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Vinyltriphenylphosphonium salt mediated synthesis of functionalized coumarins

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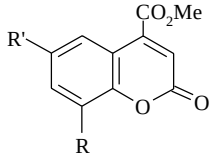
Abstract—Protonation of the reactive 1:1 intermediate produced in the reaction between triphenylphosphine and dimethyl acetylenedicarboxylate by hydroquinone, resorcinol, catechol or pyrogallol leads to vinylphosphonium salts, which undergo Michael addition with the conjugate base of the hydroxy acid to produce highly functionalized 2-oxo-2*H*-chromene derivatives in good yields.

1. Introduction

There has been considerable interest in the 2-oxo-2*H*-chromene (coumarin) ring system, both with regard to natural product chemistry, and to the pharmacological activity of several of its derivatives.[1,2] In addition, other 2-oxo-2*H*-chromenes are of interest as a result of their toxicity,[3] carcinogenicity,[4] and photodynamic effects.[5] The majority of naturally occurring coumarins are highly oxygenated.[1] There have been many reported studies on the synthesis of 2-oxo-2*H*-chromene ring structures.[1,2,6–10] We have recently described[11] a new and operationally convenient approach to the synthesis of 4-carboxymethyl-coumarins **1** based on the aromatic electrophilic substitution reaction between the conjugate base of substituted phenols and a vinyltriphenylphosphonium salt. As part of our current studies on the development of new routes to heterocyclic and carbocyclic systems, we now report the reaction between hydroxylated phenols and dimethyl acetylenedicarboxylate (DMAD) in the presence of triphenylphosphine. Thus, reaction of DMAD and triphenylphosphine in the presence of hydroquinone, resorcinol, catechol, or pyrogallol leads to functionalized 4-carboxymethyl-2-oxo-2*H*-chromenes. The reactions of tertiary phosphorus compounds with DMAD and, on occasion, other acetylenic systems have been discussed with emphasis upon the synthesis of phosphorus heterocycles.[12]



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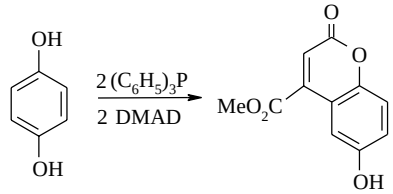
2. Results and discussion

2.1. Hydroquinone

The reaction of hydroquinone with two equivalents of DMAD in the presence of two equivalents of triphenylphosphine was carried out in refluxing toluene. The pale yellow crystals separated from the reaction mixture were identified as methyl 6-hydroxy-2-oxo-2*H*-chromene-4-carboxylate (**2**) (Scheme 1). No other compound was obtained from the tarry residue by column chromatography.

Compound **2** results from the initial addition of triphenylphosphine to the acetylenic ester and a subsequent protonation of the reactive 1:1 adduct, followed by electrophilic attack of the vinyltriphenylphosphonium cation on the aromatic ring at the *ortho* position relative to the strong



2 (50% based on hydroquinone)

Scheme 1.

Keywords: aromatic substitution; ring formation; coumarin derivatives; vinylation; triphenylphosphine.

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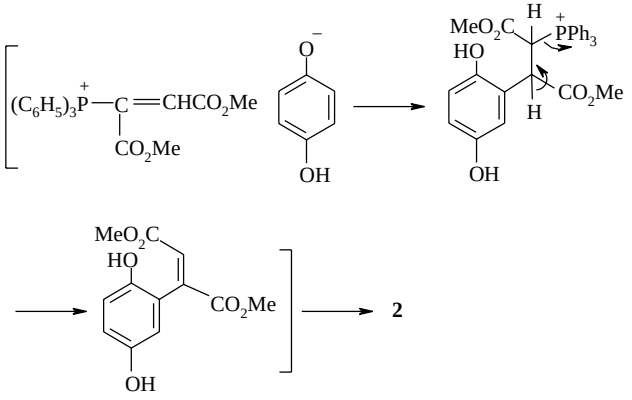
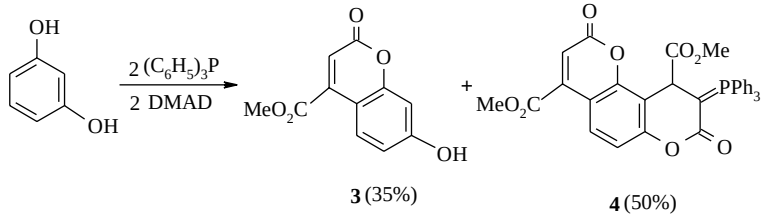


Scheme 2.

