C=C<u>H</u>), 4.20(m,4H,2C<u>H</u>$_2$), 1.37(t, $^3J_{HH}$ = 7.10Hz,6H,2C<u>H</u>$_3$); $\delta\ ^{31}P$ 6.37.

2(*E*): NMR($CDCl_3$): δ_H 10.46 (d, $^3J_{HH}$ = 7.30Hz, 1H, C<u>H</u>O), 6.79 (dd, $^3J_{HH}$ = 7.30Hz, $^3J_{HP}$ = 35.44 Hz, 1H, C=C<u>H</u>), 4.23(m, 4H, 2C<u>H</u>$_2$), 1.38(t, $^3J_{HH}$ = 7.06Hz, 6H, 2C<u>H</u>$_3$), $\delta\ ^{31}P$ 3.93. Total yield of **2(*E*)** and **2(*Z*)**: 54.6%. **MS**, m/z(rel intensity): 228(M+2, 22), 226(M^+, 65). Anal. Calcd. for $C_7H_{12}ClO_4P$: C, 37.10; H, 5.34. Found: C, 37.54; H, 5.70.

3(R = Ph): NMR($CDCl_3$): δ_H 8.43 (br, N<u>H</u>), 7.72 (d, $^3J_{HH}$ = 9.9Hz, 1H, N=C*H*,), 7.45 (dd, $^3J_{HP}$ = 13.04 Hz, $^3J_{HH}$ = 9.9Hz, 1H, C=C<u>H</u>), 4.15(m, 4H, 2C<u>H</u>$_2$), 1.35(t, $^3J_{HH}$ = 7.03Hz, 6H, 2C<u>H</u>$_3$), $\delta\ ^{31}P$ 10.44; yield: 72.5%.

3(R = MeCO): NMR($CDCl_3$): δ_H 8.43 (br, N<u>H</u>), 7.72 (d, $^3J_{HH}$ = 9.9Hz, 1H, N=C*H*,), 7.45 (dd, $^3J_{HP}$ = 13.04 Hz, $^3J_{HH}$ = 9.9Hz, 1H, C<u>H</u>=C), 4.14(m, 4H, 2CH_2), 1.34(t, $^3J_{HH}$ = 7.28Hz, 6H, 2CH_3), $\delta\ ^{31}P$ 8.77; yield: 77.6%. **MS** (m/z): 284 (M+2, 12), 282(M^+, 33).

4(R = H): NMR($CDCl_3$): δ_H 8.06 (s,1H,N=C<u>H</u>), 6.80 (s,1H,C=C<u>H</u>), 8.26(br,NH), 4.16(m, 4H,2C<u>H</u>$_2$), 1.35(t, $^3J_{HH}$ = 6.90Hz,6H,2C<u>H</u>$_3$), $\delta\ ^{31}P$ 7.53; yield: 50.6%. **MS** (m/z): 204(M^+). Anal. Calcd. for $C_7H_{13}N_2O_3P$: C, 41.18; H, 6.37; N, 13.73. Found: C, 41.26; H, 6.48; N, 13.64.

4(R = Me): NMR($CDCl_3$): δ_H 7.46 (s,1H,N=C<u>H</u>), 6.74(s,1H,C=C<u>H</u>), 4.12(m,4H,2C<u>H</u>$_2$), 2.96(s,3H,NC<u>H</u>$_3$), 1.33(dt, $^3J_{HH}$ = 7.06Hz, $^3J_{HP}$ = 3.39Hz, 6H, 2CH_3), $\delta\ ^{31}P$ 5.66; yield: 60.6%. **MS** (m/z): 218 (M^+). Anal. Calcd. for $C_8H_{15}N_2O_3P$: C, 44.04; H, 6.88; N, 12.84. Found: C, 44.30; H, 6.96; N, 12.62.

4(R = Ph): NMR($CDCl_3$): δ_H 7.72 (s, 1H, N=C<u>H</u>), 6.95 (s, 1H, C=C<u>H</u>), 4.01(m, 4H, 2C<u>H</u>$_2$), 1.19(t, $^3J_{HH}$ = 7.04Hz, 6H, 2C<u>H</u>$_3$), $\delta\ ^{31}P$ 5.66; yield: 66.4%. **MS** (m/z): 280 (M^+). Anal. Calcd. for $C_{13}H_{17}N_2O_3P$: C, 55.71; H, 6.07; N, 10.00. Found: C, 55.98; H, 6.47; N, 9.78.

