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NEW STRATEGY FOR THE SYNTHESIS OF PHOSPHONYL PYRAZOLES

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Abstract : Phosphonyl hydrazones react with DMF/$POCl_3$ to afford 3-phosphonyl pyrazoles. Phosphonyl methylene hydrazones react with DMF/$POCl_3$ to provide 4-phosphonyl pyrazoles. 5-Phosphonyl pyrazoles are obtained from the reaction of phosphonyl chlorovinylaldehydes with phenylhydrazine.

Pyrazoles have recently been exploited as herbicides, acaricides and insecticides. Many compounds have been produced commercially [1]. To a large degree, the biological activity is attributed to the nature of substituents in pyrazole ring. Furthermore, it is known that the phosphonyl group could regulate important biological functions[2]. It is conceivable that molecular modification of pyrazole rings introducing organophosphorus functionalities might be expected to exhibit

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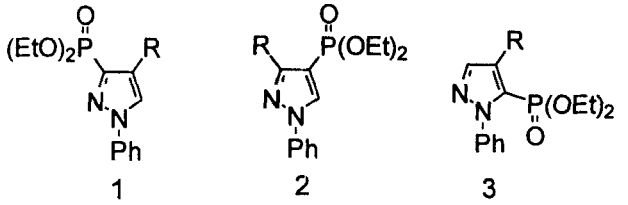
potential pesticide activity. Although some synthetic approaches to phosphonyl pyrazoles have been reported[3], there is still much active research in this area.

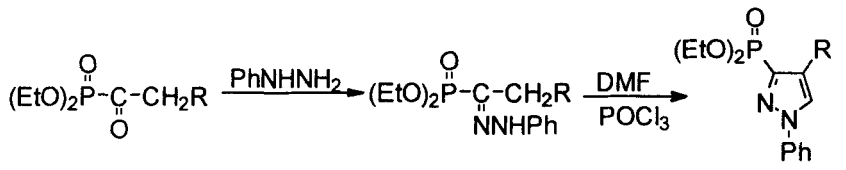
In this note we report about an efficient and facile strategy for the synthesis of phosphonyl pyrazoles. It is necessary to develop respective synthetic approachs, depending on the position of the phosphonyl group in pyrazole ring.



1 2 3

a.R=H; b.R=Me; c.R=Ph

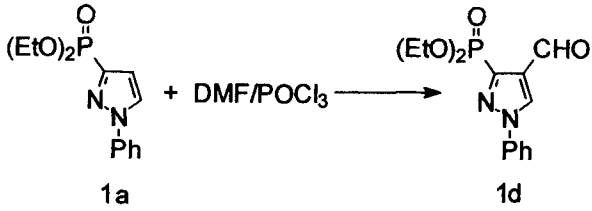
Compounds **1-3** were prepared as representative examples of phosphonyl pyrazoles. According to the method of synthesis of pyrazoles from hydrazones with the Vilsmeier reagent[4], we designed a similar route for preparation of phosphonyl pyrazoles. The reaction of phosphonyl hydrazones **5** with the Vilsmeier reagent (DMF/$POCl_3$) in equimolar ratio affords 1-phenyl-3-diethoxy phosphonyl pyrazoles **1** (**Scheme 1**).



4 5 1

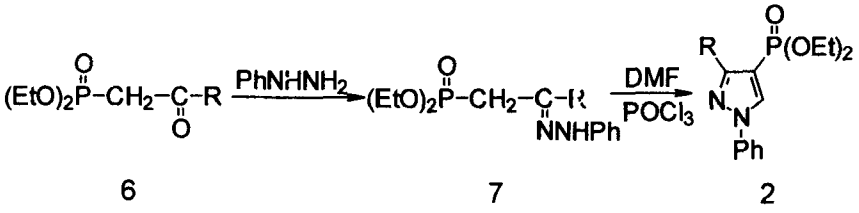
Scheme 1

When R = H, the byproduct of this reaction is compound **1d** because another mole of the Vilsmeier reagent (DMF/$POCl_3$) reacts further with product **1** (R=H) in the manner of formylation[4a,d,e](**Scheme 2**).



Scheme 2

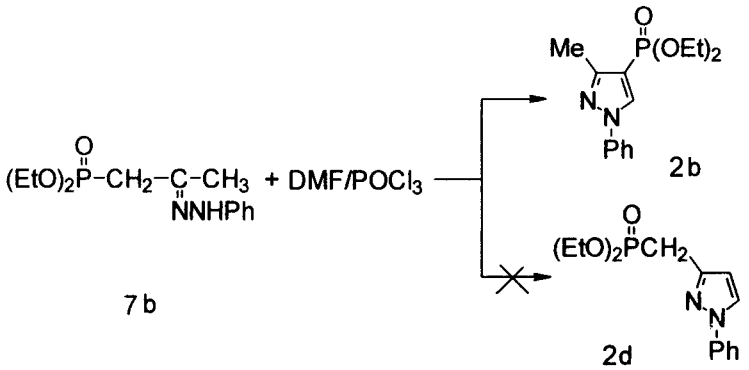
1-Phenyl-4-diethoxy phosphonyl pyrazoles **2** are obtained by reaction of phosphonyl methylene hydrazones **7** with DMF/$POCl_3$ (**Scheme 3**).