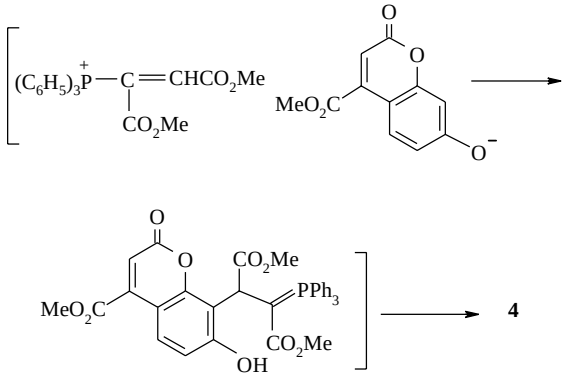
obtained from resorcinol. The products were identified as methyl 7-hydroxy-2-oxo-2*H*-chromene-4-carboxylate (**3**) and dimethyl 2,8-dioxo-9-(1,1,1-triphenylphosphanylidene)-9,10-dihydro-2*H*,8*H*-pyrano[2,3-*f*]-chromene-4,10-dicarboxylate (**4**) (Scheme 3). Compound **3** is formed by a mechanism similar to that outlined in Scheme 2 for 2-oxo-2*H*-chromene derivative **2**. Although, we have not yet established the mechanism of formation of phosphorane **4** in an experimental manner, a possible explanation is proposed in Scheme 4.

2.3. Catechol

Under the reaction conditions given for resorcinol, two products were isolated from the reaction mixture of catechol (Scheme 5). Structures **5** and **7** were assigned to the isolated



Scheme 3.



Scheme 4.

activating group. The 2-oxo-2*H*-chromene derivative **2** is presumably produced by intramolecular lactonization of the unsaturated diester (Scheme 2).

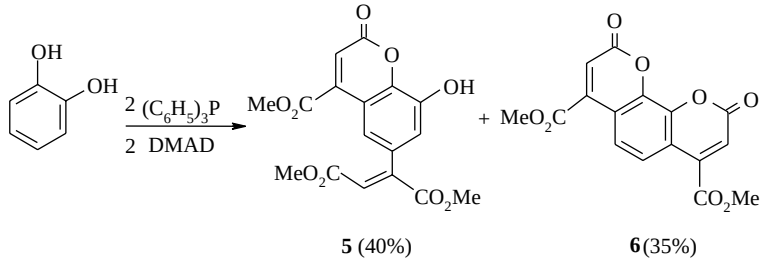
2.2. Resorcinol

Two compounds were separated from the reaction mixture

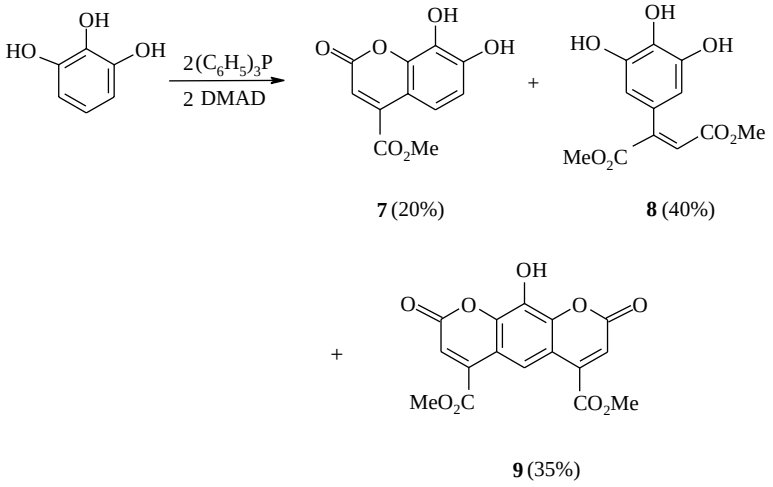
products on the basis of their elemental analyses and IR, ^{1}H- and ^{13}C NMR spectra. IR spectroscopy was applied to distinguish the tricyclic ring structure **6** from the phenol derivative **5**. Thus, the IR spectrum of the latter showed a strong OH stretching band at about 3350 cm^{-1}. The (*E*)-configuration of the carbon–carbon double bond in **5** is based on the chemical shift of the olefinic proton.[13]

