Generation and utilisation of P-cyclic α-methoxycarbonylmethylenephosphoranes

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Phosphonium salts **3** obtained by the quaternisation of 1-aryl-2,5-dihydro-1H-phospholes **2** with methyl bromoacetate are suitable precursors of the corresponding heterocyclic phosphoranes **5**. They were generated *in situ* using DBU at ambient temperature. The phosphoranes (**5**) were used in Wittig reaction with benzaldehydes and in acylation with methyl (chloroformyl)formate to afford in the latter case, heterocyclic α,β-bis(methoxycarbonyl)-β-oxophosphoranes (**7**).

Keywords: phosphorus heterocycles, phosphoranes/ylides, Wittig reaction, acylation

β-Oxophosphoranes and their derivatives form a special group of compounds that are of synthetic utility.[1] We discovered an unexpected reaction involving the interaction of cyclic P-trialkylphenylphosphine oxides and dialkyl acetylenedicarboxylates to afford β-oxophosphoranes (stabilised phosphonium ylides).[2,3] A more general approach was described by Aitken and co-workers involving the acylation of phosphoranes by α-oxo-acid chlorides.[4-7] This route is of practical importance as the starting materials are easily available.[4,5]

We wished to apply the acylation approach, to extend the scope of P-cyclic β-oxophosphoranes. Note that the novel reaction described is suitable only for the preparation of phosphoranes with trialkylphenyl substituent on the phosphorus atom.[3] Because of the lack of X-ray data for the novel products,[3] an alternative synthesis was envisaged to obtain an independent evidence for their structure.

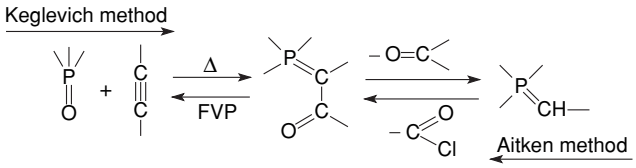
Aitken, moreover, utilised the β-oxophosphoranes in the synthesis of di- or monosubstituted acetylenes by flash vacuum pyrolysis.[4-7] Our approach applying the reaction of cyclic phosphine oxides and dialkyl acetylenedicarboxylates to furnish β-oxophosphoranes followed by deacylation[8] represents a retro synthetic route (Scheme 1).

Results and discussion

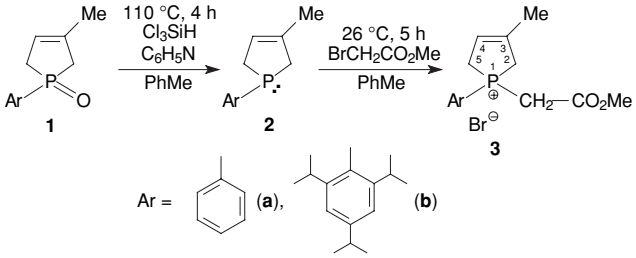
In order to synthesise the methoxycarbonylmethyl phosphonium salts **3a** and **3b** as precursors of the corresponding heterocyclic phosphoranes (see later), 2,5-dihydro-1H-phosphole oxides **1a** and **1b** were first deoxygenated by trichlorosilane in the presence of pyridine[9] to afford phosphines **2a** and **2b**. These were then quaternised by methyl bromoacetate under mild conditions to give the phosphonium salts **3a** and **3b** (Scheme 2).

Phosphonium salts **3a** and **3b** were characterised by ^{31}P, ^{13}C and ^{1}H NMR, as well as by mass spectroscopic methods. The conversion of the phosphonium salts **3** to phosphoranes **5** was studied on the phenyl-substituted model compound (**3a**).

