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SHORT COMMUNICATIONS

Phosphorylation of Amino(aryl)methylphosphonates by the Atherton–Todd Reaction

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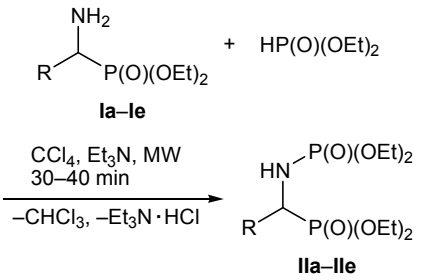
Among amidophosphate derivatives, promising are *N*-(α-phosphoryl)amidophosphates possessing two four-coordinate phosphorus atoms. These organophosphorus compounds exhibit biological activity and are used as chelating ligands for complex formation with some metal ions [1, 2]. They are usually synthesized by phosphorylation of amino phosphonates with diethyl chlorophosphate [3].

We were the first to perform phosphorylation of amino(aryl)methylphosphonates having a primary amino group under the Atherton–Todd reaction conditions. The reactions of amino(aryl)methylphosphonates **Ia**–**Ie** with diethyl phosphonate and carbon tetrachloride in the presence of triethylamine were carried out at room temperature, on heating at 110ºC, and under microwave irradiation. The reactions under microwave irradiation were complete in 30–40 min, and the corresponding *N*-(α-phosphoryl)amidophosphates **IIa**–**IIe** were obtained in 63–93% yield. No reaction occurred at room temperature, whereas after heating for 24 h at 110°C compounds **IIa**–**IIe** were isolated in poor yields (15–20%) due to predominant formation of pyrophosphate on prolonged heating.



R = Ph (**a**), 4-MeC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**), 4-$Me_2NC_6H_4$ (**d**), 3-$O_2NC_6H_4$ (**e**).

The product structure was confirmed by their ^{1}H, ^{13}C, and ^{31}P NMR spectra and elemental analyses. Compounds **IIa**–**IIe** displayed in the ^{31}P NMR spectra doublet signals at δ_P 6.2–6.8 and 22.2–22.6 ppm with coupling constants of 40.2–42.7 Hz. In the ^{1}H NMR spectra of **IIa**–**IIe**, the NCH proton characteristically resonated at δ 4.4–4.6 ppm, and the corresponding carbon signal appeared in the ^{13}C NMR spectra as a doublet at δ_C 51.3–53.8 ppm (J_{PC} = 153–156 Hz).

Diethyl aryl(diethoxyphosphorylamino)methylphosphonates IIa–IIe (*general procedure***).** Carbon tetrachloride, 20 mmol (3.08 g, 2.11 ml), triethylamine, 15 mmol (1.52 g, 1.08 ml), and aminophosphonate **Ia**–**Ie**, 10 mmol, were added in succession to 10 mmol (1.38 g, 1.29 ml) of diethyl phosphonate. The reaction was carried out in an open vessel under microwave irradiation (102 W, 115°C). The precipitate of triethylamine hydrochloride was filtered through a glass filter, the filtrate was cooled and evaporated on a rotary evaporator, and the residue was subjected to column chromatography on silica gel using chloroform–methanol (50 : 1) as eluent.

Diethyl α-[(diethoxyphosphoryl)amino]benzylphosphonate (IIa). Reaction time 40 min. Yield 3.22 g (85%), oily substance. ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 6.78 d and 22.20 d ($^3J_{PP}$ = 41.3 Hz) [3].

Diethyl α-[(diethoxyphosphoryl)amino]-4-methylbenzylphosphonate (IIb). Reaction time 35 min. Yield 3.46 g (88%), oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.06 t (3H, C**H**$_3$CH$_2$OPNH, ^3J = 7.2 Hz), 1.12 t (3H, C**H**$_3$CH$_2$OPNH, ^3J = 7.2 Hz), 1.27 t (3H, C**H**$_3$CH$_2$OPCH, ^3J = 6.8 Hz), 1.33 t (3H, C**H**$_3$CH$_2$OPCH, ^3J = 6.8 Hz), 1.88 br.s (1H, NH), 2.19 s (3H, C**H**$_3$C$_6$H$_4$), 3.65–3.70 m (2H, NHPOC**H**$_2$),

3.90–3.95 m (2H, NHPOC**H**$_2$), 3.97–4.02 m (2H, CHPOC**H**$_2$), 4.12–4.17 m (2H, CHPOC**H**$_2$), 4.47 d.t (1H, PCH, ^2J = 23.1, ^3J = 12.1 Hz), 7.15 d and 7.28 d (2H each, C_6H_4, ^3J = 8.4 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.72 s and 16.02 s (**C**H_3CH_2O-PNH), 16.12 s and 16.42 s (**C**H_3CH_2OPCH), 21.14 s (**C**$H_3C_6H_4$), 51.94 d (PCH, $^1J_{CP}$ = 154.3 Hz), 63.09 s and 63.13 s (CH_2OPNH), 63.37 s and 63.41 s (**C**H_2OPCH); 127.68 s, 129.17 s, 133.45 s, 137.91 s (C_6H_4). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 6.70 d and 22.27 d ($^3J_{PP}$ = 42.7 Hz). Found, %: C 49.02; H 7.51; N 4.14. $C_{16}H_{29}NO_6P_2$. Calculated, %: C 48.85; H 7.43; N 3.56.

