Heteroatom Chemistry
Volume 9, Number 4, 1998

Organophosphorus Chemistry 30 [1]. The Behavior of 4-Hydroxycoumarin toward Methylenetriphenylphosphoranes (Wittig Reagents) and Alkyl Phosphites

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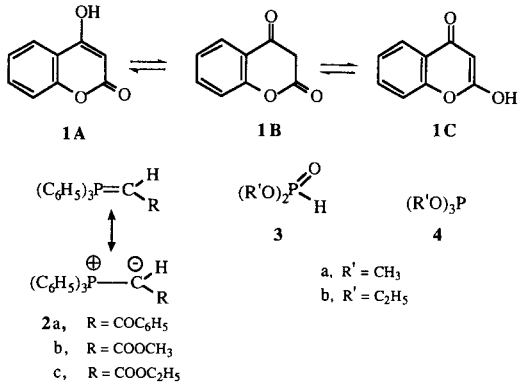
Received 22 October 1997; revised 12 February 1998

ABSTRACT: *4-Hydroxycoumarin (**1**) reacted with Wittig reagents (**2**) to give 4-benzoylmethylcoumarin (**5A**) or [3-(4-hydroxycoumarinyl)]carbonylmethylenetriphenylphosphorane (**6**) depending upon the nature of the phosphorus ylide used. Dialkyl phosphonates (**3a,b**) and trialkyl phosphites (**4a,b**) converted **1** into the respective O-alkyl ethers (**11a,b**). The ground-state structure of **1** is discussed in the light of experimental results. Compatible elementary and spectroscopic results were gained for the new products.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9:427–431, 1998

INTRODUCTION

4-Hydroxycoumarin (4HC, **1**) comprises the structural nucleus of many natural products and pesticides [2,3]. Its ground-state structure (**1A** ⇌ **1B** ⇌ **1C**) has long been a subject of arguments [3–5]. During the initial chemical characterization of **1,** it was recognized to be the enol tautomer of 2,4-chromandione (**1B**) [4]. However, it was reported that it can also react as the 2-hydroxychromone tautomer **1C** [5]. The tautomerism of **1** has been studied by many chemical methods [5–8]; none of which, however, has considered the reaction of **1** with organophosphorus reagents that show well-documented activities toward carbonyl functions [9]. In order to fill this gap, we have now studied the behavior of **1** with resonance-stabilized methylenetriphenylphosphoranes (Wittig reagents, **2a–c**) as well as with dialkyl phosphonates (**3,ab**) and trialkyl phosphites (**4a,b**).



RESULTS AND DISCUSSION

Compound **1** has been found to react with benzoylmethylenetriphenylphosphorane (**2a**) in boiling toluene to give a colorless crystalline product for which structure **5** was assigned. Triphenylphosphine oxide (TPPO) was also isolated and identified in this reaction.

Dedicated to Prof. Heinrich Nöth on the occasion of his seventieth birthday.

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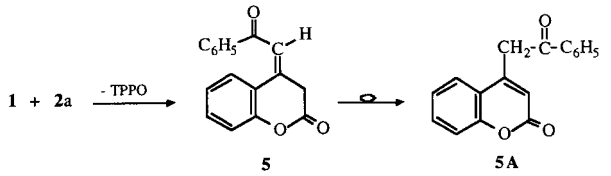
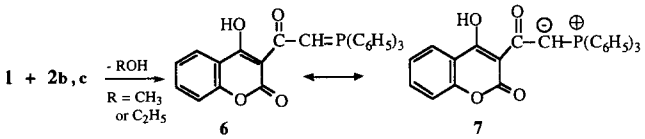
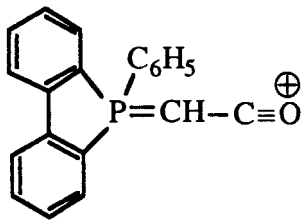


The IR spectrum of **5** (in KBr) showed a lactone-carbonyl absorption band at 1700 cm^{-1}. Its ^{1}H-NMR spectrum (in DMSO, δ ppm) showed a multiplet in the 7.70–6.60 region (10H, aromatics) as well as a singlet (2H) at 4.75. This indicates that the initially formed product **5** makes only a minor contribution to the state of the molecule and it has undergone prototropic rearrangement to the tautomeric form **5A.** This conclusion is supported by the presence of ion peaks at *m/z* 77, 187, 105, 159, 145, and 119 in the mass spectrum of **5A** that can originate via cleavage of the molecular ion peak at *m/z* 270 along axes *x, y,* and *z* to produce cations **a–f,** respectively (Chart 1).

