Facile Synthesis of Phosphonates via Catalyst-Free Multicomponent Reactions in Water

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Abstract: Stable derivatives of phosphonates were prepared using multicomponent reactions of dialkyl acetylenedicarboxylate with 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone or 4-hydroxycoumarin in the presence of trimethyl or triphenyl phosphite in water in good yields.

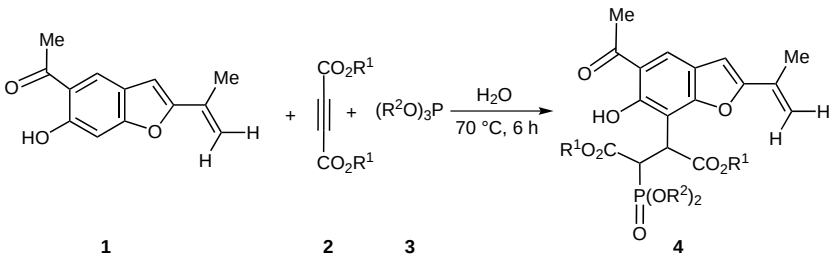
Key words: phosphonates, triphenyl phosphate, trimethyl phosphate, triethyl phosphate

One powerful tool used to combine economy with environmental concern is to perform organic reactions in water in two or more synthetic steps without isolation of any intermediate, thus reducing time and saving money, energy, and raw materials.[1] Phosphorus-containing organic compounds have diverse biological activity and have attracted noteworthy synthetic and pharmacological interest.[2,3] Phosphonates have important applications in flame retardancy,[4,5] organic synthesis,[6] and biological applications.[3c,7] Furthermore, phosphonates have been used as substitutes for the corresponding esters and acids of high-biological activity[8,9] and as suitable probes for designing antibodies on the basis of transition-state models. A large number of methods has appeared describing novel syntheses of organophosphorus compounds.[10–14] Hence, we describe herein the reaction of dialkyl acetylenedicarboxylate with a trivalent phosphorus nucleophile such as trimethyl phosphite or triphenyl phosphite in the presence of 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone[15,16] or 4-hydroxycoumarin.

1-(6-Hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone (**1**) has been extracted from the roots of *Petasites hybridus*. This compound is very soluble in water and has been shown to have potent biological and medicinal properties.[15,16]

The reaction of 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone (**1**) and dialkyl acetylenedicarboxylate **2** in the presence of trimethyl phosphite or triphenyl phosphite **3** produces dialkyl 2-(dialkoxyphosphoryl)succinate **4** in good yield (Scheme 1).[17]

The ^{1}H NMR spectrum of **4a** displayed two singlets at δ = 2.12 and 2.58 ppm for the methyl protons, two singlets at δ = 3.72 and 3.84 ppm for the methoxy protons, and two sets of doublet of doublets for the vicinal methine protons at δ = 3.94 and 5.15 ppm, which appeared with $^2J_{HP}$ and $^3J_{HP}$ values of 20.4 and 11.7 Hz, respectively. The methoxy groups of the phosphoranyl moiety are diastereotopic and show two separate doublets at δ = 2.87 (3 H, d, J_{HP} = 11.2 Hz, MeO) and 3.78 (3 H, d, $^3J_{HP}$ = 11.2 Hz, MeO) ppm. The hydroxy proton was observed as a broad



1 2 3 4

2, 3, 4	R^1	R^2	Yield (%) of 4
a	Me	Me	87
b	Et	Me	78
c	*i*-Pr	Me	75
d	Me	Ph	72
e	Et	Ph	70

Scheme 1 Reaction of phosphites, activated acetylenes, and 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone

