Efficient synthesis of ether phosphonates using trichloroacetimidate and acetate coupling methods

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A series of ether phosphonates have been prepared by trichloroacetimidate and acetate coupling methods. Trichloroacetimidates or acetates were treated with primary and secondary alcohols as O-nucleophiles in the presence of catalytic TMSOTf to afford 21 examples of diethyl alkoxysubstitutedphenyl)methyl phosphonates via C–O bond formation in 55–90% yields and short reaction time.

Introduction

Phosphonates are an important class of organic compounds showing remarkable applications as isosteric analogs of natural phosphate esters.1,2 Phosphonates are key intermediates in a variety of synthetically important reactions. The reaction of stabilized phosphate carbanions (ylides) with aldehydes or ketones to afford E-selective alkenes is known as Horner–Wadsworth–Emmons reaction (a modified Wittig reaction).3,4 A number of methods have been reported for the preparation of phosphonates. The Michaelis–Arbuzov reaction5–7 is an abundant method for the preparation of phosphonates via P–C bond formation. It involves the reaction of an aryl/alkyl halide with trialkyl phosphite to give alkyl phosphate. Hirao method8,9 shows the palladium-catalyzed cross-coupling of dialkylphosphate with aromatic electrophiles for the synthesis of arylphosphonates via aryl C–P bond formation. Recently, α-functional phosphonates, α-aminophosphonates,10 α-acetoxyphosphonates11 and α-hydroxyphosphonates12–15 showed interesting medicinal applications as antiviral agents and attracted the attention of many research groups. Abramov and Pudovik method16,17 described the reaction of aldehydes with di and trialkyl phosphate in the presence of a base to afford α-hydroxyphosphonates. An efficient use of α-hydroxy phosphonates enables a mild process for the preparation of α-substituted methyl phosphonates with promising biological activities.

The use of trichloroacetimidate and acetate methods are well recognized in organic and carbohydrate synthesis via C–O or C–C bond formations.18–21 Earlier we described the reaction of O-phthalimidomethyl trichloroacetimidate and O-diphenylmethyl trichloroacetimidate with C-nucleophiles in the presence of TMSOTf to afford a series of N-substituted phthalimides,20 and benzhydryl derivatives.21 Also, we showed the preparation of a number of N-protected non proteinogenic α-amino acid esters using trichloroacetimidate or acetate coupling methods via C–C bond formation from the corresponding methyl 2-benzamido-2-hydroxacetate and benzyl[(methoxycarbonyl)(hydroxy)methylcarbamate substrates and C-nucleophiles.22

The strategies of both trichloroacetimidate and acetate methods involve the transformation of the substrate hydroxyl group into an excellent leaving group, such as trichloroacetimidate or acetate by the reaction with trichloroacetanilide or acetic anhydride, respectively. The successive addition of poor nucleophiles (alcohols) to these active intermediates in the presence of Lewis acid give interesting products via C–O bond formations, Fig. 1.

These findings motivated the development of a series of diethyl alkoxysubstitutedphenyl)methyl phosphonate 6–8(a–f), 10 and 12 using trichloroacetimidate and acetate coupling methods via C–O bond formation.

Results and discussion

Nucleophilic addition of diethyl phosphate to benzaldehydes 1a–d in 1 : 1 molar ratio using triethylamine as a base gave the diethyl(hydroxy)aryl methyl phosphonates 2a–d in good yields (Scheme 1). The base-catalyzed addition reaction of trichloroacetanilide to α-hydroxyphosphonates 2a–d hydroxy group in the presence of DBU gave the desired diethyl 2-(2,2,2-trichloro-1-iminoethoxy)[3,4-dimethoxyphenoxy]methylphosphonates 3a–d, in 80–94% yield, Scheme 1. The reactions of α-hydroxyphosphonates 2b–d with acetic anhydride in the presence of DMAP (N,N-dimethyl aminopyridine) at room temperature afforded diethylmethylcarbonyloxy-(4-methoxyphenoxy)methylphosphonates 4b–d, Scheme 1.

The structure assignment of α-hydroxyphosphonates 2a–d, active intermediates trichloroacetimidate derivatives 3a–d and acetate derivatives 4b–d were based on 1H, 13C and 31P NMR spectroscopic and elemental analysis are shown in the experimental part.
Both active intermediates trichloroacetimidates 3a–d and acetates 4b–d are excellent precursors for the structure modification of the diethyl phosphonate residue via trichloroacetimidate and acetate coupling methods. However, our early results concerning this synthetic method applying diethyl 2-(2,2,2-trichloro-1-iminoethoxy)(phenyl)methyl phosphonate (3a) failed to give us the desired products. Thus the reaction of trichloroacetimidate 3a with isobutyl alcohol in the presence of a catalytic amount of TMSOTf at room temperature did not give diethyl 2-methylpropyloxy(phenyl)methyl phosphonate (5a) and instead decomposition was observed and a complex mixture was obtained, Scheme 2. On the other hand, trichloroacetimidates 3b–d reacted with a variety of O-nucleophile acceptors (alcohols) in the presence of catalytic amount of TMSOTf at room temperature and readily gave a series of functionalized ether phosphonates 6–8 (a–f), Scheme 2, Table 1. Similarly, the acetate derivatives 4b–d reacted with a variety of O-nucleophile acceptors (alcohols) in the presence of a catalytic amount of TMSOTf at room temperature in dichloromethane and readily gave a series of functionalized ether phosphonates 6–8 (a–f), Scheme 2, Table 1. A comparative study of both trichloroacetimidate and acetate methodologies was carried out to examine the efficiency of reaction time and % of yield in both methods. The results showed that, although all compounds were prepared in good yields, there was a slight improvement in the % of yield and in the reaction time (monitored by TLC) using the trichloroacetimidate method, see Experimental section.

