SHORT PAPER

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One-pot synthesis and dynamic studies of stable dialkyl-2-(1*H*-isoindol-1,3(2*H*)-dione-2-yl)-3-(triphenylphosphoranylidene) butanedioate ylides†

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The title compounds were prepared in high yield by protonation of the reactive 1:1 intermediates produced in the reaction between triphenylphosphine and dialkyl acetylenedicarboxylate by phthalimide, followed by nucleophilic addition of the imidic nitrogen anion to the vinyl phosphonium salts. A dynamic NMR study was also performed.

Keywords: dialkyl-2-(1*H*-isoindol-1,3(2H)-dione-2-yl)-3-(triphenylphosphoranylidene)butanedioate ylides

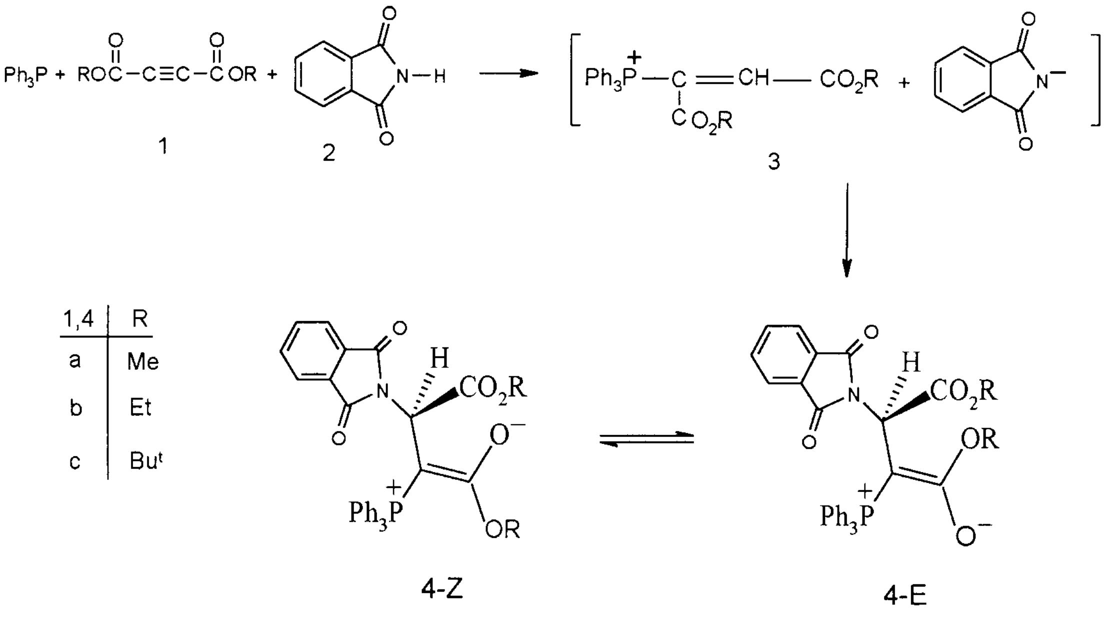
Phthalimide is one of the longest known nitrogen heterocyclic compounds that has been used in the classical Gabriel procedure for the synthesis of amines.[1,2] Such methodology has found utility in the synthesis of wide variety of N-substituted alkyl,[3,4] aryl[5–7] and allyl[8,9] phthalimides. Some substituted phthalimides have demonstrated cytotoxicity[10] and anticancer properties.[11]

In the literature some reactions have been reported between imides and phosphorus compounds.[12,13] Recently the reaction of phthalimide with ethyl propiolate in the presence of a catalytic amount of triphenylphosphine has been reported to give dehydroamino acids, with the nucleophilic α-addition to alkynotes as a key step.[14] In this paper we report the reaction of phthalimide as a proton donor source, trivalent phosphorus nucleophile and dialkyl acetylenedicarboxylate in a one-pot synthesis of the title compounds as stable ylides containining the phthalimide unit (Scheme 1).

Results and discussion

On the basis of the well established chemistry of trivalent phosphorus nucleophiles,[15–20] phosphorus ylides produced in the nucleophilic reaction between triphenylphosphine and dialkyl acetylenedicarboxylate **1** and subsequent protonation of the high reactive 1:1 adduct by phthalimide **2** leads to the vinyltriphenylphosphonium salt **3**, followed by attack of the phthalimide anion on the vinyl triphenylphosphonium cation to form the phosphorane **4**–*E* and **4**–*Z* (**4**–*Z* exclusively in the case of **4c**).

