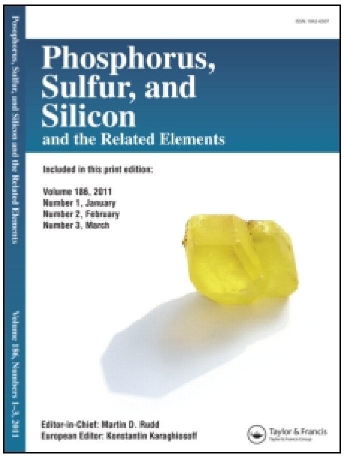

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Synthesis of Phosphorus Ylides Using 2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-*N*-phenylacetamide Derivatives

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*A convenient synthesis of highly functionalized phosphorus ylides has been achieved by the reaction of dimethyl acetylenedicarboxylate with 2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-*N*-phenylacetamides in the presence of triphenylphosphine. The protonation of the resulting zwitterion by 2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-*N*-phenylacetamide and its derivatives gave stable phosphor-ylenes. The intramolecular cyclization of ylide **2d** in toluene at reflux gave the pyrazoloimidazole derivative **3d** in a high yield.*

Keywords Dimethyl acetylenedicarboxylate; isoindole; triphenylphosphine

INTRODUCTION

Phosphorus ylides are becoming of increased importance in the synthesis of heterocyclic compounds.[1,2] The most intensive studies in this field have been carried out by Yavari and colleagues.[3,4] Phosphorus ylides have numerous synthetic applications for a wide variety of industrial and biological fields. They are ideal compounds in many cases due to their simple preparations and high reactivity with a large number of reagents, which usually proceed in high yields. In view of our general interest in the chemistry of heterocyclic compounds we previously reported the preparation of pyrazole and 2-pyrone derivatives by

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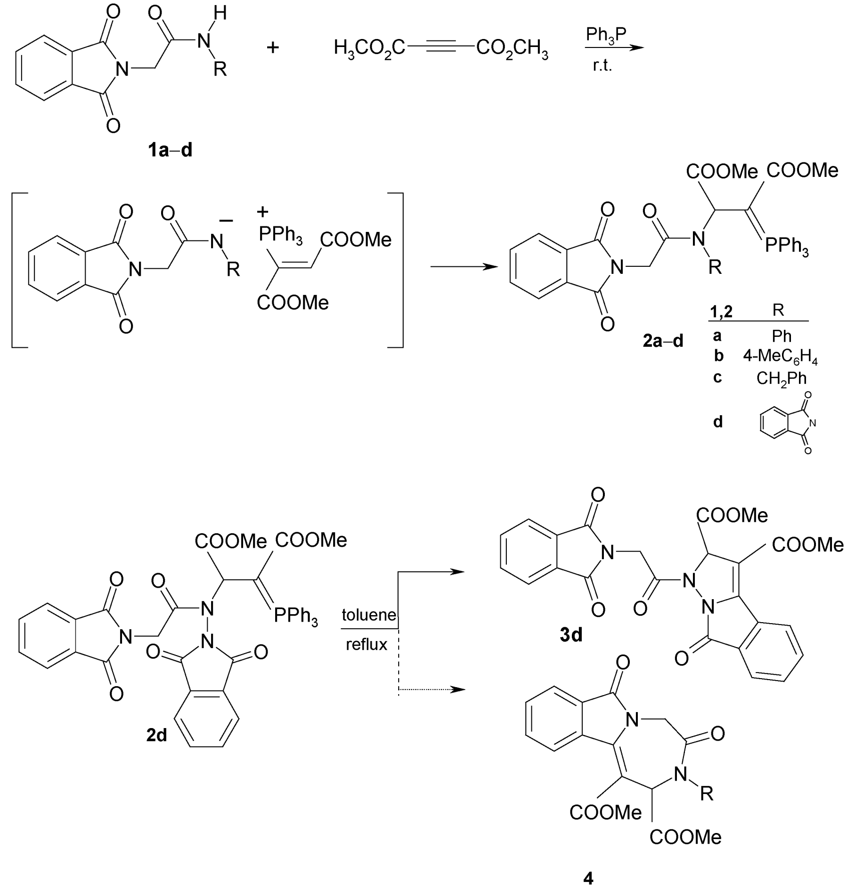
Address correspondence to Kazem Saidi, Department of Chemistry, Shahid Bahonar, University of Kerman, P.O. Box 76169-133, Kerman, Iran. E-mail: saidik@mail.uk.ac.ir the reaction of chlorocarbonyl phenyl ketene with hydrazones[5] and 1,3-diketones.[6] In this investigation we wish to report an efficient route to the synthesis of a pyrazolo[5,1-*a*]isoindole. The reaction of dimethyl acetylenedicarboxylate with 2-(1,3-dioxo-1,3- dihydroisoindol-2-yl)-*N*-phenylacetamides in the presence of triphenylphosphine was carried out, and the results are reported here.