According to the presumed mechanism, the TMSOTf is used to eliminate the trichloroacetimidate and acetate leaving groups with the subsequent formation of carbocation. This carbocation could be stabilized by an efficient electron donor and a phenyl group but it is insufficient. In contrast there was good stabilization in the case of a phenyl residue bearing an electron-donating –OR group at the 4-position. The final step is the nucleophilic attack of the weak alcohol nucleophiles at the stabilized carboxion to form the desired products 6–8 (a–f) via an overall S_N1 mechanism. The attempted reaction of diethyl 2-methylpropyloxy(4-methoxyphenyl)methyl phosphonate (6a) with isopropyl alcohol under the same reaction conditions, in the presence of a catalytic amount of TMSOTf at room temperature in dichloromethane, failed to give the corresponding isopropyl ether phosphonate derivative 6b via transetherification, Scheme 2.

Structure assignment of ether derivatives 6–8 (a–f) were based on 1H, 13C and 31P-NMR spectral and physicochemical analysis. The 1H-NMR spectrum of 6a shows an interesting doublet signal at δ = 4.52 ppm with coupling constant 15.0 Hz typically associated with CHP. This chemical shift is common for all isolated phosphonate derivatives 6–8 (a–f) with chemical shift ranging from 4.37–4.93 ppm and with coupling constant ranging from 12–18 Hz. The 1H-NMR spectrum exhibit signals at δ 0.90, 0.93, 1.84–1.97 and 3.16–3.28 ppm due to two CH₃, CH₃ and CH₂ groups, respectively of the isobutyl-residue and signals at δ 1.24–1.28 and 4.02–4.12 ppm.
due to two OCH₂CH₃ residue. The ¹³C NMR spectrum of 6a shows interesting doublet signals at δ 16.3, 16.4, 62.7, 63.0, 76.9 and 77.5 ppm having coupling constants JCP 6.0, 6.0, 6.8, 6.8, 32.4 and 169.6 Hz corresponding to CH₃, CH₂, OCH₃, OCH₂P, CH₂OCHP and CHP groups, respectively. These signals are common for all isolated products, which confirm the C-O bond formation. The previously mentioned signals are good evidences for either the C-P coupling, the diastereotopic nature or both for these individual groups. The ³¹P-NMR spectrum of 6a showed a single signal at δ = 19.5 ppm corresponding to phosphonate phosphorus and was used as an indicator for the purity of the products.

The trichloroacetimidate method proved to be an excellent method for the structure modification of diethyl hydroxy(substituted phenyl)methylphosphonate 2a–d. Next, the use of an interesting derivatized alcohols was explored: (5-methyl-2-phenyl-1,3-dioxan-5-yl)methanol 9 and 2-(N-methyl-N-phenylamino)ethanol 11. The dioxane derivative 9 was prepared by heating 1,1,1-tris(hydroxymethyl)ethane with benzaldehyde in the presence of toluene-p-sulfonic acid in benzene and this compound is known to possess potential medicinal chemistry relevance. Thus the reaction of trichloroacetimidate 3a–b with dioxane derivative 9 in the presence of a catalytic amount of TMSOTf at room temperature in dichloromethane and gave diethyl(5-methyl-2-phenyl-1,3-dioxan-5-yl)methoxy(substituted phenyl)methyl phosphonate 10a–b in 62–70% yields, Scheme 3. Also trichloroacetimidate 3a reacted with 2-(N-methyl-N-phenylamino)ethanol (11) in the presence of a catalytic amount of TMSOTf at room temperature in dichloromethane and gave diethyl 2-(N-methyl-N-phenylamino)ethoxy(4-methoxyphenyl)methyl phosphonate 12 in 29% yield, Scheme 3.

**Conclusion**

In conclusion, an efficient and very simple method for the synthesis of various ether phosphonates by trichloroacetimidate and acetate coupling methods is described. Trichloroacetimidates 3a–d or acetates 4b–d were treated with Lewis acid followed by reaction with O-nucleophiles to afford the desired products via C-O bond formation. Both methods gave good yields of desired products in short reaction times, and generally slightly better results were obtained using the trichloroacetimidate method. Applications of this methodology to synthesize various phosphonate analogues of alcohols containing primary and secondary hydroxy groups as O-nucleophiles are under progress in our laboratory.