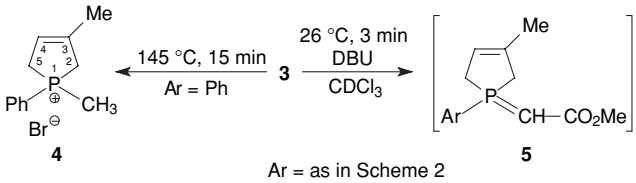
First, the thermal stability of **3a** was investigated. On heating at 145 °C in an inert atmosphere, **3a** was converted surprisingly to the methyl-phenylphosphonium salt **4** (Scheme 3). Product **4** was characterised by NMR and mass spectroscopy. The mechanism of the decomposition was not studied. However, a similar transformation has been described for methoxycarbonylmethyl-triphenylphosphonium bromide.[10]



Scheme 1



Scheme 2



Scheme 3

The dehydrobromination was attempted under phase transfer catalytic conditions using K_2CO_3/acetonitrile at 26 °C, or NaOH/H_2O–dichloromethane where the starting phosphonium salt (**3**) was assumed to act as a catalyst. These experiments did not give the required phosphorane. In the first case, the starting material (**3a**) was recovered, while in the other example, the phosphonium salt (**3a**) was hydrolysed to dihydrophosphole oxide **1a**. In the next experiments, tertiary amines were applied as the base. The use of triethylamine did not lead to HBr elimination, DBU was, however, a suitable dehydrobrominating agent at room temperature. In an NMR tube experiment, phosphorane **5a** could be detected at δ_P 33.5 after a 30 min reaction time (Scheme 3).

Compound **5a** was found to be extremely water-sensitive. This is quite unusual. It was converted to the dihydrophosphole oxide **1a** on standing or during the work-up. In a

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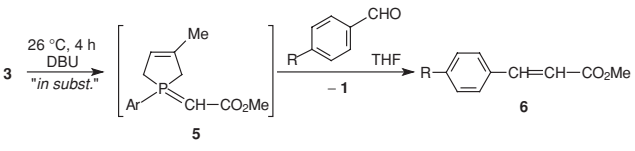
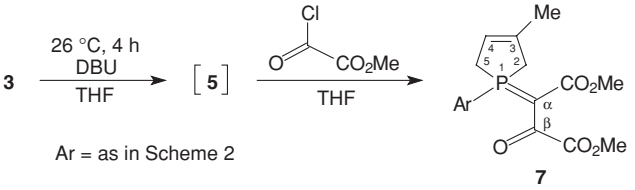


Ar		R	Yield of **6** [%]	E/Z ratio of **6** [%][a]
C_6H_5 (**a**)		MeO	49	80/20
C_6H_5 (**a**)		H	53	84/16
C_6H_5 (**a**)		NO_2	41	58/42
2,4,6-tri $^iPrC_6H_2$	(**b**)	MeO	56	52/48
2,4,6-tri $^iPrC_6H_2$	(**b**)	H	58	60/40
2,4,6-tri $iPrC_6H_2$	(**b**)	NO2	39	42/58

[a]On the basis of GC-MS.

Scheme 4



Scheme 5

similar experiment, the ^{31}P NMR signal of triisopropylphenyl phosphorane **5b** was observed at δ_P 29.1 as an unstable species.

On the basis of the above experiences, phosphoranes **5a** and **5b** were generated *in situ* and were used in Wittig reaction, as the simplest test to identify them. Accordingly, the mixture of the phosphonium salt (**3a** and **3b**) and the benzaldehyde derivative (neat or in the case of 4-nitrobenzaldehyde in THF) was treated with DBU at 26 °C furnishing the expected methyl cinnamates **6** (Scheme 4).

GC-MS measurements indicated that the products (**6**, R is listed in Scheme 4) obtained in 39–58% yield consisted of two isomers in which the *E/Z* ratio varied over a relatively wide range (84/16–42/58) (see Scheme 4).

The phosphoranes (**5a** and **5b**) generated *in situ* were acylated. DBU was added to the tetrahydrofuran solution of phosphonium salts **3a** and **3b**, followed after 5 min by methyl (chloroformyl)formate. The work-up procedure involving purification by column chromatography to provide the β-oxophosphoranes **7a** and **7b**, respectively, in *ca* 40% yield (Scheme 5). The products (**7a** and **7b**) were characterised by ^{31}P, ^{13}C and ^1H NMR, as well as mass spectra.

In the light of the above, it is possible to prepare a new family of P-cyclic β-oxophosphoranes with simple aryl-substituents on the phosphorus atom. The alternative synthesis of β-oxophosphoranes can be regarded to be an independent proof for the structure of the novel products.