When **1** was allowed to react with carbomethoxymethylenetriphenylphosphorane (**2b**) in boiling toluene, a yellow crystalline compound (**A**) was obtained as a sole product. The same compound was also isolated when **1** was reacted with ylide **2c** under similar conditions. It was formulated as [3-(4-hydroxycoumarinyl)-]carbonylmethylenetriphenylphosphorane (**6**) for the following reasons: (a) Its ^{31}P-NMR spectrum (in $CDCl_3$, vs. 85% H_3PO_4) showed a positive chemical shift at δ 14.77 that matches a phosphorus-ylide structure [10]. Its resonance structure **7** appears thus to make only a minor contribution to the ground state of the molecule. (b) Elementary analyses and molecular weight determination (MS) for **6** corresponded to $C_{29}H_{21}O_4P$, and the base peak in its mass spectrum, which appears at *m/z* 301, corresponds to cation **a.** (c) The main features of the IR spectrum of **6** (in KBr, cm^{-1}) were the presence of absorption bands at 3500 (OH, br), 1700 ($\rangle$C=O), 1615 (C=C, aromatic), 1490 (C=P) [11], and 1440 [P-C(phenyl)] [11]. (d) The ^{1}H-NMR spectrum of **6** (in $CDCl_3$, δ) showed a multiplet (19H) at 8.00–7.15 due to the aromatic protons along with a doublet (1H, $^2J_{HP}$ = 25 Hz) at 6.15 due to the exocyclic methine proton.





The new complex phosphorus ylide **6** reacts with aromatic aldehydes (e.g., benzaldehyde) and with heteroaryl aldehydes (e.g., 2-methyl-5-methoxy-6-formyl-7-hydroxychromone (**9**) to give the respective ethylenes **8** and **10.** TPPO was also isolated and identified in both cases (Scheme 1).

Compatible elementary and spectroscopic measurements were recorded for **8** and **10.** Thus, for example, combustion values and a molecular weight determination (MS) for **10** corresponded to $C_{23}H_{16}O_8$. Its IR spectrum (KBr, cm^{-1}) showed bands at 1735 (C=O, lactone), 1650 (C=O, aryl and γ-pyrone), 1615 (C=C, ethylenic), and 1535, 1495 (C=C, aromatic). The ^{1}H-NMR spectrum of **10** (DMSO, δ) revealed that the CH_3 protons that are attached to a doubly bonded carbon atom resonate at 2.28 (3H, d, J_{HH} = 1.5 Hz). The vinyl proton on the same γ-pyrone ring (**Ha**) gives a diffused quartet at 6.02 also

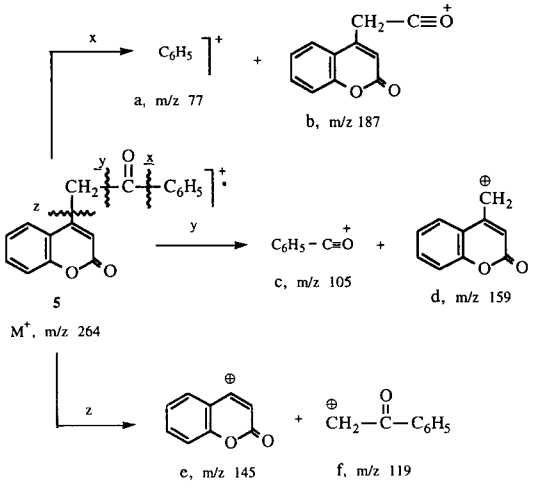
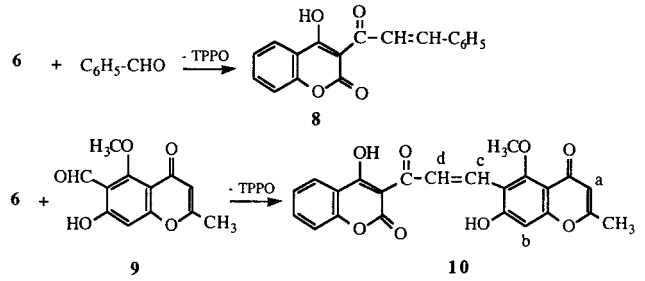


