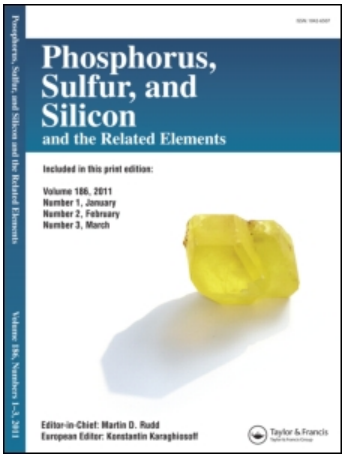

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Synthesis of Electron-Poor Pyrazole Derivatives from In-Situ Generated Stabilized Phosphorus Ylides

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Protonation of the highly reactive 1:1 intermediates produced in the reaction between triphenylphosphine and dialkyl acetylenedicarboxylates by derivatives of N-aminophthalimide 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. Intermolecular Wittig reaction of the stabilized phosphorus ylides leads to the corresponding electron-poor pyrazole derivatives in fairly good yields.

Keywords Electron-poor pyrazole derivatives; intermolecular Wittig reaction; *N*-aminophthalimide; phosphorus ylide; 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 has 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,

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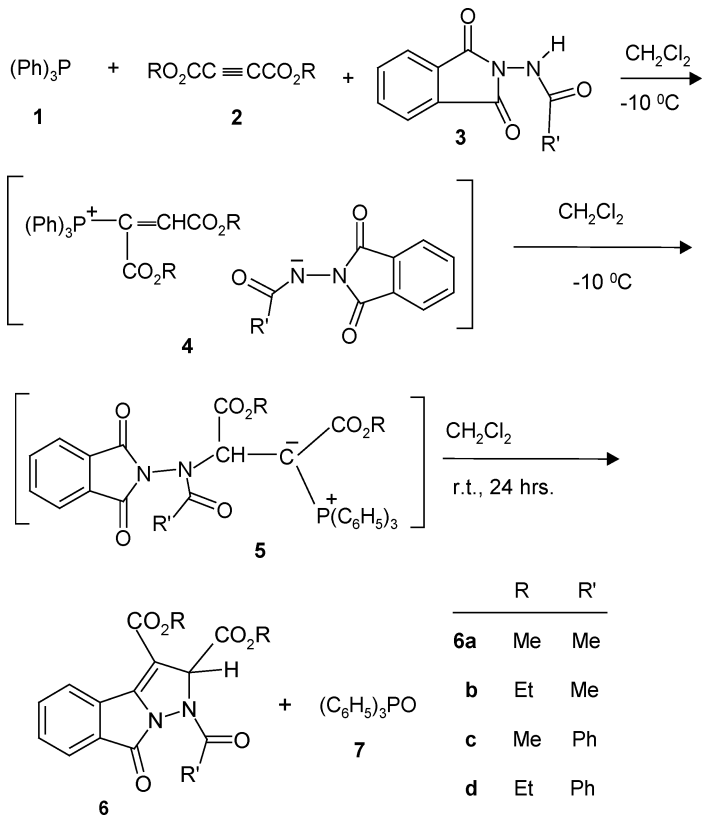
anti-convulsant, antihistaminic, antibiotics, anti-depressant, and CNS regulant properties.[2–11] β-additions of nucleophiles to the vinyl group of vinylic phosphonium salts, leading to the formation of new alkylidenephosphoranes, have attracted much attention as a very convenient and synthetically useful method in organic synthesis.[12] Organophosphorus compounds have been extensively employed in organic synthesis as useful reagents, as well as ligands, in a number of transition metal catalysts.[13] In the past, we have established a convenient, one-pot method for preparing stabilized phosphorus ylides utilizing in situ generation of the phosphonium salts.[14,15] In this article, we report synthesis of electron-poor pyrazole derivatives from *in-situ* generated stabilized phosphorus ylides in fairly good yields (Scheme 1).



	R	R'
6a	Me	Me
b	Et	Me
c	Me	Ph
d	Et	Ph

SCHEME 1

RESULTS AND DISCUSSION

Reactions are known in which an α,β-unsaturated carbonyl compound is produced from phosphonium salts[13–15] Thus, compounds **6** may result from an initial addition of triphenylphosphine **1** to the acetylenic esters **2** and concomitant protonation of the 1:1 adducts by the amide derivative of *N*-aminophthalimide (**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**. Intramolecular Wittig reaction of **5** results in the formation of the corresponding electron-poor pyrazole derivatives in fairly good yields (Scheme 1). TLC indicates that the reaction was complete after 24 h in CH_2Cl_2 at room temperature. The reaction proceeds smoothly and cleanly (in all cases the reaction works efficiently with high coversions) and no side reactions were observed. The mechanism of the reaction has not been established experimentally, and therefore, only a proposed mechanism is shown in Scheme 1.

