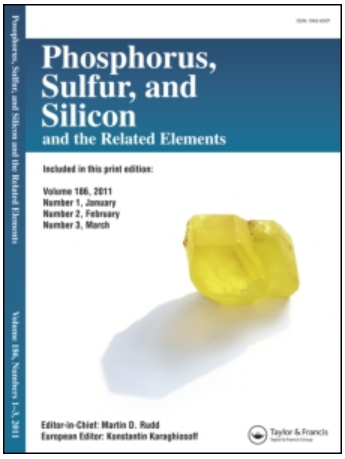

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ORGANOPHOSPHORUS CHEMISTRY 22[1]. REACTION OF 3-FORMYL-4-CHROMONE WITH TER- AND PENTA-VALENT PHOSPHORUS COMPOUNDS

Wafaa M. Abdou[a]; Maha D. Khidre[a]; Mohamed R. Mahran[a]
[a] Department of Pesticide Chemistry, National Research Centre, Cairo, A. R. Egypt

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ORGANOPHOSPHORUS CHEMISTRY 22[1]. REACTION OF 3-FORMYL-4-CHROMONE WITH TER- AND PENTA-VALENT PHOSPHORUS COMPOUNDS

WAFAA M. ABDOU, MAHA D. KHIDRE and
MOHAMED R. MAHRAN

Department of Pesticide Chemistry, National Research Centre, Dokki, Cairo, A. R. Egypt

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Trialkyl phosphites (**2**) and dialkyl phosphonates (**5**) attack the aldehydic carbonyl-carbon of 3-formyl-4-chromone (**1**), yielding the corresponding α-alkoxy (**4**), and α-hydroxy-phosphonates (**6**), respectively.

On the other hand, the reaction of **1** with ylide-phosphoranes (**10**) proceeded according to the Wittig reaction mechanism, to give the respective ethylenes **13**. Identity of the isolated products are based on analytical, chemical and spectroscopic data.

Key words: 3-Formyl-4-chromone; alkyl phosphites; ylide-phosphoranes.

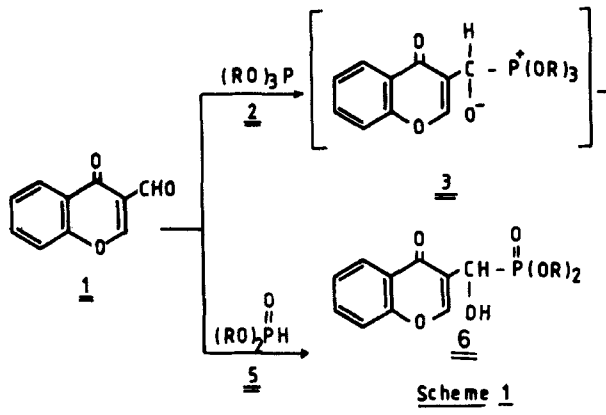
INTRODUCTION

Although 3-formyl-4-chromone (**1**) is known to undergo a number of reactions with nucleophiles,[2–4] its behavior toward phosphorus nucleophiles has not hitherto been reported. In view of the marked potentialities of chromones,[3–6] the present study has been undertaken to prepare a number of new organophosphorus derivatives of 3-formyl-4-chromone (**1**) for biological testing. We have also extended the scope to include reactions between **1** and resonance stabilized[7] ylides **10**.

In compound **1**, both the γ-pyrone and the aldehydic carbonyl functions appear in the reactions of the molecule. Even though the γ-pyrone carbonyl group does not enter into the usual reactions of the ketone function, there are cases in which both groups taking part in the reactions.[8]

RESULTS AND DISCUSSION

Upon conducting the reaction of **1** (also known, as 4-oxo-4H-chromene-3-carboxaldehyde) with trialkyl phosphites (**2**) in the absence of a solvent at 100°C, colorless crystalline 1:1 adducts, formulated as α-alkoxy-phosphonates **4** were obtained in good yield. The assigned phosphonate structure **4** is based on the following reasons: **i)** Correct combustion values and molecular weights (MS) were obtained for all the new products. **ii)** The IR spectra of these compounds revealed the presence of γ-pyrone carbonyl absorption at ~1635 cm^{-1} (recorded with **1** at 1645 cm^{-1})[9] and lack of the characteristic absorption band attributable to the stretching frequency of the aldehydic carbonyl function in the region 1700 cm^{-1} (recorded with **1** at