**Experimental**

Solvents were purified and dried in the usual way. The boiling range of the petroleum ether used was 40–60 °C. Thin-layer chromatography (TLC) utilized silica gel 60 F254 plastic plates (E. Merck, layer thickness 0.2 mm). Detection was by UV absorption. Melting points were determined on a Buchi 510 melting point apparatus. The ¹H, ¹³C and ³¹P NMR spectra were recorded at 300 MHz, 75.5 and 194.4 MHz, respectively (Bruker AC 300) in CDCl₃ with tetramethylsilane as an internal standard. The NMR analysis were performed at Organic Chemistry Department Masaryk University, Brno, Czech Republic. Elemental analyses were performed on a Flash EA-1112 instrument at the Microanalytical Laboratory, Faculty of Science, Suez Canal University, Ismailia, Egypt. 3,4-Dimethoxylbenzaldehyde 1c and 3-methoxy-4-(prop-2-ynyloxy)benzaldehyde 1d was prepared by alkylation of vaniline as described in the literature.

**Diethyl hydroxy(substitutedphenyl)methyl phosphonate 2a–d**

To a mixture of (20.7 g, 0.15 mol) of diethyl phosphonate and 1.09 g (0.011 mol) of triethylamine was added (0.15 mol) of aldehydes 1a–d portion wise during a period of 1 h at 50–70 °C. The reaction mixture was subsequently stirred at 70 °C for 2 h. After cooling it was left over night to give white crystals, filter...
**Table 1** Synthesis of ether phosphonate derivatives 6–8(a–f) and the comparative results between trichloroacetimidate and acetate coupling methods

<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
<th>TCI and Ac yield (time)</th>
<th>No.</th>
<th>Structure</th>
<th>TCI and Ac yield (time)</th>
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<td>6a</td>
<td><img src="image1" alt="Structure" /></td>
<td>81% (2 h), 76% (4 h)</td>
<td>7d</td>
<td><img src="image2" alt="Structure" /></td>
<td>78% (3 h), 59% (4 h)</td>
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<tr>
<td>6b</td>
<td><img src="image3" alt="Structure" /></td>
<td>72% (2 h), 64% (5 h)</td>
<td>7e</td>
<td><img src="image4" alt="Structure" /></td>
<td>79% (1 h), 73% (5 h)</td>
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<tr>
<td>6c</td>
<td><img src="image5" alt="Structure" /></td>
<td>75% (3 h), 71% (5 h)</td>
<td>7f</td>
<td><img src="image6" alt="Structure" /></td>
<td>86% (2 h), 79% (4 h)</td>
</tr>
<tr>
<td>6d</td>
<td><img src="image7" alt="Structure" /></td>
<td>82% (2 h), 76% (5 h)</td>
<td>8a</td>
<td><img src="image8" alt="Structure" /></td>
<td>79% (2 h), 75% (2 h)</td>
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<tr>
<td>6e</td>
<td><img src="image9" alt="Structure" /></td>
<td>67% (2 h), 71% (3 h)</td>
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<td><img src="image10" alt="Structure" /></td>
<td>74% (1 h), 66% (3 h)</td>
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Table 1 (Contd.)

<table>
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<th>No.</th>
<th>Structure</th>
<th>TCI and Ac yield (time)</th>
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<td>71% (3 h), 56% (4 h)</td>
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<td>86% (1 h), 77% (4 h)</td>
<td>8d</td>
<td><img src="image4.png" alt="Image" /></td>
<td>81% (3 h), 72% (3 h)</td>
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<tr>
<td>7b</td>
<td><img src="image5.png" alt="Image" /></td>
<td>78% (1 h), 68% (4 h)</td>
<td>8e</td>
<td><img src="image6.png" alt="Image" /></td>
<td>71% (2 h), 63% (3 h)</td>
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<tr>
<td>7c</td>
<td><img src="image7.png" alt="Image" /></td>
<td>86% (2 h), 74% (4 h)</td>
<td>8f</td>
<td><img src="image8.png" alt="Image" /></td>
<td>79% (2 h), 69% (4 h)</td>
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</table>

*Abbrev. TCI: trichloroacetimidate method, Ac: acetate method.
and wash with cold toluene and then recrystallized from toluene to give pure crystals.

Diethyl hydroxy(phenyl)methyl phosphonate (2a)

27.5 g, yield 76% white crystals. Mp 80–81 °C. 1H NMR spectrum, (300 MHz, CDCl3), δ, ppm (J, Hz): 1.19–1.34 (m, 6H, 2CH2), 3.82 (s, 3H, OCH3), 3.91–4.10 (m, 4H, 2CH2), 3.54 (bs, 1H, OH), 5.00 (d, JHP = 8.0 Hz, 1H, CHP), 7.24–7.46 (m, 5H, H-Ar). 13C-NMR (75.0 MHz, CDCl3), δ, ppm: 16.3 (d, JCP = 4.0, CH3), 16.4 (d, JCP = 4.0, CH3), 55.3 (OCH3), 62.7 (d, JCP = 7.6, CH2OP), 70.2 (d, JCP = 158.4, CHP), 127.1, 127.2, 128.1, 128.3, 136.8 (C-Ar). 31P-NMR (194.4 MHz, CDCl3), δ, ppm: 21.6 [P]. Found, %: C, 53.89; H, 6.94. For C11H17O4P (244.1). Calculated, %: C, 54.10; H, 7.02.