RESULTS AND DISCUSSION

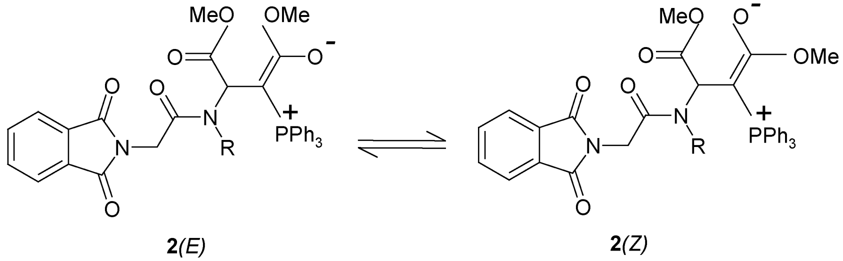
A readily available and relatively inexpensive compound such as dimethyl acetylene-dicarboxylate, which is an electron-deficient ester, reacts rapidly at r.t. with triphenylphosphine.[7] The key step in this transformation involves the generation of a zwitterion[8] and protonation of the 1:1 adduct by 2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-*N*-phenylacetamides to form a positively charged ion. This positively charged ion is attacked by the nitrogen atom of the conjugate base of the N—H acid leading to the formation of a new C—N bond to form a stable phosphor-ylene. Reflux of compounds **2a–c** in toluene led to the decomposition of these products, and no formation of the seven-membered ring compound **4** was observed. In the case of **2d**, removal of triphenylphosphine oxide was achieved by heating at 110°C, resulting in the formation of a five-membered heterocyclic ring in high yields (**3d**), which was further identified and characterized by its spectroscopic data (Scheme 1).[9]

Reaction of equimolar quantities of the starting compounds followed by work-up produced compounds **2a–d**. The structures of these products were deduced from their ^1H and ^{13}C NMR and IR spectral data. The rotation about the partial double bond in the *E* and *Z* isomers was slow on the NMR time scale at ambient temperature. The presence of a mixture of the *E* and *Z* isomers for compounds **2a–d** was proven by their ^{13}C NMR and ^1H NMR data (Scheme 2).[10] The mass spectrum of **2a** revealed the molecular ion peak at m/z 684 and the base peak at m/z 277, which corresponds to $C_{18}H_{14}OP$. The ^1H NMR spectrum of this compound showed four sharp lines at 2.78, 2.89, 3.68, and 3.80 ppm due to the methoxy protons and two doublets at 4.85 ($^3J_{PH} = 20.4$ Hz) and 5.16 ppm ($^3J_{PH} = 19.1$ Hz) for the methine protons of the two rotamers.

The ^{13}C NMR spectrum of **2a** showed two doublets at 41.3 ($^1J_{PC} = 134.9$ Hz) and 40.8 ppm ($^1J_{PC} = 138.8$ Hz), which are due to the P=C carbon atom for the major and minor isomer, respectively. The ratio of two geometrical isomers was approximately 7:3 based on the ^1H NMR spectrum. The IR spectrum of **2a** showed two ester absorptions at 1759



SCHEME 1



SCHEME 2

and 1666 cm^{-1}. Conjugation with the negative charge appeared to be a plausible factor in the reduction of the wave number of one of the carbonyl absorption bands as shown in Scheme 2.

The mass spectrum of compound **3d** showed the molecular ion peak at m/z 475 and base peak at m/z 149, which corresponds to $C_8H_7NO_2$. The ^1H NMR spectrum of **3d** showed two singlets at 3.78 and 3.81 ppm for the two methoxy groups, a multiplet for the methylene protons, and a singlet for the methine proton. The ^{13}C NMR spectrum of this product displayed the signal for the methylene carbon atom at 48.8, signals for the two methoxy groups at 52.2 and 52.3, and a signal for the carbon atom of the methine group at 58.2 ppm. The resonances of the carbonyl groups appeared at 164.7–168.7 ppm. The IR spectrum of this compound revealed strong absorptions at 1761, 1720, and 1665 cm^{-1} due to the carbonyl groups.