Scheme 3

The hydrazones should have two isomers in theory. However, when the phosphonyl hydrazones **5** and the phosphonyl methylene hydrazones **7** were prepared, only one isomer could be detected. This isomeric configuration was not assigned, but it was readily converted to the corresponding pyrazoles in good yield.

In the case of the phosphonyl methylene hydrazone **7b** ($R=CH_3$), 4-diethoxyphosphonyl pyrazole **2b** was obtained instead of 3-diethoxy phosphonyl methylene pyrazole **2d** (**Scheme 4**).

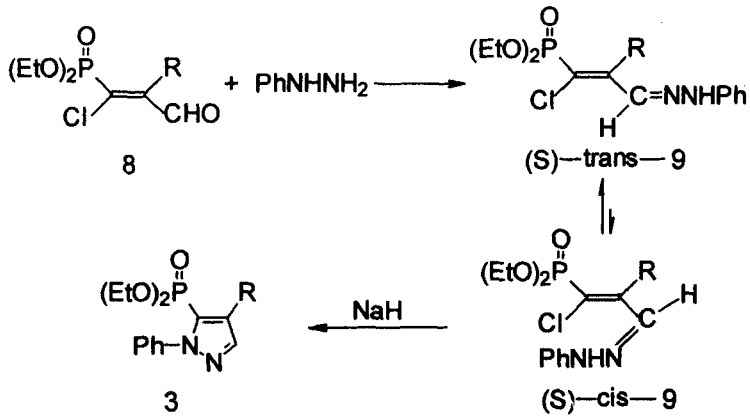


Scheme 4

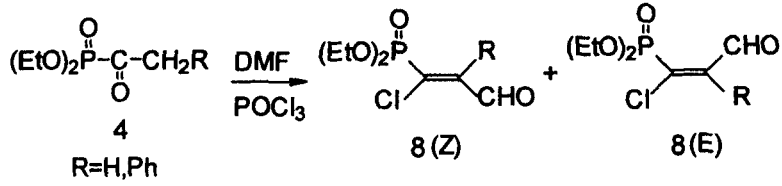
This may be rationalized that the electrophilic substitution of the Vilsmeier reagent on the methylene group took place more readily than on the methyl group because of the electron withdrawing effect of the phosphonyl group.

1-Phenyl-5-diethoxyphosphonyl pyrazoles **3** were readily prepared by the action of **8** on phenylhydrazine in presence of sodium hydride (**Scheme 5**). Hydrazone **9** (R=H) could be separated in absence of sodium hydride. The (S)-trans conformation of **9** is more stable than the (S)-cis conformation at room temperature. However in the presence of sodium hydride (S)-trans **9** can be cyclized to give **3** via (S)-cis **9** because of the low rotational energy barrier between C_1 and C_2 of **9**.

The intermediates **8** were obtained from the reaction of ketophosphonates **4** with the Vilsmeier reagent ($DMF/POCl_3$) (**Scheme 6**).



Scheme 5



Scheme 6

This reaction led stereoselectively to the products **8** (R=H) with the (Z)-configuration along with a small amount of the (E)-isomer (Z/E = 93/7). The E or Z configuration was obtained from the coupling constant between phosphorus nucleus and double bond proton. The coupling constant of E isomer is far larger than that of Z isomer. ^{31}P NMR shows that the Z isomer is found at a lower field than the E isomer. The difference is approximately 2.5 ppm. In addition, aldehydic proton shift of Z isomer is found at a lower field than that of E isomer.

Moreover, when the pure Z or E isomers is refluxed in ethyl acetate about 10 h respectively, the equilibration of the geometrical isomers (Z $\rightleftharpoons$ E)

takes place, and the ratio of Z/E (93/ 7) is almost the same in each case. No matter which Z or E isomer the compound **8** (R=H) is, it always reacts with phenylhydrazine to give 1-phenyl-5-diethoxy phosphonyl-4-substituted pyrazoles **3**.

In summary, we have developed a convenient method for preparing 3-, 4-, or 5-phosphonyl pyrazoles respectively. Other aspects of this process including N-alkylation and R group variants are under investigation.

