Stereoselective synthesis of 3-[2-(dialkoxyphosphoryl)-1,2-dialkoxycarbonyl-ethyl]-4-hydroxycoumarins by reaction between trialkyl phosphites, dialkyl acetylenedicarboxylates and 4-hydroxycoumarin

Mohammad Anary-Abbasinejad*, Khadijeh Charkhati and Alireza Hassanabadi

Department of Chemistry, Islamic Azad University, Yazd Branch, PO Box 89195-155, Yazd, Iran

A three-component reaction between trialkyl phosphites, dialkyl acetylenedicarboxylates and 4-hydroxycoumarin is described as a simple and efficient route for the synthesis of 3-[2-(dialkoxyphosphoryl)-1,2-dialkoxycarbonyl-ethyl]-4-hydroxycoumarins in high yields.

Keywords: dialkyl acetylenedicarboxylates, trialkyl phosphites, 4-hydroxycoumarin, phosphonates, stereoselective synthesis

The synthesis of coumarin and its derivatives has attracted considerable attention from organic and medicinal chemists for many years as a large number of natural products contain this heterocyclic nucleus. They are widely used as additives in food, perfumes, cosmetics, pharmaceuticals[1] and optical brighteners[2] and dispersed fluorescent and laser dyes.[3] Among the various substituted coumarins, 4-hydroxycoumarins substituted on their C-3 position represents a significant class of compounds as biologically active compounds[4,5] and useful scaffolds, which can be used for the synthesis of 3,4-substituted compounds.[6–9] The existing methods for the synthesis of 3-substituted 4-hydroxycoumarins include direct synthesis of the target compound[10–13] or C3-alkylation/substitution of 4-hydroxycoumarin.[14]

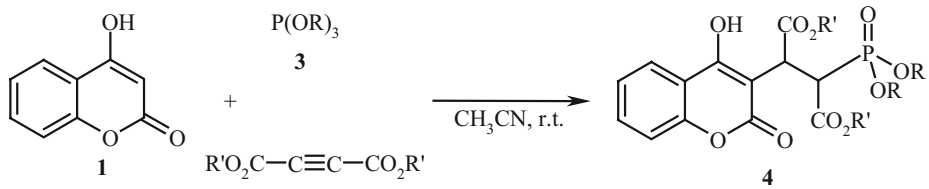
The reaction of trimethyl phosphite and dimethyl acetylenedicarboxylate (DMAD) in the presence of alcohols is reported to produce phosphite ylide derivatives which are stable at low temperatures, but are converted to phosphonate derivatives by warming or by treatment with water.[15] There are some other recent reports on the reaction between phosphites and acetylenic esters in the presence of an acidic organic compound, all of them proceeding through a phosphite ylide intermediate.[16-22] In continuation of our works on the reaction between trivalent phosphorus nucleophiles and acetylenic esters in the presence of organic NH, OH, or CH-acids,[17-23] here we report the results of our study on the reaction between dialkyl acetylenedicarboxylates (DAADs) and trialkyl phosphites in the presence of 4-hydroxycoumarin.

Results and discussion

The reaction of DAAD **2** with trialkyl phosphite **3** in the presence of 4-hydroxycoumarin **1** leads to 3-[2-(dialkoxyphosphoryl)-1,2-dialkoxycarbonyl-ethyl]-4-hydroxycoumarins **4** in high yields (Scheme 1).

Products **4a–f** were all new compounds and their structures were deduced from their elemental analyses and spectral data. The mass spectrum of compound **4a** showed the molecular ion peak at 414. The ^{1}H NMR spectrum of compound **4a** displayed two doublets (J_{HP} = 11 Hz) at 3.41 and 3.47 ppm for two $POCH_3$ groups and two singlets at 3.54 and 3.67 ppm for two methoxycarbonyl groups. Two signals were observed at 3.99 (dd, $^3J_{HH}$ = 11 Hz, $^2J_{HP}$ = 21 Hz) and 4.89 ppm (dd, $^3J_{HH}$ = 11 Hz, $^3J_{HP}$ = 5 Hz) for two vicinal methine protons. Aromatic protons resonated between 7.35 and 7.69 ppm. A broad signal was observed at 12.62 ppm for the OH proton and disappeared by addition of D_2O to d_6-DMSO solution of **4a**. The ^{13}C NMR spectrum of compound **4a** showed 17 distinct resonances in agreement with the proposed structure. The structural assignments made on the basis of the NMR spectra of compound **4a** were supported by its IR spectrum, the ester carbonyl groups exhibited strong absorption bands at 1731 and 1690 cm^{-1}.