2.4. Pyrogallol

The reaction of 1,2,3-trihydroxybenzene (pyrogallol) with DMAD in the presence of triphenylphosphine proceeded in boiling toluene, and finished in a few hours. Three compounds were separated from the reaction mixture and identified as methyl 7,8-dihydroxy-2-oxo-2*H*-chromene-4-carboxylate (**7**), dimethyl (*E*)-2-(3,4,5-trihydroxyphenyl)-2-butenedioate (**8**), and dimethyl 10-hydroxy-2,8-dioxo-2*H*,8*H*-pyrano-[3,2-*g*]chromene-4,6-dicarboxylate (**9**) (Scheme 6). ^{1}H NMR spectroscopy was applied to distinguish structure **7** from **8** and **9**. Thus the NMR spectrum of **7** displayed an AX pattern for the aromatic protons, while compounds **8** and **9** exhibited single lines



Scheme 5.



Scheme 6.

at δ=6.47 and 8.47, respectively. The assignment of the *E* configuration of **8** is based on the chemical shift of the vinylic proton.[13] Partial assignment of the ^{13}C resonances in compounds **7**–**9** are given in Section 4.

3. Conclusions

We anticipate that the reactions described herein represent a simple entry into the synthesis of polyfunctional coumarin derivatives of potential interest. The present method carries the advantage that, not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modification. The one-pot nature of the present procedure makes it an acceptable alternative to multistep approaches.[1,2,9] The present coumarin synthesis complements the older established methods and offers significant advantages for the synthesis of coumarins having acid sensitive functional groups. In contrast, the well-known von Pechmann synthesis[14] entails acidic conditions and frequently affords low and erratic yields.

4. Experimental

DMAD, triphenylphosphine, resorcinol, hydroquinone, catechol and pyrogallol were obtained from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C and H were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^1H-, ^{13}C- and ^{31}P NMR spectra were measured with a Brucker DRX-500 AVANCE spectrometer at 500.13, 125.77 and 202.45 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Aldrich silica gel 70–230 mesh.

4.1. General procedure

To a magnetically stirred solution of triphenylphosphine (1.06 g, 4 mmol) and hydroquinone (0.22 g, 2 mmol) in toluene (20 mL) was added dropwise a mixture of DMAD (0.57 g, 4 mmol) in toluene (3 mL) at −5°C for 10 min. The reaction mixture was then allowed to warm up to room temperature and refluxed for 8 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography using hexane–ethyl acetate (2:1) as eluent. The solvent was removed under reduced pressure and the product was recrystallized from hexane–ethyl acetate (1:2).

4.1.1. Methyl 6-hydroxy-2-oxo-2*H*-chromene-4-carboxylate (2). Pale yellow crystals, mp 205–207°C (from 1:2 hexane–ethyl acetate), yield 50%; IR (KBr) (ν_{max}/cm^{-1}): 3200 (OH), 1722 (C=O ester), 1679 (C=O lactone); MS, *m/z* (%): 220 (M^+, 59), 192 (18), 161 (84), 133 (26), 105 (33), 77 (10), 51 (55). Anal. Calcd for $C_{11}H_8O_5$ (220.18): C, 60.00; H, 3.66. Found: C, 59.8; H, 3.8%. ^1H NMR (acetone-d_6 solution): δ 3.98 (3H, s, OCH_3), 6.85 (1H, s, CH), 7.17 (1H, dd, $^3J_{HH}$=8.9 and $^4J_{HH}$=2.8 Hz, CH), 7.26 (1H, d, $^3J_{HH}$=8.9 Hz, CH), 7.68 (1H, d, $^4J_{HH}$=2.8 Hz, CH), 8.76 (1H, s, OH); ^{13}C NMR (acetone-d_6 solution): δ 52.58 (OCH_3), 111.36 (CH), 116.28 (C), 117.73, 119.31 and 120.39 (3CH), 142.20 (CCO_2CH_3), 147.98 and 153.94 (2C–O), 159.38 and 164.24 (2C=O).

4.1.2. Methyl 7-hydroxy-2-oxo-2*H*-chromene-4-carboxylate (3). Pale yellow crystals, mp 170–172°C (from 1:2 hexane–ethyl acetate), yield 35%; IR (KBr) (ν_{max}/cm^{-1}): 3180 (OH), 1719 and 1673 (C=O), 1583 (C=C); MS, *m/z* (%): 220 (M^+, 38), 161 (72), 133 (41), 105 (37), 51 (62). Anal. Calcd for $C_{11}H_8O_5$ (220.18): C, 60.00; H, 3.66. Found: C, 60.2; H, 3.7%. ^1H NMR (DMSO-d_6 solution): δ 3.89 (3H, s, OCH_3), 6.54 (1H, s, CH), 6.74 (1H, d, $^4J_{HH}$=2.3 Hz, CH), 6.81 (1H, dd, $^3J_{HH}$=8.9 and $^4J_{HH}$=2.3 Hz, CH), 7.90 (1H, d, $^3J_{HH}$=8.9 Hz, CH), 9.10 (1H, s, OH); ^{13}C NMR ($CDCl_3$ solution): δ 53.56 (OCH_3), 103.13 (CH), 108.12 (C), 114.01, 114.05 and 128.38 (3 CH), 143.43 (CCO_2CH_3), 156.25 and 160.23 (2C–O), 162.21 and 164.83 (2C=O).