EXPERIMENTAL

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

General Procedure for Preparation of Phosphonyl pyrazoles 1 or 2:

$POCl_3$ (0.25mol) was added dropwise to DMF (10ml) with stirring under nitrogen atmosphere at 0～10 ℃ .The mixture was stirred at room temperature for 0.5h. Then phosphonyl hydrazones **5** or **7** (0.05mol) were dropped into the mixture at 0～10℃. The reaction was kept at 20～80℃ for 5～10h. After completion of the reaction, the reaction mixture was directly separated by plate chromatography to give the corresponding phosphonyl pyrazoles **1a,b,c** or **2a,b,c**. If the reaction mixture was hydrolyzed first, **1a** and **1d** can be obtained respectively by preparative chromatography. We used ethyl acetate and petroleum ether (4:1) as eluent.

1a: Mobile liquid, **NMR($CDCl_3$):** δ_H 6.55(d, 1H, C-CH=C), 7.78(d, 1H, N-CH=C), δ_P 8.36, yield(%): 30.3. **MS** (m/z): 280

1b: Mobile liquid, **NMR($CDCl_3$):** δ_H 7.76 (s,1H,N-CH), δ_P 10.89, yield(%): 61.2. **MS** (m/z): 294

1c: Viscous liquid, **NMR($CDCl_3$):** δ_H 8.05(s,1H,N-CH), δ_P 10.28, yield(%): 72.5. **MS** (m/z): 356

1d: Mobile liquid, **NMR($CDCl_3$).** δ_H 8.51(s,1H,N-CH), 10.27(s,1H,CHO), δ_P 6.97; yield(%): 59.4. **MS** (m/z): 308

2a: Mobile liquid, **NMR($CDCl_3$):** δ_H 7.90(d,1H,N=CH), 7.92(d,1H,N-CH), δ_P 14.10, yield(%): 45.9. **MS** (m/z): 280

2b: Mobile liquid, **NMR($CDCl_3$):** δ_H 8.22(s,1H,N-CH), δ_P 14.46, yield(%): 80.7. **MS** (m/z): 294

2c: Viscous liquid, **NMR($CDCl_3$):** δ_H 8.46(s,1H,N-CH), δ_P 14.06, yield(%): 71.3. **MS** (m/z): 356

General Procedure for Preparation of Phosphonyl pyrazole 3:

DMF (0.12mol) in 5ml $CH_2Cl_2$was added dropwise to $POCl_3$ (0.12mol) in 15ml CH_2Cl_2 at 5～10℃ under nitrogen atmosphere, then the mixture was stirred at 30℃ for 30 minutes. Ketophosphonate **4** (0.02mol) in 5ml CH_2Cl_2 was added dropwise at 15℃. The reaction mixture was stirred at 35℃ 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 **8** could

be obtained respectively. $PhNHNH_2$ (0.5mmol) in CH_2Cl_2 (0.5 ml) was added into compound **8** (0.5mmol) in CH_2Cl_2(0.5 ml) at 20℃, followed with NaH (1mmol). The reaction mixture was kept at 30℃ for 2h and isolated by preparative chromatography (using ethyl acetate : petroleum ether (3 : 1) as developing solvent) to afford phosphonyl pyrazole **3a**. Hydrazone **9** (R=H) could be obtained in absence of NaH.

3a: Mobile liquid, **NMR($CDCl_3$):** δ_H 7.72 (s, 1H, N=CH), 6.95 (s, 1H, C-CH=C), δ_P 5.66, yield(%): 60.6. **MS** (m/z): 280

8(Z) (R=H): NMR($CDCl_3$): δ_H 10.14 (d, $^3J_{HH}$ = 6.79 Hz, 1H), 6.94 (dd, $^3J_{HH}$ = 6.79 Hz, $^3J_{HP}$ = 13.56 Hz, 1H), δ_P 6.37.

8(E) (R=H): NMR($CDCl_3$): δ_H 10.46 (d, $^3J_{HH}$ = 7.3, 1H, CHO), 6.79 (dd, $^3J_{HH}$ = 7.3 Hz, $^3J_{HP}$ = 35.44 Hz, 1H, C=CH), δ_P 3.93.

Total yield(%) of **8(E)** and **8(Z)**: 54.6. **MS** (m/z): 225 (M-1)

9 (R=H): NMR($CDCl_3$): δ_H 7.72 (d, 1H, N=CH, $^3J_{HH}$ = 9.9 Hz), 7.45 (dd, $^3J_{HP}$ = 10.44 Hz, $^3J_{HH}$ = 9.9 Hz, 1H,C-CH=C), 8.43 (br,1H, NH), δ_P 10.44, yield(%): 81.7. **MS** (m/z): 316

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