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Synthesis of phosphonate derivatives using multicomponent reaction of alkyl bromides

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Abstract: An effective one-pot synthesis of phosphonate derivatives using the reaction of activated acetylenic compounds and alkyl bromides in the presence of trialkyl phosphites in water at room temperature that provided good yields of products.

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

Introduction

Performing organic reactions in aqueous medium has a number of advantages because of water would be significantly secure, profuse, nontoxic, environmentally friendly, and economical compared to organic solvents. Moreover, water shows single reactivity and selectivity that is different from those in conservative organic solvents [5]. Therefore, the expansion of a catalyst that is not only stable toward water but also simply recyclable seems highly attractive. Multicomponent reactions (MCRs) have some advantages to classic different reaction methodes, such as lower costs, shorter reaction time, and less side products, as well as environmentally friendly features [6]. Hence, MCRs are essential subject in the synthesis of many chief heterocyclic compounds such as pyran derivatives at the present time. [1-9].

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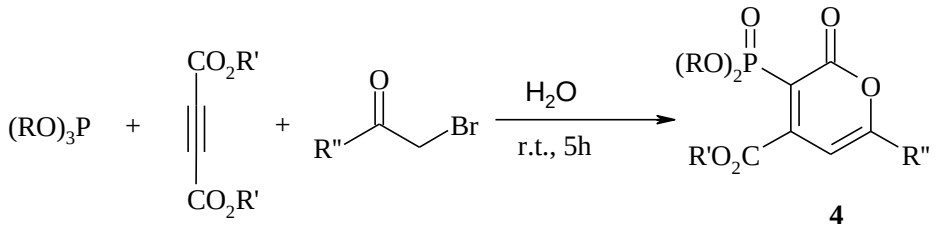
Recently, there has been enormous emphasis on the green and sustainable chemistry, where high importance has been given for the development of novel and eco-friendly methodologies which can decrease or remove the utilization and making of unsafe industrial wastes.10Among the solvents, water is the best green, accessible and low-cost solvent for the increasing the velocity of organic process for water-insoluble starting materials.11 Also all of organic products precipitate in water, remain in solution and could be extracted by filtration[13].

Results and discussion

We describe synthesis of phosphonate derivatives **4** in good yields in water through the reaction of trivalent phosphorus nucleophile **1** with dialkyl acetylenedicarboxylate **2** and alkyl bromides **3** (Scheme **1**).



1 **2** **3** **4**

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 **5** results from initial addition of trialkyl phosphite to the acetylenic compound and subsequent attack of the resulting anion **5** to the carbon of alkyl bromides **3** to yield intermediate **6** which apparently cyclizes, under the reaction conditions employed to generate the phosphonate derivatives **4** (Scheme **2**).

