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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 dielz-alder reaction of activated acetylenes with phosphoryl-2-oxo-2*H*-pyran is described. In these reactions, phosphoryl-2-oxo-2H-pyran is synthesized via the reaction of dialkyl acetylene dicarboxylates and alkyl bromides in the presence of trialkyl phosphites under solvent-free conditions at 50oC that provided good yields of products.

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

## Introduction

Functionalized benzene is a chief group of compounds in organic chemistry, natural product chemistry, and materials science [1-4]. Multicomponent reaction of benzene ring is an interesting option in benzene synthesis. For instance, a [2+2+2] synthesis has been reached by transition metal catalyzed reactions [5-7], and a [4+2] synthesis was catalyzed by transition metal reactions or by thermal reactions [5, 8, 9]. The chemistry of aromatic with carboxylate groups has obtained considerable notice due to the diversity of bridging facilities of these compounds in the creation of inorganic organic skeletons. Especially, benzenecarboxylate ligands have been exhibited building blocks effects in the design of metal organic materials with wanted topologies owing to their full coordination modes [10-12].

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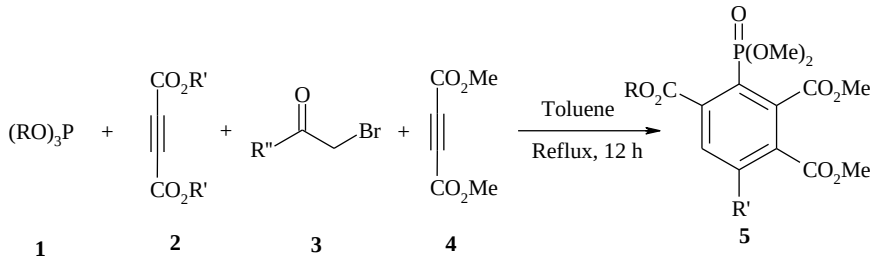
Carbon nucleophiles (anions of carbon acids, organometallics, ylides, enamines, enol ethers, etc.) frequently add to alkynes only in the presence of some activating substituent, reaction-facilitating solvents, specific coordination sites or catalysts [13].

In many cases, cyclic products such as benzene derivatives are achieved. Consequently, in this report we investigate the synthesis of benzene derivatives using the reaction of phosphoryl-2-oxo-2*H*-pyran with dialkyl acetylenedicarboxylate without any catalyst.

## Results and discussion

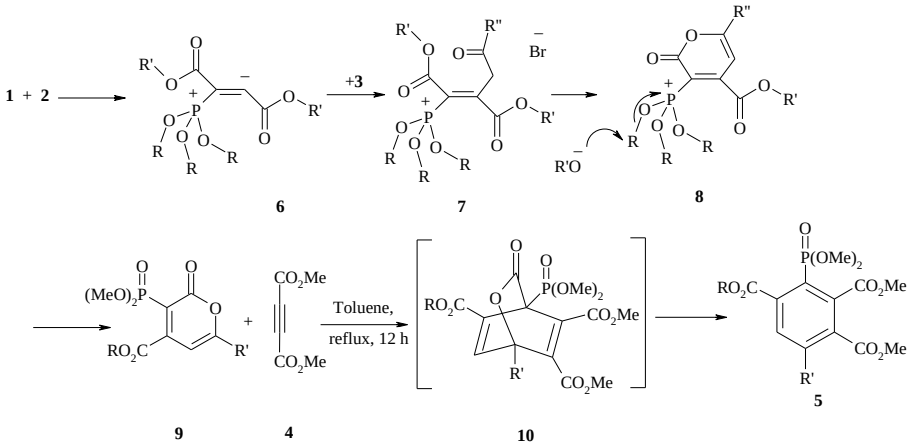
We describe synthesis of phosphonate derivatives **5** in good yields under reflux conditions through the reaction of trivalent phosphorus nucleophile **1** with dialkyl acetylenedicarboxylate **2**, alkyl bromides **3** and dimethyl acetylenedicarboxylate (Scheme **1**).




| 5 | R | R' | R" | Yield (%) of **5** |
|---|---|---|---|---|
| **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 **5a** showed one doublet at 3.78 (d $^3J_{HP}$ 11.8 Hz) ppm for two methoxy groups of phosphoranyl moiety, three singlet at ($\delta$ 3.85, 3.87, 3.92 ppm) for methoxy protons and one singlet at ($\delta$ 8.72 ppm) for methin proton. The $^{13}$C NMR spectrum of **5a** showed three singlets at ($\delta$ 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 $\delta$ = 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 **9.** Phosphonate **9** react with DMAD to produce intermediate **10** that after elimination of $CO_2$ compound **5** is produced (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 5:***

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 (5a).-** Pale yellow powder, Yield: 0.69 g (85%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1745, 1740, 1738, 1697, 1587, 1469, 1357, 1284, 1129 cm$^{-1}$. $^{1}H$ NMR (500 MHz, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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) ($\nu_{max}$/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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 18.8.

**Trimethyl3-(dimethoxyphosphoryl)-6-(4-methoxyphenyl)-1,2,4-benzene tericarboxylate (5c).** Yellow powder, Yield: 0.73 g (83%). IR (KBr) ($\nu_{max}$/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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 19.8.

**Trimethyl3-(dimethoxyphosphoryl)-6-(4-methylphenyl)-1,2,4-benzene tericarboxylate (5d).-** Yellow powder, Yield: 0.63 g (82%). IR (KBr) ($\nu_{max}$/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, $CDCl_3$): $\delta$ 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, $^{3}J_{HH}$ = 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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 20.7.

**Trimethyl3-(dimethoxyphosphoryl)-6-(4-Nitrophenyl)-1,2,4-benzene tericarboxylate (5e).-** Yellow powder, Yield: 0.63 g (87%). IR (KBr) ($\nu_{max}$/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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 22.4.

**4-ethyl1,2-dimethyl3-(dimethoxyphosphoryl)-6-(4-bromophenyl)-1,2,4-benzene tericarboxylate (5f).** Pale yellow powder, Yield: 0.79 g (85%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1738, 1735, 1730, 1695, 1578, 1457, 1355, 1298 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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**, alkyl bromides **3** and dimethyl acetylenedicarboxylate under reflux conditions in toluene in good yield. The advantages of these reactions involve good yield and easy reaction workup procedures.

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