Diethyl hydroxy(4-methoxyphenyl)methyl phosphonate (2b)

34.4 g, yield 84% white crystals. Mp 90–91 °C. 1H NMR spectrum, (300 MHz, CDCl3), δ, ppm (J, Hz): 1.19–1.29 (m, 6H, 2CH2), 3.80 (s, 3H, OCH3), 3.89–4.10 (m, 4H, 2CH2), 4.33 (bs, 1H, OH), 4.95 (d, JHM = 9.0 Hz, 1H, CHP), 6.87 (d, J = 9.0 Hz, 2H, H-Ar), 7.39–7.43 (m, 2H, H-Ar). 13C-NMR (75.0 MHz, CDCl3), δ, ppm: 16.3 (d, JCP = 4.0, CH3), 16.4 (d, JCP = 4.0, CH3), 55.2 (OCH3), 62.9 (d, JCP = 7.6, CH2OP), 63.2 (d, JCP = 7.6, CH2OP), 70.3 (d, JCP = 161.6, CHP), 113.0, 113.7, 128.4, 128.5, 128.8, 159.5 (C-Ar). 31P-NMR (194.4 MHz, CDCl3), δ, ppm: 21.7 [P]. Found, %: C, 52.39; H, 6.81. For C15H21O6P (328.1). Calculated, %: C, 52.55; H, 6.98.

Diethyl hydroxy(3,4-dimethoxyphenyl)methyl phosphonate (2c)

40.6 g, yield 89% white crystals. Mp 101–103 °C. 1H NMR spectrum, (300 MHz, CDCl3), δ, ppm (J, Hz): 1.16–1.26 (m, 6H, 2CH2), 3.83 (s, 3H, OCH3), 3.88 (s, 3H, OCH3), 3.92–4.02 (m, 4H, 2CH2), 4.62 (bs, 1H, OH), 4.89 (d, JHP = 9.0 Hz, 1H, CHP), 6.81 (d, J = 9.0 Hz, 1H, H-Ar), 6.95–7.07 (m, 1H, H-Ar), 7.08 (s, 1H, H-Ar). 13C-NMR (75.0 MHz, CDCl3), δ, ppm: 16.3 (d, JCP = 4.0, CH3), 16.4 (d, JCP = 4.0, CH3), 55.8 (OCH3), 55.9 (OCH3), 62.9 (d, JCP = 7.6, CH2OP), 63.2 (d, JCP = 7.6, CH2OP), 70.4 (d, JCP = 161.6, CHP), 110.5, 110.8, 110.9, 129.3, 148.7, 148.8 (C-Ar). 31P-NMR (194.4 MHz, CDCl3), δ, ppm: 21.7 [P]. Found, %: C, 51.12; H, 6.89. For C15H21O6P (340.1). Calculated, %: C, 51.31; H, 6.96.

Diethyl hydroxy(3-methoxy-4-(prop-2-yn-1-yloxy)phenyl) methyl phosphonate (2d)

36.9 g, yield 75% white crystals. Mp 87–88 °C. 1H NMR spectrum, (300 MHz, CDCl3), δ, ppm (J, Hz): 1.19–1.37 (m, 6H, 2CH2), 2.50 (t, J = 3.0 Hz, 1H, CHJ), 3.86 (s, 3H, OCH3), 3.92–4.17 (m, 4H, 2CH2), 4.39 (bs, 1H, OH), 4.74 (d, J = 3.0 Hz, 2H, OCH3), 4.93 (d, JHP = 9.0 Hz, 1H, CHP), 6.99–7.12 (m, 3H, H-Ar). 13C-NMR (75.0 MHz, CDCl3), δ, ppm: 16.3 (d, JCP = 4.0, CH3), 16.4 (d, JCP = 4.0, CH3), 55.9 (OCH3), 65.8 (OCH3), 63.0 (d, JCP = 7.6, CH2OP), 63.2 (d, JCP = 7.6, CH2OP), 70.5 (d, JCP = 160.8, CHP), 75.8 (C=CH), 78.5 (C=CH), 110.9, 114.0, 119.5, 130.7, 146.6, 149.6 (C-Ar). 31P-NMR (194.4 MHz, CDCl3), δ, ppm: 21.5 [P]. Found, %: C, 54.68; H, 6.43. For C15H21O6P (328.1). Calculated, %: C, 54.88; H, 6.45.

Preparation of diethyl 2-(2,2,2-trichloro-1-iminoethoxy)(substitutedphenyl) methyl phosphonate 3a–d

A stirred solution of diethyl hydroxy(substitutedphenyl)methyl phosphonate 2a–d (10.0 mmol) in dry dichloromethane (30 mL) was treated with trichloroacetonitrile (2.9 mL, 20 mmol) and DBU (0.8 mL, 5.0 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure and the product was purified by column chromatography 5% triethylamine in dichloromethane, to give 3a–d as whistish oil.

