A facile synthesis of stable heterocyclic fused ring phosphorus ylides

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Stable crystalline phosphorus ylides were obtained in excellent yields from the 1:1:1 addition reaction between triphenylphosphine, dialkyl acetylenedicarboxylates, and strong NH-acids, such as 7-azaindole. These stabilised phosphoranes exist as a mixture of two geometrical isomers as a result of restricted rotation around the carbon–carbon partial double bond resulting from conjugation of the ylide moiety with the adjacent carbonyl group.

Keywords: acetylenic ester, NH-acid, stable phosphorus ylide, triphenylphosphine

Development of simple synthetic routes for widely-used organic compounds from readily available reagents is one of the major tasks in organic chemistry.[1] Phosphorus ylides are reactive systems, which take part in many valuable reactions in organic synthesis.[2-4] These ylides are most often prepared by treatment of a phosphonium salt with a base, and phosphonium salts are usually made from the phosphine and an alkyl halide.[2-10] Phosphonium salts are also obtained by Michael addition of phosphorus nucleophiles to activated olefines among other methods.[2-4] We describe here an efficient synthetic route of 7-azaindole-containing stable phosphorus ylides. The 7-azaindole moiety has the important pharmaceutical property and it has been used for medicinal chemistry purposes. It has also employed in agrochemistry.[11,12] Thus, reaction of triphenylphosphine with dialkyl acetylenedicarboxylates (**1**) in the presence of strong NH-acid (**2**) leads to the vinyls triphenylphosphonium salt (**3**), followed by attack of the 7-azaindole anion on the vinyl triphenylphosphonium cation to form the phosphorane (**4**-*E*) and (**4**-*Z*) in excellent yields (see Scheme 1).

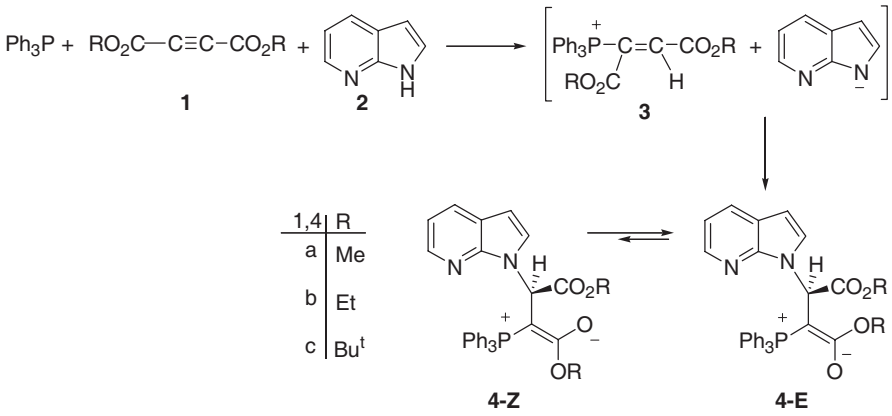
The reaction of 7-azaindole with dialkyl acetylenedicarboxylates (**1**) in the presence of triphenylphosphine proceeded at room temperature in ethyl acetate, and was finished after 12h. The ^{1}H and ^{13}C NMR spectra of the crude product clearly indicated the formation of phosphorane (**4**). Any product other than (**4**) could not be detected by NMR spectroscopy. The structures of compounds (**4a–c**) were deduced from their IR, ^{1}H, ^{13}C and ^{31}P NMR spectra. The mass spectra of these stable ylides displayed molecular ion peaks at appropriate *m/z* values. Any initial fragmentation involves loss of the side chains. The ^{1}H, ^{13}C and ^{31}P NMR spectra of ylides (**4a–b**) are consistent with the presence of two isomers but, only one geometrical isomer was observed for di-*tert*-butyl derivative of (**4c**), presumably, because of the bulky tert-butyl group. The ylides moiety of these compounds is strongly conjugated with the adjacent carbonyl group and rotation about the partial double bond in (**4**-*E*) and (**4**-*Z*) geometrical isomers (see Scheme 1) is slow on the NMR timescale at ambient temperature.

Experimental

Melting points and IR spectra were measured on an Electrothermal 9100 apparatus and a Shimadzu IR-460 spectrometer respectively. ^{1}H, ^{13}C, and ^{31}P NMR spectra were obtained from a Bruker DRX-500 AVENCE instrument with $CDCl_3$ as solvent at 500.1, 125.8, and 202.4 MHz respectively. The mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer operating at an ionisation potential of 70 eV. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyser. Triphenylphosphine, dialkyl acetylenedicarboxylates (**1a–c**) and 7-azaindole (**2**) were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

