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Application of H_2O as the Green Solvent for the Synthesis of Phosphonates *via* Multicomponent Reactions

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Abstract

Phosphonate derivatives were prepared using multicomponent reactions of dialkyl acetylenedicarboxylate with 4-hydroxycumarine in the presence of trimethyl or triphenyl phosphite in good yields.

Key words*: Triphenyl Phosphite; Dialkyl Acetylenedicarboxilates; Multicomponent reactions; Triethyl phosphite.*

Introduction

Multicomponent reactions (MCRs), with three or more reactants combine in a one-pot procedure to give a single product, have become increasingly popular during the last decade [1-7]. They are economically and environmentally advantageous because multi-step syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic, and hazardous solvents after each step. Phosphonates have important applications in flame retardancy [8, 9], organic synthesis [10], and biological applications [11]. Also, phosphonates have been used as substitutes of the corresponding esters and acids of high biological activity [12, 13] and as suitable probes for designing antibodies on the basis of transition state models. A large number of methods have appeared describing novel syntheses of organophosphorus compounds [14]. In this research another class of synthesized compounds is chromenes. The reaction of dialkyl acetylenedicarboxylate and 4-hydroxycumarine in the presence of trimethyl or triphenyl phosphite leads to phosphonate derivatives 4 in high yields (Scheme 1).

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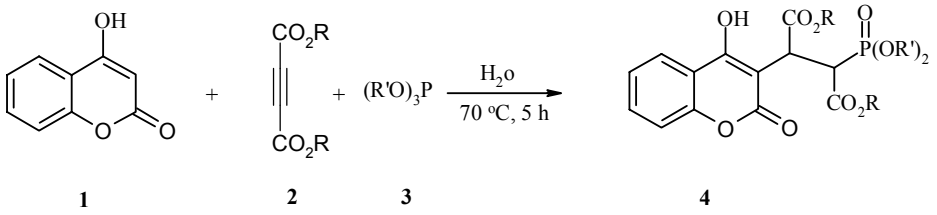


1 2 3 4

2, 3, 4	R	R'	Yield (%) of **4**
a	Me	Me	85
b	Et	Me	80
c	Me	Ph	72
d	Et	Ph	68

Scheme 1. Reaction of phosphites, activated acetylenes and 4-hydroxycumarine.

Experimental

Melting points were measured on an Electrothermal 9100 aparatus. Elemental analyses for the C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H, ^{13}C, and ^{31}P spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1, 125.8, and 202.4 MHz, respectively. ^{1}H, ^{13}C, and ^{31}P spectra were obtained for solutions in $CDCl_3$ using TMS as internal standard or 85% H_3PO_4 as external standard. All the chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and are used without further purification.

General procedure for the preparation of compounds 4a-d

To a magnetically stirred solution of dialkyl acethylenedicarboxylate **2** (2 mmol) and 4-hydroxycumarine **1** (2 mmol) in H2O (10 mL) was added trimethyl or triphenyl phosphite 3 (2 mmol). The reaction mixture was then stirred for 5 h at 70 °C. The completion of reaction was confirmed by TLC (EtOAc–hexane 6:1). The resulting precipitate was separated by filtration and washed by EtOH to afford the pure title compounds.

Dimethyl 2-(dimethoxyphosphoryl)-3-(4-hydroxy-2-oxo-2H-chromen-3-yl) succinate (4a)

Colorless crystals, m.p. 185-187 °C, 0.70 g, yield 85%. IR (KBr) (ν_{max}/cm^{-1}): 3235, 1732, 1740, 1754 cm^{-1}. Anal. Calcd for $C_{17}H_{19}O_{10}P$ (414.30): C, 49.28; H, 4.62. Found: C, 49.36; H, 4.74%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.92 (3 H, d $^{3}J_{HP}$ 11.2 Hz, MeO), 3.65 (3 H, s, MeO), 3.72 (3 H, d $^{3}J_{HP}$ 11.2 Hz, OMe), 3.85 (3 H, s, MeO), 3.92 (1 H, dd $^{2}J_{HP}$ 20.4 Hz $^{3}J_{HH}$ 11.7 Hz, CH), 5.12 (1 H, dd $^{3}J_{HH}$ 11.7 Hz $^{3}J_{HP}$ 8.7 Hz, CH), 6.95-7.92 (4 H, m, 4 CH), 8.12 (1 H, s, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 43.8 (CH), 48.2 (d $^{1}J_{PC}$ 134.4 Hz, CH), 51.8 (OMe), 52.3 (d $^{2}J_{PC}$ 8.2 Hz, MeO), 53.4 (MeO), 54.0 (d, $^{2}J_{PC}$ 8.2 Hz, MeO), 115.4 (C), 122.4 (CH), 123.8 (C), 125.4 (CH), 126.8 (CH), 127.5 (C), 132.6 (CH), 149.6 (C),

165.2 (C=O), 167.5 (d $^{2}J_{PC}$ 5.4 Hz, C=O), 172.6 (d $^{3}J_{PC}$ 21.5 Hz, C=O). ^{31}P NMR (202 MHz, $CDCl_3$): δ 18.6. MS, *m/z* (%): 414 (M^+, 20), 252 (48), 162 (86), 31 (100).