Diethyl 2-(2,2,2-trichloro-1-iminoethoxy)(phenyl)methyl phosphonate (3a)

1.92 g, yield 91% brownish oil. 1H NMR spectrum, (300 MHz, CDCl3), δ, ppm (J, Hz): 1.16–1.29 (m, 6H, 2CH2), 3.78 (s, 3H, OCH3), 3.94–4.17 (m, 4H, 2CH2), 6.22 (d, JHP = 15.0 Hz, 1H, CHP), 6.95–7.53 (m, 5H, H-Ar), 8.55 (bs, 1H, NH). 31P-NMR (194.4 MHz, CDCl3), δ, ppm: 16.4 [P]. Found, %: C, 40.04; H, 4.32; N, 3.48. For C15H21Cl2N2O4P (387.1). Calculated, %: C, 40.18; H, 4.41; N, 3.60.

Diethyl[2,2,2-trichloro-1-iminoethoxy](4-methoxyphenyl) methyl phosphonate (3b)

3.6 g, yield 87% brownish oil. 1H-NMR spectrum, (300 MHz, CDCl3), δ, ppm (J, Hz): 1.20–1.27 (m, 6H, 2CH2), 3.76 (s, 3H, OCH3), 3.97–4.16 (m, 4H, 2CH2), 6.20 (d, JHP = 15.0 Hz, 1H, CHP), 6.86 (d, J = 9.0 Hz, 2H, H-Ar), 7.44 (d, J = 6.0 Hz, 2H, H-Ar).
Diethyl(2,2,2-trichloro-1-iminoethoxy)(3,4-dimethoxyphenyl) methyl phosphonate (4c)

3.8 g, yield 80% brownish oil. ¹H-NMR spectrum, (300 MHz, CDCCl₃), δ, ppm (J, Hz): 2.22 (m, 3H, CH₃), 2.50 (s, 1H, CH), 3.85 (s, 3H, OCH₃), 3.99–4.16 (m, 4H, CH₂), 2.19 (CH₂), 3.74 (CP), 6.07 (d, JCP = 12.0 Hz, 1H, CHP), 6.99–7.28 (m, 3H, H-Ar), 6.02 (d, JCP = 6.0 Hz, 3H, CH₃), 7.19 (m, 4H, 2CH₂), 6.32 (d, JCP = 6.0 Hz, 2CH₂), 6.35 (d, JCP = 6.0 Hz, CH₂OP), 70.3 (d, JCP = 172.9, CHP), 73.1 (CCH₃), 73.8 (CCH₃), 119.0, 120.9, 121.0, 125.7, 149.4 (C=O), 169.2 (CO). ³¹P-NMR (194.4 MHz, CDCCl₃), δ, ppm: 16.3 (P). Found, %: C, 51.85; H, 6.54. For C₁₅H₂₁O₇P (346.1). Calculated, %: C, 52.02; H, 6.69.

Diethyl(2,2,2-trichloro-1-iminoethoxy)(3-methoxy-4-propargyloxyphenyl) methyl phosphonate (4d)

2.44 g, yield 66% whitish oil. ¹H NMR spectrum, (300 MHz, CDCCl₃), δ, ppm (J, Hz): 1.13 (t, J = 6.0 Hz, 3H, CH₃), 1.31 (t, J = 6.0 Hz, 3H, CH₃), 2.21 (s, 3H, COCH₃), 2.27 (s, 1H, CH), 3.38 (s, 1H, CH₂OCH₃), 3.92–4.13 (m, 4H, CH₂, 2CH₂), 7.44 (d, J = 3.0 Hz, 2H, CH₃), 6.57 (d, JHP = 12.0 Hz, 1H, CHP), 6.98–7.08 (m, 3H, H-Ar), 1.15 (t, J = 6.0 Hz, 3H, CH₃), 1.27 (s, 3H, CH₃), 2.19 (CH₂), 3.74 (CH₂), 6.35 (d, JCP = 6.0 Hz, 2CH₂), 6.38 (d, JCP = 6.0 Hz, CH₂OP), 70.3 (d, JCP = 172.9, CHP), 73.1 (CCH₃), 73.8 (CCH₃), 119.0, 120.9, 121.0, 125.7, 149.4 (C=O), 169.2 (CO). ³¹P-NMR (194.4 MHz, CDCCl₃), δ, ppm: 17.9 (P). Found, %: C, 55.04; H, 6.19. For C₁₅H₂₁O₇P (370.1). Calculated, %: C, 55.13; H, 6.26.