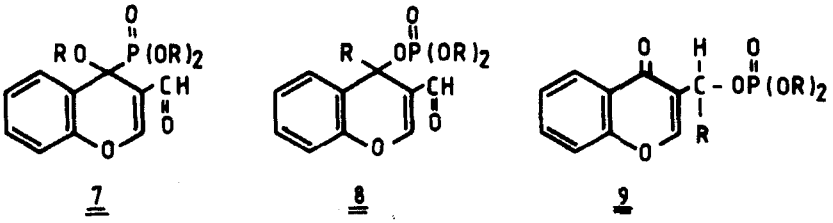


^{31}PNMR

2-6	R	4	6
a	CH_3	24.3	27.6
b	C_2H_5	26.5	28.3
c	i - C_3H_7	22.6	28.55

1695 cm^{-1}). In addition, they exhibited intense bands corresponding to the >P=O (bonded), —C—O—C, and —P—O—C (alkyl) stretching vibrations.[10]

iii) The ^{1}H NMR (δ) spectrum of **4a** lacked a signal due to —C(=O)—H (recorded with **1** at 10.3); instead a new signal appeared at 5.23 (1H, d, J_{HP} = 22 Hz) due to the exocyclic methine proton. The two methoxyl groups attached to the phosphorus atom appeared as two doublets (6H, each with $^3J_{HP}$ = 13.5 Hz) at 3.5 and 3.6 ppm. Moreover, a doublet resonated for the methoxyl group at 3.15 ($^4J_{HP}$ = 4.5 Hz).[10] A multiplet is visible for the aromatic protons centered at 7.88, while the ring-vinyl proton gave a singlet at 8.47. **iv)** ^{31}P NMR spectrum (*vs.*, 85% H_3PO_4) of **4a** had a signal at 24.3 ppm, indicating a phosphonate structure.[11] Based upon the above arguments, these data are most adequately accommodated in structure **4** and rule out other possible structures like **7–9**.



Actually, the ^{13}C NMR spectra offered strong evidence in support of the assigned structure **4**. ^{13}C NMR (δ)[10] of compound **4a** (in $CDCl_3$), exhibited signals at 54.7 and 55.15 (2d, —P—O—C), 59.53 (d, $CO\underline{C}H_3$), 62.9 (d, $\underline{C}OCH_3$), and at 176.34 ppm (>C=O, γ-pyrone).

We conclude that the phosphorus of the phosphite adds slowly to the aldehydic carbonyl-carbon[12,13] to yield the alkoxyphosphonium cation **3**, which undergoes intermolecular dealkylation by the anionic centre, (Scheme 1) to give the expected dialkoxyphosphonates **4**.[14–15]