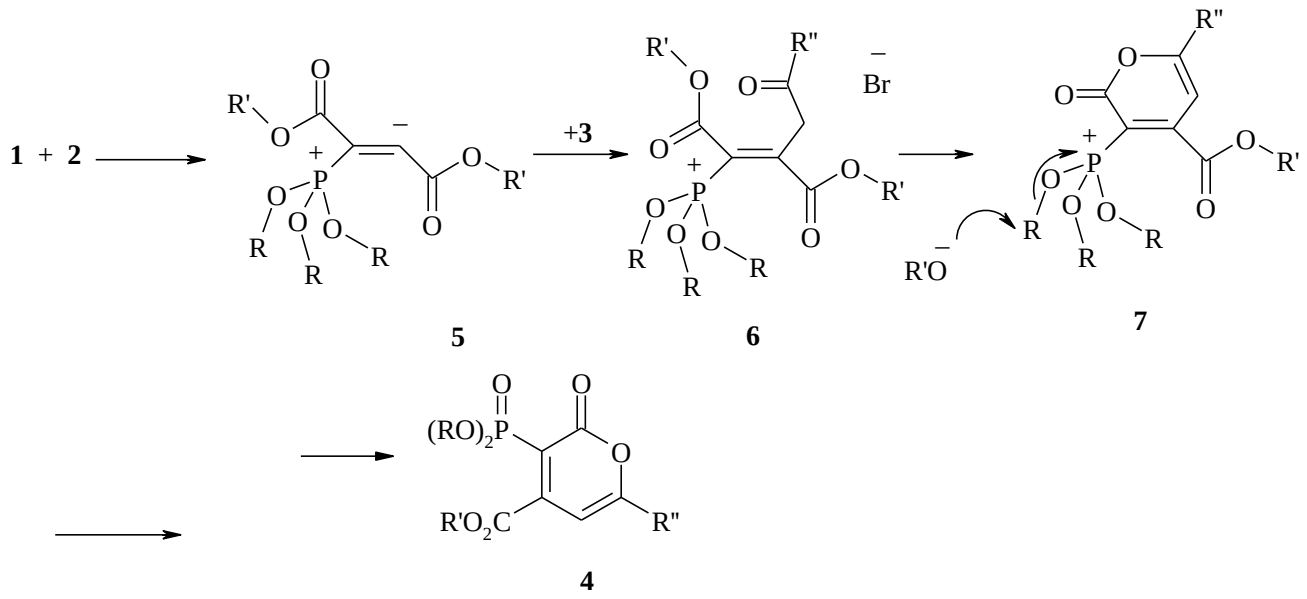
Conclusion

In summary synthesis of phosphonate derivatives is performed using the reaction of trivalent phosphorus nucleophile **1** with dialkyl acetylenedicarboxylate **2** and, alkyl bromides **3** in water in good yield. The advantages of these reactions involve good yield and easy reaction workup procedures.

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.



Scheme 2: Proposed mechanism.

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) in toluene at reflux conditions. After 2 h dimethyl acetylenedicarboxylate was added to mixture of reaction slowly. The reaction mixture was stirred for 12 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 **5**.

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, $^3J_{HH}$ =7.4 Hz, Me), 3.78 (6 H, d $^3J_{HP}$ 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, $^3J_{HH}$ =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, $^2J_{PC}$ = 11.2 Hz, 2 MeO), 61.5 (CH_2O), 133.2 (d, $^2J_{PC}$ = 10.8 Hz, C), 133.8 (d, $^3J_{PC}$ = 21.7 Hz, CH), 134.8 (d, $^2J_{PC}$ = 11.5 Hz, C), 138.2 (d, $^3J_{PC}$ = 21.4 Hz, C), 139.7 (C), 147.5 (d, $^1J_{PC}$ = 138.7 Hz, C), 160.2 (d, $^3J_{PC}$ = 24.2 Hz, C=O), 161.4 (C=O), 168.7 (d, $^3J_{PC}$ = 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 (4b):

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, $^3J_{HH}$ =7.5 Hz, Me), 1.34 (3 H, t, $^3J_{HH}$ =7.4 Hz, Me), 3.79 (6 H, d $^3J_{HP}$ 11.5 Hz, 2 MeO), 3.84 (MeO), 3.87 (MeO), 4.28 (2 H, q, $^3J_{HH}$ =7.5 Hz, CH_2O), 4.32 (2 H, q, $^3J_{HH}$ =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, $^2J_{PC}$ = 9.2 Hz, 2 MeO), 61.2 (CH_2O), 62.5 (CH_2O), 132.4 (d $^2J_{PC}$ = 8.7 Hz, C), 133.5 (d, $^3J_{PC}$ = 21.4 Hz, CH), 134.3 (d $^2J_{PC}$ = 9.5 Hz, C), 137.4 (d $^2J_{PC}$ = 10.2 Hz, C), 139.8 (C), 147.5 (d $^1J_{PC}$ = 140.2 Hz, C), 9.2 (C), 159.6 (d, $^3J_{PC}$ = 21.7 Hz, C=O), 160.7 (C=O), 162.8 (d, $^3J_{PC}$ = 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, $^3J_{HP}$ = 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, $^3J_{HH}$ = 7.6 Hz, 2 CH), 7.75 (2 H, d, $^3J_{HH}$ = 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, $^2J_{PC}$ = 9.4 Hz, 2 MeO), 55.4 (MeO), 112.8 (2 CH), 124.8 (2 CH), 125.6 (d $^2J_{PC}$ = 9.7 Hz, C), 126.2 (C), 126.6 (d, $^3J_{PC}$ = 21.8 Hz, C),127.2 (d, $^3J_{PC}$ = 22.5 Hz, CH), 127.8 (d, $^2J_{PC}$ = 8.7 Hz, C), 144.2 (d $^1J_{PC}$ = 141.2 Hz, C), 146.8 (C), 155.7 (C), 159.7 (d, $^3J_{PC}$ = 21.4 Hz, C=O), 160.7 (d, $^3J_{PC}$ = 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, $^3J_{HP}$ = 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%.

Acknowledgments

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