General procedure for the preparation of diethyl alkloyo(substitutedphenyl) methyl phosphonate 6–8(a-f), 10 and 12

A solution of trichloroacetimide 3a–d or acetate 4b–d (1.0 mmol) in dichloromethane (40 mL) was added O-nucleophiles (alcohol) (1.0 mmol) and TMSOTf (0.1 mmol). The reaction mixture was stirred at room temperature till completion of the reaction (TLC monitored and the time was recorded). The reaction mixture was neutralized with solid sodium bicarbonate, filtered and concentrated in vacuo. The residue was purified by flash chromatography 1:2 pet. ether/ethyl-acetate to give the pure alkoxy phosphonates 6–8(a-f), 10 and 12 as colorless oil.
Diethyl 1-methylthiophosphoryl(4-methylphosphoryl)methyl phosphate (6b)

0.26 g, yield 83% colorless oil. 1H NMR spectrum, (300 MHz, CDCl3), δ ppm (J, Hz): 1.08 (d, J = 6.0 Hz, 3H, CH3), 1.14 (d, J = 6.0 Hz, 3H, CH3), 1.19–1.25 (m, 6H, 2CH3), 3.57–3.76 (m, 1H, CH), 3.87 (s, 3H, OCH3), 3.92–4.09 (m, 4H, 2CH2), 4.64 (d, JHP = 18.0 Hz, 1H, CHP), 6.84 (d, J = 9.0 Hz, 2H, H-AR), 7.33–7.36 (m, 2H, H-AR). 13C-NMR (75.0 MHz, CDCl3), δ ppm: 13.6 (d, JCp = 6.0, CH3), 16.4 (d, JCp = 6.0, CH3), 20.9 (CH3), 23.0 (CH3), 55.1 (OCH3), 62.7 (d, JCp = 8.0, CH2OP), 63.1 (d, JCp = 8.0, CH2OP), 71.3 (d, JCp = 13.6, CHOCHP), 75.5 (d, JCp = 171.4, CHP), 113.6, 113.7, 117.6, 129.3, 159.6 (C-AR). 31P-NMR (194.4 MHz, CDCl3), δ ppm: 20.0 (P). Found, %: C, 56.78; H, 8.73. For C16H27O5P (330.2). Calculated, %: C, 58.17; H, 8.24.

Diethyl 2-phenylthiophosphoryl(4-methylphosphoryl)methyl phosphate (6f)

0.15 g, yield 39% colorless oil. 1H NMR spectrum, (300 MHz, CDCl3), δ ppm (J, Hz): 1.13–1.21 (m, 6H, 2CH3), 2.84–2.89 (m, 2H, CH2), 3.59–3.69 (m, 2H, CH2), 3.73 (s, 3H, OCH3), 3.89–4.01 (m, 4H, 2CH2), 4.56 (d, JHP = 15.0 Hz, 1H, CHP), 6.83 (d, J = 9.0 Hz, 2H, H-AR), 7.14–7.28 (m, 7H, H-AR). 13C-NMR (75.0 MHz, CDCl3), δ ppm: 16.3 (d, JCp = 6.0, CH3), 16.4 (d, JCp = 6.0, CH3), 36.2 (C7H8), 55.7 (OCH3), 62.8 (d, JCp = 8.0, CH2OP), 63.2 (d, JCp = 8.0, CH2OP), 71.3 (CH3) (d, JCp = 13.6, CHOCHP), 78.4 (d, JCp = 170.6, CHP), 113.7, 113.8, 126.2, 126.5, 128.2, 128.9, 129.3, 129.4, 138.6, 159.7, 159.8, 163.6 (C-AR). 31P-NMR (194.4 MHz, CDCl3), δ ppm: 19.1 (P). Found, %: C, 63.26; H, 7.13. For C20H27O5P (378.2). Calculated, %: C, 63.48; H, 7.19.

Diethyl 2-methylthiophosphoryl(3,4-dimethoxyphosphoryl)methyl phosphate (7a)

0.23 g, yield 65% colorless oil. 1H NMR spectrum, (300 MHz, CDCl3), δ ppm (J, Hz): 0.86 (d, J = 3.0 Hz, 3H, CH3), 0.89 (d, J = 3.0 Hz, 3H, CH3), 1.19–1.23 (m, 6H, 2CH3), 1.80–1.91 (m, 1H, CH2), 3.12–3.24 (m, 2H, CH2), 3.83 (s, 3H, OCH3), 3.85 (s, 3H, OCH3), 4.01–4.07 (m, 4H, 2CH2), 4.48 (d, JHP = 18.0 Hz, 1H, CHP), 6.79–6.92 (m, 2H, H-AR), 7.00 (s, 1H, H-AR). 13C-NMR (75.0 MHz, CDCl3), δ ppm: 16.3 (d, JCp = 5.3, CH3), 16.4 (d, JCp = 5.3, CH3), 19.1 (CH3), 19.2 (CH3), 28.4 (CH3), 55.8 (2 OCH3), 62.7 (d, JCp = 6.8, CH2OP), 63.0 (d, JCp = 6.8, CH2OP), 78.7 (d, JCp = 160.0, CHP), 76.9 (d, JCp = 32.5, CH2OCHP), 110.7, 110.8, 111.0, 120.6, 127.4, 149.0 (C-AR). 31P-NMR (194.4 MHz, CDCl3), δ ppm: 19.4 (P). Found, %: C, 56.64; H, 8.07. For C17H22O5P (360.2). Calculated, %: C, 56.66; H, 8.11.