Diethyl 2-(dimethoxyphosphoryl)-3-(4-hydroxy-2-oxo-2H-chromen-3-yl)succinate (4b)

White powder, m.p.192-194 °C, 0.71 g, yield 80%. IR (KBr) (ν_{max}/cm^{-1}): 3242, 1725, 1738, 1746 cm^{-1}. Anal. Calcd for $C_{19}H_{23}O_{10}P$ (442.35): C, 51.59; H, 5.24. Found: C, 51.48; H, 5.18%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (3 H, t, $^{3}J_{HH}$ 7.4 Hz, Me), 1.38 (3 H, t, $^{3}J_{HH}$ 7.5 Hz, Me), 3.04 (3 H, d $^{3}J_{HP}$ 11.6 Hz, MeO), 3.75 (3 H, d $^{3}J_{HP}$ 11.6 Hz, MeO), 4.02 (1 H, dd $^{2}J_{HP}$ 21.2 Hz $^{3}J_{HH}$ 12.4 Hz, CH), 4.21 (2 H, q, $^{3}J_{HH}$ 7.5 Hz, CH2O), 4.27 (2 H, q, $^{3}J_{HH}$ 7.4 Hz, CH_2O), 5.18 (1 H, dd $^{3}J_{HH}$ 12.0 Hz $^{3}J_{HP}$ 9.2 Hz, CH), 6.87-7.90 (4 H, m, 4 CH), 8.09 (1 H, s, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.4 (Me), 14.2 (Me), 44.0 (CH), 48.8 (d $^{1}J_{PC}$ 135.4 Hz, CH), 51.7 (d $^{2}J_{PC}$ 8.5 Hz, MeO), 54.6 (d, $^{2}J_{PC}$ 8.5 Hz, MeO), 61.7 (CH_2O), 62.3 (CH_2O), 114.7 (C), 122.5 (CH), 124.3 (C), 125.8 (CH), 127.5 (CH), 128.2 (C), 132.4 (CH), 149.1 (C), 164.3 (C=O), 166.8 (d $^{2}J_{PC}$ 5.8 Hz, C=O), 173.2 (d $^{3}J_{PC}$ 22.3 Hz, C=O). ^{31}P NMR (202 MHz, $CDCl_3$): δ 17.8.

Dimethyl 2-(diphenoxyphosphoryl)-3-(4-hydroxy-2-oxo-2H-chromen-3-yl) succinate (4c)

Pale yellow crystals, m.p. 204-206 °C, 0.77 g, yield 72%. IR (KBr) (ν_{max}/cm^{-1}): 3238, 1730, 1738, 1745 cm^{-1}. Anal. Calcd for $C_{27}H_{23}O_{10}P$ (538.44): C, 60.23; H, 4.31. Found: C, 60.34; H, 4.42%. 1H NMR (500 MHz, $CDCl_3$): δ 3.74 (3 H, s, MeO), 3.87 (3 H, s, MeO), 4.12 (1 H, dd $^{2}J_{HP}$ 21.2 Hz $^{3}J_{HH}$ 12.2 Hz, CH), 5.23 (1 H, dd $^{3}J_{HH}$ 12.2 Hz $^{3}J_{HP}$ 9.2 Hz, CH), 7.14-7.96 (14 H, m, 14 CH), 8.05 (1 H, s, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 44.2 (CH), 49.5 (d $^{1}J_{PC}$ 135.8 Hz, CH), 52.0 (OMe), 52.8 (MeO), 121.2 (d, $^{3}J_{PC}$ 6.4 Hz, 2 CH), 122.3 (d, $^{3}J_{PC}$ 10.2 Hz, C), 123.0 (d, $^{3}J_{PC}$ 5.6 Hz, 2 CH), 124.6 (CH), 126.2 (CH), 127.4 (CH), 128.2 (CH), 128.8 (CH), 130.4 (m, 4 CH), 130.8 (CH), 132.4 (C), 132.7 (C), 148.6 (d $^{2}J_{PC}$ 9.5 Hz, C), 150.8 (m, 2 C), 163.5 (C=O), 168.2 (d $^{2}J_{PC}$ 17.0 Hz, C=O), 175.3 (C=O).