All the compounds **4a–c** are stable solid powders whose structures are fully supported by elemental analysis, ^{1}H, ^{13}C and ^{31}P NMR and 1R spectral data. The mass spectra of these compounds displayed the molecular ion peak at *m/z* 551 and 579 for **4a**, **4b** and *m/z* 534 (M^+-CO_2Bu^t) for **4c**, respectively. The ^{1}H NMR data of compounds **4a** and **4b** showed the **4**–*Z* and **4**–*E* rotamers in about 55–65% to 45–35% mole ratio while phosphorane **4c** was purely found as the the *Z* rotamer.



Scheme 1

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

The ^1H NMR spectrum of **4a** exhibited two sets of sharp lines at δ 3.19 and 3.77 ppm for the *Z* rotamer and δ 3.66 and 3.73 ppm for the *E* rotamer arising from methyl protons of esters. The shift at 3.19 of the methyl group of the *Z* rotamer is shielded, because of the anisotropic effect of the phenyl groups of triphenylphosphine. Also the ^1H NMR spectrum of **4a** displayed signals for methine protons as two sets of doublets at δ 4.83 and 4.85 ppm respectively ($^3J_{HP}$ 16.0 Hz and 17.5 Hz), in agreement with the *E* and *Z* rotamers. The ^1H NMR spectrum of **4b** is similar to that of **4a** except for its ester group, which exhibits characteristic signals with appropriate chemical shafts. The ^1H NMR spectrum of **4c** shows a different pattern from those of **4a** and **4b**. It also shows one doublet and two sharp singlet signals for methine and methyl protons respectively which is in accord to the single rotamer *Z*.

In addition to the evidence for two rotamers of **4a** and **4b** and one rotamer of **4c** from the ^1H and ^{13}C NMR data, further evidence was obtained from ^{31}P NMR spectra. In each spectrum of both **4a** and **4b** compounds two singlets ^{31}P signals were observed at about δ24 ppm (downfield from 85% H_3PO_4) for *E* and *Z* rotamers, respectively. These shifts are similar to those observed for stable phosphorus ylides (Ph_3P=C).[21,22]

The variable temperature ^1H NMR of compound **4a** was also studied in $CDCl_3$. The ^1H NMR spectrum of **4a** displays two isomers, which are appreciably broadened by increasing temperature. At about 51°C in $CDCl_3$ the four methyl signals coalesced and appeared as two fairly broad bands. Also, the resonance of the vicinal methine protons of $CHCO_2R$, which appears as two sets of doublets for the *E* and *Z* isomers, coalesced at 39°C. The behaviour is fully reversible on cooling to room temperature.

From the coalescence temperature of the methyl protons and using the expression

$$k = \pi\Delta\nu/\sqrt{2} \tag{1}$$

the first order rate constant (k_c) for C=C bond rotation in **4a** was calculated to be 177.6 s^{-1} at 51°C. The expression (Z) from the absolute rate theory[23] with a transmission coefficient of 1 was applied to calculate the free enthalpy of activation as 65.5 kJ/mol.

Table 1 ^1H, ^{13}C and ^{31}P NMR data for compounds **4a–c**.