CHART 1



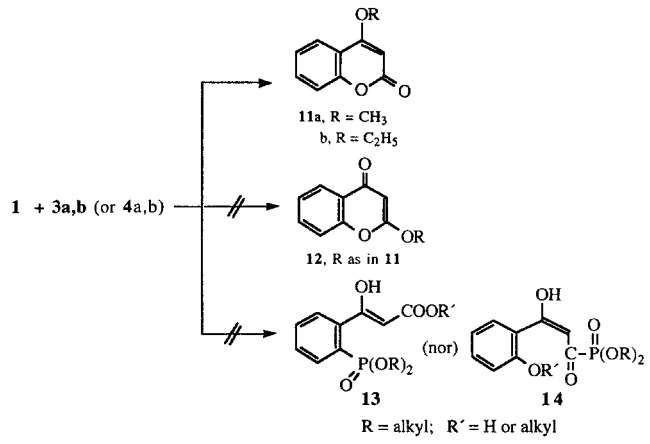
SCHEME 1

with J_{HH} = 1.5 Hz, indicating an allylic type of coupling with the CH_3 protons [12]. The aromatic proton of the benzo-γ-pyrone moiety (H**b**) gives a singlet at 6.7, while aromatic protons of the coumarin nucleus (4H) appear as a multiplet in the 8.05–7.37 region. The spectrum also shows a singlet at 3.89 (3H, OCH_3) and two doublets (each with J_{HH} = 16 Hz) at 8.30 (H**c**) and 8.90 (H**d**), indicating thus that protons of the exocyclic ethylenic group are oriented *E* with respect to one another.

When **1** was allowed to react with dimethyl phosphonate (**3a**) at 100°C in the absence of a solvent, it yielded a colorless crystalline product in ~75% yield that was proved to be 8-methoxycoumarin (**11a**) by comparing its mp as well as its IR and ^{1}H-NMR spectra with those of a reference sample [5,13]. Similarly, **1** reacted with diethyl phosphonate (**3b**) to give 4-ethoxycoumarin (**11b**) [4] in a 70% yield. Alkyl ethers **11a,b** were produced both upon reacting **1** with trimethyl phosphite (**4a**) and triethyl phosphite (**4b**), respectively, at 100°C in the absence of solvent (Scheme 2).

CONCLUSION

Results of the present investigation indicate that both the 2,4-chromandione form (**1B**) and its enol tautomer (**1A**) appear to be involved in the reactions of **1** with ylides **2.** Thus, **1** reacts with **2a** via **1B** and with **2b,c** via **1A.** Noteworthy, involvement of the latter form **1A** is more frequent than **1B** in many other types of condensation reactions [7,8] that produce 3-substituted-4-hydroxycoumarin derivatives (cf. Ref. [6]). However, only the enol form **1A** could be recognized in the reaction of **1** with alkyl phosphites (**3a,b** and **4a,b**). On the other hand, no evidence for the involvement of the 2-hydroxychromone tautomer (**1C**) was found in the aforementioned investigations, at least under the prevailing experimental conditions.



SCHEME 2

The reactions of **1** with ylides **2b,c** to give **6** reprepresent a facile and direct approach for producing new models of complex ylidenetriphenylphosphoranes (Wittig reagents). Furthermore, use can be made of this finding for incorporating two heterocyclic moieties of anticipated biological activities in one and the same molecule via reaction of **6** with the appropriate heterocyclic or heteroaryl aldehyde. For example, compound **10** incorporates both the 4-hydroxycoumarinyl moiety that is found in many drugs used as anticoagulants [14] and the benzo-γ-pyrone (chromone) residue that is common in drugs used for treatment of cardiovascular disorders [15–17].