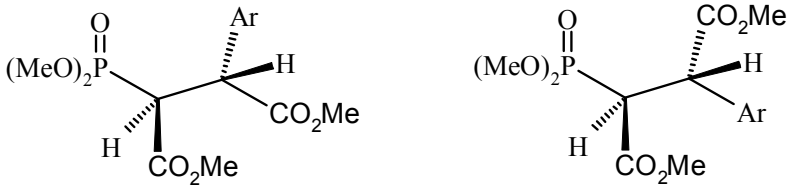
Diethyl 2-(diphenoxyphosphoryl)-3-(4-hydroxy-2-oxo-2H-chromen-3-yl) succinate (4d)

Yellow powder, m.p. 212-214 °C, 0.76 g, yield 68%. IR (KBr) (ν_{max}/cm^{-1}): 3242, 1738, 1745, 1752. Anal. Calcd for $C_{29}H_{27}O_{10}P$ (566.49): C, 61.49; H, 4.80. Found: C, 61.57; H, 4.86%. 1H NMR (500 MHz, $CDCl_3$): δ 1.36 (3 H, t, $^{3}J_{HH}$ 7.6 Hz, Me), 1.42 (3 H, t, $^{3}J_{HH}$ 7.6 Hz, Me), 4.16 (1 H, dd $^{2}J_{HP}$ 21.5 Hz $^{3}J_{HH}$ 12.0 Hz, CH), 4.24 (2 H, q, $^{3}J_{HH}$ 7.6 Hz CH_2O), 4.34 (2 H, q, $^{3}J_{HH}$ 7.6 Hz, CH_2O), 5.27 (1 H, dd $^{3}J_{HH}$ 12.5 Hz $^{3}J_{HP}$ 9.6 Hz, CH), 7.16-8.04 (14 H, m, 14 CH), 8.10 (1 H, s, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.2 (Me), 13.8 (Me), 44.6 (CH), 50.2 (d $^{1}J_{PC}$ 136.4 Hz, CH), 61.2 (CH_2O), 62.3 (CH_2O), 121.5 (d, $^{3}J_{PC}$ 6.8 Hz, 2 CH), 122.7 (d, $^{3}J_{PC}$ 10.6 Hz, C), 123.4 (d, $^{3}J_{PC}$ 6.3 Hz, 2 CH), 125.4 (CH), 126.7 (CH), 128.2 (CH), 128.8 (CH), 129.3 (CH), 130.8 (m, 4 CH), 131.3 (CH), 132.9 (C), 133.5 (C), 149.2 (d $^{2}J_{PC}$ 10.4 Hz, C), 151.3 (m,

2 C), 164.2 (C=O), 169.3 (d $^2J_{PC}$ 18.4 Hz, C=O), 176.2 (C=O).

Result and discussion

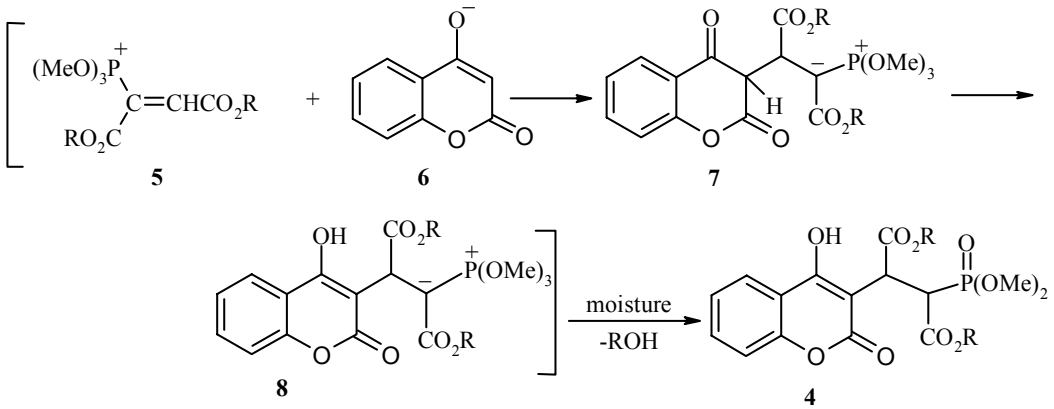
The ^{1}H NMR spectrum of **4a** displayed signals for vicinal methine protons at δ = 3.92 and 5.12, which appeared as two set of doublet doublets with $^2J_{HP}$ and $^3J_{HP}$ values of 20.4 and 8.7 Hz, respectively. The methoxy groups of the phosphoranyl moiety are diastereotopic and show two separate doublets at δ = 2.92 and 3.72. The hydroxy proton was observed as a broad singlet at δ = 8.12 which disappeared with addition of D_2O. Observation of $^3J_{HH}$ = 11.7 Hz for the vicinal methine protons in **4a** specifys the supremacy of anti arrangement. Since compound **4a** possesses two stereogenic centers, two diastereomers with anti HCCH arrangements are possible (Figure 1). The observation of $^3J_{CP}$ of 21.5 Hz for the CO_2Me group and $^3J_{CP}$ of zero for C of naphthalene moiety is in agreement with the (*2R, 3S*) or (*2S, 3R*) diastereoisomer [15].



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

Figure 1. Two diastereomers of **4a** with anti arrangement.

A proposed mechanism for the formation of compound **4** is shown in Scheme 2. Under the reaction conditions, ylide **7** isomerizes to ylide **8** and hydrolysis of **8** leads to phosphonate derivative **4**.



Scheme 2. Proposed mechanism for the formation of **4**.

Conclusion

We found that the reaction of activated acetylenic compounds with trimethyl phosphite or triphenyl phosphite in the presence of 4-hydroxycumarin leads to a facile synthesis of some functionalized phosphonates in water as green solvent without using any catalyst.

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