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Synthesis of phosphonate derivatives using multicomponent reaction of phosphites

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Abstract: An effective one-pot synthesis of phosphonate derivatives using multicomponent reaction of activated acetylenes with alkyl bromide and trialkyl phosphites is described. In these reactions, phosphoryl-2-oxo-2H-pyran is synthesized under solvent-free conditions at room temperature that provided good yields of products.

Keywords: 2*H*-pyran, Trialkyl phosphite, Dialkyl acetylenedicarboxylates.

Introduction

Heterocyclic compounds hold a prominent position in medicinal chemistry owing to their wide spectrum of biological activities such as antimalarial,[1] antimicrobial [2], antitumor [3], anticancer [4], antidepressant [5], antiviral [6], antidiabetic [7], anti-inflammatory [8] and anti-HIV [9]. Moreover, they also contribute in the feld of material science [10], dyes and pigment science [11] as well as agrochemistry [12]. Therefore, there is considerable thrust for the development of efficient synthetic strategies for producing these compounds. MCRs open diverse avenues to create novel concatenations in one pot fashion leading to diverse biologically potent heterocyclic scaffolds [13, 14]. Having a cascade of reactions occurring in one pot is highly beneficial in the context of modern trends for organic synthesis, where sustainability is as relevant as efficiency and selectivity.

Multicomponent reactions being atom economic, efficient and extremely convergent in nature offer a number of advantages over stepwise sequential approaches [15–17] and could be performed in the presence of nanocatalyst and produce heterocyclic compounds [18-20]. Consequently, in this report we investigate the synthesis of phosphoryl-2-oxo-2*H*-pyran derivatives using the reaction of with activated acetylenes with alkyl bromide and trialkyl phosphites without any catalyst.

Results and discussion

We describe synthesis of phosphonate derivatives **5** in good yields under solvent-free conditions through the reaction of trivalent phosphorus nucleophile **1** with dialkyl acetylenedicarboxylate **2** and alkyl bromides **3** (Scheme **1**).

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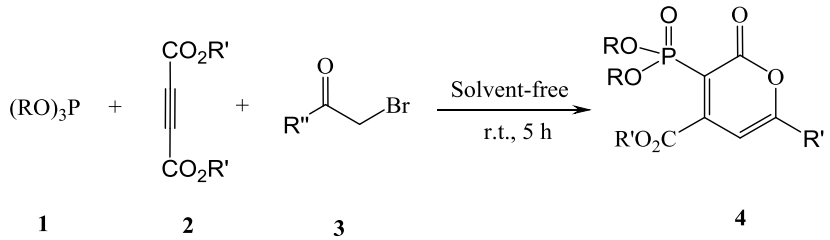
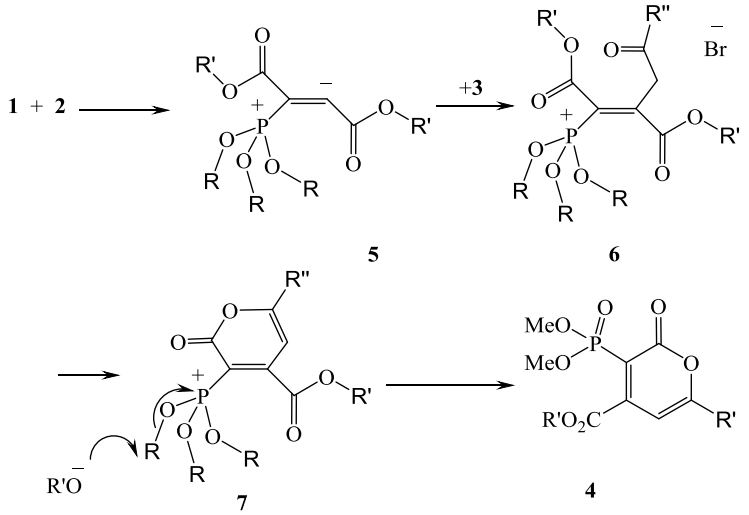


