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A mild and efficient method for the synthesis of phosphoryloxy phosphonates via one-pot reactions in water

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Abstract: A synthesis of phosphoryloxy phosphonate derivatives is described via reaction between acid chlorides, dialkyl(aryl)phosphites and N-methylimidazole in water.

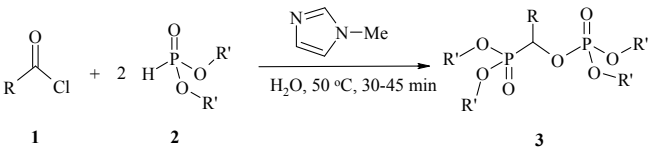
Keywords: Acid Chlorides. Diphenylphosphite. *N*-methylimidazole. Phosphoryloxy phosphonate.One-pot reactions.

Introduction

The use of water as a green media for organic synthesis has become an important research area. Other than the economical and environmental benefits, water also exhibits unique physical and chemical properties which lead to unique reactivity and selectivity in comparison with organic solvents. Thus, the development of organic reaction in water medium is necessitating in the present days [1-8]. Phosphorus compounds containing the P–C bond are not particularly abundant in nature but they have diverse biological activity and have attracted considerable synthetic and pharmacological interest [9], 10 Phosphonates have important applications in flame retardancy [11, 12], organic synthesis [13], and biological applications [14, 15]. Also, phosphonates have been used as substitutes of the corresponding esters and acids of high biological activity [16, 17] and as convenient probes for designing antibodies on the basis of transition state models. These investigations have been supported by organic synthesis; therefore, development of protocols for obtaining phosphonates of complex structures is inevitably important [18-20]. Hence, a large number of methods have appeared describing novel synthesis of phosphonate systems [21-23].

As part of our current studies on the development of new routes in organic compounds synthesis, we report an efficient synthetic route to phosphoryloxy phosphonate derivatives. Thus, the reaction of acid chlorides (1) with dialkyl(aryl)phosphites (2) in the presence of N-methylimidazole in water led to phosphoryloxy phosphonate derivatives 3 in good yield (Scheme 1).

Scheme 1. Synthesis of phosphoryloxy phosphonate derivatives.



1 **2** **3**

1, 3	R	R'	Yield % of 3
a	4-NO_2-C_6H_4	Ph	83
b	Ph	Et	92
c	4-OMe-C_6H_4	Et	86
d	Et	Me	78
e	Et	Ph	75
f	^{t}Bu	Me	75
g	^{t}Bu	Ph	74

The structures of compounds **3a-3g** were determined on the basis of their ^{1}H, ^{13}C, ^{31}P NMR, IR spectra, and elemental analyses data. The ^{1}H NMR spectrum of **3a** in $CDCl_3$ exhibited one doublet of doublet at δ = 6.25 (1 H, dd, $^2J_{PH}$ = 14.3 Hz and $^3J_{PH}$ = 10.7 Hz, CH), for the methine proton and multiplets at δ = 6.98–8.12 for the aromatic protons. The ^{13}C NMR spectrum of **3a** exhibited 32 signals in agreement with the proposed structure. The ^{1}H and ^{13}C-decoupled ^{31}P NMR spectrum of **3a** exhibited two sharp singlet at δ = -10.25 ($^3J_{PP}$ = 40.2 Hz), 12.4 ($^3J_{PP}$ = 40.2 Hz) ppm. Partial assignments