CONCLUSION

In summary, we have found a new and efficient method for preparing compounds **6** from triphenylphosphine, dialkyl acetylenedicarboxylates, and derivatives of *N*-aminophthalimide (Scheme 1). Other aspects of this process are under investigation.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a Shimadzu IR-460 spectrometer. UV spectra were recorded on a Shimadzu UV-2100 spectrophotometer. ^1H and ^{13}C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500 and 125 MHz, respectively (Me_4Si as internal standard).

General Procedure for the Preparation of Compounds 6a–d

To a magnetically stirred solution of triphenylphosphine **1** (1 mmol) and the amide derivative of *N*-aminophthalimide **3** (1 mmol) in CH_2Cl_2 (6 mL) was added dropwise a mixture of the respective dialkyl acetylenedicarboxylate **2** (1 mmol) in CH_2Cl_2 (4 mL) at $-10^\circ C$ over a period of 15 min. The mixture was allowed to warm up to room temperature and was stirred for 24 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 pyrazoles **6a–d**.

1-Acetyl-8-oxo-2,8-dihydro-1H-pyrazolo[5,1-a]isoindole-2,3-dicarboxylic Acid Dimethyl Ester (6a)

Yellow crystals; m.p.: 161.0–162.6°C; Yield: 75%; UV (EtOH 95%), ($\lambda_{max/nm}$, log ε): 235, 5.23; 281, 5.62; 294, 5.28; IR(KBr) (υ_{max}, cm^{-1}): 2946 (CH, aliphatic); 1751, 1712, 1651 (CO, carbonyl); 1218 (C—O, ester).^{1}H NMR ($CDCl_3$)δ: 2.43 (s, 3H, $COCH_3$); 3.79 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3); 6.08 (s, 1H, NCH); 7.71 (m, 2H, arom-H); 7.87 (d,$^3J_{HH}$ = 7.2 Hz, 1H, arom-H)); 8.43 (d,$^3J_{HH}$ = 7.2 Hz, 1H, arom-H).^{13}C NMR ($CDCl_3$)δ: 22.1 (CH_3); 52.2 (OCH_3), 53.3 (OCH_3), 71.0 (NCH), 103.0 (C=C), 124.4 (arom-C), 126.8 (arom-C), 127.7 (arom-C), 132.7 (arom-C), 133.3 (arom-C), 133.4 (arom-C), 147.1 (C=C), 159.7 (CO), 162.2 (CO), 167.0 (CO), 174.3 (CO). Found: C, 58.38; H, 4.49; N, 8.31%. $C_{16}H_{14}N_2O_6$ requires C, 58.18; H, 4.27; N, 8.48%.

1-Acetyl-8-oxo-2,8-dihydro-1H-pyrazolo[5,1-a]isoindole-2,3-dicarboxylic Acid Diethyl Ester (6b)

Yellow crystals; m.p.: 111.0–112.0°C; Yield: 65%; UV (EtOH 95%), ($\lambda_{max/nm}$, log ε): 203, 5.08; 278, 4.50; 353, 5.13. IR (KBr) (υ_{max} cm^{-1}): 2931 (CH, aliphatic), 1743, 1704, 1650 (CO, carbonyl), 1280, 1180 (C—O, ester).^{1}H NMR ($CDCl_3$)δ: 1.35 (t, $^3J_{HH}$ = 7.5 Hz, 3H, CH_3), 1.44 (t, $^3J_{HH}$ = 7.5 Hz, 3H, CH_3), 2.43 (s, 3H, $COCH_3$); 4.23 (q, $^3J_{HH}$ = 7.5 Hz, 2H, OCH_2), 4.34 (q, $^3J_{HH}$ = 7.5 Hz, 2H, OCH_2), 6.05 (s, 1H, NCH), 7.66–7.88 (m, 4H, arom-H).^{13}C NMR ($CDCl_3$)δ: 14.0 (CH_3), 14.3 (CH_3), 22.1 ($COCH_3$), 61.5 (OCH_2), 62.4 (OCH_2), 71.4 (NCH), 104.3 (C=C), 124.4 (arom-C), 124.5 (arom-C), 126.8 (arom-C), 127.7 (arom-C), 130.0 (arom-C), 132.6 (arom-C), 135.1 (C=C), 146.9 (CO), 159.7 (CO), 161.8 (CO), 167.5 (CO). Found: C, 60.10; H, 5.19; N, 7.98%. $C_{18}H_{18}N_2O_6$ requires C, 60.33; H, 5.06; N, 7.82%.