EXPERIMENTAL

Dimethyl Acetylenedicarboxylate (DMAD) and triphenylphosphine were obtained from Merck (Darmstadt, Germany) and were used without further purification. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Mass spectra were recorded on a Shimadzu QP-2000A mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Mattson 1000 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were obtained with a Bruker DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively. Overlaping signals, for witch the assignment to the *E* or *Z* isomer was not possible, are marked with an asterix. Microanalytical data for compound **3d** was obtained from National Iran Oil Company chemistry lab (Tehran) on a Heraeus CHN-O Rapid analyzer. All of the amides used were prepared according to the literature procedures.[11,12]

General Procedure for the Preparation of 2

To a magnetically well-stirred solution of triphenylphosphine (1 mmol, 0.262 g) and **1a–d** (1 mmol) in ethyl acetate (10 mL) was added dropwise a mixture of DMAD (1 mmol, 0.142 g) in ethyl acetate (5 mL) at the r.t. The reaction mixture was then allowed to stirr for 24 h. The solvent was removed under reduced pressure, and the residual solid recrystallized from 1:1 hexane-ethyl acetate.

2-[2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-acetyl]-phenylamino-3-(triphenyl-λ-5-phosphanylidene)-succinic Acid Dimethyl Ester (2a)

White crystals, 0.616 g, (yield 90%), m.p. 172°C; IR (KBr) (ν_{max}, cm^{-1}): 1782, 1759, 1726 and 1666 (C=O). MS, *m/z*: 684 (M^{+}, 0.3%), 278 (34%), 277 (100%), 199 (38%), 183 (32%), 77 (42%).

Major isomer, *Z*-**2a** (72%), ^{1}H NMR (CDCl$_3$): δ 2.89 (s, 3H, OCH$_3$), 3.68 (s, 3H, OCH$_3$), 4.85 (m, 2H, CH$_2$), 5.18 (d, $^{3}J_{PH} = 20.4$ Hz, 1H, P=C—CH), 7.06–7.81 (m, 48H, arom-H)*; ^{13}C NMR (CDCl$_3$): δ 41.3 (d, $^{1}J_{PC} = 134.9$ Hz, P=C)*, 49.3 (CH$_2$), 48.4 (OCH$_3$), 52.0 (OCH$_3$), 60.3 (d, $^{2}J_{PC} = 17.4$ Hz, P=C—CH), 123.0 (CH), 126.5 (d, $^{1}J_{PC} = 92.2$ Hz, C-*i*), 128.0 (CH), 128.2 (CH), 129.0 (d, $^{3}J_{PC} = 12.3$ Hz, C-*m*), 131.9 (C), 132.30 (C), 132.29 (CH), 133.5 (d, $^{4}J_{PC} = 8.2$ Hz, C-*p*)*, 133.7 (d, $^{2}J_{PC} = 9.8$ Hz, C-*o*)*, 138.4 (CH), 167.6 (C=O amide), 168.5 (C=O phthalimide), 170.4 (d, $^{2}J_{PC} = 18.5$ Hz, C=O ester)*, 172.2 (d, $^{3}J_{PC} = 13.3$ Hz, C=O ester)*.

Minor isomer, *E*-**2a** (28%), ^{1}H NMR (CDCl$_3$): δ 2.78 (s, 3H, OCH$_3$), 3.80 (s, 3H, OCH$_3$), 4.80 (m, 2H, CH$_2$), 5.16 (d, $^{3}J_{PH} = 19.1$ Hz, 1H, P=C—CH); ^{13}C NMR (CDCl$_3$): δ 47.6 (CH$_2$), 48.7 (OCH$_3$), 52.2 (OCH$_3$), 61.4 (d, $^{2}J_{PC} = 12.5$ Hz, P=C—CH), 122.9 (CH), 127.0 (d, $^{1}J_{PC} = 91.5$ Hz, C-*i*), 127.3 (CH), 127.6 (CH), 128.7 (d, $^{3}J_{PC} = 12.2$ Hz, C-*m*), 132.1 (C), 132.30 (C), 132.31 (CH), 138.0 (CH), 167.5 (C=O amide), 168.1 (C=O phthalimide).

2-[2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-acetyl]-p-tolylamino-3-(triphenyl-λ-5-phosphanylidene)-succinic Acid Dimethyl Ester (2b)

White crystals, 0.650 g, (yield 93%), m.p. 180°C; IR (KBr) (ν_{max}, cm^{-1}): 1784, 1753, 1715 and 1665 (C=O). MS, *m/z*: 698 (M^{+}, 0.2%), 278 (36%), 277 (100%), 262 (14%), 199 (18%), 183 (19%), 77 (47%).

