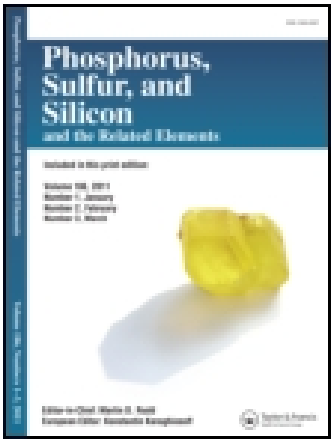

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Triphenylphosphine Catalyzed Stereoselective Addition of 3,5-Diphenyl-1*H*-pyrazole to Acetylenic Esters

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*Protonation of the highly reactive 1:1 intermediates produced in the reaction between triphenylphosphine and dialkyl acetylenedicarboxylates by 3,5-diphenyl-1*H*-pyrazole leads to vinyltriphenylphosphonium salts. The cation in these salts undergoes an addition reaction with the counter anion in CH_2Cl_2 at room temperature to yield the corresponding stabilized phosphorus ylides. Elimination of triphenylphosphine from the stabilized phosphorus ylides leads to the corresponding electron-poor* N*-vinyl pyrazoles in fairly high yields. The reaction is fairly stereoselective.*

Keywords Catalyst; dialkyl acetylenedicarboxylates; electron-poor *N*-vinyl pyrazoles; phosphorus ylide; triphenylphosphine; vinyltriphenylphosphonium salts

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]

β-Additions of nucleophiles to the vinyl group of vinylic phosphonium salts leading to the formation of new alkylidenephosphoranes has attracted much attention as a very convenient and synthetically useful method in organic synthesis.[12,13] Organophosphorus compounds have

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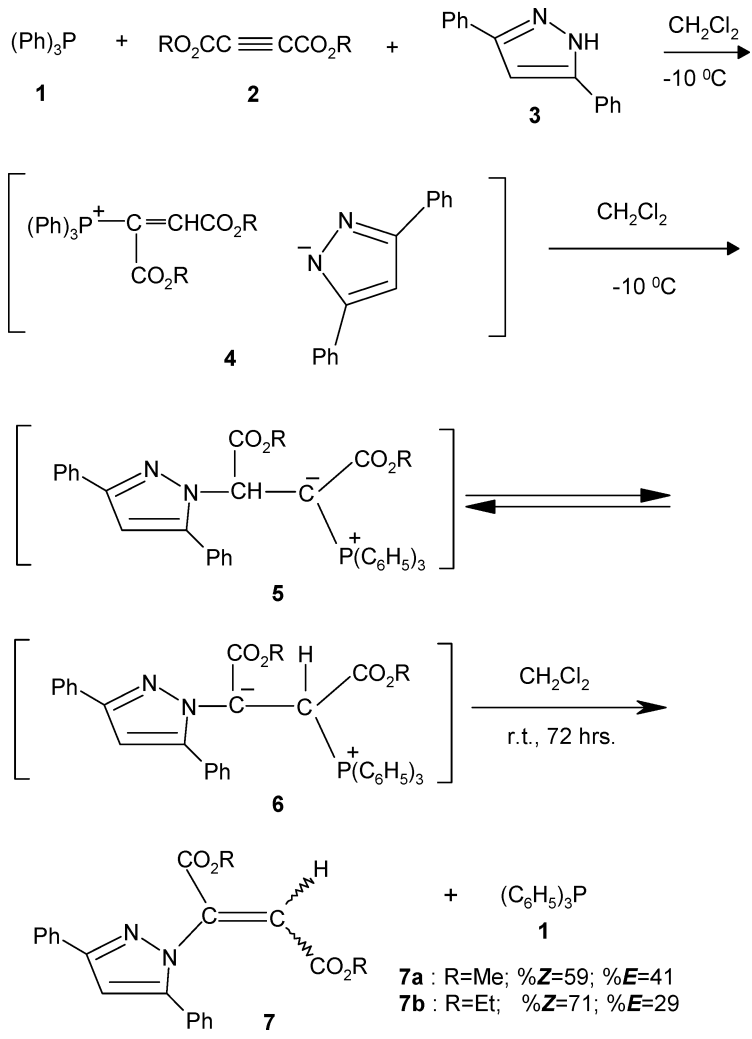
been extensively employed in organic synthesis as useful reagents as well as ligands in a number of transition metal catalysts.[14] Phosphorus ylides are a class of special type of zwitterions, which bear strongly nucleophilic electron rich carbanions. The electron distribution around the P^+—C^- bond 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.[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] These ylides are usually prepared by treatment of a phosphonium salt with a base, and phosphonium salts are usually obtained from a phosphine and an alkyl halide. Phosphonium salts are also prepared by Michael addition of phosphorus nucleophiles to activated olefins and in other ways.[12] The phosphonium salts are most often converted to the ylide by treatment with a strong base, though weaker bases can be used if the salt is acidic enough.[12] In recent years, we have established a one-pot method for the synthesis of stabilized ylides.[17–25] In this article, we wish to describe the stereoselective preparation of electron-poor *N*-vinyl pyrazoles from the dialkyl acetylenedicarboxylates and 3,5-diphenyl-1*H*-pyrazole in the presence of triphenylphosphine in fairly high yields (Scheme 1).