4	R	R'	R''	Yield (%) of **4**
a	Me	Me	CO_2Et	85
b	Me	Et	CO_2Et	80
c	Et	Me	CO_2Et	83
d	Et	Et	CO_2Et	82
e	Me	Me	4-MeO-C_6H_4	87
f	Me	Me	4-Me-C_6H_4	85

Scheme 1: Synthesis of phosphonate derivatives

The ^{1}H NMR spectrum of **4a** showed one doublet at 3.78 (d $^3J_{HP}$ 11.8 Hz) ppm for two methoxy groups of phosphoranyl moiety, three singlet at (δ 3.85, 3.87, 3.92 ppm) for methoxy protons and one singlet at (δ 8.72 ppm) for methin proton. The ^{13}C NMR spectrum of **5a** showed three singlets at (δ 51.8, 52.2, 52.6 ppm) for methoxy groups and one doublet for two methoxy groups of the phosphoranyl moiety at 53.7 (d, $^2J_{PC}$ = 11.2 Hz) and resonance of methin group at 133.8 (d, $^3J_{PC}$ = 21.7 Hz) along with resonance of carbonyl groups at 160.2 (d, $^3J_{PC}$ = 24.2 Hz), 161.4, 168.7 (d, $^3J_{PC}$ = 19.7 Hz), 169.4 ppm in agreement with the proposed structure. ^{31}P NMR signals was found at δ = 17.8 ppm. On the basis of the well established chemistry of trivalent phosphorus nucleophiles it is reasonable to guess that phosphonate derivatives **6** results from initial addition of trialkyl phosphite to the acetylenic compound and subsequent attack of the resulting anion **6** to the carbon of alkyl bromides **3** to yield intermediate **7** which apparently cyclizes, under the reaction conditions employed to generate the phosphonate derivatives **4** (Scheme **2**).



Scheme 2: Proposed mechanism

Experimental Section

General

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ^{1}H, ^{13}C and ^{31}P NMR spectra were obtained with a Bruker FT-500 spectrometer in $CDCl_3$, and tetramethylsilane (TMS) was used as an internal standard or 85% H_3PO_4 as external standard. Mass spectra were recorded with a Finnigan Mat TSQ-70 spectrometer. Infrared (IR) spectra were acquired on a Nicolet Magna 550-FT spectrometer. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4 % of the calculated values. Acetylenic ester, phenacyl bromide or its derivatives and triphenylphosphine were obtained from Fluka and were used without further purification.

***General procedure for the preparation of phosphonate derivatives* 4**

To a stirred mixture of alkyl bromides **3** (2 mmol) and dialkyl acetylenedicarboxylate **2** (2 mmol) was added trialkyl phosphite **1** (2 mmol) at room temperature. The reaction mixture was stirred for 5 h. After completion of reaction (monitored by TLC), solvent is evaporated and viscous residue was purified by column chromatography on silica gel (Merck 230-400 mesh) using n-hexane-EtOAc (7:1) as eluent to afford **4**.

1-Ethyl 2,3,5-trimethyl 4-(dimethoxyphosphoryl)-1,2,3,5-benzene tertacarboxylate (4a):

