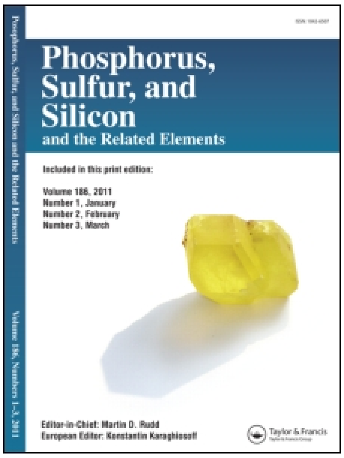

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The Reaction of Phenylhydrazine with Sterically Congested Stabilized Phosphorus Ylides in the Presence of Silica Gel Powder in Solvent-Free Conditions: A Novel Synthesis of Fully Substituted Pyrazole Derivatives

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*Reactions of sterically congested stabilized phosphorus ylides with phenylhydrazine in the presence of silica gel powder in solvent-free conditions proceed smoothly at 100° C to afford dialkyl 2-(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)-2-butenedioates in good yields. The structures of the products were deduced from their IR, ^1H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate* m/z *values. The ^1H NMR ($CDCl_3$) spectra of the compounds show the presence of two estereoisomers (**E** and **Z**) for each pyrazoles. The relative population of **E** and **Z** isomers were determined* via *their ^1H NMR spectra The reaction is fairly stereoselective.*

Keywords Phenylhydrazine; phosphorus ylide; pyrazole; silica gel; solvent-free conditions

INTRODUCTION

Pyrazole derivatives are in general well-known nitrogen-containing heterocyclic compounds, and various procedures have been developed for their syntheses.[1–5] The chemistry of pyrazole derivatives have been the subject of much interest due to their importance for various applications and their widespread potential and proven biological and pharmacological activities such as anti-inflammatory, antipyretic, analgesic, antimicrobial, antiviral, antitumor, antifungal, pesticidal, anticonvulsant, antihistaminic, antibiotics, anti-depressant, and CNS regulant properties.[2–11]

Organophosphorus compounds[12,13] have been extensively employed in organic synthesis as useful reagents as well as ligands in a number of transition metal catalysts.[14] Phosphorus ylides are a class of special

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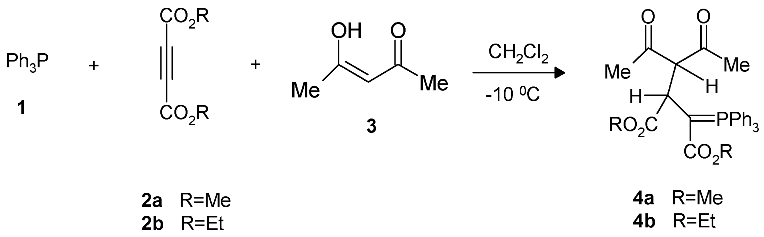
type of zwitterions, which bear strongly nucleophilic electron rich carbanions. The electron distribution around the $P^+–C^-$ bond and its consequent chemical implications had been probed and assessed through theoretical, spectroscopic, and crystallographic investigations[15]; They are excellent ligands and excel in their ligating functions the unstabilized ylides because of their ambidentate and chemically differentiating character. Proton affinity of these ylides can be used as a molecular guide to assess their utility as synthetic reagents and their function as ligands in coordination and organometallic chemistry.[14,16] The nucleophilicity at the ylidic carbon is a factor of essential mechanistic importance in the use of these ylides as Wittig reagents. Phosphorus ylides are important reagents in synthetic organic chemistry, especially in the synthesis of naturally occurring products, compounds with biological and pharmacological activity.[12,13] In recent years, we have established a one-pot method for the synthesis of stabilized ylides.[17–25]