RESULTS AND DISCUSSION

Reactions are known in which an α, β-unsaturated carbonyl compound is produced from phosphonium salts.[25] Thus, The compound **5** may result from initial addition of triphenylphosphine (**1**) to the acetylenic esters **2** and concomitant protonation of the 1:1 adducts by the 3,5-diphenyl-1*H*-pyrazole (**3**) to form the corresponding triphenylphosphonium salts **4**. Addition of the anion in **4** to the vinyltriphenylphosphonium cation leads to the formation of the stabilized phosphorus ylides **5** (Scheme 1) that undergoes intramolecular proton transfer leading to formation of sterically congested electron-poor*N*-vinyl pyrazoles **7** via zwitterionic intermediate **6** (Scheme 1). In this reaction triphenylphosphine acts as a catalyst. TLC indicated that the reaction was completed after 72 h in CH_2Cl_2 at room temperature. We reduced the



SCHEME 1

amount of triphenylphosphine to 50% of mole ratio. In all cases where we have used triphenylphosphine as a catalyst in the range of 50% to 100% of molar ratio, the reaction time amounted to 72 h. In all cases where we have used triphenylphosphine as a catalyst in the range below 50% of mole ratio, the reaction time was longer than 72 h. The reaction proceeds smoothly and cleanly and no side reactions were observed. In the absence of triphenylphosphine no products were observed. Based on TLC monitoring of the reaction and NMR analyses

of the products, in this reaction, *Z* and *E* stereoisomers of **7a** and **7b** were observed. Relative population of *E* and *Z* isomers were determined via their ^{1}H NMR spectra (**7a**: $\%Z = 59$, $\%E = 41$; **7b**: $\%Z = 71$, $\%E = 29$) and therefore, the reaction is fairly stereoselective. The mechanism of the reaction has not been established experimentally and therefore only proposed mechanism is shown in the Scheme 1. The structures **7a–b** were deduced from their IR, ^{1}H and ^{13}C NMR spectra.

CONCLUSION

In summary, we have found a new and efficient method for preparing sterically congested electron-poor*N*-vinyl pyrazoles (**7**) from triphenylphosphine (**1**), dialkyl acetylenedicarboxylates (**2**) and 3,5-diphenyl-1*H*-pyrazole (**3**) (Scheme 1). We believe the reported method offers a simple and efficient route for the preparation of substituted electron-poor*N*-vinyl pyrazole **7a–b** (Scheme 1). Its ease of work up and fairly good yields make it a useful addition to modern synthetic methodologies. Other aspects of this process are under investigation.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Mattson-1000 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured with a Bruker Spectrospin spectrometer at 250 and 62.5 MHz, respectively (Me_4Si as internal standard).