Observation of $^3J_{HH}$ = 11 Hz for the vicinal protons in compound **4a** indicates an *anti* arrangement for these protons.[24,25] Since compound **4a** possesses two stereogenic centres, two diastereoisomers with *anti* HCCH arrangements

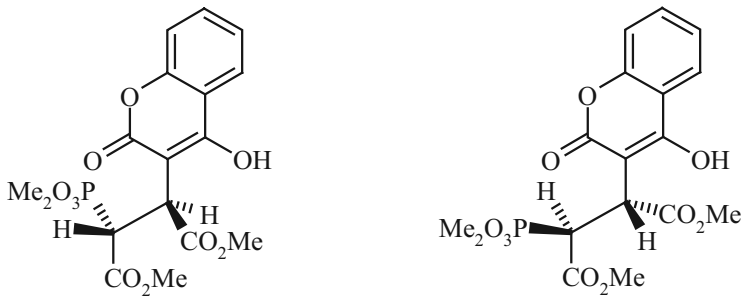


4	R	R'	Yield* (%)
a	Me	Me	89
b	Et	Me	90
c	n-Bu	Me	91
d	Me	Et	90
e	Et	Et	91
f	n-Bu	Et	88

* Isolated yields

Scheme 1 Three-component reaction between trialkyl phosphites, DAADs and 4-hydroxycoumarin.

* Correspondent. E-mail: mohammadanary@yahoo.com



(2*R*,3*S*) - **4a** (2*S*,3*R*) - **4a**

Scheme 2 Two enantiomers of phosphonate **4a**.

are possible (Scheme 2). The three-bond carbon–phosphorus coupling, $^3J_{CP}$, depends on configuration, as expected, transoid couplings being larger than cisoid ones. The observation of $^3J_{CP}$ of 21 Hz for the ester C=O group and $^3J_{CP}$ of 0 Hz for the C-3 of coumarin ring is in agreement with the (*2R,3S*)-**4a** and its mirror image (*2S,3R*)-**4a** geometries.[26] The same diasteromers were observed for compounds **4b–f**. Any traces of the other diastereomer were not detected by the NMR spectra of compounds **4a–f**.

A reasonable mechanism for the formation of compound **4a** is presented in Scheme 3. The initial addition of trimethyl phosphite on DMAD leads to a diionic intermediate that is protonated by 4-hydroxycoumarin to produce the vinyl phosphonium **5**. The conjugate addition of anion **6** to cation **5** afforded the phosphite ylide **7** which then hydrolyses to product **4a**.

In summary, we report here that three-component reaction between trialkyl phosphites, dialkyl acetylenedicarboxylates and 4-hydroxycoumarin provides a simple and efficient one-pot route for the synthesis of 3-[2-(dialkoxyphosphoryl)-1,2-dialkoxycarbonyl-ethyl]-4-hydroxycoumarins in good yields.

Experimental

Melting points were determined with an electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS–O analyser. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer.^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker DRX-500 AVANCE spectrometer in d_6-DMSO using TMS as internal standard or 85% H_3PO_4 as external standard. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

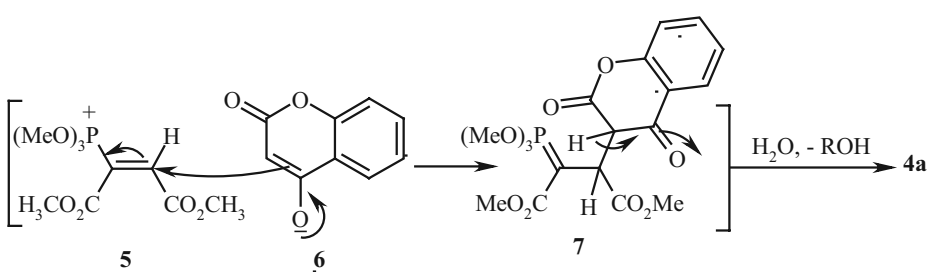
General procedure for preparation of compounds **4a–g** *by reaction between dialkyl acetylenedicarboxylates, trialkyl phosphites and 4-hydroxycoumarin*