Diethyl 1-methylthiophosphoryl(3,4-dimethoxyphosphoryl)methyl phosphate (7b)

0.26 g, yield 74% colorless oil. 1H NMR spectrum, (300 MHz, CDCl3), δ ppm (J, Hz): 1.08 (d, J = 6.0 Hz, 6H, 2CH3), 1.11–1.22 (m, 6H, 2CH3), 3.54–3.62 (m, 1H, CH), 3.80 (s, 3H, OCH3), 3.88 (s, 3H, OCH3), 3.92–4.06 (m, 4H, 2CH2), 4.59 (d, JHP = 18.0 Hz, 1H, CHP), 6.76–6.91 (m, 2H, H-AR), 6.99 (s, 1H, H-AR). 13C-NMR (75.0 MHz, CDCl3), δ ppm: 16.3 (d, JCp = 5.3, CH3), 16.4 (d, JCp = 5.3, CH3), 21.0 (CH3), 23.0 (CH3), 55.7 (OCH3), 55.8 (OCH3), 62.8 (d, JCp = 6.8, CH2OP), 63.1 (d, JCp = 6.8, CH2OP), 71.5 (OCH) (d,
Diethyl propargyloxy(3,4-dimethoxyphenyl)methyl phosphate (7c)

0.19 g, yield 56% colorless oil. 1H NMR spectrum, (300 MHz, CDCl3), δ ppm (J, Hz): 1.05 (t, J = 6.0 Hz, 3H, CH3), 1.15 (t, J = 6.0 Hz, 3H, CH3), 2.39 (s, 1H, CH), 3.72 (s, 3H, OCH3), 3.82 (s, 3H, OCH3), 3.87–3.94 (m, 2H, CH2), 3.99–4.17 (m, 4H, 2CH2), 4.75 (d, JHP = 15.0 Hz, 1H, CHP), 6.70–6.91 (m, 3H, H-Ar). 31P-NMR (75.0 MHz, CDCl3), δ ppm: 16.2 (d, JCP = 6.0, CH3), 16.3 (d, JCP = 6.0, CH3), 55.7 (OCH3), 55.8 (OCH3), 56.3 (d, JCP = 15.9, CH2OCH3), 62.8 (d, JCP = 6.8, CH2OP), 63.2 (d, JCP = 6.8, CH2OP), 75.6 (C(=CH)), 75.7 (d, JCP = 172, CHP), 78.4 (C(=CH)), 110.8, 111.2, 121.3, 125.6, 148.9, 149.4 (C-Ar). 31P-NMR (194.4 MHz, CDCl3), δ ppm: 19.0 (P). Found, %: C, 55.95; H, 6.60. For C16H23O8P (342.1). Calculated, %: C, 56.14; H, 6.77.

Diethyl 4-chlorobutoxy(3,4-dimethoxyphenyl)methyl phosphate (7d)

0.27 g, yield 69% colorless oil. 1H NMR spectrum, (300 MHz, CDCl3), δ ppm (J, Hz): 1.19 (t, J = 6.0 Hz, 3H, CH3), 1.34 (t, J = 6.0 Hz, 3H, CH3), 1.50–1.72 (m, 4H, 2CH2), 3.51–3.70 (m, 2H, CH2), 3.88 (s, 3H, OCH3), 3.90 (s, 3H, OCH3), 4.02–4.10 (m, 2H, CH2), 4.53 (d, JHP = 15.0 Hz, 1H, CHP), 6.71–6.87 (m, 2H, H-Ar), 7.63 (s, 1H, H-Ar). 13C-NMR (75.0 MHz, CDCl3), δ ppm: 16.3 (d, JCP = 6.0, CH3), 16.4 (d, JCP = 6.0, CH3), 27.3 (CH2), 29.3 (CH2), 44.7 (C(=CH2)), 55.4 (OCH3), 56.9 (OCH3), 62.6 (d, JCP = 6.8, CH2OP), 63.5 (d, JCP = 6.8, CH2OP), 71.4 (d, JCP = 13.6, C(=CH2)OCH3), 78.1 (d, JCP = 170.6, CHP), 110.5, 112.0, 121.8, 126.4, 149.0, 149.7 (C-Ar). 31P-NMR (194.4 MHz, CDCl3), δ ppm: 19.2 (P). Found, %: C, 51.56; H, 7.01. For C16H23ClO8P (394.1). Calculated, %: C, 51.71; H, 7.15.

Diethyl benzylxyloxy(3,4-dimethoxyphenyl)methyl phosphate (7e)