The reactions of **1** with alkyl phosphites (**3a,b** and **4a,b**) produce the respective alkyl ethers (**11a,b**) directly and in a high percentage yield. This new approach is superior to that of other conventional procedures that either give poor yields of **11a,b** or undesired by-products [3,4,13]. Apparently, **1** reacts with alkyl phosphites (**3,4**) more as a hydroxy compound [18,19] than as a lactone or cyclic ester [20]. In the latter cases, ring cleavage to give phosphonates (cf. Ref. [13]) or α-ketophosphonates (cf. Ref. [14]) is expected.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were measured in KBr, on a Perkin–Elmer Infracord Spectrometer model 157 (Grating). The PMR spectra were run on a Varian Gemini 200 (200 MHz) instrument using TMS as an internal reference. The ^{31}P-NMR spectrum was recorded, relative to external H_3PO_4 (85%), with a Varian FT-80 spectrometer. The mass spectra were run at 70 eV on Kratos MS-50 equipment and on a Varian MAT 311A spectrometer. Elemental analyses were carried out at the Microanalysis Laboratory, Cairo University. The solvents were dried by usual techniques. Trialkyl phosphites were purified by treatment with sodium ribbon followed by fractional distillation. Dialkyl phosphonates were freshly distilled. 4-Hydroxycoumarin is commercially available from Merck–Schuchardt Co.

Action of Phosphorus Ylide **2a** *on 4-Hydroxycoumarin* **1**

A mixture of **1** (0.8 g, 0.01 mol) and benzoylmethylenetriphenylphosphorane **2a** [21] (2.1 g, 0.011 mol) in toluene (50 mL) was refluxed for 30 hours. The reaction mixture was 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 light petroleum ether. The column was developed with light petroleum ether containing increasing amounts of chloroform and then with pure ethyl alcohol.

The fraction (up to 6:4 v/v) yielded colorless needles, mp 156°C (ca. 82% yield) of triphenylphosphine oxide [22], (mp, mixed mp, and comparative IR spectra).

Elution with 100% ethyl alcohol afforded compound **5,** as colorless crystals (from cyclohexane) (0.7 g, 53.4%) charring over 300°C. Anal. calcd for $C_{17}H_{12}O_3$ (264.283): C, 77.26; H, 4.58. Found: C, 77.17; H, 4.47. IR (KBr) cm^{-1}: 1700 (C=O, lactone), 1664 (C=C), ^{1}H-NMR (DMSO): δ = 4.75 (s, 2H, CH_2) and 6.6–7.7 (m, 10H, Ar-H). MS: *m/z* = 264 (M^+, 39%).

Action of Phosphorus Ylides **2b** *and/or* **2c** *on 4-Hydroxycoumarin* **1**

A mixture of **1** (0.8 g, 0.01 mol) and carbomethoxymethylenetriphenylphosphorane **2b** [23] (1.8 g, 0.011 mol) in toluene (50 mL) was refluxed for 20 hours. The solid product was crystallized from cyclohexane to afford yellow crystals of mp 225°C (1.9 g, 82.5%) and identified as 3-(4-hydroxycoumarinyl)-carbonylmethylenetriphenylphosphorane (**6**).

Anal. calcd for $C_{29}H_{21}O_4P$ (464.467): C, 74.99; H, 4.56; P, 6.67. Found: C, 75.1; H, 4.48; P, 6.7. IR (KBr) cm^{-1}; 3500 (OH), 1700 (C=O), 1615 (C=C, aromatic), 1490 (C=P), and 1440 (C–P phenyl). ^{1}H-NMR ($CDCl_3$): δ 6.15 (d, 1H, CH–P, J_{HP} = 25 Hz) and 7.15–8.00 ppm (m, 19H, Ar-H). ^{31}P-NMR ($CDCl_3$)δp = 14.77. MS: *m/z* = 464 (M^+, 75%).

Compound **6** was also obtained as the sole product in a 78% yield by the reaction of **1** with carboethoxymethylenetriphenylphosphorane **2c** [23] in refluxing toluene for 22 hours (mp, mixed mp, and comparative IR spectra).

Action of Aldehydes on **6:** *General Procedure*

A mixture of **6** (5.1 g, 0.011 mol) and benzaldehyde (0.01 mol) and/or 2-methyl-5-methoxy-6-formyl-7-hydroxychromone (**9**), respectively, in 50 mL of toluene was refluxed for 10–12 hours (TLC). After removal of the volatile materials, in vacuo, the solid product was redissolved in methanol (50 mL) and evaporated to dryness in the presence of silica gel (10 g). The mixture was then added to a column previously charged with silica gel in light petroleum ether (br 60–80°C). The column was eluted with light petroleum ether containing increasing amounts of chloroform and then with pure chloroform.