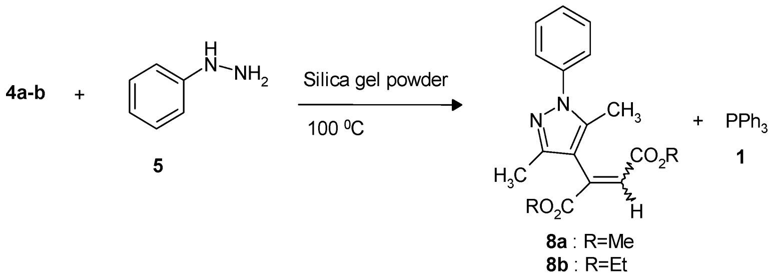
Environmentally friendly synthesis of organic compounds without using of organic solvents has come several steps closer in recent years.[26] Organic reactions using conventional organic solvents especially chlorinated hydrocarbons have posed a serious threat to the environment owing to their toxicity and volatile nature.[26] In this regard, solvent free catalytic organic reaction has received tremendous attention in recent times.[27] Silica gel as an additive promotes many condensation reactions in solvent-free conditions.[28,29] As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds,[30–32] we sought to develop a convenient preparation of fully substituted pyrazole derivatives **8a–b** (Scheme 1, Scheme 2 and Scheme 3).



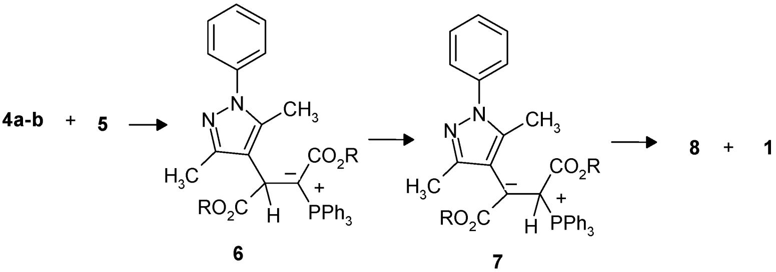
SCHEME 1

RESULTS AND DISCUSSION

Sterically congested stabilized phosphorus ylides **4a-b** were prepared based on previously reported procedure (Scheme 1).[25] The phenylhydrazine **5** and stabilized phosphorus ylides **4** in the presence of silica



SCHEME 2

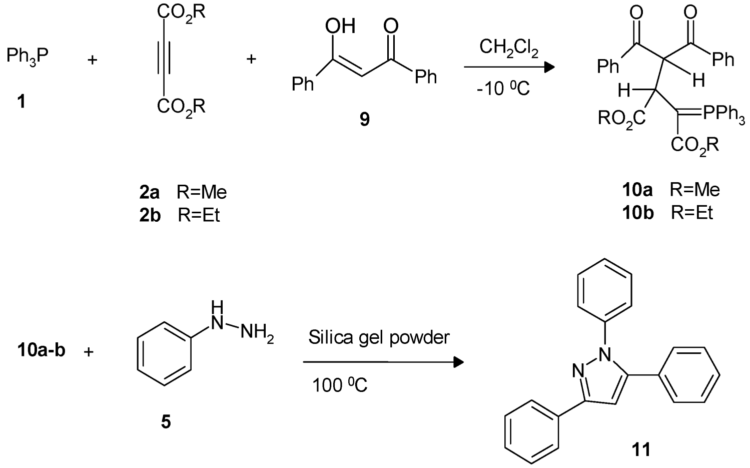


SCHEME 3

gel powder undergo a smooth 1:1 condensation reaction in solvent-free conditions at 100°C to produce fully substituted pyrazole derivatives **8** (Scheme 2). TLC indicated the formation of pyrazoles **8** and triphenylphosphine **1** on the silica gel surface. The reaction proceeds smoothly and cleanly under reaction conditions and no side reactions were observed. In the absence of the silica gel powder, the compounds **4** were not reacted with phenylhydrazine **5** under reaction conditions (100°C, 5 h) in the solvent-free system. The reaction also was not occurred in dichloromethane solutions after several days. The ^1H NMR ($CDCl_3$) spectra of compounds **8** show the presence of two estereoisomers (***E*** and ***Z***) for each pyrazoles **8**. The relative population of ***E*** and ***Z*** isomers were determined via their ^1H NMR spectra (See Experimental section). The reaction is fairly stereoselective. We have also used electron-poor hydrazine derivatives (such as benzohydrazide, isonicotinohydrazide and 2,4-dinitrophenylhydrazine) in this reaction, but no corresponding products **8** were observed and in the all cases decomposition of the starting materials were observed. Fairly week nucleophilicity of electron-poor hydrazine derivatives relative to the phenylhydrazine **5** may be plausible factor in the reduction of their reactivity toward this reaction.