Experimental

The ^{31}P-, ^{13}C- and ^1H NMR spectra were taken on a Bruker DRX-500 spectrometer operating at 202.4, 160.4 125.7, and 500 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 or TMS. The couplings are given in Hz. FAB mass spectrometry was performed on a ZAB-2SEQ instrument. GC-MS measurements were performed on a Fisons GC 8000/MD 800 apparatus. A 25m × 0.25mm × 0.25μm DB-5ms capillary column was used in the GC unit in the range of 60–290 °C applying helium (0.8 ml/min) as the carrier gas. The temperature of the ion source was 200 °C, while the ionisation energy was 70 eV.

General procedure for the preparation of phosphonium salts (**3**): To the solution of phospholene oxide (**1**) (2.6 mmol) of dry toluene (20 ml) of pyridine (0.63 ml, 7.8 mmol) and of trichlorosilane (0.29 ml, 2.9 mmol) were added under N_2 atmosphere. The mixture was refluxed for 4 hours, then the precipitate was filtered. The solution of the arylphospholene (**2**) so obtained was treated with 0.49 ml (5.2 mmol) of methyl bromoacetate. After a 5 h stirring at room temperature, the precipitated phosphonium salt (**3**) was filtered off and dried.

The following products were thus prepared:

α-*Methoxycarbonylmethyl-3-methyl-1-phenyl-2,5-dihydro-1H-phosphoniumbromide* (**3a**): Yield: 0.78 g (92%) as a white powder (that decomposes above 75 °C), ^{31}P NMR ($CDCl_3$) δ 44.1; ^{13}C NMR ($CDCl_3$) δ 19.5 (d, J = 11.5, C_3–CH_3), 29.4 (d, J = 53.0, C_α)[a], 31.7 (d, J = 53.5, C_5)[a], 32.9 (d, J = 56.0, C_2)[a], 53.5 (OCH_3), 118.2 (d, J = 80.9, $C_{1'}$), 120.3 (d, J = 5.8, C_4), 129.9 (d, J = 13.0, $C_{3'}$)[b], 132.2 (d, J = 10.3, $C_{2'}$)[b], 134.6 (d, J = 2.5, $C_{4'}$), 137.4 (d, J = 10.7, C_3), 165.9 (d, J = 3.7, C=O), [a,b]may be reversed; ^1H NMR δ 1.88 (s, 3H, C_3–CH_3), 3.23–3.44 (m, 2H, CH_2), 3.61 (s, 3H, OCH_3), 3.90–4.06 (m, 2H CH_2), 5.01 (d, J_{PH} = 14.0, 2H, C(α)H_2), 5.65 (d, J_{PH} = 32.0, 1H, CH=), 7.50–8.17 (m, 5H, ArH); FAB-MS, 249 (M^+); M^+_{found} = 249.1024, $C_{14}H_{18}O_2P$ requires 249.1044.

α-*Methoxycarbonylmethyl-3-methyl-1-(2,4,6-triisopropylphenyl)-2,5-dihydro-1H-phosphonium bromide* (**3b**): Yield: 0.88 g (90%) as a white powder, m.p. 85–86 °C; ^{31}P NMR ($CDCl_3$) δ 40.1; ^{13}C NMR ($CDCl_3$) δ 19.2 (d, J = 11.2, C_3–CH_3), 23.5 ($CH(CH_3)_2$), 25.2 ($CH(CH_3)_2$), 25.3 ($CH(CH_3)_2$), 33.0 (d, J = 43.9, C_α)[a], 33.4 (d, J = 47.4, C_5)[a], 33.8 (d, J = 5.5, *o*-$CHMe_2$), 34.4 (*p*-$CHMe_2$), 36.5 (d, J = 54.3, C_2)[a], 53.4 (OCH_3), 111.1 (d, J = 78.9, $C_{1'}$), 119.8 (d, J = 6.3, C_4), 124.5 (d, J = 11.9, $C_{3'}$), 137.2 (d, J = 10.9, C_3), 155.4 (d, J = 11.7, $C_{2'}$), 156.5 ($C_{4'}$), 165.4 (d, J = 4.7, C=O), [a]may be reversed; ^1H NMR δ 1.27 (d, J = 6.9, 6H, $CH(CH_3)_2$), 1.36 (d, J = 6.3, 12H, $CH(CH_3)_2$) 2.03 (s, 3H, C_3–CH_3), 2.85–3.02 (m, 1H, $CHMe_2$) 3.08–3.22 (m, 2H, $CHMe_2$), 3.69 (s, 3H, OCH_3), 4.38 (dd, J_{PH} = 14.1, J_{HH} = 2.7, 2H, C(α)H_2), 5.75 (d, J_{PH} = 33.3, 1H, CH=), 7.23 (s, 2H, ArH); FAB-MS, 375 (M^+); M^+_{found} = 375.2427, $C_{23}H_{36}O_2P$ requires 375.2453.