Pale yellow powder, Yield: 0.69 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 1745, 1740, 1738, 1697, 1587, 1469, 1357, 1284, 1129 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (3 H, t, $^{3}J_{HH}$ =7.4 Hz, Me), 3.78 (6 H, d $^{3}J_{HP}$ 11.8 Hz, 2 MeO), 3.85 (3 H, s, MeO), 3.87 (3 H, s, MeO), 3.92 (3 H, s, MeO), 4.26 (2 H, q, $^{3}J_{HH}$ =7.4 Hz, CH_2O), 8.72 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.0 (Me), 51.8 (MeO), 52.2 (MeO), 52.6 (MeO), 53.7 (d, $^{2}J_{PC}$ = 11.2 Hz, 2 MeO), 61.5 (CH_2O), 133.2 (d, $^{2}J_{PC}$ = 10.8 Hz, C), 133.8 (d, $^{3}J_{PC}$ = 21.7 Hz, CH), 134.8 (d, $^{2}J_{PC}$ = 11.5 Hz, C), 138.2 (d, $^{3}J_{PC}$ = 21.4 Hz, C), 139.7 (C), 147.5 (d, $^{1}J_{PC}$ = 138.7 Hz, C), 160.2 (d, $^{3}J_{PC}$ = 24.2 Hz, C=O), 161.4 (C=O), 168.7 (d, $^{3}J_{PC}$ = 19.7 Hz, C=O), 169.4 (C=O) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ 19.2. MS, *m/z* (%): 432 (M^{+}, 10), 401 (86), 45 (88), 31 (100). Anal. Calcd for $C_{17}H_{21}O_{11}P$ (432.32): C 47.23, H 4.90; Found: C 47.36, H 5.06%.

1,5-Diethyl2,3-dimethyl4-(dimethoxyphosphoryl)-1,2,3,5-benzene tertacarboxylate (5b):

Yellow powder, Yield: 0.67 g (80%) IR (KBr) (ν_{max}/cm^{-1}): 1744, 1739, 1695, 1487, 1376, 1295 cm^{-1}.- MS, *m/z* (%): 446 (M^{+}, 15), 415 (66), 45 (68), 31 (100).- Anal. Calcd for $C_{18}H_{23}O_{11}P$ (446.34): C 48.44, H 5.19; Found: C 48.52, H 5.32%.- ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (3 H, t, $^{3}J_{HH}$ =7.5 Hz, Me), 1.34 (3 H, t, $^{3}J_{HH}$ =7.4 Hz, Me), 3.79 (6 H, d $^{3}J_{HP}$ 11.5 Hz, 2 MeO), 3.84 (MeO), 3.87 (MeO), 4.28 (2 H, q, $^{3}J_{HH}$ =7.5 Hz, CH_2O), 4.32 (2 H, q, $^{3}J_{HH}$ =7.4 Hz, CH_2O), 8.54 (1 H, s, CH) ppm.- ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.6 (Me), 14.0 (Me), 51.7 (MeO), 52.4 (MeO), 53.6 (d, $^{2}J_{PC}$ = 9.2 Hz, 2 MeO), 61.2 (CH_2O), 62.5 (CH_2O), 132.4 (d $^{2}J_{PC}$ = 8.7 Hz, C), 133.5 (d, $^{3}J_{PC}$ = 21.4 Hz, CH), 134.3 (d $^{2}J_{PC}$ = 9.5 Hz, C), 137.4 (d $^{2}J_{PC}$ = 10.2 Hz, C), 139.8 (C), 147.5 (d $^{1}J_{PC}$ = 140.2 Hz, C), 9.2 (C), 159.6 (d, $^{3}J_{PC}$ = 21.7 Hz, C=O), 160.7 (C=O), 162.8 (d, $^{3}J_{PC}$ = 22.5 Hz, C=O), 167.4 (C=O) ppm.- ^{31}P NMR (202 MHz, $CDCl_3$): δ 18.8.

Trimethyl3-(dimethoxyphosphoryl)-6-(4-methoxyphenyl)-1,2,4-benzene tericarboxylate (4c):