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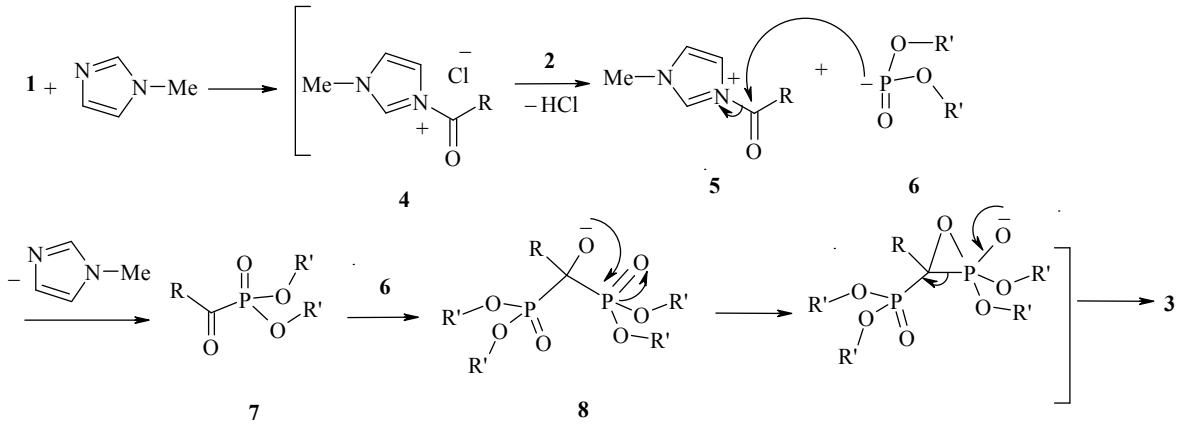
of these resonances are given in the Experimental section. Mechanistically, it is conceivable that the reaction involves the initial formation of a 1:1 zwitterionic intermediate **4** between acid chlorides and *N*-methylimidazole, which undergoes reaction with **2** to produce cationic ion **5** and anionic ion **2** after elimination of HCl. Intermediate **5** would be attacked by negative charge in **6** and loss of *N*-methylimidazole to produce **7** that would be attacked by negative charge in **6** again and finally compound **3** was produced in good yield (see Scheme 2).

Scheme 2. Proposed mechanism for synthesis of phosphoryloxy phosphonate derivatives.



Because of releasing of HCl during the reaction, the small quantity of *N*-methylimidazole to have become protonated as the reaction proceeds. Also, decomposition of the insignificant quantity of acid chlorides has occurred on the reaction timescale. For these reasons, quantity of *N*-methylimidazole and acid chloride in these reactions are excess.

In summary, the reaction between acid chlorides and dialkyl(aryl)phosphites in the presence of *N*-methylimidazole, provides a simple one-pot entry into the synthesis of phosphoryloxy phosphonate derivatives of potential synthetic and pharmacologically interest. The present method carries the advantage of being performed under the one-pot conditions, and requiring no activation or modification of the educts. In addition, phosphoryloxy phosphonate derivatives using commercially available starting materials are synthesized.

Exprimental

N-methylimidazole, acid chlorides, and dialkyl(aryl)phosphite were obtained from *Fluka* and were used without further purification. Mp: Electrothermal-9100 apparatus. IR spectra: *Shimadzu IR-460* spectrometer. ^{1}H and ^{13}CNMR spectra: *Bruker DRX-500 Avance* instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, respectively; δ in parts per million, J in hertz. EIMS (70 eV): *Finnigan-MAT-8430* mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a *Heraeus CHN-O-Rapid* analyzer.

General Procedure

N-methylimidazole (1 mmol) was added slowly to a mixture of acid chlorides **1** (excess) and **2** (4 mmol) in 5 ml of water at 50^{o}C. After completion of the reaction (30-45 min) as indicated by TLC (*n*-hexane**s**/EtOAc 8:1), the resulting solid was removed by filtration, washed with water (5 mL) and diethylether (1 mL) and dried to afford pure title compounds. The dried product thus obtained showed a single spot on TLC and was pure enough for all analytical purposes.

Diphenyl[[diphenoxyphosphoryl)oxy](4-nitrophenyl) methyl]phosphonate **(3a)**

Yellow powder, mp 174-176ºC; yield: 1.02 g (83%). IR (KBr) (ν_{max}/cm^{-1}): 1524, 1478, 1356, 1289, 1145 and 1087. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 6.25 (1 H, dd, $^2J_{PH}$ = 14.3 Hz and $^3J_{PH}$ = 10.7 Hz, CH), 6.98-7.32 (20 H, m, 20 CH), 7.66 (2 H, d, ^3J = 8.5 Hz, 2 CH), 8.12 (2 H, d, ^3J = 8.5 Hz, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 74.8 (dd, $^1J_{CP}$ = 181.3 Hz and $^2J_{CP}$ = 6.7 Hz, CH), 119.8 (d, $^3J_{CP}$ = 5.1 Hz, 2 CH), 120.1 (d, $^3J_{CP}$ = 4.8 Hz, 2 CH), 120.3 (d, $^3J_{CP}$ = 4.1 Hz, 2 CH), 123.6 (d, $^3J_{CP}$ = 4.2 Hz, 2 CH), 125.7 (2 CH), 125.8 (CH), 126.4 (CH), 129.0 (2 CH), 129.1 (2 CH), 129.8 (2 CH), 129.9 (2 CH), 130.0 (d, $^3J_{CP}$ = 7.4 Hz, 2 CH), 131.0 (2 CH), 132.5 (dd, $^2J_{CP}$ = 10.2 Hz and $^3J_{CP}$ = 6.4 Hz, C), 148.4