1,3-Dimethyl-1-phenyl-2,5-dihydro-1H-phosphonium bromide: Heating 0.20 g (0.80 mmol) of phospholium bromide **3a** at 145 °C for 15 min in nitrogen atmosphere afforded 0.13 g (85 %) of phosphonium salt **4** as an amorphous solid. ^{31}P NMR ($CDCl_3$) δ 44.0; ^{13}C NMR ($CDCl_3$) δ 9.3 (d, J_{PC} = 49.8, P–CH_3), 19.2 (d, J_{PC} = 11.0, C_3–CH_3), 30.5 (d, J_{PC} = 52.2, C_5)[a], 33.9 (d, J_{PC} = 55.5, C_2)[a], 119.6 (d, J_{PC} = 80.8, $C_{1'}$), 120.2 (d, J_{PC} = 4.9, C_4), 129.6 (d, J_{PC} = 12.9, $C_{3'}$)[b], 132.0 (d, J_{PC} = 10.0, $C_{2'}$)[b], 134.2 (d, J_{PC} = 2.6, $C_{4'}$), 137.2 (d, J_{PC} = 8.4, C_3); ^1H NMR δ 1.79 (s, 3H, C_3–CH_3), 2.61 (d, J_{PH} = 15.0, 3H, P–CH_3), 3.07–3.39 (m, 2H, CH_2), 3.64–3.79 (m, 2H, CH_2), 5.55 (d, J_{PH} = 31.5, 1H, CH=), 7.42–7.95 (m, 5H, ArH); FAB-MS, 191 (M^+); M^+_{found} = 191.0978, $C_{12}H_{16}P$ requires 191.0990.

General procedure for the Wittig reactions: To 0.3 mmol of the corresponding arylphosphonium bromide (**3a** or **3b**) and 3.0 mmol of an aldehyde in 5 ml of THF was added 0.05 ml (0.3 mmol) of DBU by a syringe on stirring at room temperature under N_2. After a 4 h reaction, the volatiles were removed *in vacuo* and the residue was passed through a silica gel column using 3% methanol in chloroform as the eluant. The fraction containing the isomers of cinnamate **6** was analysed by GC–MS. For isolated yields and isomeric ratios, see the table of Scheme 4. The products (**6**) identified by EI–MS were of *ca* 94–98% purity according to GC.

6–1, R = MeO: EI–MS (relative intensity) 192 (M^+, 79%), 161 (M–MeO, 100%), 133 (M–CO_2Me, 30%); **6–2**, R = MeO: EI–MS (relative intensity) 192 (M^+, 80%), 161 (M–MeO, 100%), 133 (M–CO_2Me, 35%).

6–1, R = H: EI–MS (relative intensity) 162 (M^+, 58%), 131 (M–MeO, 100%), 103 (M–CO_2Me, 64%), 77 (37%); **6–2**, R = H: EI–MS (relative intensity) 162 (M^+, 54%), 131 (M–MeO, 100%), 103 (M–CO_2Me, 71%), 77 (40%).

6–1, R = NO_2: EI–MS (relative intensity) 207 (M^+, 48%), 176 (M–MeO, 100%), 130 (176–NO_2, 35%); **6–2**, R = NO_2: EI–MS (relative intensity) 207 (M^+, 43%), 176 (M–MeO, 100%), 130 (176–NO_2, 41%).