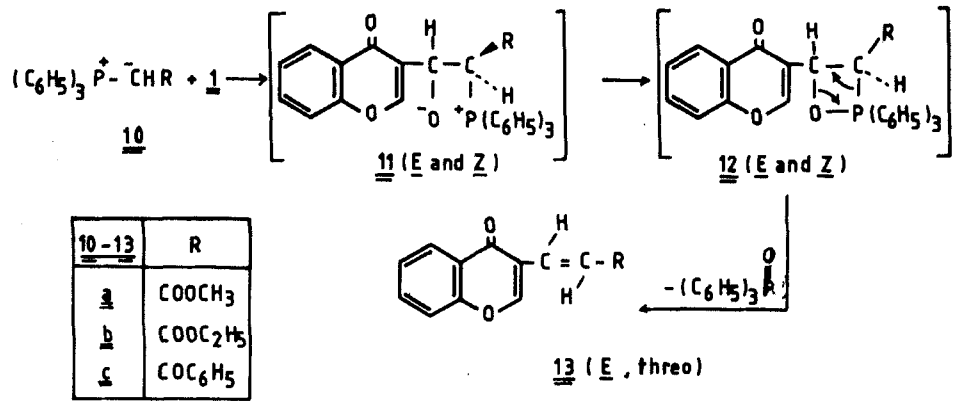
Further, treatment of **1** with dialkyl phosphonates (**5a–c**) led to the production of colorless crystalline 1:1 adducts as inferred from their elemental analyses and molecular weight determinations (MS). The reaction products, believed to have structures **6a–c** (Scheme 1), dissolve in aqueous sodium hydroxide solution and do not respond positively to ferric chloride color reaction. Upon treatment of **6a** with an ethereal diazomethane solution, it could be recovered, practically unchanged. On the other hand, compound **6a** regenerated the chromone **1** when heated above its melting point under reduced pressure. In favor of the assigned α-hydroxy phosphonate structure **6** are: **i)** The IR spectrum of **6a** showed strong absorption bands at 3210 (—OH), 1635 (>C=O, γ-pyrone), 1220 (P=O, bonded) and 1020 cm^{-1} (P—O—C).[10] **ii)** The ^1H NMR. (δ)[10] spectrum of **6a** disclosed the presence of signals at 8.4 (1H, s, ring-vinyl-H), 7.72 (4H, m, Ar-H), 5.35 (1H, d, $^2J_{HP}$ = 18.5 Hz, CH), 4.8 (1H, broad, OH, D_2O exchangeable) and at 3.55, 3.7 (6H, 2d, $^3J_{HP}$ = 12 Hz, —P—O—CH_3). The ^{31}P NMR spectrum of **6a** had a signal at 27.6 ppm indicating a phosphonate structure.

Further evidence for structure **6** was gained from ^{13}C-NMR (δ) spectrum of **6a** which showed the presence of >C=O (γ-pyrone). Also the presence of HC(OH)P— was supported by a doublet at δ 60.47 ppm. Moreover, other signals coincide with chemical shifts expected for the proposed structure.

Data on the biological activity of the new organophosphorus compounds will be published later.

Next, the reaction of 3-formyl-4-chromone (**1**) with stabilized methylenetriphenylphosphorane (**10**) was also investigated. When **1** was allowed to react with one equivalent of methoxy-(**10a**), ethoxy-(**10b**) and/or phenylcarbonylmethylenetriphenylphosphorane (**10c**) in toluene at ambient temperature for 4 h, the respective ethylene-derivatives **13a–c** accompanied with triphenylphosphine oxide were obtained, respectively, in good yields. Carrying out the reaction using two moles of the phosphonium ylide instead of one, led to the same results. The structure of the α,β-unsaturated ketones **13** is well established by the following physical and spectroscopic data: (**1**) Elemental analyses and molecular weight determinations. (**2**) The characteristic bands in the infrared spectrum of **13b** appeared at 1715 cm^{-1} (>C=O, ester), 1640 (>C=O, γ-pyrone), 1450 (—O—C, stretching) and at 1622 cm^{-1} (>C=C<, exocyclic). (**3**) ^1H NMR spectrum of **13b** had signals at δ 1.3 (3H, t, —CH_3), δ 4.23 (2H, q, —CH_2). Moreover, the exo-cyclic vinyl protons (AB) resonated as two doublets at δ 6.17 and 7.1, with J_{HH} = 17 Hz. Aromatic protons fall in the region 7.26–8.9 (4H, m), while the ring-vinyl proton resonated at δ 8.35 ppm. (**4**) In the MS spectrum of **13b,** a signal for m/z = 244 (M^+) was present.

Remarkably, compounds **13** could be present in *Z* or *E* configuration. However, the *E* isomer seems to be the only structure that represents the alkenes **13**. In favor of this conclusion, is the large coupling constant (J_{HH} = ~16 Hz) between the two hydrogens of the exocyclic AB system in the PMR spectrum. Moreover, *E*-selective



10-13	R
a	$COOCH_3$
b	$COOC_2H_5$
c	COC_6H_5

Scheme 2

carbonyl olefination is generally accepted,[7,16-19] for the reactions of aldehydes with stabilized Wittig reagents of type **10**.

