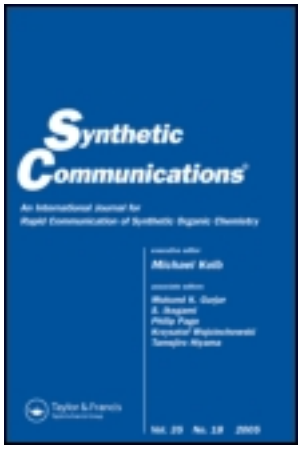

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POLYETHYLENE GLYCOL–PROMOTED DIALKYL, ARYL/HETEROARYL PHOSPHONATES

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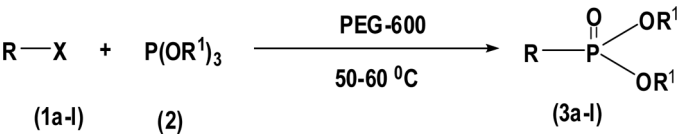
GRAPHICAL ABSTRACT



Abstract *A new, straightforward polyethylene glycol–promoted method for Michaelis–Arbuzov rearrangement has been described.*

Keywords Aryl/heteroaryl phosphonates; dialkyl; PEG-600

INTRODUCTION

The Michaelis–Arbuzov rearrangement is one of the most versatile pathways for the formation of carbon–phosphorus bonds and their diverse biological activity.[1,2] Two main flaws that preclude wider use of this reaction are the drastic reaction are conditions such as long reaction time in high temperatures and the formation of a mixture of phosphorylated products,[3] which consequently decrease the yield of the desired product. To overcome these drawbacks, many catalysts such as iodine,[4] alkali–metal-iodide,[5] trimethyl silylhalide (TMSX),[6] $BF_3 \cdot OEt_2$,[7] and ionic liquid[8] have been tried, but none of them was found to be satisfactory. The present method for the Arbuzov reaction in polyethylene glycol (PEG) overcomes these difficulties. PEG has many advantages such as thermal stability and recoverability; it is environmentally benign and a biologically acceptable medium for drug delivery not only as an ecofriendly solvent but also as a catalyst.[9]

SYNTHESIS AND DISCUSSION

In the present procedure, trialkyl phosphite (**2**), a safe and easy reagent to handle, has been employed as an effective phosphite ion source, and neither

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additives are needed nor promoters to enhance this reaction because PEG serves as an ecofriendly medium and also acts as a reaction-promoting catalyst under mild conditions.

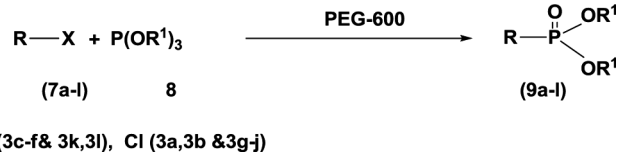
To date, it is the first feasible method for the Arbuzov reaction of various alkyl/aryl/heteroaryl halides with trialkyl phosphite in PEG medium. The advantages are many: simple and mild experimental conditions, less reaction time, cost-effectiveness due to recyclability of PEG, and applicability to various substituted alkyl, aryl, and heterocyclic halide substrates. It is an innovative and efficient green chemical approach to synthesize phosphonates while avoiding hazardous solvents and toxic reagents.

The synthetic route for the new alkyl, aryl, and heterocyclic phosphonates (**3a–l**) in good yields (72–82%) involved reaction of alkyl, aryl, and heterocyclic halides (**1a–l**) with trialkyl phosphites (**2**) in PEG at 50–60 °C (Scheme 1). The chemical structures of **3a–l** were confirmed by elemental analysis; infrared (IR); ^{1}H, ^{13}C, and ^{31}P NMR; and mass spectral data. The methoxy protons gave two distinct doublets in the region of δ 3.78–3.63 ($J = 10.9$–10.2 Hz), 3.72–3.40 ($J = 10.9$–10.2 Hz),[10] indicating their magnetic nonequivalence, and the methyleneoxy protons resonated as multiplets at δ (4.21–4.01).[11] The methoxy carbon chemical shifts appeared as a doublet at δ 59.0–52.5 (d, $J = 6.7$–6.4 Hz).[10] Similarly in diethyl phosphonate, the methyleneoxy carbons also resonated as a doublet at δ 62.3–61.4 (d, $J =$ 6.9 Hz).[11] The ^{31}P NMR signals were observed in the range 19.2–26.2 ppm.[11] Liquid chromatography/mass spectrometry (LCMS) data were recorded for **3a, 3c, 3f, 3i**, and **3l**, and they gave $M^{+\cdot}$ ions at their respective m/z values.