General Procedure for the Preparation of Compounds 7a–b

To a magnetically stirred solution of triphenylphosphine **1** (0.262 g, 1 mmol) and the 3,5-diphenyl-1*H*-pyrazole **3** (0.22 g, 1 mmol) in CH_2Cl_2 (5 mL) was added dropwise a mixture of the respective dialkyl acetylenedicarboxylate **2** (0.13 mL, 1 mmol) in CH_2Cl_2 (2 mL) at -10°C over a period of 15 min. The mixture was allowed to warm up to room temperature and stirred for 74 h. The solvent was removed under reduced pressure, and the viscous residue was purified by silica gel column chromatography using ethyl acetate-light petroleum ether (1:8) as eluent. The solvent was removed under reduced pressure yielding the *N*-vinyl pyrazoles (**7a–b**).

Dimethyl 2-(3,5-Diphenyl-1H-pyrazol-1-yl)-2-butenedioate (7a)

Colorless oil; yield 75%; IR (neat) (υ_{max} , cm^{-1}): 3026 (CH, arom); 2954 (CH , alipha); 1727 (C=O , ester); 1612 (C=C, alkene); 1524 (C=N). %E =41, %Z = 59.

^{1}H NMR ($CDCl_3$) for *E* stereoisomer δ_H: 3.66 and 3.73 (6 H, 2s, 2 OCH_3); 6.15 (1 H, 1 s, =CH); 6.76 (1 H, 1 s, H-pyrazol); 7.26–7.88 (10 H, m, arom.).

^{13}C NMR ($CDCl_3$) for *E* stereoisomer δ_C : 52.31 and 52.89 (2 OCH_3); 107.98, 126.13, 127.86, 128.75, 129.09 (12CH); 129.40, 142.13, 146.11, 153.46 (5C); 162.95 and 164.96 (C=O of ester).

^{1}H NMR ($CDCl_3$) for *Z* stereoisomer δ_H: 3.58 and 3.64 (6H, 2 s, 2OCH_3); 6.81(1H, 1s, H-pyrazol); 7.01(1H, 1s, =CH); 7.26–7.88(10H, m, arom).

^{13}C NMR ($CDCl_3$) for *Z* stereoisomer δ_C : 52.14 and 53.11(2OCH_3); 104.36, 125.88, 128.61, 128.71, 128.85(12CH); 129.44, 137.86, 146.27, 152.85 (5C); 162.95 and 163.86 (C=O of ester).

Diethyl 2-(3,5-Diphenyl-1H-pyrazol-1-yl)-2-butenedioate (7b)

Colorless oil; yield 75%, IR (neat) (υ_{max} , cm^{-1}) : 3020 (CH, arom); 2956 (CH , alipha); 1727 (C=O , ester); 1612 (C=C, alkene); 1524 (C=N). %E =29, %Z = 79.

^{1}H NMR ($CDCl_3$) for *E* stereoisomer δ_H: 1.23 and 1.26 (6H, 2s, $^3J_{HH}$ = 7.2 Hz, 2CH_3 of 2OEt) 4.07 and 4.19 (4H, 2q, $^3J_{HH}$ = 7.2 Hz, 2OCH_2 of 2OEt); 6.22 (1H, 1s, H-pyrazol); 6.76 (1H, 1s, =CH); 7.33–7.89 (10H, m, arom).

^{13}C NMR ($CDCl_3$) for *E* stereoisomer δ_C: 13.69 and 14.07 (2CH_3); 61.12 and 62.29 (2$OCH_2$of 2OEt); 107.66, 126.08, 127.07, 128.70, 128.80 (12CH); 130.28, 132.64, 141.84, 153.30 (5C); 162.42 and 164.47 (C=O of ester).

^{1}H NMR ($CDCl_3$) for *Z* stereoisomer δ_H: 1.01 and 1.07 (6H, 2s, $^3J_{HH}$ = 7.2 Hz, 2CH_3 of 2OEt) 4.02and 4.10 (4H, 2q, $^3J_{HH}$ = 7.2 Hz, 2OCH_2 of 2OEt); 6.82 (1H, 1s, H-pyrazol); 7.07 (1H, 1s, =CH); 7.33–7.89 (10H, m, arom).

^{13}C NMR ($CDCl_3$) for *Z* stereoisomer δ_C: 13.69 and 13.95 (2CH_3); 61.45 and 62.47 (2$OCH_2$of 2OEt); 104.19, 125.82, 127.79, 128.62, 128.80 (12CH); 129.04, 138.10, 146.05, 152.67 (5C); 162.32 and 163.65 (C=O of ester).

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