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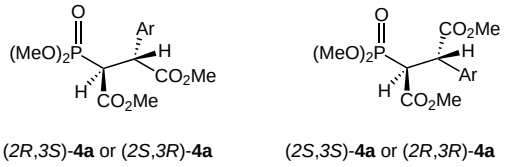
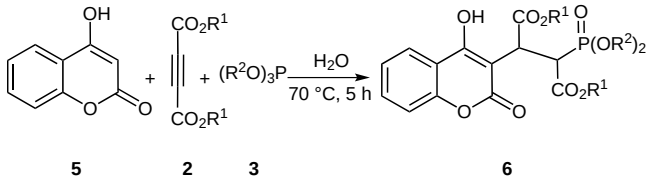
singlet at δ = 8.22 ppm, which disappeared with addition of D_2O. Observation of $^3J_{HH}$ = 12.0 Hz for the vicinal methine protons in **4a** implies an *anti* arrangement. Since compound **4a** possesses two stereogenic centers, two diastereomers with *anti* HCCH arrangements are possible (Figure 1). The observation of $^3J_{CP}$ = 22.4 Hz for the CO_2Me group and $^3J_{CP}$ = 0 Hz for C of the benzene moiety is in agreement with the *2R*,*3S* or *2S*,*3R* diastereomer.



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

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

Under similar conditions, the reaction of 4-hydroxycoumarin (**5**) and dialkyl acetylenedicarboxylate **2** in the presence of trimethyl phosphite or triphenyl phosphite **3** produced dialkyl 2-(dialkoxyphosphoryl)succinate **6** in good yield (Scheme 2).[18]



5 **2** **3** **6**

2, **3**, **6**	R^1	R^2	Yield (%) of **6**
a	Me	Me	85
b	Et	Me	80
c	Me	Ph	72
d	Et	Ph	68

Scheme 2 Reaction of phosphites, activated acetylenes, and 4-hydroxycoumarin

The ^{1}H NMR spectrum of **6a** displayed signals for vicinal methine protons at δ = 3.92 and 5.12 ppm, which appeared as two doublet of 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 ppm. The hydroxy proton was observed as a broad singlet at δ = 8.12 ppm, which disappeared with addition of D_2O. Observation of $^3J_{HH}$ = 11.7 Hz for the vicinal methine protons in **6a** once again indicates an *anti* arrangement. Since compound **6a** possesses two stereogenic centers, two diastereomers with *anti* HCCH arrangements are possible (Figure 1).

A proposed mechanism for the formation of compound **6** is shown in Scheme 3. On the basis of phosphorus nucleophilic chemistry,[12,19] it is reasonable to presume that compound **6** results from initial addition of the phosphite to the activated acetylenic compound and following protonation of the reactive 1:1 adduct, attack of the 4-hydroxycoumarin **8** to cation **7** to generate ylide **9** which isomerizes, under the reaction conditions employed, to ylide **10**. Hydrolysis of **10** leads to phosphonate derivative **6**.

In conclusion, we found that the reaction of activated acetylenic compounds with trimethyl phosphite or triphenyl phosphite in the presence of 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone or 4-hydroxycoumarin leads to a facile synthesis of some functionalized phosphonates in water as the solvent without needing a catalyst.

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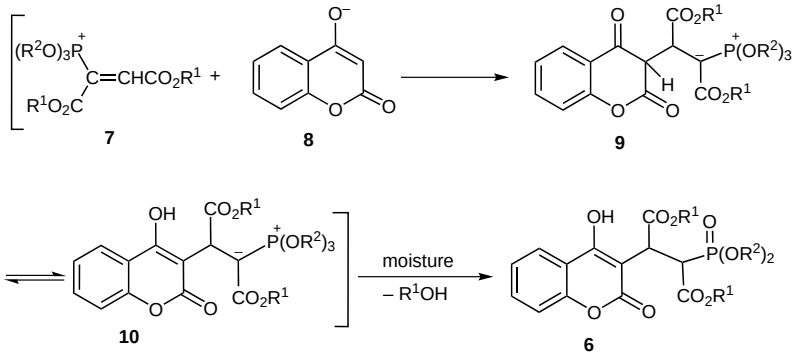

7 **8** **9** **10** **6**

Scheme 3 Proposed mechanism for the formation of **4**

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(17) **General Procedure for the Preparation of Compounds 4**
To a magnetically stirred solution of dialkyl acetylenedicarboxylate **2** (2 mmol) and 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone (**1**, 2 mmol) in H_2O was added trimethyl or triphenyl phosphite **3** (2 mmol). The reaction mixture was stirred for 6 h, and, after completion of reaction (monitored by TLC), the mixture was purified by silica gel column chromatography (Merck 230–400 mesh) using *n*-hexane–EtOAc as eluent to give compound **4**.