(d, $^2J_{CP}$ = 8.7 Hz, C), 149.8 (C), 149.9 (d, $^2J_{CP}$ = 9.6 Hz, C), 150.0 (d, $^2J_{CP}$ = 8.5 Hz, C), 150.3 (d, $^2J_{CP}$ = 8.6 Hz, C), ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = -10.25 ($^3J_{PP}$ = 40.2 Hz), 12.4 ($^3J_{PP}$ = 40.2 Hz) ppm. Anal. Calc. for $C_{31}H_{25}NO_9P_2$ (617.48): C, 60.30; H, 4.08; N, 2.27 found: C, 60.27; H, 3.94; N, 2.18%.

Diethyl[[diethyloxyphosphoryl)oxy](phenyl)methyl]phosphonate **(3b)**

Yellow powder, mp 140-142ºC; yield: 92%. IR (KBr) (ν_{max}/cm^{-1}): 1575, 1480, 1473, 1348, 1285 and 1248. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.27 (6 H, t, $^3J_{HH}$ = 7.3 Hz, 2 CH_3), 1.33 (6 H, t, $^3J_{HH}$ = 7.4 Hz, 2 CH_3), 4.25 (2 H, m, OCH_2), 4.32 (2 H, m, OCH_2), 4.48 (2 H, m, OCH_2), 4.53 (2 H, m, OCH_2), 6.16 (1 H, dd, $^2J_{PH}$ = 13.0 Hz and $^3J_{PH}$ = 10.4 Hz, CH), 6.87 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.45 (1 H, t, ^3J = 7.5 Hz, CH), 7.79 (2 H, d, ^3J = 7.5 Hz, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.4 (d, $^3J_{CP}$ = 5.6 Hz, 2 CH_3), 14.6 (d, $^3J_{CP}$ = 6.4 Hz, 2 CH_3), 62.0 (d, $^2J_{CP}$ = 8.4 Hz, OCH_2), 62.3 (d, $^2J_{CP}$ = 8.5 Hz, OCH_2), 62.5 (d, $^2J_{CP}$ = 7.4 Hz, OCH_2), 62.7 (d, $^2J_{CP}$ = 7.6 Hz, OCH_2), 76.1 (dd, $^1J_{CP}$ = 176.5 Hz and $^2J_{CP}$ = 6.7 Hz, CH), 120.1 (d, $^3J_{CP}$ = 6.2 Hz, 2 CH), 129.4 (2 CH), 132.0 (CH), 132.8 (d, $^2J_{CP}$ = 9.5 Hz, C) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = -11.45 ($^3J_{PP}$ = 39.2 Hz), 9.45 ($^3J_{PP}$ = 39.2 Hz) ppm.