Yellow powder, Yield: 0.73 g (83%). IR (KBr) (ν_{max}/cm^{-1}): 1742, 1738, 1735, 1697, 1587, 1464, 1373, 1225 cm^{-1}.- MS,*m/z* (%): 466 (M^{+}, 20), 435 (88), 107 (68), 31 (100).- Anal. Calcd for $C_{21}H_{23}O_{10}P$ (466.38): C 54.08, H 4.97; Found: C 54.23, H 5.18%.-^{1}H NMR (500 MHz, $CDCl_3$): δ 3.72 (6 H, d, $^{3}J_{HP}$ = 12.5 Hz, 2 MeO), 3.85 (3 H, s, MeO), 3.87 (3 H, s, MeO), 3.90 (MeO), 3.94 (MeO), 7.32 (2 H, d, $^{3}J_{HH}$ = 7.6 Hz, 2 CH), 7.75 (2 H, d, $^{3}J_{HH}$ = 7.6 Hz, 2 CH), 8.62 (1 H, s, CH) ppm.- ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 51.4 (MeO), 52.0 (MeO), 52.3 (MeO), 53.6 (d, $^{2}J_{PC}$ = 9.4 Hz, 2 MeO), 55.4 (MeO), 112.8 (2 CH), 124.8 (2 CH), 125.6 (d $^{2}J_{PC}$ = 9.7 Hz, C), 126.2 (C), 126.6 (d, $^{3}J_{PC}$ = 21.8 Hz, C),127.2 (d, $^{3}J_{PC}$ = 22.5 Hz, CH), 127.8 (d, $^{2}J_{PC}$ = 8.7 Hz, C), 144.2 (d $^{1}J_{PC}$ = 141.2 Hz, C), 146.8 (C), 155.7 (C), 159.7 (d, $^{3}J_{PC}$ = 21.4 Hz, C=O), 160.7 (d, $^{3}J_{PC}$ = 22.3 Hz, C=O), 167.4 (C=O) ppm.- ^{31}P NMR (202 MHz, $CDCl_3$): δ 19.8.

Trimethyl3-(dimethoxyphosphoryl)-6-(4-methylphenyl)-1,2,4-benzene tericarboxylate (4d):

Yellow powder, Yield: 0.63 g (82%). IR (KBr) (ν_{max}/cm^{-1}): 1745, 1740, 1738, 1695, 1587, 1465, 1357, 1215 cm^{-1}.- MS, *m/z* (%): 450 (M^{+}, 15), 419 (66), 91 (86), 31 (100). -Anal. Calcd for $C_{21}H_{23}O_9P$ (450.38): C 56.00, H 5.15; Found: C 56.22, H 5.28%.- ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.28 (Me), 3.75 (6 H, d, $^{3}J_{HP}$ =

11.5 Hz, 2 MeO), 3.84 (3 H, s, MeO), 3.87 (3 H, s, MeO), 3.92 (3 H, s, MeO), 7.32 (2 H, d, $^3J_{HH}$ = 7.5 Hz, 2 CH), 7.75 (2 H, d, $^3J_{HH}$ = 7.5 Hz, 2 CH), 8.57 (1 H, s, CH), ppm.- ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 22.5 (Me), 51.4 (MeO), 52.3 (MeO), 52.7 (MeO), 53.7 (d, $^2J_{PC}$ = 10.2 Hz, 2 MeO), 121.8 (C), 123.5 (2 CH), 125.4 (2 CH), 125.8 (d, $^2J_{PC}$ = 11.2 Hz, C), 126.2 (d, $^3J_{PC}$ = 21.2 Hz, C), 127.2 (d, $^3J_{PC}$ = 21.4 Hz, CH), 127.8(d, $^2J_{PC}$ = 10.8 Hz, C), 133.4 (C), 134.7 (C), 144.3 (d $^1J_{PC}$ = 138.7 Hz, C), 160.2 (d, $^3J_{PC}$ = 23.2 Hz, C=O), 165.3 (d, $^3J_{PC}$ = 22.4 Hz, C=O), 167.8 (C=O) ppm.- ^{31}P NMR (202 MHz, $CDCl_3$): δ 20.7.