The fraction (up to 8:2 v/v) afforded yellow crystals (cyclohexane) of compound **8** (2.5 g, 77.9%) mp 125°C. Anal. calcd for $C_{18}H_{12}O_4$ (292.294): C, 73.96; H, 4.14. Found: C, 73.99; H, 4.04. IR (KBr) cm^{-1}: 1725 (C=O), 1605 (C=C, ethylenic), 1530, and 1491 (C=C, aromatic). ^{1}H-NMR: δ = 7.2–7.85 (m, 9H, Ar–**H**), 8.12 (d, 1H, C**H,** J_{HH} = 16 Hz) and 8.49 (d, 1H, **CH,** J_{HH} = 16 Hz), MS: *m/z* = 292 (M^+, 48.5%). Compound **8** was obtained from the reaction of **6** with benzaldehyde.

Elution with pure chloroform gave compound **10** as yellow crystals (3.4 g, 73.9%) mp 222°C (cyclohexane) from the reaction of **6** with **9.** Anal. calcd for $C_{23}H_{16}O_8$ (420.381): C, 65.71; H, 3.84. Found: C, 65.78; H, 3.76. IR (KBr) cm^{-1}; 3408 (OH), 1735 (C=O, lactone), 1650 (C=O pyrone), 1615 (C=C, ethylenic), 1545, and 1495 (C=C, aromatic). ^{1}H-NMR (DMSO): δ = 2.28 (d, 3H, C**H**$_3$, J_{HH} = 1.5 Hz), 3.89 (s, 3H, OC**H**$_3$), 6.02 (q, 1H, **Ha,** J_{HH} = 1.5 Hz), 6.7 (s, 1H, **Hb**), 7.37–8.05 (m, 4H, Ar–**H**), 8.3 (d, 1H, **Hc,** J_{HH} = 16 Hz), 8.9 (d, 1H, **Hd,** J_{HH} = 16 Hz), and 12.05 (s, 1H, O**H**). MS *m/z* = 420 (M^+, 5%). TPPO was also isolated and identified [22] in both cases.

Action of Trialkyl Phosphites **3a,b** *on* **1:** *General Procedure*

A mixture of **1** (0.8 g, 0.01 mol) and trimethyl-**3a** or triethyl phosphite **3b** (5 mL) was heated in the absence of solvent at 100°C for 6–8 hours (TLC). After removal of the volatile materials in vacuo, the residue was triturated with light petroleum ether and left to cool. The solid was collected and recrystallized from cyclohexane to give 8-methoxycoumarin **11a** or 4-ethoxycoumarin **11b.**

Compound **11a** was obtained as colorless crystals (0.73 g, 84%) mp 127°C. Anal. calcd for $C_{10}H_8O_3$ (176.174): C, 68.18; H, 4.58. Found: C, 68.21; H, 4.49. IR (KBr) cm^{-1}: 1730 (C=O, lactone), 1625, 1605, 1490 (C=C, aromatic), and 1390 (C–O, stretching). No OH band was present in the 3600–3400 region. ^{1}H-NMR ($CDCl_3$) δ 3.95 (s, 3H, OC**H**$_3$), 5.65 (s, 1H, ring methine-**H**), and 7.15–7.85 ppm (m, 4H, Ar–**H**). MS: *m/z* = 176 (M^+, 20%).

Compound **11b** was obtained as colorless needles (0.76 g, 82%) mp 138°C. Anal. calcd for $C_{11}H_{10}O_3$ (190.201): C, 69.46; H, 5.3. Found: C, 69.42; H, 5.23. IR (KBr) cm^{-1}: 1710 (C=O, lactone), 1620, 1600, 1560, 1490. ^{1}H-NMR ($CDCl_3$) δ 1.5 (t, 3H, OCH_2–C**H**$_3$), 4.2 (q, 2H, OC**H**$_2$–CH_3), 5.65 (s, 1H, ring methine-**H**), and 7.25–7.85 ppm (m, 4H, Ar–**H**). MS: *m/z* = 190 (M^+, 75%).

Action of Dialkyl Phosphonates **4a** *and* **4b** *on 1: General Procedure*

When the reaction of **1** with dimethyl **4a** and/or diethyl phosphonate **4b** was carried out in the absence

of solvent at 100°, it was completed after 50–55 hours (TLC) and yielded colorless crystals (cyclohexane) identified as **11a** (~75% yield) or **11b** (70% yield) (mp, mixed mp, and comparative IR spectra).

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