Diethyl[[diethyloxyphosphoryl)oxy](4-methoxyphenyl)methyl]phosphonate **(3c)**

White powder, mp 155-157ºC; yield: 86%. IR (KBr) (ν_{max}/cm^{-1}): 1534, 1477, 1342, 1315, and 1278. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.24 (6 H, t, $^3J_{HH}$ = 7.2 Hz, 2 CH_3), 1.37 (6 H, t, $^3J_{HH}$ = 7.4 Hz, 2 CH_3), 3.75 (3 H, s, MeO), 4.27 (2 H, m, CH_2), 4.32 (2 H, m, CH_2), 4.47 (2 H, m, CH_2), 4.52 (2 H, m, CH_2), 6.34 (1 H, dd, $^2J_{PH}$ = 14.3 Hz and $^3J_{PH}$ = 11.5 Hz, CH), 7.43 (2 H, d, $^3J_{HH}$ = 8.5 Hz, 2 CH), 8.27 (2 H, d, $^3J_{HH}$ = 8.4 Hz, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.4 (d, $^3J_{CP}$ = 5.6 Hz, 2 CH_3), 14.5 (d, $^3J_{CP}$ = 6.4 Hz, 2 CH_3), 52.4 (MeO), 62.4 (d, $^2J_{CP}$ = 8.5 Hz, CH_2), 62.7 (d, $^2J_{CP}$ = 8.6 Hz, CH_2), 62.8 (d, $^2J_{CP}$ = 7.4 Hz, CH_2), 62.9 (d, $^2J_{CP}$ = 7.6 Hz, CH_2), 75.7 (dd, $^1J_{CP}$ = 187.4 Hz and $^2J_{CP}$ = 9.7 Hz, CH), 129.5 (d, $^3J_{CP}$ = 6.8 Hz, CH), 129.7 (d, $^3J_{CP}$ = 6.7 Hz, CH), 131.8 (CH), 132.0 (CH), 132.8 (dd, $^2J_{CP}$ = 9.5 Hz and $^3J_{CP}$ = 4.7 Hz, C), 140.1 (C) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = -11.25 ($^3J_{PP}$ = 39.4 Hz), 10.34 ($^3J_{PP}$ = 39.4 Hz) ppm.

Dimethyl[[dimethoxyphosphoryl)oxy]propyl]phosphonate **(3d)**

Yellow powder, mp 115-117ºC; yield: 0.43 g (78%). IR (KBr) (ν_{max}/cm^{-1}): 1541, 1487, 1452, 1328, and 1254. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.28 (3 H, m, CH_3), 1.65 (2 H, m, CH_2), 3.72 (3 H, d, $^3J_{PH}$ = 5.4 Hz, CH_3), 3.78 (3 H, d, $^3J_{PH}$ = 5.6 Hz, CH_3), 3.80 (3 H, d, $^3J_{PH}$ = 6.2 Hz, CH_3), 3.82 (3 H, d, $^3J_{PH}$ = 6.2 Hz, CH_3), 5.24 (1 H, m, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 12.5 (d, $^3J_{CP}$ = 4.8 Hz, CH_3), 28.3 (dd, $^2J_{CP}$ = 7.4 Hz and $^3J_{CP}$ = 4.2 Hz, CH_2), 51.4 (d, $^2J_{CP}$ = 6.0 Hz, OCH_3), 51.8 (d, $^2J_{CP}$ = 6.2 Hz, OCH_3), 52.0 (d, $^2J_{CP}$ = 5.8 Hz, OCH_3), 52.3 (d, $^2J_{CP}$ = 5.8 Hz, OCH_3), 78.4 (dd, $^1J_{CP}$ = 195.2 Hz and $^2J_{CP}$ = 9.7 Hz, CH) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = -11.65 ($^3J_{PP}$ = 34.5 Hz), 12.32 ($^3J_{PP}$ = 34.5 Hz) ppm. Anal. Calc. for $C_7H_{18}O_7P_2$ (276.16): C, 30.44; H, 6.57 found: C, 30.34; H, 6.40%.

Diphenyl{[diphenoxyphosphoryl)oxy]propyl}methyl]phosphonate **(3e)**

Yellow powder, mp 154-156ºC; yield: 75%. IR (KBr) (ν_{max}/cm^{-1}): 1654, 1547, 1325, 1245, 1189, and 1048. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.16 (3 H, t, ^3J = 7.2 Hz, Me), 2.18 (2 H, m, CH_2), 5.22 (1 H, m, CH), 6.79-7.37 (20 H, m, 20 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 9.9 (d, $^2J_{CP}$ = 10.7 Hz, Me), 24.6 (dd, $^2J_{CP}$ = 14.2 Hz and $^3J_{CP}$ = 8.4 Hz, CH_2), 75.6 (dd, $^1J_{CP}$ = 171.6 Hz and $^2J_{CP}$ = 7.4 Hz, CH_2), 120.1 (d, $^3J_{CP}$ = 6.5 Hz, 2 CH), 120.2 (d, $^3J_{CP}$ = 6.8 Hz, 2 CH), 120.5 (d, $^3J_{CP}$ = 5.7 Hz, 2 CH), 120.7 (d, $^3J_{CP}$ = 5.8 Hz, 2 CH), 125.5 (2 CH), 125.7 (2 CH), 129.4 (2 CH), 129.7 (2 CH), 129.8 (2 CH), 128.9 (2 CH), 149.9 (d, $^2J_{CP}$ = 10.4 Hz, C), 150.1 (d, $^2J_{CP}$ = 10.3 Hz, C), 150.4 (d, $^2J_{CP}$ = 9.8 Hz, C), 150.5 (d, $^2J_{CP}$ = 9.5 Hz, C) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = -10.15 ($^3J_{PP}$ = 39.0 Hz), 9.54 ($^3J_{PP}$ = 39.1 Hz) ppm. Anal. Calc. for $C_{27}H_{26}O_7P_2$ (524.44): C, 61.84; H, 5.00 found: C, 61.74; H, 4.87%.