To a magnetically stirred solution of trialkyl phosphite (2 mmol) and 4-hydroxycoumarin (2 mmol) in acetonitrile (15 mL) was added dropwise a mixture of dialkyl acetylenedicarboxylate (2 mmol) in acetonitrile (3 mL) at room temperature over 2 min. The reaction mixture was then stirred for 24 h. The solvent was removed under reduced pressure and diethyl ether (20 mL) was added. The solid was filtered off and washed with diethyl ether (20 mL) to afford the pure product.

3-[2-(Dimethoxyphosphoryl)-1,2-dimethoxycarbonyl-ethyl]-4-hydroxycoumarin **(4a):** Yield: 89%; White powder, m.p. 194–196 °C, IR (KBr)(ν_{max}, cm^{-1}): 3150 (OH), 1731, 1690 (C=O, ester). Anal. Calcd for $C_{17}H_{19}O_{10}P$: C, 49.28; H, 4.62. Found: C, 49.04; H, 4.43%. MS (*m/z*,%): 414 (M^+, 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.41 and 3.47 (6 H, 2 d, $^3J_{HP}$ = 11 Hz, 2 $POCH_3$), 3.54 and 3.67 (6 H, 2 s, 2 OCH_3), 3.99 (1 H, dd, $^3J_{HH}$ = 11 Hz, $^2J_{HP}$ = 21 Hz, CH), 4.89 (1 H, dd, $^3J_{HH}$ = 11 Hz, $^3J_{HP}$ = 5 Hz, CH), 7.35 (2 H, m, aromatic), 7.61 (1 H, t, $^3J_{HH}$ = 8 Hz, aromatic), 7.69 (1 H, d, $^3J_{HH}$ = 8 Hz, aromatic), 12,62 (1 H, broad s, OH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 40.7 (d, $^2J_{CP}$ = 1 Hz, CH), 43.6 (d, $^1J_{CP}$ = 131 Hz, CP), 52.2 and 52.3 (2 OCH_3), 52.5 and 52.7 (2 d, $^2J_{CP}$ = 11 Hz, 2 $POCH_3$), 101.9, 116.9, 117.2, 124.6, 125.0, 133.4, 153.0, 162.3, 162.9 (coumarin moiety), 169.5 (d, $^2J_{CP}$ = 5 Hz, C=O), 172.2 (d, $^3J_{CP}$ = 21 Hz, C=O). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ 21.8.

3-[2-(Diethoxyphosphoryl)-1,2-dimethoxycarbonyl-ethyl]-4-hydroxycoumarin **(4b):** Yield: 90%; White powder, m.p. 207–210 °C, IR (KBr)(ν_{max}, cm^{-1}): 3130 (OH), 1733, 1702 (C=O, ester). Anal. Calcd for $C_{19}H_{23}O_{10}P$: C, 51.59; H, 5.24%. Found: C, 51.74; H, 5.38%. MS (*m/z*,%): 442 (M^+, 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (6 H, m, 2 CH_3), 3.32 and 3.49 (6 H, 2 s, 2 OCH_3), 3.60 (4 H, m, 2 OCH_2), 3.80 (1 H, dd, $^3J_{HH}$ = 11 Hz, $^2J_{HP}$ = 21 Hz, CH), 4.72 (1 H, dd, $^3J_{HH}$ = 11 Hz, $^3J_{HP}$ = 5 Hz, CH), 7.20 (2 H, m, aromatic), 7.44 (1 H, t, $^3J_{HH}$ = 8 Hz, aromatic), 7.77 (1 H, d, $^3J_{HH}$ = 8 Hz, aromatic), 12,60 (1 H, broad s, OH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 16.19 and 16.27 (2 d, $^3J_{CP}$ = 2 Hz, 2 CH_3), 40.7 (d, $^2J_{CP}$ = 1 Hz, CH), 43.7 (d, $^1J_{CP}$ = 130 Hz, CP), 52.7 and 52.9 (2 OCH_3), 62.5 and 62.7 (2 d, $^2J_{CP}$ = 6 Hz, 2 $POCH_2$), 101.6, 116.6, 116.7, 124.1, 124.6, 132.9, 152.5, 162.2, 162.6 (coumarin moiety), 169.3 (d, $^2J_{CP}$ = 5 Hz, C=O), 172.4 (d, $^3J_{CP}$ = 21 Hz, C=O). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ 21.6.