4.1.3. Dimethyl 2,8-dioxo-9-(1,1,1-triphenylphosphanylidene)-9,10-dihydro-2*H*,8*H*-pyrano[2,3-*f*]-chromene-4,10-dicarboxylate (4). Yellow crystals, mp 196–198°C (from

1:1 hexane–ethyl acetate), yield 50%; IR (KBr) (ν_{max}/cm^{-1}): 1728 (C=O); MS, *m/z* (%): 594 (M^++2, 6), 534 (83), 445 (34), 330 (84), 262 (85), 183 (63), 108 (37). Anal. Calcd for $C_{34}H_{25}O_8P$ (592.51): C, 68.92; H, 4.25. Found: C, 68.7; H, 4.3%. ^{1}H NMR ($CDCl_3$ solution): δ 3.39 and 3.98 (6H, 2s, $2OCH_3$), 4.24 (1H, d, $^3J_{PH}$=9.6 Hz, P–C–CH), 6.72 (1H, s, CH), 7.11 (1H, d, *J*=9.0 Hz, CH), 7.5–7.8 (15H, m, $3C_6H_5$), 8.14 (1H, d, *J*=9.0 Hz, CH); ^{13}C NMR ($CDCl_3$ solution): δ 37.80 (d, $^2J_{PC}$=11.4 Hz, P–C–*C*H), 38.4 (d, $^1J_{PC}$=130 Hz, P=C), 52.05 and 53.17 ($2OCH_3$), 110.03 and 110.92 (2C), 114.43 and 116.15 (2CH), 123.5 (d, $^1J_{PC}$=94 Hz, C^{ipso}), 126.71 (CH), 129.2 (d, $^3J_{PC}$=12.4 Hz, C^m), 132.92 (C^p), 133.90 (d, $^2J_{PC}$=9.9 Hz, C^o), 142.74 and 151.71 (2C–O), 157.08, 159.76, 164.48 and 172.85 (4C=O); ^{31}P NMR ($CDCl_3$ solution): δ 22.70 (Ph_3P^+–C).

4.1.4. Dimethyl (*E*)-2-[8-hydroxy-4-(methoxycarbonyl)-2-oxo-2*H*-chromene-6-yl]-2-butenedioate (5). Light yellow crystals, mp 141–143°C (from 1:2 hexane–ethyl acetate), yield 40%; IR (KBr) (ν_{max}/cm^{-1}): 3385 (OH), 1743 (C=O ester), 1716 (C=O lactone); MS, *m/z* (%): 362 (M^+, 83), 331 (16), 303 (33), 271 (39), 243 (12), 185 (11), 101 (14), 75 (24), 59 (40). Anal. Calcd for $C_{17}H_{14}O_9$ (362.29): C, 56.36; H, 3.89. Found: C, 56.4; H, 3.9%. ^{1}H NMR ($CDCl_3$ solution): δ 3.80, 3.97 and 4.00 (9H, 3s, $3OCH_3$), 6.32 (1H, s, CH), 6.52 (1H, br s, OH), 7.00 (1H, s, CH), 7.31 (1H, d, $^4J_{HH}$=2.0 Hz, CH), 7.98 (1H, d, $^4J_{HH}$=2.0 Hz, CH); ^{13}C NMR ($CDCl_3$ solution): δ 52.20, 52.94 and 53.40 ($3OCH_3$), 116.47 (C), 116.53, 117.19, 118.43 and 120.25 (4CH), 130.35, 142.20 and 143.40 (3C), 144.08 and 147.20 (2C–O), 158.34, 163.57, 165.12 and 167.84 (4C=O).