Major isomer, *Z*-**2b** (68%), ^{1}H NMR (CDCl$_3$): δ 2.28 (s, 3H, CH$_3$), 2.96 (s, 3H, OCH$_3$), 3.72 (s, 3H, OCH$_3$), 4.84 (m, 2H, CH$_2$), 5.15 (d, $^{3}J_{PH} = 18.6$ Hz, 1H, P=C—CH), 7.14–7.81 (m, 46H, arom-H)*; ^{13}C NMR (CDCl$_3$): δ 21.1 (CH$_3$), 41.1 (d, $^{1}\mathrm{J}_{PC} = 138.3$ Hz, P=C)*, 49.1 (OCH$_3$), 50.1 (CH$_2$), 52.1 (OCH$_3$), 60.1 (d, $^{2}J_{PC} = 17.6$ Hz, P=C—CH)*, 126.4 (d, $^{1}J_{PC} = 92.6$ Hz, C-*i*), 128.0 (CH), 128.6 (d, $^{3}J_{PC} = 12.9$ Hz, C-*m*), 128.8 (CH), 131.2 (CH), 132.0 (CH), 132.1 (C), 133.6 (d, $^{4}J_{PC} = 7.8$ Hz, C-*p*)*, 133.9 (d, $^{2}J_{PC} = 9.7$ Hz, C-*o*)*, 135.7 (C)*, 137.5 (C)*, 167.6 (C=O amide), 168.8 (C=O phthalimide), 170.3 (d, $^{2}J_{PC} = 16.3$ Hz, C=O ester)*, 172.8 (d, $^{3}J_{PC} = 11.7$ Hz, C=O ester)*.

Minor isomer, *E*-**2b** (32%), ^{1}H NMR (CDCl$_3$): δ 2.41 (s, 3H, CH$_3$), 2.82 (s, 3H, OCH$_3$), 3.81 (s, 3H, OCH$_3$), 4.91 (m, 2H, CH$_2$), 5.17 (d, $^{3}J_{PH} = 20.0$ Hz, 1H, P=C—CH); ^{13}C NMR (CDCl$_3$): δ 21.3 (CH$_3$), 48.8 (CH$_2$), 49.3 (OCH$_3$), 52.3 (OCH$_3$), 126.9 (d, $^{1}J_{PC} = 94.3$ Hz, C-*i*), 128.3 (CH), 128.9 (d, $^3J_{PC} = 11.7$ Hz, C-*m*), 129.5 (CH), 131.2 (CH), 132.1 (CH), 132.4 (C), 168.4 (C=O amide), 169.3 (C=O phthalimide).

2-Benzyl[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-acetyl]-benzylamino-3-(triphenyl-λ-5-phosphanylidene)-succinic Acid Dimethyl Ester (2c)

White crystals, 0.635 g, (yield 91%), m.p. 185°C; IR (KBr) (ν_{max}, cm^{-1}): 1782, 1760, 1723, 1660. MS,*m/z*: 698 (M$^+$, 0.2%), 278 (18%), 277 (55%), 262 (100%), 199 (10%), 183 (91%).

Major isomer, *Z*-**2c** (75%), ^{1}H NMR (CDCl$_3$): δ 3.01 (s, 3H, OCH$_3$), 3.78 (s, 3H, OCH$_3$), 4.47 (d, $^3J_{PH} = 16.2$ Hz, 1H, P=C—CH), 4.54 (m, 2H, CH$_2$), 4.73 (m, 2H, CH$_2$), 7.19–7.85 (m, 48H, arom-H)*; ^{13}C NMR (CDCl$_3$): δ 39.7 (d, $^1J_{PC} = 134.2$ Hz, P=C)*, 47.5 (CH$_2$)*, 48.0 (CH$_2$)*, 49.0 (OCH$_3$), 52.4 (OCH$_3$), 58.6 (d, $^2J_{PC} = 18.9$ Hz, P=C—CH)*, 123.2 (CH), 126.3 (CH), 127.0 (d, $^1J_{PC} = 91.8$ Hz, C-*i*), 126.8 (CH), 128.2 (C), 128.8 (d, $^3J_{PC} = 12.2$ Hz, C-*m*), 131.9 (CH), 132.2 (CH), 132.5 (C)*, 133.6 (d, $^4J_{PC} =$ 9.9 Hz, C-*p*)*, 133.7 (d, $^2J_{PC} = 11.2$ Hz, C-*o*)*, 167.9 (C=O, amide)*, 168.2 (C=O phthalimide)*, 170.1 (d, $^2J_{PC} = 17.2$ Hz, C=O ester)*, 173.2 (d, $^3J_{PC} = 12.0$ Hz, C=O ester)*.