Representative Analytical Data for Compound 4a
White powder; mp 138–140 °C; yield: 0.81 g (87%). IR (KBr): ν_{max} = 3225, 1740, 1735, 1724, 1678, 1587, 1128 cm^{-1}. Anal. Calcd (%) for $C_{21}H_{25}O_{10}P$ (468.39): C, 53.85; H, 5.38. Found: C, 53.92; H, 5.47. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.12 (3 H, s, Me), 2.58 (3 H, s, Me), 2.87 (3 H, d $^3J_{HP}$ = 11.2 Hz, MeO), 3.72 (3 H, s, MeO), 3.78 (3 H, d $^3J_{HP}$ = 11.2 Hz, OMe), 3.84 (3 H, s, MeO), 3.94 (1 H, dd $^2J_{HP}$ = 20.4 Hz, $^3J_{HH}$ = 12.0 Hz, CH), 4.78 (1 H, d, ^2J = 3.5 Hz, CH), 5.15 (1 H, dd, $^3J_{HH}$ = 12.0 Hz, $^3J_{HP}$ = 8.7 Hz, CH), 5.30 (1 H, s, CH), 5.73 (1 H, d, ^2J = 3.5 Hz, CH), 7.82 (1 H, s, CH), 8.22 (1 H, s, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 18.6 (Me), 27.3 (Me), 44.2 (CH), 48.5 (d, $^1J_{PC}$ = 134.4 Hz, CH), 52.0 (OMe), 52.8 (d, $^2J_{PC}$ = 8.2 Hz, MeO), 53.6 (MeO), 54.6 (d, $^2J_{PC}$ = 8.2 Hz, MeO), 110.8 (d, $^3J_{PC}$ = 5.8 Hz, C), 111.4 (CH), 112.3 (CH_2), 117.5 (C), 121.0 (C), 122.4 (CH), 137.5 (C), 154.2 (C), 157.4 (C), 159.2 (C), 167.5 (d, $^2J_{PC}$ = 5.4 Hz, C=O), 172.6 (d, $^3J_{PC}$ = 22.4 Hz, C=O), 192.8 (C=O). ^{31}P NMR (202 MHz, $CDCl_3$): δ = 18.6. MS: m/z (%) = 468 (10) [M^+], 359 (56), 109 (100), 31 (86).

(18) **General Procedure for the Preparation of Compounds 6**
To a magnetically stirred solution of dialkyl acetylenedicarboxylate **2** (2 mmol) and 4-hydroxycoumarin (**5**, 2 mmol) in H_2O was added trimethyl or triphenyl phosphite **3** (2 mmol). The reaction mixture was then stirred for 5 h. After completion of reaction (monitored by TLC), the mixture was purified by silica gel column chromatography (Merck 230–400 mesh) using *n*-hexane–EtOAc as eluent to give compound **6**.

Representative Analytical Data for Compound 6a
Colorless crystals; mp 185–187 °C; yield 0.70 g (85%). IR (KBr): ν_{max} = 3235, 1754, 1740, 1732 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. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.92 (3 H, d, $^3J_{HP}$ = 11.2 Hz, MeO), 3.65 (3 H, s, MeO), 3.72 (3 H, d, $^3J_{HP}$ = 11.2 Hz, OMe), 3.85 (3 H, s, MeO), 3.92 (1 H, dd, $^2J_{HP}$ = 20.4 Hz, $^3J_{HH}$ = 11.7 Hz, CH), 5.12 (1 H, dd, $^3J_{HH}$ = 11.7 Hz, $^3J_{HP}$ = 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, $^1J_{PC}$ = 134.4 Hz, CH), 51.8 (OMe), 52.3 (d, $^2J_{PC}$ = 8.2 Hz, MeO), 53.4 (MeO), 54.0 (d, $^2J_{PC}$ = 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, $^2J_{PC}$ = 5.4 Hz, C=O), 172.6 (d, $^3J_{PC}$ = 21.5 Hz, C=O). ^{31}P NMR (202 MHz, $CDCl_3$): δ = 18.6. MS: *m/z* (%) = 414 (20) [M^+], 252 (48), 162 (86), 31 (100).

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