4.1.5. Dimethyl 2,9-dioxo-2,3,4,9-tetrahydropyrano-[3,2-*h*]-chromene-4,7-dicarboxylate (6). Pale yellow crystals, mp 197–199°C (from ethanol), yield 35%; IR (KBr) (ν_{max}/cm^{-1}): 1713 (C=O); MS, *m/z* (%): 330 (M^+, 83), 302 (16), 271 (85), 243 (26), 187 (14), 100 (10), 59 (18). Anal. Calcd for $C_{16}H_{10}O_8$ (330.25): C, 58.19; H, 3.05. Found: C, 58.4; H, 3.2%. ^{1}H NMR ($CDCl_3$ solution): δ 4.04 (6H, s, $2OCH_3$), 7.13 (2H, s, 2CH), 8.25 (2H, s, 2CH); ^{13}C NMR ($CDCl_3$ solution): δ 53.50 ($2OCH_3$), 118.23 (2C), 121.69 (2CH), 122.03 (2CH), 141.28 (2C), 141.62 (2C–O), 157.93 (2C=O), 163.54 (2C=O).

4.1.6. Methyl 7,8-dihydroxy-2-oxo-2*H*-chromene-4-carboxylate (7). Yellow crystals, mp 215–217°C (from 1:2 hexane–ethyl acetate), yield 15%; IR (KBr) (ν_{max}/cm^{-1}): 3325 and 3200 (OH), 1721 (C=O ester), 1700 (C=O lactone); MS, *m/z* (%): 236 (M^+, 85), 208 (58), 177 (57), 150 (19), 93 (35), 63 (36), 39 (46). Anal. Calcd for $C_{11}H_8O_6$ (236.18): C, 55.94; H, 3.41. Found: C, 55.6; H, 3.4%. ^{1}H NMR ($CDCl_3$ solution): δ 3.97 (3H, s, OCH_3), 6.59 (1H, s, CH), 6.89 (1H, d, *J*=8.9 Hz, CH), 7.58 (1H, d, *J*=8.9 Hz, CH), 8.79 (2H, br s, 2OH); ^{13}C NMR ($CDCl_3$ solution): δ 57.75 (OCH_3), 114.28 (C), 117.66, 119.31 and 123.03 (3CH), 137.37 (CCO_2CH_3), 148.77, 149.16 and 154.69 (3C–O), 164.54 and 169.70 (2C=O).

4.1.7. Dimethyl (*E*)-2-(3,4,5-trihydroxyphenyl)-2-butenedioate (8). Colorless crystals, mp 172–175°C (from ethyl acetate), yield 20%; IR (KBr) (ν_{max}/cm^{-1}): 3445, 3400 and 3280 (OH), 1706 (C=O); MS, *m/z* (%): 268 (M^+, 55), 236 (18), 209 (25), 150 (32), 121 (10), 44 (86). Anal. Calcd for $C_{12}H_{12}O_7$ (268.22): C, 53.73; H, 4.51. Found: C, 53.4; H, 4.4%. ^{1}H NMR (DMSO-d_6 solution): δ 3.66 and 3.79 (6H, 2s, $2OCH_3$), 6.17 (1H, s, CH), 6.47 (2H, s, 2CH), 9.05 (3H, br s, 3OH); ^{13}C NMR (DMSO-d_6 solution): δ 52.12 and 52.70 ($2OCH_3$), 106.52 (2CH), 112.57 (C), 122.80 (CH), 137.26 (C), 146.71 (2C–OH), 149.56 (C–OH), 165.68 and 168.56 (2C=O).

4.1.8. Dimethyl 10-hydroxy-2,8-dioxo-2*H*,8*H*-pyrano-[3,2-*g*]-chromene-4,6-dicarboxylate (9). Yellow crystals, mp 262–264°C (from 1:2 hexane–ethyl acetate), yield 45%; IR (KBr) (ν_{max}/cm^{-1}): 3365 (OH), 1740 and 1719 (C=O). MS, *m/z* (%): 346 (M^+, 84), 318 (29), 287 (49), 259 (14), 87 (16), 59 (24). Anal. Calcd for $C_{16}H_{10}O_9$ (346.25): C, 55.50; H, 2.91. Found: C, 55.4; H, 2.8%. ^{1}H NMR (DMSO-d_6 solution): δ 3.94 (6H, s, $2OCH_3$), 6.94 (2H, s, 2CH), 8.47 (1H, s, CH), 10.55 (1H, br s, OH). ^{13}C NMR (DMSO-d_6 solution): δ 53.79 ($2OCH_3$), 113.01 (2C), 114.77 (2C), 119.25 (2CH), 133.09 (CH), 142.38 (2C–O), 145.15 (C–O), 159.04 and 164.27 (4C=O).

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