The preparation of dimethyl 2-(7-azaindole-1-yl)-3-(triphenylphosphanylidene)butanedioate (**4a**). To a magnetically stirred solution of 7-azaindole (0.18 g, 1 mmol) and triphenylphosphine (0.26 g, 1 mmol) in 8 ml of acetone was added, dropwise, a mixture of dimethyl acetylenedicarboxylate (0.14 g, 1 mmol) in 4 ml of acetone at –5°C over 10 min. After 12 h stirring at room temperature, the product was filtered off and recrystallised from acetone. Colourless crystals, m.p. 187–189°C, 0.51 g, yield 97%. IR (ν_{rnax}, cm^{-1}): 1621 and 1735(C=O). MS(*m/z*, %): 522(M, 4), 463(M-CO_2Me, 25), 405(M-heterocyclic, 65), 262(PPh_3, 100), 183(PPh_2, 19), 118(heterocyclic, 10), 108(PPh, 14), 77(Ph, 4); Anal. Calcd for $C_{31}H_{27}N_2PO_4$ C, 71.26; H, 5.17; N, 5.36, Found: C, 71.12; H, 5.09; N, 5.32

Major isomer (70%): ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 3.2 and 3.7(6H, 2s, 2OMe), 5.62(1H, d, $^3J_{HP=}$ 17.4 Hz, P–C–CH), 6.48 and 6.88(2H$_{arom}$, $C_7H_5N_2$), 7.34–7.56(15H, m, $3C_6H_5$). 7.77, 7.84 and 8.01(3H$_{arom}$, $C_7H_5N_2$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 43.70(d, $^1J_{PC}$=127.5 Hz, P=C), 49.28 and 52.56(2s, 2OMe), 56.07(d, $^2J_{PC}$=16.5 Hz, P–C–CH), 99.34, 115.04, 120.42, 126.13, 129.72, 141.40



Scheme 1

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and 146.97(7C, $C_7H_5N_2$), 127.26(d, $^1J_{PC}$= 92.3 Hz, C_{ipso}), 128.51 (d, $^3J_{PC}$=12.0 Hz, C_{meta}), 132.06(d, $^4J_{PC}$= 2.3 Hz, C_{para}), 133.47 (d, $^2J_{PC}$=12.0Hz, C_{ortho}), 170.33(d, $^3J_{PC}$= 13.0 Hz, C=O ester), 172.48 (d, $^2J_{PC}$= 12.3 Hz, P-C=C). **31**P NMR (202.4 MHz, $CDCl_3$): δ_P 23.86 (Ph_3P^+–C).

Minor isomer (30%): **1**H NMR (500.1 MHz, $CDCl_3$):δ_H 3.66 and 3.70(6H, 2s, 2OMe), 5.60(1H, d, $^3J_{PH}$=17.0 Hz, P–C–CH), 6.48 and 6.88(2H_{arom}, $C_7H_5N_2$), 7.34–7.56(15H, m, 3C_6H_5), 7.79, 7.86 and 8.03(3H_{arom}, $C_7H_5N_2$). **13**C NMR (125.8 MHz, $CDCl_3$): δ_C 42.72 (d, $^1J_{PC}$=127.4 Hz, P=C), 50.31 and 52.4(2s, 2OMe), 55.93(d, $^2J_{PC}$=16.4 Hz, P–C–CH), 109.34, 115.04, 120.44, 126.10, 129.75, 141.46 and 146.92(7C, $C_7H_5N_2$), 125.82 (d, $^1J_{PC}$= 91.5 Hz, C_{ipso}), 128.74(d, $^3J_{PC}$= 12.0 Hz, C_{meta}), 131.93(d, $^4J_{PC}$= 2.2 Hz, C_{para}), 132.27(d, $^2J_{PC}$=12.0 Hz, C_{ortho}), 170.69(d, $^3J_{PC}$=18.9 Hz, C=O ester), 172.65(d, $^2J_{PC}$=15.0 Hz, P-C=C). **31**P NMR (202.4 MHz, $CDCl_3$): δ_P 24.63(Ph_3P^+–C).

Selected data for diethyl 2-(7-azaindole-l-yl)-3-(triphenylphosphanylidene)-butanedioate (**4b**). White powder, m.p. 163–165°C, 0.52g, yield 94%. IR (ν_{rnax}, cm^{-1}): 1621 and 1745(C=O). MS(*m/z*, %): 550(M, 3), 477(M-CO_2Et, 8), 385(M-heterocyclic, 40), 262(PPh_3, 100), 183(PPh_2, 22), 118(heterocyclic, 38), 108(PPh, 80), 77(Ph, 8); Anal. Calcd for $C_{33}H_{31}N_2PO_4$ C, 72.00; H, 5.64; N, 5.09, Found: C, 72.21; H, 5.61; N, 5.11.