The mechanism of the reaction between the phenylhydrazine **5** and stabilized phosphorus ylides **4** in the presence of silica gel powder in solvent-free conditions has not been established experimentally. However, a possible explanation is proposed in Scheme 3. The structures of the products were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values (See Experimental section).

We have also used Sterically congested stabilized phosphorus ylides[25] **10a–b** in this reaction (Scheme 4), but no corresponding products **8** were observed and in the all cases decomposition of the starting materials and formation of 1,3,5-triphenylpyrazole **11** were observed.



SCHEME 4

The presence of fairly bulky phenyl groups in **10a–b** relative to the methyl groups in **4a–b** may be plausible factor for the different behavior of their reactivity toward this reaction (Scheme 1, Scheme 2 and Scheme 4).

CONCLUSIONS

In summary, we have found a new and efficient method for preparing fully substituted pyrazole derivatives **(8)** from triphenylphosphine **(1)**, dialkyl acetylenedicarboxylates **(2)**, acetylacetone **(3)** and phenylhydrazine **(5)** in the presence of silica gel powder in solvent-free conditions (Scheme 1, Scheme 2, and Scheme 3). We believe the reported method offers a simple and efficient route for the preparation of fully substituted pyrazole derivatives **8a-b** (Scheme 2). Its ease of work up and good yields make it a useful addition to modern synthetic methodologies. Other aspects of this process are under investigation.

EXPERIMENTAL

^{1}H (250 MHz) and ^{13}C (62.5 MHz) NMR measurements were recorded on a Brucker 250 spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. IR spectra were measured on a Mattson-1000 FTIR spectrophotometer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Flash chromatography columns were prepared from Merck silica gel powder.

General Procedure for the Preparation of Compounds 8a-b

Stabilized phosphorus ylides **4a-b** were prepared based on previously reported procedure.[25]

Homogenous mixture of stabilized phosphorus ylide 4 (1 mmol), phenylhydrazine 5 (0.1 ml, 1 mmol) and powdered silica gel (0.7 g) were heated in a oven at 100°C (5 h for **4a** and 4 h for **4b**) and then placed over a column of silica gel (12 g). The column chromatography was washed using ethyl acetate-light petroleum ether (1:10) as eluent. The solvent was removed under reduced pressure and the products were obtained as light yellow oils. The relative population of ***E*** and ***Z*** stereoisomers for the compounds **8a-b** was determined via their ^{1}H NMR spectra. The characterization data of the new compounds are given below.

Dimethyl 2-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)-2-butenedioate 8a