EXPERIMENTAL

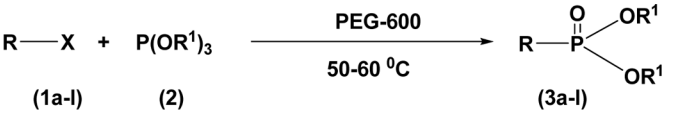
Chemistry

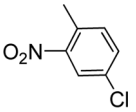
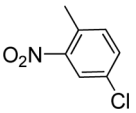
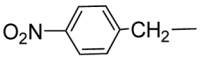
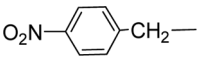
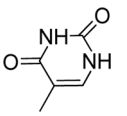
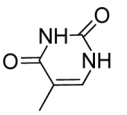
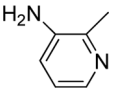
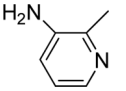
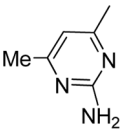
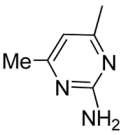
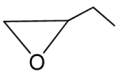
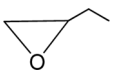
Chemicals purchased from Sigma-Aldrich, Merck, and Lancaster were used as such without further purification. All solvents used for spectroscopic and other physical studies were of reagent grade and were further purified as described in the literature methods.[12] IR spectra were recorded as KBr pellets and Nujol mulls on a Perkin-Elmer 283 unit. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker 400-MHz NMR spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C, and 161.9 MHz for ^{31}P NMR in $CDCl_3$ and referenced to tetramethylsilane (TMS) (^{1}H and ^{13}C) and 85% H_3PO_4(^{31}P), respectively. LCMS mass spectra were recorded on a Jeol SX102 DA/600 mass spectrometer. Elemental analyses were performed on a Thermo Finnigan Insturment at University of Hyderabad, Hyderabad, India.



Scheme 1.

Table 1. Synthesis of phosphonate derivatives



Compound	R	R^1
3a		Me
3b		Et
3c		Me
3d		Et
3e		Me
3f		Et
3g		Me
3h		Et
3i		Me
3j		Et
3k		Me
3l		Et

General Procedure for the Preparation of 3a–l

A mixture of alkyl/aryl halide (1 mmol), trialkyl phosphite (1.3 mmol), and PEG-600 (3 g) were placed in a 50-mL round-bottomed flask, and the mixture was stirred at 50–60 °C for 2–4 h. The reaction progress was monitored by thin-layer chromatography (TLC) (ethyl acetate–hexane, 3:7). After completion of the reaction, the reaction mixture was cooled in a dry ice–acetone bath to precipitate the PEG and extract it with ether. The ether extract was dried over $MgSO_4$ and evaporated. The resulting product, though seen as a single compound by TLC, was further purified by passing it over a column of silica gel. The recovered PEG was reused.

Selected Data

Dimethyl-4-chloro-2-nitrophenylphosphonate (3a). Yield 81%, semisolid; ^{1}H NMR ($CDCl_3$): δ 7.68 (1H, d, $J = 6.9$ Hz, Ar-H), 7.38 (1H, s, Ar-H), 7.31 (1H, d, $J = 7.8$ Hz, Ar-H), 3.78 (3H, d, $J = 10.5$ Hz, -OCH_3), 3.72 (3H, d, $J = 10.2$ Hz, -OCH_3); ^{13}C NMR: 148.2, 135.4, 130.4, 128.9, 122.2, 117.6, 52.5 (d, $J = 6.2$ Hz, -OCH_3); ^{31}P NMR: δ 24.3; IR (KBr) cm^{-1}: 1243 (P=O), 1018 (P-C); LCMS m/z: 264 (100, $M^{+\cdot}$), 266 (32, M + 2). Anal. calcd. for $C_8H_9NO_5PCl$: C, 36.24; H, 3.39; N, 5.28. Found: C, 36.20; H, 3.36; N, 5.22.

Diethyl-4-chloro-2-nitrophenylphosphonate (3b). Yield 82%, semisolid; ^{1}H NMR ($CDCl_3$): δ 7.57 (1H, d, $J = 8.1$ Hz, Ar-H), 7.26 (1H, s, Ar-H), 7.20 (1H, d, $J = 6.9$ Hz, Ar-H), 4.16–4.01 (4H, m, -OCH_2), 1.18 (6H, t, $J = 5.1$ Hz, -CH_3); ^{13}C NMR: 149.1, 134.6, 131.2, 129.2, 122.7, 116.4, 61.4 (d, $J = 5.9$ Hz, -OCH_2), 16.7 (-CH_3); ^{31}P NMR: δ 26.2; IR (KBr) cm^{-1}: 1234 (P=O), 971 (P-C); Anal. calcd. for $C_{10}H_{13}NO_5PCl$: C, 40.95; H, 4.43; N, 4.77. Found: C, 40.92; H, 4.38; N, 4.72.