Di(tert-butyl)[[dimethoxyphosphoryl)oxy]propyl]phosphonate **(3f)**

White powder, mp 111-113ºC; yield: 0.46 g (75%). IR (KBr) (ν_{max}/cm^{-1}): 1557, 1480, 1467, 1334, and 1228. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.14 (9 H, s, Me_3C), 3.74 (3 H, d, $^3J_{PH}$ = 5.5 Hz, CH_3), 3.76 (3 H, d, $^3J_{PH}$ = 5.5 Hz, CH_3), 3.82 (3 H, d, $^3J_{PH}$ = 5.8 Hz, CH_3), 3.85 (3 H, d, $^3J_{PH}$ = 5.8 Hz, CH_3), 5.22 (1 H, dd, $^3J_{PH}$ = 5.8 Hz, $^3J_{PH}$ = 4.2 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 28.7 (d, $^3J_{CP}$ = 5.6 Hz, Me_3C), 34.6 ($^2J_{CP}$ = 8.5 Hz and $^3J_{CP}$ = 5.0 Hz, Me_3C), 52.3 (d, $^2J_{CP}$ = 7.4 Hz, OCH_3), 52.5 (d, $^2J_{CP}$ = 7.4 Hz, OCH_3), 53.4 (d, $^2J_{CP}$ = 8.0 Hz, OCH_3), 53.5 (d, $^2J_{CP}$ = 8.0 Hz, OCH_3), 80.4 (dd, $^1J_{CP}$ = 194.3 Hz and $^2J_{CP}$ = 8.6 Hz, CH) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = -12.0 ($^3J_{PP}$ = 35.1 Hz), 11.45 ($^3J_{PP}$ = 35.1 Hz) ppm. Anal. Calc. for $C_9H_{22}O_7P_2$ (304.21): C, 35.53; H, 7.29 found: C, 35.58; H, 7.32%.

Diphenyl[[diphenoxyphosphoryl)oxy] (tert-butyl) methyl]phosphonate (**3g)**

White powder, mp 115-117ºC; yield: 74%. IR (KBr) (ν_{max}/cm^{-1}): 1562, 1480, 1475, 1345, and 1214. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.23 (9 H, s, *Me*$_3$C), 4.94 (1 H, dd, $^3J_{PH}$ = 7.2 Hz, $^3J_{PH}$ = 5.6 Hz, CH), 6.79-7.37 (20 H, m, 20 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 29.4 (d, $^3J_{CP}$ = 5.4 Hz, *Me*$_3$C), 34.6 (dd, $^2J_{CP}$ = 8.9 Hz and $^3J_{CP}$ = 6.0 Hz, Me$_3$*C*), 82.4 (dd, $^1J_{CP}$ = 198.4 Hz and $^2J_{CP}$ = 8.7 Hz, CH), 120.1 (d, $^3J_{CP}$ = 6.5 Hz, 2 CH), 120.2 (d, $^3J_{CP}$ = 6.8 Hz, 2 CH), 120.5 (d, $^3J_{CP}$ = 5.7 Hz, 2 CH), 120.7 (d, $^3J_{CP}$ = 5.8 Hz, 2 CH), 125.5 (2 CH), 125.7 (2 CH), 129.4 (2 CH), 129.7 (2 CH), 129.8 (2 CH), 128.9 (2 CH), 149.9 (d, $^2J_{CP}$ = 10.4 Hz, C), 150.1 (d, $^2J_{CP}$ = 10.3 Hz, C), 150.4 (d, $^2J_{CP}$ = 9.8 Hz, C), 150.5 (d, $^2J_{CP}$ = 9.5 Hz, C) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = -10.34 ($^3J_{PP}$ = 31.5 Hz), 11.25 ($^3J_{PP}$ = 31.5 Hz) ppm.

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