Compound	^1H/^{13}C/^{31}P	δ (ppm) ($CDCl_3$ – Me_4Si)
4a		**Major rotamer**
	^1H	3.19 and 3.77 (6H, 2s, 2OCH_3), 4.83 (1H, d, $^3J_{HP}$ 16.1 Hz, P-C-*CH*), 7.47–7.85 (19H, m, 3C_6H_5 and C_6H_4).
	^{13}C	37.35 (d, $^1J_{CP}$ 126.3 Hz, P=*C*), 49.78 and 53.56 (2s, 2O*Me*), 55.76 (d, $^2J_{pc}$ 17.3 Hz P-C-*CH*), 123.37 (s, 2CH, C_6H_4), 127.50 (d, $^1J_{PC}$ 92.0 Hz, C_{ipso}), 129.21 (d, $^3J_{PC}$ 12.3 Hz, C_{meta}), 132.44 (d, $^4J_{PC}$ 1 Hz C_{para}), 132.75 (s, 2C, C_6H_4), 133.89 (s, 2CH, C_6H_4), 134.09 (d, $^2J_{PC}$ 10.0 Hz, C_{orto}), 167.97 (2C=O, phthlimide), 169.81 (d, $^3J_{PC}$ 14.0 Hz, C=O ester), 171.7 (d, $^3J_{PC}$ 20.9 Hz, C=O ester).
	^{31}P	23.84 (s, ph_3P=C).
		Minor rotamer
	^1H	3.66 and 3.73 (6H, 2s, 2OCH_3). 4.85 (1H, d, $^3J_{HP}$ 17.5 Hz, P-C-*CH*), 7.47–7.85 (19H, m, 3C_6H_5 and C_6H_4).
	^{13}C	39.51 (d, $^1J_{CP}$ 131.0 Hz, P=*C*), 51.18 and 53.28 (2s, 2O*Me*), 55.13 (d, $^2J_{PC}$ 17.3 Hz, P-C-*CH*), 123.36 (s, 2CH, C_6H_4), 126.8 (d, $^1J_{PC}$ 92.3 Hz, C_{ipso}); 129.11 (d, $^3J_{PC}$ 12.3 Hz, C_{meta}), 132.45 (d, $^4J_{PC}$ 1.0 Hz, C_{para}), 132.65 (s, 2C, C_6H_4), 133.99 (s, 2CH, C_6H_4), 134.07 (d, $^2J_{PC}$ 6.5 Hz, C_{orto}), 167.96 (2C=O, phthalimide), 169.64 (d, $^3J_{PC}$ 13.7Hz, C=O ester), 171.8 (d, $^3J_{PC}$ 21.0 Hz, C=O ester).
	^{31}P	24.00 (s, ph_3P=C).
4b		**Major rotamer**
	^1H	0.49 and 1.27 (6H, 2t, $^3J_{HH}$ 7.1 and 7.06 Hz, 2O-C-CH_3), 3.71 and 4.12 (4H, 2m, 2O-CH_2-C), 4.82 (1H, d, $^3J_{HP}$ 16.4 Hz, P-C-*CH*), 7.44–7.79 (19H, m, 3C_3H_5 and C_6H_4).
	^{13}C	14.41 and 14.59 (2s, 2O-C-*C*), 37.43 (d, $^1J_{CP}$ 129.9 Hz, P=*C*), 55.92 (d, $^2J_{PC}$ 17.6 Hz, P-C-*CH*), 58.35 and 62.24 (2s, 2O-*C*-C), 123.39 (s, 2CH, C_6H_4), 127.72 (d, $^1J_{PC}$ 91.3 Hz, C_{ipso}), 129.08 (d, $^3J_{PC}$ 12.2 Hz, C_{meta}), 132.36 (d, $^4J_{PC}$ 1.0 Hz, C_{para}), 132.79 (s, 2C, C_6H_4), 133.82 (s, 2CH, C_6H_4), 134.12 (d, $^2J_{PC}$ 9.8 Hz, C_{orto}), 168.04 (2C=O, phthalimide), 169.13 (d, $^3J_{PC}$ 12.9 Hz, C=O ester), 171.35 (d, $^3J_{PC}$ 12.9 Hz, C=O ester).
	^{31}P	23.91 (s, ph_3P=C).
		Minor rotamer
	^1H	1.19 and 1.32 (6H, 2t, $^3J_{HH}$ 7.0 and 7.1 Hz, 2O-C-CH_3), 3.82 and 4.19 (4H, 2m, 2O-CH_2-C), 4.81 (1H, d, $^3J_{HP}$ 17.9 Hz, P-C-*CH*), 7.44–7.79 (19H, m, 3C_6H_5 and C_6H_4).
	^{13}C	14.63 and 15.21 (2s, 2O-C-*C*), 39.19 (d, $^1J_{CP}$ 138.3 Hz, P=*C*), 55.27 (d, $^2J_{pc}$ 17.4 Hz, P-C-*CH*), 59.34 and 62.09 (2s, 2O-*C*-C), 123.34 (s, 2CH, C_6H_4), 127.07 (d, $^1J_{PC}$ 91.5 Hz, C_{ipso}), 129.14 (d, $^3J_{PC}$ 12.1 Hz, C_{meta}), 132.42 (d, $^4J_{PC}$ 1.0 Hz, C_{para}), 132.70 (s, 2C, C_6H_4), 133.92 (s, 2CH, C_6H_4), 134.11 (d, $^2J_{PC}$ 5.8 Hz, C_{orto}), 168.03 (2C-O, phthalimide), 168.95 (d, $^3J_{PC}$ 15.0 Hz, C=O ester), 171.21 (d, $^3J_{PC}$ 12.5 Hz, C=O ester).
	^{31}P	24.02 (s, ph_3P=C).
4c		**Only one rotamer**
	^1H	0.98 and 1.52 (18H, 2s, sC*MEe*$_3$); 4.64 (1H, d, $^3J_{HP}$ 17.3 Hz, P-C-*CH*); 746–7.83 (19H, m, 3C_6H_5 and C_6H_4)
	^{13}C	28.58 and 28.84 (2s, 2O-C*Me*$_3$), 36.91 (d, $^1J_{CP}$ 131.0 Hz, P=*C*), 56.62 (d, $^2J_{PC}$ 17.5 Hz, P-C-*CH*), 78.71 and 81.52 (2s, 2O-*C*-Me_3), 123.71 (s, 2CH, C_6H_4), 128.23 (d, $^1J_{PC}$ 94.3 Hz, C_{ipso}), 129.94 (d, $^3J_{PC}$ 12.2 Hz, C_{meta}), 132.20 (d, $^4J_{PC}$ 1.5 Hz, C_{para}), 132.81 (s, 2C, C_6H_4), 132.62 (s, 2CH, C_6H_4), 134.17 (d, $^2J_{PC}$ 9.1 Hz, C_{orto}), 167.93 (2C=O, phthalimide), 168.25 (d, $^3J_{PC}$ 11.8 Hz, C=O ester), 170.19 (d, $^3J_{PC}$ 16.1 Hz, C=O ester).
	^{31}P	23.38 (s, ph_3P=C).