Major isomer (77%): **1**H NMR (500.1 MHz, $CDCl_3$): δ_H 0.51 and 1.23(6H, 2t, $^3J_{HH}$= 7.0 and 7.1Hz, 2O–C–CH_3), 3.78 and 4.13(4H, 2m, 2O–CH_2–C), 5.60(1H, d, $^3J_{HP}$= 17.6 Hz, P–C–CH), 6.46 and 6.86(2H_{arom}, $C_7H_5N_2$), 7.44–7.72(15H, m, 3C_6H_5), 7.77, 7.86 and 8.04 (3H_{arom}, $C_7H_5N_2$), **13**C NMR (125.8 MHz, $CDCl_3$): δ_C 13.95 and 14.23(2s, 2O-C-CH_3), 43.36(d, $^1J_{PC}$= 127.0 Hz, P=C), 56.08(d, $^2J_{PC}$= 16.8 Hz, P–C–CH), 57.84 and 61.13(2s, 2O–CH_2-C), 99.20, 115.09, 120.46, 126.41, 128.92, 141.48 and 147.08(7C, $C_7H_5N_2$), 126.80(d, $^1J_{PC}$=92.0 Hz, C_{ipso}), 128.65(d, $^3J_{PC}$= 12.0 Hz, C_{meta}), 131.97(d, $^4J_{PC}$= 2.3 Hz, C_{para}), 133.62(d, $^2J_{PC}$= 9.8 Hz, C_{ortho}), 169.83(d, $^3J_{PC}$= 13.0 Hz, C=O ester), 171.91 (d, $^2J_{PC}$= 13.7 Hz, P-C=C). **31**P NMR (202.4 MHz, $CDCl_3$): δ_P 23.87(Ph_3P^+–C).

Minor isomer (23 %): **1**H NMR (500.1 MHz, $CDCl_3$): δ_H 1.20 and 1.29(6H, 2t, $^3J_{HH}$= 7.1and 7.2 Hz, 2O–C–CH_3), 3.99 and 4.23(4H, 2m, 2O–CH_2–C), 5.63(1H, d, $^3J_{HP}$= 17.5 Hz, P–C–CH), 6.46 and 6.86(2H_{arom}, $C_7H_5N_2$), 7.44–7.72(15H, m, 3C_6H_5), 7.77, 7.86 and 8.04(3H_{arom}, $C_7H_5N_2$). **13**C NMR (125.8 MHz, $CDCl_3$): δ_C 14.23 and 14.99(2s, 2O-C-CH_3), 43.73(d, $^1J_{PC}$= 134.0 Hz, P=C), 55.81(d, $^2J_{PC}$= 17.0 Hz, P–C–CH), 58.51 and 61.32(2s, 2O–CH_2-C), 99.20, 115.09, 120.42, 126.45, 128.92, 141.44 and 147.08(7C, $C_7H_5N_2$), 127.49 (d, $^1J_{PC}$= 92.1 Hz, C_{ipso}), 128.65(d, $^3J_{PC}$= 12.1 Hz, C_{meta}), 131.97 (d, $^4J_{PC}$= 2.3 Hz, C_{para}), 133.62(d, $^2J_{PC}$= 9.8 Hz, C_{ortho}), 170.41 (d, $^3J_{PC}$= 16.1 Hz, C=O ester), 171.74(d, $^2J_{PC}$= 15.8 Hz, P-C=C).**31** P NMR (202.4 MHz, $CDCl_3$): δ_P 24.78 (Ph_3P^+–C).

Selected data for Di-*tert*-buthyl 2-(7-azaindole-l-yl)-3-(triphenylphosphanylidene)-butanedioate (**4c**). White powder, m.p. 155–157°C, 0.58 g, yield 96 %. IR (ν_{rnax}, cm^{-1}): 1736 and 1630 (C=O). Mz (*m/z*, %): 606(M, 3), 506(M-2CO_2tBu, 100), 262(PPh_3, 40), 183 (PPh_2, 26), 118(heterocyclic, 20), 108(PPh, 9), 77(Ph, 8); Anal. Calcd. for $C_{37}H_{39}N_2PO_4$ C, 73.26; H, 6.43; N, 4.62, Found: C, 73.20; H, 6.39; N, 4.66. **1**H NMR (500.1 MHz, $CDCl_3$): δ_H 1.04 and 1.56(18H, 2s, 2CMe_3), 5.51(1H, d, $^3J_{HP}$=17.0 Hz, P–C–CH), 6.49 and 6.84(2H_{arom}, $C_7H_5N_2$), 7.34–7.58(15H, m, 3C_6H_5). 7.76, 7.83 and 8.11(3H_{arom}, $C_7H_5N_2$), **13**C NMR (125.8 MHz, $CDCl_3$): δ_C 28.28 and 28.49(2s, 2OCMe_3), 43.34(d, $^1J_{PC}$= 127.4 Hz, P=C), 56.6(d, $^2J_{PC}$= 16.7 Hz, P–C–CH), 80.6 and 80.99(2s, 2OCMe_3), 100.42, 115.76, 120.51, 125.52, 129.07, 142.35 and 148.94(7C, $C_7H_5N_2$), 127.24 (d, $^1J_{PC}$= 91.7 Hz, C_{ipso}), 128.53(d, $^3J_{PC}$= 12.0Hz, C_{meta}), 131.88 (d, $^4J_{PC}$=2.1 Hz, C_{para}), 133.65(d, $^2J_{PC}$= 9.5 Hz, C_{ortho}), 169.48 (d, $^3J_{PC}$= 12.8 Hz, C=O ester), 170.91(d, $^2J_{PC}$=13.2 Hz, P-C=C).**31** P NMR (202.4 MHz, $CDCl_3$): δ_P 23.61(Ph_3P^+–C).

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