According to the Wittig reaction mechanism,[7,16] the reaction is a two-stage process (Scheme 2) initiated by nucleophilic attack of the ylide on the aldehydic carbonyl-carbon atom to give two possible isomeric betaines **11** (*E* and *Z*). Subsequent decomposition is then believed to occur by way of a four-centered cyclic intermediate **12** which eleminates triphenylphosphine oxide to form the *E* alkene **13**. We presume that the formation of *E* isomer is attained, almost exclusively, with complete exclusion of the *Z* isomer, since betaine formation is reversible[20] and frequently the *Z*-alkenes having electron withdrawing groups at the α-carbon (cf. **12**, $\diagdown$C=O$\diagup$) isomerized to the thermodynamically more stable *E*-isomer.[16,20,21]

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were run on a Perkin Elmer Infracord Spectrometer Model 197 (Grating) in KBr. The ^1H NMR spectra were recorded on a Bruker Spectrometer Model WH-90 and the chemical shifts were recorded in δ ppm relative to TMS. The ^{31}P NMR spectra were taken on Varian CFT-20 (*vs.* 85% H_3PO_4). The mass spectra were performed at 70 eV on MS-50 Kratos (A.E.I.) Spectrometer provided with data system. Elemental analyses were carried out at the "Microanalysis Laboratory, National Research Centre, Cairo."

Reaction of 3-Formyl-4-Chromone (**1**) *with Trialkyl Phosphites* (**2**)

General procedure: A mixture of **1**[22] (0.01 mol) and trialkyl phosphite (trimethyl-, triethyl- or triisopropyl phosphite) (4 ml) was heated in the absence of solvent at 100°C for *ca.* 6 h. After removing the volatile materials, *in vacuo*, the residue was triturated with light petroleum and left to cool, the solid so formed was collected, and recrystallized from a suitable solvent to give compounds **4**. Physical and analytical data for compounds **4** are presented in Tables I–III.

Reaction of 3-Formyl-4-Chromone (**1**) *with Dialkyl Phosphonates* (**5**)

General procedure: A mixture of **1** (0.01 mol) and dialkyl phosphonate (dimethyl-, diethyl- or diisopropyl phosphonate) (5 ml) was heated in the absence of solvent at 100°C for 10 h. After the reaction was completed (TLC), the volatile material was evaporated, *in vacuo*, the residual substance was

TABLE I

Physical characteristics of **4**, **6** and **13**

Compound	Yield in %	m.p. °C	Mol. Form. (M. Wt)	Anal. (Calcd./Found) C	H	P	M^+ m/z	—OH	IR cm^{-1} C=O (pyrone)	P=O	P—O—C
4a	74	147[a]	$C_{13}H_{15}O_6P$	52.35	5.06	10.38	298	—	1635	1265	1015
			(298.24)	52.18	5.04	10.27					
b	78	128[b]	$C_{16}H_{21}O_6P$	56.46	6.22	9.10	340	—	1645	1275	1025
			(340.32)	56.36	6.17	8.88					
c	80	133[c]	$C_{19}H_{27}O_6P$	59.67	7.11	8.10	382	—	1630	1280	985
			(382.41)	59.57	7.06	7.95					
6a	77	178[b]	$C_{12}H_{13}O_6P$	50.71	4.61	10.90	284	3210	1635	1220	1020
			(284.22)	50.67	4.56	10.84					
b	85	122[b]	$C_{14}H_{17}O_6P$	53.84	5.48	9.92	312	3390	1630	1215	1010
			(312.27)	53.76	5.44	9.78					
c	82	136[b]	$C_{16}H_{21}O_6P$	56.46	6.22	9.10	340	3290	1640	1230	1030
			(340.33)	56.57	6.20	8.89					
13a	70	92[d]	$C_{13}H_{10}O_4$	67.82	4.37	—	230	1710	1645	—	1618
			(230.22)	68.31	4.27			C=O, ester			CH=CH
b	68	141[e]	$C_{14}H_{12}O_4$	68.84	4.95	—	244	1715	1640	—	1622
			(244.25)	68.50	7.87			C=O, ester			CH=CH
c	88	165[e]	$C_{18}H_{12}O_3$	78.24	4.37	—	276	1670	1635	—	1610
			(276.29)	77.93	4.29			C=O, benzoyl			CH=CH