Dimethyl-4-nitrobenzylphosphonate (3c). Yield 77%, semisolid; ^{1}H NMR ($CDCl_3$): δ 8.11 (2H, d, $J = 8.3$ Hz, Ar-H), 8.01 (2H, d, $J = 8.2$ Hz, Ar-H), 3.64 (3H, d, $J = 10.9$ Hz, -OCH_3), 3.50 (3H, d, $J = 10.9$ Hz, -OCH_3), 3.22–3.06 (2H, q, -P-CH_2); ^{13}C NMR: 147.2, 139.2, 130.7, 123.9, 53.2 (d, $J = 6.7$ Hz, -OCH_3), 33.7 (P-CH_2); ^{31}P NMR: δ 23.2; IR (KBr) cm^{-1}: 1237 (P=O), 967 (P-C); LCMS m/z: 245 ($M^{+\cdot}$). Anal. calcd. for $C_9H_{12}NO_5P$: C, 44.08; H, 4.89; N, 5.71. Found: C, 43.98; H, 4.86; N, 5.68.

Diethyl-4-nitrobenzylphosphonate (3d). Yield 80%, semisolid; ^{1}H NMR ($CDCl_3$): δ 8.14 (2H, d, $J = 7.9$ Hz, Ar-H), 8.03(2H, d, $J = 8.1$ Hz, Ar-H), 4.12–4.02 (4H, m, -OCH_2), 3.25–3.03 (2H, q, -P-CH_2), 1.20 (6H, t, $J = 5.6$ Hz, -CH_3); ^{13}C NMR: 146.7, 139.5, 130.4 123.4, 62.3 (d, $J = 6.9$ Hz, -OCH_2), 34.2 (P-CH_2), 16.0 (-CH_3); ^{31}P NMR: δ 24.2; IR (KBr) cm^{-1}: 1249 (P=O), 1027 (P-C). Anal. calcd. for $C_{11}H_{16}NO_5P$: C, 48.35; H, 5.86; N, 5.12. Found: C, 48.30; H, 5.79; N, 5.04.

Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-yl-phosphonate (3e). Yield 72%, semisolid; ^{1}H NMR ($CDCl_3$): δ 8.20 (2H, s, -NH), 6.71 (1H, d, $J = 7.5$ Hz, Ar-H), 3.62 (3H, d, $J = 10.2$ Hz, -OCH_3), 3.56 (3H, d, $J = 10.8$ Hz, -OCH_3); ^{31}P NMR: δ 21.3; IR (KBr) cm^{-1}: 3412 (-NH), 1726 (C=O), 1261 (P=O), 1031 (P-C); Anal. calcd. for $C_6H_9N_2O_5P$: C, 32.72; H, 4.09; N, 12.72. Found: C, 32.65; H, 4.03; N, 12.65.

Diethyl-2, 4-dioxo-1,2,3,4-tetrahydropyrimidine-5-yl-phosphonate (3f). Yield 76%, semisolid; ^{1}H NMR ($CDCl_3$): δ 8.20 (2H, s, -NH), 6.79 (1H, d, $J = 7.5$ Hz, Ar-H), 4.21–4.13 (4H, m, -OCH_2), 1.14 (6H, t, $J = 7.1$ Hz, -CH_3); ^{31}P NMR: δ19.2; IR (KBr) cm^{-1}: 3380 (-NH), 1716 (C=O), 1237 (P=O), 954 (P-C); LCMS m/z; 248 ($M^{+\cdot}$). Anal. calcd. for $C_8H_{13}N_2O_5P$: C, 38.70; H, 5.24; N, 11.29. Found: C, 38.64; H, 5.19; N, 11.21.

Dimethyl-3-amino pyridin-2-yl phosphonate (3g). Yield 80%, semisolid; ^{1}H NMR ($CDCl_3$): δ 8.12 (1H, d, $J = 8.2$ Hz, Ar-H), 7.55 (1H, t, $J = 7.6$ Hz, Ar-H), 7.12 (1H, d, $J = 6.5$ Hz, Ar-H), 5.91 (2H, s, -NH_2), 3.62 (3H, d, $J = 10.5$ Hz, -OCH_3), 3.42 (3H, d, $J = 10.2$ Hz, -OCH_3); ^{13}C NMR: 145.1, 143.2, 129.2, 126.1, 123.9, 59.0 (d, $J = 6.4$ Hz, -OCH_3); ^{31}P NMR: δ 20.3; IR (KBr) cm^{-1}: 3365 (-NH_2), 1240 (P=O), 960 (P-C). Anal. calcd. for $C_7H_{11}N_2O_3P$: C, 41.58; H, 5.44; N, 13.86. Found: C, 41.50; H, 5.40; N, 13.81.