$$\Delta G^{\ddagger} = 19.14\ T_c\ (10.32 + \log T_c/K_c) \qquad (2)$$

The spectral changes can be easily interpreted in terms of mesomeric canonical[24–26] forms in **4a**.

Experimental

All melting points are uncorrected. Elemental analyses were performed using a Heraeus CHN-O rapid analyser. IR spectra were measured on a Shimadzu IR-470 spectrometer. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker DRX-250 advance spectrometer at 250.13, 62.90 and 101.25 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionisation potential of 70 eV. Triphenylphosphine, dialkyl acetylenedicarboxylates and phthalimide were obtained from Fluka and Merck and were used without purification.

Di-methyl-2-(1H-isoindol-1-3(2H)-dione-2-yl)-3-(triphenylphosphoranylidene)-butanedioate **4a***:* To a magnetically stirred mixture of phthalimide (0.264 g, 2 mmol) and triphenylphosphine (0.524 h, 2 mmol) in ethylacetate (6 ml) was added dropwise a solution of dimethyl acetylenedicarboxylate (0.284 g, 2 mmol) in ethylacetate (2 ml) at –5°C over 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 45 min. The precipitate was filtered off and washed with cold diethylether (3 × 4 ml) and the product **4a** was obtained as white powder (1.07 g, 97%) m.p. 184–185°C (decom.); IR (KBr) υ_{max}/cm^{-1} 1702 and 1747 (C=O), 1643 (C=C); Ms (*m/z*, %) 551(M$^+$, 7), 492 (51), 405 (14), 262 (100), 230 (34), 183 (100), 108 (27) (Found: C, 69.5 H, 4.6; N, 2.4. $C_{32}H_{26}NO_6P$ requires C, 69.7; H, 4.7; N, 2.5 %). The other compounds were prepared by a similar procedure.

Selected data for **4b***:* White-yellow powder (1.10 g, 95%) m.p. 135–136°C (dec); 1R (KBr) υ_{max}/cm^{-1} 1707 and 1746 (C=O), 1601 (C=C); Ms (*m/z*, %) 579 (M$^+$ 2), 506 (38), 262 (100), 183 (100), 148 (29), 108 (63) (Found: C, 70.4; H, 5.1; N, 2.3. $C_{34}H_{30}NO_6P$ requires C, 70.5; H, 5.2; N, 2.4%).

Selected data for **4c***:* Bright yellow powder (1.19 g, 94%) m.p. (120–121°C (dec); IR (KBr) υ_{max}/cm^{-1} 1708 and 1742 (C=O), 1647 (C=C); Ms (*m/z*, %) 534 (M$^+$ – CO_2Bu^t, 2), 478 (3), 334 (7), 262 (100), 216 (94), 183 (94), 142 (72), 102 (61), 57 (100) (Found: C, 71.7; H, 6.1; N, 2.1. $C_{38}H_{38}NO_6P$ requires C, 71.8; H, 6.0; N, 2.2%).

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