3-[2-(Dibutoxyphosphoryl)-1,2-dimethoxycarbonyl-ethyl]-4-hydroxycoumarin **(4c):** Yield: 91%; White powder, m.p. 190–192 °C, IR (KBr)(ν_{max}, cm^{-1}): 3110 (OH), 1732, 1691 (C=O, ester). Anal. Calcd. for $C_{23}H_{31}O_{10}P$: C, 55.42; H, 6.27%. Found: C, 55.54; H, 6.11%. MS (*m/z*,%): 498 (M^+, 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (6 H, m, 2 CH_3), 1.08 (4 H, m, 2 CH_2), 1.32 (4 H, m, 2 CH_2), 3.50 and 3.65 (6 H, 2 s, 2 OCH_3), 3.77 (4 H, m, 2 OCH_2), 3.97 (1 H, dd, $^3J_{HH}$ = 9 Hz, $^2J_{HP}$ = 19 Hz, CH), 4.88 (1 H, dd, $^3J_{HH}$ = 9 Hz, $^3J_{HP}$ = 4 Hz, CH), 7.35 (2 H, m, aromatic), 7.61 (1 H, t, $^3J_{HH}$ = 8 Hz, aromatic), 7.95 (1 H, d, $^3J_{HH}$ = 8 Hz, aromatic), 12,63 (1 H, broad s, OH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.1 and 14.2 (2 CH_3), 18.8 and 18.9 (2 CH_2), 32.5 and 32.6 (2 CH_2), 40.6 (d, $^2J_{CP}$ = 1 Hz, CH), 44.3 (d, $^1J_{CP}$ = 131 Hz, CP), 53.1 and 53.3 (2 OCH_3), 66.5



Scheme 3 Suggested mechanism for formation of compound **4a**.

and 66.6 (2 d, $^2J_{CP}$ = 7 Hz, 2 $POCH_2$), 102.2, 117.0, 117.1, 124.5, 125.0, 133.3, 152.9, 162.6, 162.9 (coumarin moiety), 169.6 (d, $^2J_{CP}$ = 5 Hz, C=O), 172.4 (d, $^3J_{CP}$ = 21 Hz, C=O). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ 21.8.

3-[2-(Dimethoxyphosphoryl)-1,2-diethoxycarbonyl-ethyl]-4-hydroxycoumarin **(4d):** Yield: 90%; White powder, m.p. 182–184 °C, IR (KBr)(ν_{max}, cm^{-1}): 3110 (OH), 1725, 1684 (C=O, ester). Anal. Calcd for $C_{19}H_{23}O_{10}P$: C, 51.59; H, 5.24. Found: C, 51.31; H, 5.43%. MS (*m/z*,%): 442 (M^+, 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 and 1.20 (6 H, 2 t $^3J_{HH}$ = 7 Hz, 2 CH_3), 3.42 and 3.98 and 4.13 (5 H, 2 m, 2 OCH_2 and CH), 4.85 (1 H, dd, $^3J_{HH}$ = 11 Hz, $^3J_{HP}$ = 4 Hz, CH), 7.35 (2 H, m, aromatic), 7.61 (1 H, t, $^3J_{HH}$ = 8 Hz, aromatic), 7.96 (1 H, d, $^3J_{HH}$ = 8 Hz, aromatic), 12,62 (1 H, broad s, OH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.7 and 14.8 (2 CH_3), 40.7 (CH), 43.8 (d, $^1J_{CP}$ = 130 Hz, CP), 53.6 and 53.8 (2 d, $^2J_{CP}$ = 11 Hz, 2 $POCH_3$), 61.8 and 61.9 (2 OCH_2), 102.3, 116.9, 117.2, 124.6, 125.0, 133.3, 153.0, 162.5, 162.9 (coumarin moiety), 169.1 (d, $^2J_{CP}$ = 5 Hz, C=O), 171.7 (d, $^3J_{CP}$ = 21 Hz, C=O). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ 21.9.