0.32 g, yield 81% colorless oil. 1H NMR spectrum, (300 MHz, CDCl3), δ ppm (J, Hz): 1.17 (t, J = 6.0 Hz, 3H, CH3), 1.25 (t, J = 6.0 Hz, 3H, CH3), 3.86 (s, 3H, OCH3), 3.99 (s, 3H, OCH3), 4.02–4.12 (m, 4H, 2CH2), 4.37 (d, JHP = 12.0 Hz, 1H, CHP), 4.61 (dd, J = 9.0, 12.0 Hz, 2H, CH2), 6.83 (d, J = 9.0 Hz, 1H, H-Ar), 6.94–6.96 (m, 1H, H-Ar), 7.05 (s, 1H, H-Ar), 7.29 (s, 5H, H-Ar). 13C-NMR (75.0 MHz, CDCl3), δ ppm: 16.3 (d, JCP = 6.0, CH3), 16.4 (d, JCP = 6.0, CH3), 55.8 (OCH3), 55.9 (OCH3), 62.7 (d, JCP = 6.8, CH2OP), 63.2 (d, JCP = 6.8, CH2OP), 71.4 (d, JCP = 14.3, CH2OCH3), 76.6 (d, JCP = 171.4, CHP), 110.8, 110.9, 111.2, 111.3, 121.1, 121.2, 126.7, 127.9, 128.2, 132.3, 137.1, 149.1 (C-Ar). 31P-NMR (194.4 MHz, CDCl3), δ ppm: 19.5 (P). Found, %: C, 60.87; H, 6.74. For C20H27O8P (394.2). Calculated, %: C, 60.91; H, 6.90.
13C-NMR (75.0 MHz, CDCl3), δ ppm: 19.4 (P). Found, %: C, 61.95; H, 7.14. For C24H33O7P (464.2). Calculated, %: C, 62.06; H, 7.16.

**Diethyl(5-methyl-2-phenyl-1,3-dioxan-5-yl)methoxy(4-
methoxyphenyl)methyl phosphonate (10b)**

0.35 g, yield 70% colorless oil. ¹H NMR spectrum, (300 MHz, CDCl3), δ ppm (J, Hz): 0.87 (s, 3H, CH3), 1.19 (t, J = 6.0 Hz, 3H, CH3), 1.26 (t, J = 6.0 Hz, 3H, CH3), 3.63–3.75 (m, 4H, 2CH2), 3.59–3.79 (m, 2H, CH2), 3.88 (s, 3H, OCH3), 3.96 (s, 3H, OCH3), 4.01–4.15 (m, 4H, 2CH2), 4.63 (d, JHP = 15.0 Hz, 1H, CHP), 5.38 (s, 3H, CH3), 6.84–7.00 (m, 2H, H-Ar), 7.05 (s, 1H, H-Ar), 7.28–7.37 (m, 5H, H-Ar). 13C-NMR (75.0 MHz, CDCl3), δ ppm: 16.4 (d, JCP = 6.0, CH3), 16.5 (d, JCP = 6.0, CH3), 19.1 (CH3), 35.0 (C), 55.8 (OCH3), 55.9 (OCH3), 55.8 (OCH3), 55.8 (OCH3), 62.8 (d, JCP = 7.8, CH2OP), 63.1 (d, JCP = 7.8, CH2OP), 63.1 (d, JCP = 7.8, CH2OP), 72.9 (d, JCP = 14.3, CH2OCHP), 72.3 (OCH2), 73.3 (OCH2), 79.0 (d, JCP = 170.6, CHP), 101.8 (OCH), 110.8, 111.1, 111.2, 120.8, 120.9, 121.6, 122.8, 123.8, 139.3, 149.3 (C-Ar). 31P-NMR (194.4 MHz, CDCl3), δ ppm: 19.2 (P). Found, %: C, 60.62; H, 6.85. For C25H35O5P (494.2). Calculated, %: C, 60.72; H, 7.13.

**Diethyl 2-(N-methyl-N-phenylamino)ethyloxy(4-
methoxyphenyl)methyl phosphonate (12)**

0.12 g, yield 29% colorless oil. ¹H NMR spectrum, (300 MHz, CDCl3), δ ppm (J, Hz): 1.21 (t, J = 6.0 Hz, 3H, CH3), 1.26 (t, J = 6.0 Hz, 3H, CH3), 2.98 (s, 3H, CH3), 3.57–3.68 (m, 4H, 2CH2), 3.82 (s, 3H, OCH3), 3.93–4.11 (m, 4H, 2CH2), 4.58 (d, JHP = 15.0 Hz, 1H, CHP), 6.68 (d, J = 9.0 Hz, 2H, H-Ar), 6.87 (d, J = 9.0 Hz, 2H, H-Ar), 7.18–7.35 (m, 5H, H-Ar). 13C-NMR (75.0 MHz, CDCl3), δ ppm: 16.3 (d, JCP = 6.0, CH3), 16.4 (d, JCP = 6.0, CH3), 36.2 (CH2), 55.8 (OCH3), 56.8 (OCH2), 62.9 (d, JCP = 6.8, CH2OP), 63.2 (d, JCP = 6.8, CH2OP), 71.5 (d, JCP = 13.6, CH2OCHP), 75.8 (CCH2), 78.5 (CCH2), 87.6 (d, JCP = 169.9, CHP), 111.2, 111.3, 113.9, 120.5, 120.6, 126.2, 128.3, 128.6, 129.0, 138.7, 146.9, 149.7 (C-Ar); 13P-NMR (194.4 MHz, CDCl3), δ ppm: 18.9 (P). Found, %: C, 63.69; H, 6.72. For C25H35O5P (494.2). Calculated, %: C, 63.88; H, 6.76.

**Conflicts of interest**

There are no conflicts to declare.
References