Light yellow oil; yield 65%; IR (neat) ($\upsilon_{\max}$, cm^{-1}): 3063, 2954, 1727, 1597, 1504, 1431, 1380, 1249, 1149, 1025, 774, 694. %***E***=74 and %***Z***=26. ^{1}H NMR (250 MHz, $CDCl_3$) for ***E*** stereoisomer, δ_H: 2.14 and 2.15 (6 H, 2 s, 2 CH_3); 3.71 and 3.84 (6 H,2 s, 2 OCH_3); 7.09 (1 H, 1 s, =CH), 7.35–7.51 (5 H, m, arom). ^{1}H NMR (250 MHz, $CDCl_3$) for ***Z*** stereoisomer, δ_H: 2.29 and 2.32 (6 H, 2 s, 2 CH_3); 3.79 and 3.91 (6 H, 2 s, 2 OCH_3); 6.02 (1 H, 1 s, =CH), 7.35–7.51 (5 H, m, arom). ^{13}C NMR (62.5 MHz, $CDCl_3$) for *E* stereoisomer, δ_c: 11.95 and 12.50 (2 CH_3); 51.94 and 52.92 (2 OCH_3); 125.02, 127.57, 129.02, 129.65 (6 CH); 125.48, 136.90, 138.70, 139.60, 147.84 (5 C); 165.23 and 168.87 (2 C=O). ^{13}C NMR (62.5 MHz, $CDCl_3$) for ***Z*** stereoisomer, δ_c: 12.02 and 13.42 (2 CH_3); 51.89 and 52.56 (2 OCH_3); 128.31, 128.82, 129.04 and 129.65 (6 CH); 125.15, 138.98, 139.17, 141.99 and 148.08 (5 C); 165.68 and 168.32 (2 C—O). MS: *m/z* (%) (EI) 314 (M^+, 71), 282 (16), 254 (50), 243 (8), 225 (12), 215 (20), 199 (30), 195 (35), 168 (10), 154 (15), 149 (16), 128 (12), 118 (20), 104 (8), 91 (12), 78 (12), 77 (100), 65 (12), 59 (35), 51 (31), 41 (12).

Diethyl 2-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)-2-butenedioate 8b

Light yellow oil; yield 66%; IR (neat) (υ_{max} , cm^{-1}): 3062, 2985, 2931, 1728, 1596, 1504, 1434, 1380, 1248, 1164, 1033, 786, 694. %***E***=79 and %***Z***=21. ^{1}H NMR (250 MHz, $CDCl_3$) for ***E*** stereoisomer, δ_H: 1.21 and 1.32 (6 H, 2 t, $^3J_{HH} = 7.3$ Hz, 2 CH_3 of 2 OEt); 2.17 and 2.22 (6 H, 2 s, 2 CH_3); 4.06 and 4.28 (4 H, 2 q, $^3J_{HH} = 7.3$ Hz, 2 OCH_2 of 2 OEt); 7.08 (1 H, 1 s, =CH), 7.28–7.36 (5 H, m, arom). ^{1}H NMR (250 MHz, $CDCl_3$) for ***Z*** stereoisomer, δ_H: 1.24 and 1.38 (6 H, 2 t, $^3J_{HH} = 7.3$ Hz, 2 CH_3 of 2 OEt); 2.30 and 2.33 (6 H, 2 s, 2 CH_3); 4.25 and 4.37 (4 H, 2 q, $^3J_{HH} = 7.3$ Hz, 2 OCH_2 of 2 OEt); 5.99 (1 H, 1 s, =CH), 7.28-7.36 (5 H, m, arom). ^{13}C NMR (62.5 MHz, $CDCl_3$) for *E* stereoisomer, δ_c: 11.99 and 12.58 (2 CH_3); 14.06 and 14.18 (2 CH_3 of 2 OEt); 60.87 and 60.01 (2 OCH_2 of 2 OEt); 124.90, 127.45, 129.00 and 130.09 (6 CH); 125.42, 136.75, 138.45, 139.63 and 147.85 (5 C); 165.04 and 166.50 (2 C=O of ester). ^{13}C NMR (62.5 MHz, $CDCl_3$) for *Z* stereoisomer, δ_c: 12.15 and 12.25 (2 CH_3); 13.51 and 13.95 (2 CH_3 of 2 OEt); 61.18 and 61.81 (2 OCH_2 of 2 OEt); 125.07, 127.55, 129.21 and 130.07 (6 CH); 125.41, 137.20, 139.00, 139.10 and 147.50 (5 C); 164.00 and 168.09 (2 C=O). MS: *m/z* (%) (EI) 342 (M^+, 100), 313 (8), 296 (34), 271 (50), 268 (50), 250 (12), 241 (34), 229 (14), 225 (25), 199 (55), 195 (45), 173 (29), 154 (22), 149 (10), 128 (16), 118 (25), 104 (9), 91 (11), 77 (81), 65 (10), 51 (22), 42 (11).

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