3-[2-(Diethoxyphosphoryl)-1,2-diethoxycarbonyl-ethyl]-4-hydroxycoumarin **(4e):** Yield: 91%; White powder, m.p. 157–159 °C, IR (KBr)(ν_{max}, cm^{-1}): 3100 (OH), 1729, 1691 (C=O, ester). Anal. Calcd for $C_{21}H_{27}O_{10}P$: C, 53.62; H, 5.79. Found: C, 53.84; H, 5.90%. MS (*m/z*,%): 470 (M^+, 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (6 H, m, 2 CH_3), 1.11 and 1.27 (6 H, 2 t $^3J_{HH}$ = 7 Hz, 2 CH_3), 3.55–4.22 (9 H, m, 4 OCH_2 and CH), 4.70 (1 H, dd, $^3J_{HH}$ = 10 Hz, $^3J_{HP}$ = 5 Hz, CH), 7.21 (2 H, m, aromatic), 7.44 (1 H, t, $^3J_{HH}$ = 8 Hz, aromatic), 7.71 (1 H, d, $^3J_{HH}$ = 8 Hz, aromatic), 12,63 (1 H, broad s, OH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.7 and 14.8 (2 CH_3), 16.1 and 16.3 (2 d, $^3J_{CP}$ = 1 Hz, 2 CH_3), 40.7 (d, $^2J_{CP}$ = 1 Hz, CH), 43.6 (d, $^1J_{CP}$ = 130 Hz, CP), 61.7 and 61.9 (2 OCH_2), 62.5 and 62.7 (2 d, $^2J_{CP}$ = 7 Hz, 2 $POCH_2$), 101.5, 116.6, 116.8, 124.0, 124.6, 132.9, 152.5, 162.1, 162.6 (coumarin moiety), 169.4 (d, $^2J_{CP}$ = 5 Hz, C=O), 172.1 (d, $^3J_{CP}$ = 20 Hz, C=O). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ 21.7.

3-[2-(Dibutoxyphosphoryl)-1,2-dimethoxycarbonyl-ethyl]-4-hydroxycoumarin **(4f):** Yield: 88%; White powder, m.p. 148–150 °C, IR (KBr)(ν_{max}, cm^{-1}): 3110 (OH), 1729, 1691 (C=O, ester). Anal. Calcd. for $C_{19}H_{23}O_{10}P$: C, 57.03; H, 6.70%. Found: C, 56.79; H, 6.51%. MS (*m/z*,%): 526 (M^+, 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.53 (6 H, m, 2 CH_3), 0.83 (3 H, t, $^3J_{HH}$ = 7 Hz, CH_3), 0.92 (4 H, m, 2 CH_2), 1.03 (3 H, t, $^3J_{HH}$ = 7 Hz, CH_3), 1.17 (4 H, m, 2 CH_2), 3.50–4.29 (9 H, m, 4 OCH_2 and CH), 4.68 (1 H, dd, $^3J_{HH}$ = 10 Hz, $^3J_{HP}$ = 5 Hz, CH), 7.35 (2 H, m, aromatic), 7.63 (1 H, t, $^3J_{HH}$ = 8 Hz, aromatic), 7.96 (1 H, d, $^3J_{HH}$ = 8 Hz, aromatic), 12,62 (1 H, broad s, OH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.1, 14.2 and 14.4 (4 CH_3), 18.4 and 18.5 (2 CH_2), 32.1 and 32.2 (2 CH_2), 40.6 (d, $^2J_{CP}$ = 1 Hz, CH), 44.0 (d, $^1J_{CP}$ = 131 Hz, CP), 61.3 and 61.4 (2 OCH_2), 66.0 and 66.2 (2 d, $^2J_{CP}$ = 7 Hz, 2 $POCH_2$), 101.9, 116.6, 116.8, 124.1, 124.5, 132.8, 152.6, 162.1, 162.5 (coumarin moiety), 169.4 (d, $^2J_{CP}$ = 5 Hz, C=O), 172.8 (d, $^3J_{CP}$ = 21 Hz, C=O). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ 21.9.

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