Diethyl-3-amino pyridin-2-yl phosphonate (3h). Yield 81%, semisolid; ^{1}H NMR ($CDCl_3$): δ 8.14 (1H, d, $J = 8.0$ Hz, Ar-H), 7.61 (1H, t, $J = 7.2$ Hz, Ar-H), 7.10 (1H, d, $J = 6.9$ Hz, Ar-H), 5.99 (2H, s, -NH_2), 4.15–4.09 (4H, m, -OCH_2), 1.21 (6H, t, $J = 6.2$ Hz, -CH_3); ^{31}P NMR: δ 21.5; IR (KBr) cm^{-1}: 3352 (-NH_2), 1232 (P=O), 1012 (P-C). Anal. calcd. for $C_9H_{15}N_2O_3P$: C, 46.95; H, 6.52; N, 12.17. Found: C, 46.89; H, 6.44; N, 12.10.

Dimethyl-2-amino-6-methylpyrimidin-4-yl-phosphonate (3i). Yield 78%, semisolid; ^{1}H NMR ($CDCl_3$): δ 6.80 (1H, s, Ar-H), 5.50 (2H, s, -NH_2), 3.68 (3H, d, $J = 10.6$ Hz, -OCH_3), 3.40 (3H, d, $J = 10.5$ Hz, -OCH_3), 2.59 (3H, s, -CH_3); ^{31}P NMR: δ 20.9; IR (KBr) cm^{-1}: 3344 (-NH_2), 1211 (P=O), 980 (P-C); LCMS m/z: 217 ($M^{+\cdot}$). Anal. calcd. for $C_7H_{12}N_3O_3P$: C, 38.70; H, 5.52; N, 19. 35. Found: C, 38.65; H, 5.49; N, 19.30.

Diethyl-2-amino-6-methylpyrimidin-4-yl-phosphonate (3j). Yield 82%, semisolid; ^{1}H NMR ($CDCl_3$): δ 6.79 (1H, s, Ar-H), 5.55 (2H, s, -NH_2), 4.20–4.12 (4H, m, -OCH_2) 2.41 (3H, s, -CH_3), 1.18 (6H, t, $J = 10.5$ Hz, -CH_2-CH_3); ^{31}P NMR: δ 21.5; IR (KBr) cm^{-1}: 3336 (-NH_2), 1220 (P=O), 960 (P-C). Anal. calcd. for $C_9H_{16}N_3O_3P$: C, 44.08; H, 6.53; N, 17.14. Found: C, 43.97; H, 6.50; N, 17.11.

Dimethyloxiran-2-ylmethylphosphonate (3k). Yield 70%, semisolid; ^{1}H NMR ($CDCl_3$): δ 3.64 (3H, d, $J = 10.2$ Hz, -OCH_3), 3.42 (3H, d, $J = 10.1$ Hz, -OCH_3), 2.62–2.54 (2H, m, -CH_2), 2.41–2.39 (1H, m, -CH), 2.10–2.02 (2H, m, -CH_2-P); ^{31}P NMR: δ 22.9; IR (KBr) cm^{-1}: 1242 (P=O), 975 (P-C). Anal. calcd. for $C_5H_{11}O_4P$: C, 36.14; H, 6.62. Found: C, 36.08; H, 6.59.

Diethyloxiran-2-ylmethylphosphonate (3l). Yield 73%, semisolid; ^{1}H NMR ($CDCl_3$): δ 4.20–4.13 (4H, m, -OCH_2), 2.65-2.53 (2H, m, -CH_2), 2.45–2.32 (1H, m, -CH), 2.20–2.11 (2H, m, -CH_2-P), 1.12 (6H, t, $J = 10.2$ Hz, -CH_2-CH_3); ^{31}P NMR: δ 22.0; IR (KBr) cm^{-1}; 1235 (P=O), 980 (P-C); LCMS m/z: 194 ($M^{+\cdot}$). Anal. calcd. for $C_7H_{15}O_4P$: C, 43.29; H, 7.73. Found: C, 43.23; H, 7.69.

CONCLUSION

An efficient, ecofriendly green synthesis of novel alkyl, aryl, and heterocyclic phosphonates was achieved by a one-pot, two-component reaction between alkyl, aryl, and heteroaryl halides and trialkyl phosphite in PEG, which served both as reaction medium and as a catalyst. This procedure was environmentally friendly and inexpensive, and the catalyst is recyclable, making it an attractive protocol over the existing procedures for the synthesis of phosphonates.

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