Trimethyl3-(dimethoxyphosphoryl)-6-(4-Nitrophenyl)-1,2,4-benzene tericarboxylate (4e):

Yellow powder, Yield: 0.63 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1742, 1738, 1735, 1697, 1562, 1487, 1352, 1295 cm^{-1}.- MS, *m/z* (%): 481 (M^+, 10), 450 (86), 122 (82), 31 (100). - Anal. Calcd for $C_{20}H_{20}NO_{11}P$ (481.35): C 49.90, H 4.19, N 2.91; Found: C 49.78, H 4.02, N 2.75%.-^{1}H NMR (500 MHz, $CDCl_3$): δ 3.82 (6 H, d, $^3J_{HP}$ = 11.8 Hz, 2 MeO), 3.85 (3 H, s, MeO), 3.88 (3 H, s, MeO), 3.93 (3 H, s, MeO), 7.57 (2 H, d, $^3J_{HH}$ = 7.8 Hz, 2 CH), 8.62 (1 H, s, CH), 8.22 (2 H, d, $^3J_{HH}$ = 7.8 Hz, 2 CH) ppm.- ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 51.8 (MeO), 52.2 (MeO), 52.8 (MeO), 53.5 (d, $^2J_{PC}$ = 10.5 Hz, 2 MeO), 120.1 (2 CH), 122.8 (d, $^3J_{PC}$ = 20.8 Hz, C),123.6 (d, $^3J_{PC}$ = 21.5 Hz, CH), 125.6 (2 CH), 126.2 (d, $^2J_{PC}$ = 11.5 Hz, C), 127.2 (C), 127.6 (d,$^2J_{PC}$ = 11.4 Hz, C), 140.2 (C), 144.5 (C), 145.8 (d $^1J_{PC}$ = 139.2 Hz, C), 160.4 (d, $^3J_{PC}$ = 22.3 Hz, C=O), 164.8 (d, $^3J_{PC}$ = 21.7 Hz, C=O), 168.4 (C=O) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ 22.4.

4-Ethyl1,2-dimethyl3-(dimethoxyphosphoryl)-6-(4-bromophenyl)-1,2,4-benzene tericarboxylate (4f):

Pale yellow powder, Yield: 0.79 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 1738, 1735, 1730, 1695, 1578, 1457, 1355, 1298 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (3 H, t, $^3J_{HH}$ =7.5 Hz, Me), 3.85 (6 H, d, $^3J_{HP}$ = 11.5 Hz, 2 MeO), 3.87 (3 H, s, MeO), 3.92 (3 H, s, MeO), 4.26 (2 H, q, $^3J_{HH}$ =7.4 Hz, CH_2O), 7.38 (2 H, d, $^3J_{HH}$ = 7.6 Hz, 2 CH), 7.45 (2 H, d, $^3J_{HH}$ = 7.6 Hz, 2 CH), 8.58 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.7 (Me), 51.6 (MeO), 52.4 (MeO), 53.8 (d, $^2J_{PC}$ = 10.8 Hz, 2 MeO), 61.2 (CH_2O), 116.7 (C), 124.2 (2 CH), 125.2 (d, $^2J_{PC}$ = 10.2 Hz, C), 125.8 (C), 126.5 (d, $^3J_{PC}$ = 21.8 Hz, C), 126.8 (d, $^3J_{PC}$ = 22.4 Hz, CH), 127.2 (2 CH), 127.8 (d, $^2J_{PC}$ = 10.8 Hz, C), 135.4 (C), 144.2 (d $^1J_{PC}$ = 138.6 Hz, C),161.7 (d, $^3J_{PC}$ = 22.8 Hz, C=O), 165.2 (d, $^3J_{PC}$ = 22.3 Hz, C=O), 168.7 (C=O) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ 22.8. MS, *m/z* (%): 529(M^+, 15), 498 (78), 156 (68), 31 (100). Anal. Calcd for $C_{21}H_{22}BrO_9P$ (529.27): C 47.66, H 4.19; Found: C 47.74, H 4.32%.

Conclusion

In summary synthesis of phosphonate derivatives is performed using the reaction of trivalent phosphorus nucleophile **1** with dialkyl acetylenedicarboxylate **2** and alkyl bromides **3** under solvent-free conditions at room temperature in good yield. The advantages of these reactions involve good yield and easy reaction workup procedures.

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