Solv. of Cryst.: [a] alcohol/ether (v/v, 1:1).
[b] Cyclohexane.
[c] Chloroform.
[d] Aceton/light petroleum (v/v, 1:1).
[e] Light petroleum.

TABLE II

^{1}H-NMR spectral data of compounds **4, 6** and **13**

Compound[a]	^{1}H NMR (δ, ppm)[b]				
4a	—	—	3.15 (d, 3H)	3.5, 3.6 (2d, 6H)	5.23 (d, 1H)
	—	—	J_{HP} = 4.5 Hz	J_{HP} = 13.5 Hz	$^2J_{HP}$ = 22 Hz
	—	—	C—O—CH_3	P—O—CH_3	—CH
b	1.2 (d of t, 6H)	1.5 (d of t, 3H)	3.5 (qt,[c] 2H)	4.1 (d of q, 4H)	5.20 (d, 1H)
	J_{HP} = 12 Hz	J_{HP} = 4 Hz	J_{HP} = 4 Hz	J_{HP} = 12 Hz	$^2J_{HP}$ = 21.5 Hz
	J_{HH} = 6 Hz	J_{HH} = 6 Hz		J_{HH} = 4 Hz	
	P—O—C—CH_3	C—O—C—CH_3	C—O—CH_2	P—O—CH_2	—CH
c	1.1 (d of d, 12H)	1.25 (d of d, 6H)	3.2 (d of st.,[c] 1H)	4.05 (d of st., 2H)	5.6 (d, 1H)
	J_{HP} = 11.5 Hz	J_{HP} = 2.5 Hz	J_{HP} = 2.5 Hz	J_{HP} = 11.5 Hz	$^2J_{HP}$ = 21.5 Hz
	J_{HH} = 4.5 Hz	J_{HH} = 4.5 Hz	J_{HH} = 4.5 Hz	J_{HH} = 4.5 Hz	
	P—O—C—CH_3	C—O—C—CH_3	C—O—CH	P—O—CH	—CH
6a	—	—	4.8 (br., 1H)	3.55, 3.7 (2d, 6H)	5.35 (d, 1H)
	—	—	—	J_{HP} = 12 Hz	$^2J_{HP}$ = 18.5 Hz
	—	—	—OH	P—O—CH_3	—CH
b	1.25 (d of t, 6H)	—	4.9 (br., 1H)	4.15 (d of q, 4H)	5.35 (d, 1H)
	J_{HP} = 12 Hz	—	—	J_{HP} = 12 Hz	$^2J_{HP}$ = 20.0 Hz
	J_{HH} = 7 Hz	—		J_{HH} = 7 Hz	
	P—O—CH_3		—OH	P—O—CH_2	—CH
c	1.18 (d of d, 12H)	—	4.1 (br., 1H)	3.48 (d of st., 2H)	5.18 (d, 1H)
	J_{HP} = 10.5 Hz	—	—	J_{HP} = 10.5 Hz	$^2J_{HP}$ = 18.0 Hz
	J_{HH} = 7.0 Hz			J_{HH} = 7.0 Hz	
	P—O—C—CH_3		—OH	P—O—CH	—CH
13a	—	—	3.8 (s, 3H)	7.1 (d, 1H)	7.88 (d, 1H)
	—	—	—	J_{HH} = 16 Hz	J_{HH} = 16 Hz
	—	—	—O—CH_3	=CH	=CH
b	1.3 (6, 3H)	—	4.23 (q, 2H)	6.17 (d, 1H)	7.1 (d, 1H)
	J_{HH} = 6 Hz	—	J_{HH} = 6 Hz	J_{HH} = 17 Hz	J_{HH} = 17 Hz
	O—C—CH_3	—	O—CH_2	=CH	=CH