Minor isomer, *E*-**2c** (25%), ^{1}H NMR (CDCl$_3$): δ 3.10 (s, 3H, OCH$_3$), 3.72 (s, 3H, OCH$_3$), 4.33 (d,$^3J_{PH} = 18.6$ Hz, 1H, P=C—CH), 4.88 (m, 2H, CH$_2$), 5.12 (m, 2H, CH$_2$); ^{13}C NMR (CDCl$_3$): δ 50.0 (OCH$_3$), 53.0 (OCH$_3$), 123.2 (CH), 126.4 (CH), 129.0 (d, $^3J_{PC} = 14.6$ Hz, C-*m*), 132.0 (CH), 132.3 (CH).

2-[2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-2-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-acetyl]-amino-3-(triphenyl-λ-5-phosphanylidene)-succinic Acid Dimethyl Ester (2d)

White crystals, 0.715 g, (yield 95%), m.p. 210°C; IR (KBr) (ν_{max}, cm^{-1}): 1808, 1766, 1749, 1715, 1682 and 1639. MS, *m/z*: 753 (M$^+$, 0.1%), 278 (36%), 277 (100%), 199 (26%), 183 (14%).

Major isomer, *Z*-**2d** (72%), ^{1}H NMR (CDCl$_3$): δ 3.76 (s, 3H, OCH$_3$), 3.89 (s, 3H, OCH$_3$), 5.26 (d, $^3J_{PH} = 17.5$ Hz, 1H, P=C—CH), 5.89 (m, 2H, CH$_2$), 7.44–8.48 (m, 46H, arom-H)*; ^{13}C NMR (CDCl$_3$): δ 39.4 (d, $^1J_{PC} = 140.8$ Hz, P=C)*, 49.3 (CH$_2$), 52.4 (OCH$_3$), 53.3 (d, $^2J_{PC} = 17.2$ Hz, P=C—CH)*, 53.4 (OCH$_3$), 123.5 (CH), 124.6 (CH), 126.9 (C), 127.3 (d, $^1J_{PC} = 79.6$ Hz, C-*i*), 131.9 (C), 132.7 (d, $^4J_{PC} = 13.0$ Hz, C-*p*)*, 133.4 (d, $^2J_{PC} = 10.3$ Hz, C-*o*)*, 159.0 (C=O phthalimide)*, 162.1 (C=O amide)*, 166.9 (C=O phthalimide)*, 167.8 (d, $^2J_{PC} = 23.6$ Hz, C=O ester)*, 172.3 (d, $^3J_{PC} = 14.9$ Hz, C=O ester)*.

Minor isomer, *E*-**2d** (28%), ^{1}H NMR (CDCl$_3$): δ 3.70 (s, 3H, OCH$_3$), 3.86 (s, 3H, OCH$_3$), 4.67 (d, $^3J_{PH} = 17.5$ Hz, 1H, P=C—CH), 5.88 (m, 2H,

CH_2); ^{13}C NMR ($CDCl_3$): δ 49.3 (CH_2), 52.3 (OCH_3), 53.2 (OCH_3), 123.3 (CH), 124.3 (CH), 126.5 (C), 131.4 (C).

1-[2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-acetyl]-8-oxo-2,8-dihydro-1H-pyrazolo[5,1-a] isoindole-2,3-dicarboxylic Acid Dimethyl Ester (3d)

2d (0.753 g, 1 mmol) was dissolved in 20 mL of toluene and refluxed for 5 h. The solvent was removed under reduced pressure, and the solid residue was recrystallized from ethanol (10 mL). Yellow crystals, 0.375 g, (yield 75%), m.p. 150°C; IR (KBr) (ν_{max}, cm^{-1}): 1761, 1720 and 1665 (C=O). MS, *m/z*: 475 (M^+, 0.5%), 149 (100%), 60 (74%), 44 (70%). Anal. calcd. for $C_{24}H_{17}N_3O_8$ (475.4): C, 60.6; H, 3.6; N, 8.8%. Found: C, 60.3; H, 3.6; N, 8.9%; ^1H NMR ($CDCl_3$): δ 3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 5.22 (m, 2H, CH_2), 6.25 (s, 1H, CH), 7.26–7.90 (m, 8H, arom-H); ^{13}C NMR ($CDCl_3$): δ 48.8 (CH_2), 52.2 (OCH_3), 52.3 (OCH_3), 58.2 (CH), 123.7, 123.9, 128.4, 128.5, 129.8, 130.2, 131.9, 132.1, 132.1, 133.4, 134.5, 164.7 (C=O phthalimide), 165.4 (C=O amide), 165.7 (C=O phthalimide), 167.8 (C=O ester), 168.7 (C=O ester).

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