General method for the preparation of α,β-*bis(methoxycarbonyl)*-β-*oxophosphoranes* (**7**): To the solution of 1.1 mmol of phosphonium salt **3** in 10 ml of dry THF, 0.17 ml (1.1 mmol) of DBU was added under N_2 atmosphere. Five minutes later, the mixture was treated with 0.10 ml (1.1 mmol) of methyl (chloroformyl)formate and was stirred for 4 hours at room temperature. The mixture was added to 10 ml of water and extracted with 3 × 7 ml of diethylether. The organic phase was dried (Na_2SO_4) and the solvent evaporated to give the phosphorane (**7**).

2-[3-Methyl-1-phenyl-2,5-dihydro-1H-phosphole-1-ylidene]-3-oxo-succinic acid dimethyl ester (**7a**): Yield: 0.14 g (38%) as a thick oil; ^{31}P NMR ($CDCl_3$) δ 33.2; ^{13}C NMR ($CDCl_3$) δ 19.2 (J = 11.5, C_3–CH_3), 32.8 (J = 59.5, C_5), 36.3 (J = 62.4, C_2), 51.1 (MeO), 52.2 (MeO), 69.5 (J = 104.2 C_α), 121.4 (J = 5.7 C_4), 126.4 (J = 80.2, $C_{1'}$), 129.6 (J = 12.5, $C_{2'}$)*,130.3 (J = 10.6, $C_{3'}$)*, 133.1 (J = 3.1, $C_{4'}$), 138.0 (J = 10.4, C_3), 167.4 (J = 13.1, C=O), 168.0 (J = 15.4, C=O), 184.0 (J = 6.2, C_β), *tentative assignment; ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 3H, C_3–CH_3), 3.05–3.27 (m, 4H, CH_2), 3.48–3.58 (m, 4H, CH_2), 3.65 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.69 (d, J_{PH} = 32.5, 1H, CH=), 7.45–7.68 (m, 5H, ArH); FAB–MS, 335 $(M+1)^+$; $(M+H)^+_{found}$ = 335.1021, $C_{17}H_{20}O_5P$ requires 335.1048; IR (film) 1724, 1683 cm^{-1}.

2-[3-Methyl-1-(2,4,6-triisopropylphenyl)-2,5-dihydro-1H-phosphole-1-ylidene]-3-oxo-succinic acid dimethyl ester (**7b**): Yield: 0.23 g (45% as a thick oil); ^{31}P NMR ($CDCl_3$) δ 33.8; ^{13}C NMR ($CDCl_3$) δ 18.9 (J = 10.4, C_3–CH_3), 23.5 ($CH(CH_3)_2$), 24.7 ($CH(CH_3)_2$), 24.8 ($CH(CH_3)_2$), 31.8 (J = 6.0, o-$CHMe_2$), 34.1 (p-$CHMe_2$), 34.5 (J = 56.4, C_5), 37.6 (J = 59.0, C_2), 50.6 (MeO), 51.5 (MeO), 72.7 (J = 99.7, C_α), 119.7 (J = 86.2, $C_{1'}$), 120.5 (J = 6.3, C_4), 123.4 (J = 11.5, $C_{3'}$), 137.1 (J = 10.7, C_3), 153.0 (J = 2.7, $C_{4'}$), 153.7 (J = 11.2, $C_{2'}$), 166.9 (J = 14.3, C=O), 167.7 (J = 14.7, C=O), 183.2 (J = 6.2, C_β); ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 7.2, 6H, $CH(CH_3)_2$), 1.27 (d, J = 8.1, 6H, $CH(CH_3)_2$), 1.30 (d, J = 6.3, 6H, $CH(CH_3)_2$), 1.87 (s, 3H, C_3–CH_3), 2.76–2.96 (m, 1H, p-$CHMe_2$), 3.45–3.60 (m, 2H, o-$CHMe_2$), 3.59 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 5.59 (d, J_{PH} = 30.3, 1H, CH=), 7.12 (s, 2H, ArH); FAB–MS, 461 $(M+1)^+$; $(M+H)^+_{found}$ = 461.2427, $C_{26}H_{38}O_5P$ requires 461.2457; IR (film) 1732, 1672 cm^{-1}.

Gy. K. is grateful for the OTKA support (No. T 042479) of the work. We are indebted to Zoltán Nagy (Gedeon Richter Ltd.) for the GC–MS measurements.

Received 25 November 2004; accepted 11 January 2005
Paper 04/2898

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