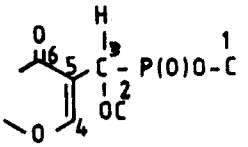
[a] The solvent is $CDCl_3$.
[b] The hydrogens of the aromatics are found in δ 7.2–8.9 ppm region.
[c] qt = Quintet.
[d] q = Quartet.
[e] st. = septet.

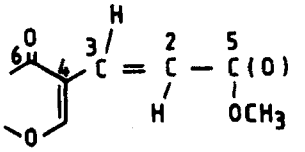
TABLE III

^{13}C-NMR spectral data[a]

Compound/ C[b,c]	C_1	C_2	C_3	C_4	C_5	C_6
4a	54.7, 55.15 (2d)	59.53 (d)	62.9 (d)	120.8 (d)	136.87 (d)	176.34
6a	54.2, 55.8 (2d)	—	60.47 (d)	121.3 (d)	136.3 (d)	176.95
13a	52.42	123.5	130.92	139.2	169.08	178.26

[a] See experimental for details of NMR experiments. Since all spectra are proton decoupled, the coupling constants listed reflect the coupling to phosphorus.
[b] The solvent is $CDCl_3$.
[c] The numbering system is as in Figures 1 and 2.





FIGURES 1 and 2

collected and recrystallized from the appropriate solvent (cf. Table 1) to give compounds **6a–c**. Percentage yields, physical and analytical data for compounds **6** are given in Tables I–III.

Adducts **6a–c** are freely soluble in 10% aqueous sodium hydroxide solution and give no color reaction with alcoholic ferric chloride.

Action of Diazomethane on **6a**. To a solution of adduct **6a** (0.5 g) in ether (10 ml) was added an ethereal solution of diazomethane (from 3 g *N*-nitrosomethylurea) and the mixture kept at 10° for 24 h. After evaporation of the solvent, compound **6a** (0.48; 95%) was recovered practically unchanged, m.p. 152°C (mp., mixed mps. and comparative IR spectra).

Action of Heat on **6a**. The hydroxy phosphonate adduct **6a** (0.5 g) was heated (bath temp., 230°C) for one hour under reduced pressure (5 mm/Hg) in a cold finger sublimator. The reaction vessel was left to cool and ethyl alcohol (5 ml) was added. The crystals which separated were recrystallized from ethanol to give the chromone **1** (identified by mp., mixed mps. and comparative IR spectra).[22] Dimethyl phosphonate was detected in the receiver by the development of a violet color on addition of 3,5-dinitrobenzoic acid in the presence of alkali.[23]

Reaction of 1 with Wittig Reagents **10**

General procedure: To a solution of the ylide **10a**,[24] **10b**[24] and/or **10c**[25] (0.01 mol) in 20 ml toluene, was added drop by drop at room temperature, a solution of 3-formyl-4-chromone (**1**, 0.01 mol) in 30 ml toluene. The reaction mixture was stirred for 4 h. The reaction mixture was then concentrated at 60°C under reduced pressure. The solid product was redissolved in methanol (100 ml) and evaporated to dryness in the presence of silica gel (5 g). The mixture was then added to a column previously charged with silica gel in cyclohexane. The column was developed with cyclohexane containing increasing amounts of chloroform. Fraction up to 8:2 v/v eluted a colorless substance, recrystallized from the suitable solvent to give **13a–c** (cf. Tables I–III).

The fraction up to 6:4 v/v afforded colorless needles, mp 156°C (ca. 80% yield) of triphenylphosphine oxide (mp., mixed mps., and comparative IR spectra).

Even when two equivalents of the ylide **10a** were used under severe reaction conditions, **10a** reacted with only the aldehydic carbonyl group in the chromone **1**, to form **13a**.

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