1-Benzoyl-8-oxo-2,8-dihydro-1H-pyrazolo[5,1-a]isoindole-2,3-dicarboxylic Acid Dimethyl Ester (6c)

Yellow crystals; m.p.: 173.0–181.0°C; Yield: 60%. UV (EtOH 95%), ($\lambda_{max/nm}$, log ε): 201, 5.88; 282, 5.30; 353, 4.87. IR (KBr) (υ_{max} cm^{-1}): 3255 (CH, arom); 2923 (CH, aliphatic); 1743, 1704 (CO, carbonyl); 1257, 1103 (C—O, ester).^{1}H NMR ($CDCl_3$)δ: 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.64 (s, 1H, NCH), 7.58–7.90 (m, 9H, arom-H).^{13}C NMR ($CDCl_3$)δ: 52.3 (OCH_3), 53.3 (OCH_3), 73.2 (NCH), 102.8 (C=C), 124.1 (arom-C), 124.5 (arom-C), 126.8 (arom-C), 127.1 (arom-C), 127.8 (arom-C), 128.7 (arom-C), 129.7 (arom-C), 130.9 (arom-C), 132.8 (arom-C), 132.9 (arom-C),

133.4 (arom-C), 134.8 (arom-C), 147.0 (C=C), 157.94 (CO), 162.4 (CO), 167.8 (CO) 172.2 (CO). Found: C, 64.43; H, 4.27; N, 7.02%; $C_{21}H_{16}N_2O_6$ requires C, 64.28; H, 4.11; N, 7.14%.

1-Benzoyl-8-oxo-2,8-dihydro-1H-pyrazolo[5,1-a]isoindole-2,3-dicarboxylic Acid Diethyl Ester (6d)

Yellow crystals; m.p.: 118.0–124.0°C; Yield: 50%. UV (EtOH 95%), ($\lambda_{max/nm}$, $\log \varepsilon$): 202, 5.23; 278, 5.62; 354, 5.28. IR (KBr) (υ_{max}, cm^{-1}): 2923 (CH, aliphatic); 1743, 1658 (CO, carbonyl), 1118, 1187 (CO, ester).^{1}H NMR ($CDCl_3$)δ: 1.26 (t, $^3J_{HH}$ = 7.5 Hz, 6H, CH_3), 4.25 (q, $^3J_{HH}$ = 7.5 Hz, 4H, OCH_2), 5.61 (s, 1H, NCH), 7.55–8.01 (m, 9H, arom-H).^{13}C NMR ($CDCl_3$)δ: 28.9 (CH_3), 30.9 (CH_3), 61.3 (OCH_2), 62.4 (OCH_2), 68.1 (NCH), 102.3 (C=C), 124.4 (arom-C), 126.9 (arom-C), 127.0 (arom-C), 128.4 (arom-C), 128.6 (arom-C), 128.7 (arom-C), 128.8 (arom-C), 139.8 (arom-C), 130.9 (arom-C), 132.0 (arom-C), 132.4 (arom-C), 132.7 (arom-C), 147.5 (C=C), 162.5 (CO), 167.4 (CO), 167.7 (CO) 172.4 (CO). Found: C, 65.55; H, 4.67; N, 6.81%. $C_{23}H_{20}N_2O_6$ requires C, 65.71; H, 4.79; N, 6.66%.

Preparation of the Amides 3a,b

Compounds **3a**, **b** were prepared by known methods[16] and identified as follows:

N-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetamide (3a)

White crystals; mp: 226.0–228.0°C; Yield: 85%. IR (KBr) (υ_{max} cm^{-1}); 3509 (NH, amide); 3029 (CH, arom); 2900 (CH, aliphatic); 1797, 1743, 1656 (CO, carbonyl); 1154, 1211 (C-N, amide).^{1}H NMR ($CDCl_3$)δ: 2.23 (s, 3H, CH_3), 7.71–7.92 (m, 5H, arom-H), 7.81 (s, 1H, NH).

N-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-benzamide (3b)

White crystals; m.p.: 307.0–309.0°C; Yield: 70%. IR (KBr) (υ_{max}, cm^{-1}): 3470 (NH, amide); 1749, 1670 (CO, carbonyl).^{1}H NMR ($CDCl_3$)δ: 7.7–8.2 (m, 9H, arom-H), 8.12 (s, 1H, NH).

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