5: NMR($CDCl_3$): δ_H 8.19 (d, 1H, $^3J_{HH}$ = 10.95Hz, N=C<u>H</u>), 8.13 (dd, 1H, $^3J_{HP}$ = 21.9Hz, $^3J_{HH}$ = 10.95Hz, C=C<u>H</u>), 11.00 (br, 1H, O<u>H</u>), 4.15(m, 4H, 2C<u>H</u>$_2$), 1.35(t, $^3J_{HH}$ = 7.12Hz, 6H, 2C<u>H</u>$_3$), $\delta\ ^{31}P$ 9.53; yield: 74.4%. **MS** (m/z): 243(M+2, 167), 241(M^+, 522). **6: NMR($CDCl_3$)**: δ_H 8.13(dd, 1H, $^3J_{HH}$= 9.38Hz, $^4J_{HP}$ = 2.1Hz, N=C<u>H</u>), 7.88(dd, 1H, $^3J_{HP}$ = 14.08Hz, $^3J_{HH}$= 9.38Hz, C=C<u>H</u>), 4.11(m, 4H, 2C<u>H</u>$_2$), 1.34(t, $^3J_{HH}$ = 7.00Hz, 6H, 2C<u>H</u>$_3$), $\delta\ ^{31}P$ 9.53; yield: 65.8%. **MS** (m/z): 205 (M^+). Anal. Calcd. for

$C_7H_{12}NO_4P$: C, 40.98; H, 5.85; N, 6.83. Found: C, 40.76; H, 5.60; N, 6.81.

7(X = H): NMR($CDCl_3$): δ_H 7.39(s, 1H, N=C<u>H</u>-N), 7.34(dd, 1H, $^4J_{HP}$= 21.87Hz, $^3J_{HH}$ = 21.87Hz, $^3J_{HH}$ = 12.70Hz, N=C<u>H</u>), 6.41(d,1H, $^3J_{HH}$ = 12.70Hz, C=C<u>H</u>), 4.14(m, 4H, 2C<u>H_2</u>), 1.35(t, $^3J_{HH}$ = 7.03Hz, 6H, 2C<u>H_3</u>), δ^{31}_P 8.29; yield: 74.4%. **MS** (m/z): 216 (M^+). Anal. Calcd. for $C_8H_{13}N_2O_3P$: C, 44.44; H, 6.02; N, 12.96. Found: C, 44.26; H, 5.98; N, 12.78.

7(X = NH_2): NMR($CDCl_3$): δ_H 7.39(t, 1H, $^3J_{HH} = {}^4J_{HP}$ = 14.35Hz, N=C<u>H</u>), 6.73(d, 1H, $^3J_{HH}$ = 14.35Hz, C=C<u>H</u>), 5.62(br,2H, N<u>H_2</u>), 4.13(m, 4H, 2C<u>H_2</u>), 1.35(m, 6H, 2C<u>H_3</u>), δ^{31}_P 8.25; yield: 57.5%. **MS**(m/z): 231 (M^+). Anal. Calcd. for $C_8H_{14}N_3O_3P$: C, 41.56; H, 6.06; N, 18.18. Found: C, 41.24; H, 6.12; N, 18.02.

8: NMR($CDCl_3$): δ_H 6.8~7.2(m, 4H, C_6<u>H_4</u>), 4.22(m, 4H, 2C<u>H_2</u>), 1.30(t, $^3J_{HH}$ = 7.16Hz, 6H, 2C<u>H_3</u>), δ^{31}_P −5.33; yield: 45.4%. **MS** (m/z): 255 (M^+). Anal. Calcd. for $C_{11}H_{14}NO_4P$: C, 51.76; H, 5.49; N, 5.49. Found: C, 51.60; H, 5.32; N, 5.28.

9: NMR($CDCl_3$): δ_H 7.55 (d, $^3J_{HH}$ = 16.68Hz, N=C<u>H</u>), 7.44 (d, $^3J_{HH}$ = 16.68Hz, C=C<u>H</u>), 6.70~7.23 (m, 4H,C_6<u>H_4</u>), 4.11(m, 4H, 2C<u>H_2</u>), 1.34(t, $^3J_{HH}$ = 6.99Hz, 6H, 2C<u>H_3</u>), δ^{31}_P 16.32; yield: 15.7%. **MS** (m/z): 281 (M^+). Anal. Calcd. for $C_{13}H_{16}NO_4P$: C, 55.52; H, 5.69; N, 4.98. Found: C, 55.28; H, 5.35; N, 4.68.

Acknowledgements

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