Diethyl α-[(diethoxyphosphoryl)amino]-4-methoxybenzylphosphonate (IIc). Reaction time 35 min. Yield 3.80 g (93%), oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.06 t (3H, C**H**$_3$CH$_2$OPNH, ^3J = 6.7 Hz), 1.11 t (3H, C**H**$_3$CH$_2$OPNH, ^3J = 6.7 Hz), 1.24 t (3H, C**H**$_3$CH$_2$OPCH, ^3J = 6.7 Hz), 1.31 t (3H, C**H**$_3$CH$_2$OPCH, ^3J = 6.7 Hz), 2.20 br.s (1H, NH), 3.79 s (3H, C**H**$_3$OC$_6$H$_4$), 3.64–3.69 m (2H, NHPOC**H**$_2$), 3.93–3.97 m (2H, NHPOC**H**$_2$), 3.98–4.03 m (2H, CHPOC**H**$_2$), 4.12–4.17 m (2H, CHPOC**H**$_2$), 4.44 d.t (1H, PCH, ^2J = 22.8, ^3J = 10.8 Hz), 6.85 d and 7.31 d (2H each, C_6H_4, ^3J = 8.3 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.76 s and 16.02 s (C**H**$_3$CH$_2$-OPNH), 16.17 s and 16.37 s (C**H**$_3$CH$_2$OPCH), 51.56 d (PCH, $^1J_{CP}$ = 156.3 Hz), 55.25 s (C**H**$_3$OC$_6$H$_4$), 62.94 s and 62.98 s (CH_2OPNH), 63.24 s and 63.28 s (**C**H_2OPCH); 113.83 s, 115.95 s, 129.00 s, 159.39 s (C_6H_4). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 6.78 d and 22.43 d ($^3J_{PP}$ = 40.6 Hz). Found, %: C 47.04; H 7.30; N 3.65. $C_{16}H_{29}NO_7P_2$. Calculated, %: C 46.95; H 7.14; N 3.42.

Diethyl α-[(diethoxyphosphoryl)amino]-4-dimethylaminobenzylphosphonate (IId). Reaction time 40 min. Yield 2.66 g (63%), oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.03 t (3H, C**H**$_3$CH$_2$OPNH, ^3J = 7.2 Hz), 1.10 t (3H, C**H**$_3$CH$_2$O-PNH, ^3J = 7.2 Hz), 1.26 t (3H, C**H**$_3$CH$_2$OPSH, ^3J = 7.2 Hz), 1.33 t (3H, C**H**$_3$CH$_2$OPCH, ^3J = 7.2 Hz), 2.08 br.s (1H, NH), 2.94 s (6H, CH_3N), 3.63–3.68 m (2H, NHPOC**H**$_2$), 3.92–3.97 m (2H, NHPOC**H**$_2$), 3.97–4.02 m (2H, CHPOC**H**$_2$), 4.12–4.16 m (2H, CHPOC**H**$_2$), 4.51 d.t (1H, PCH, ^2J = 22.5, ^3J = 10.3 Hz), 7.33 d and 7.41 d (2H each, C_6H_4, ^3J = 6.3 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.70 s and 15.78 s (**C**H_3CH_2OPNH), 16.37 s and 16.43 s (**C**H_3CH_2OPCH), 40.51 s (CH_3N), 52.28 d (PCH, $^1J_{CP}$ = 153.8 Hz), 63.05 s and 63.09 s (**C**H_2OPNH), 63.33 s and 63.37 s (**C**H_2OPCH); 127.85 s, 128.45 s, 136.73 s (C_6H_4); 153.53 s (C^p). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 6.68 d and 22.20 d ($^3J_{PP}$ = 40.2 Hz). Found, %: C 48.51; H 7.81; N 6.82. $C_{17}H_{32}N_2O_6P_2$. Calculated, %: C 48.34; H 7.64; N 6.63.

Diethyl α-[(diethoxyphosphoryl)amino]-3-nitrobenzylphosphonate (IIe). Reaction time 30 min. Yield 3.48 g (82%), oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.04 t (3H, C**H**$_3$CH$_2$OPNH, ^3J = 7.2 Hz), 1.11 t (3H, C**H**$_3$CH$_2$OPNH, ^3J = 7.2 Hz), 1.25 t (3H, C**H**$_3$CH$_2$OPCH, ^3J = 7.2 Hz), 1.32 t (3H, C**H**$_3$CH$_2$OPCH, ^3J = 7.2 Hz), 2.52 br.s (1H, NH), 3.60–3.65 m (2H, NHPOC**H**$_2$), 3.95–4.00 m (2H, CHPOC**H**$_2$), 4.01–4.05 m (2H, CHPOC**H**$_2$), 4.12–4.17 m (2H, NHPOC**H**$_2$), 4.62 d.t (1H, PCH, ^2J = 22.7, ^3J = 10.5 Hz); 7.55 d, 7.69 t, 7.84 d, 8.17 d (4H, C_6H_4). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.85 s and 15.93 s (**C**H_3CH_2OPNH), 16.33 s and 16.41 s (**C**H_3CH_2OPCH), 53.81 d (PCH, $^1J_{CP}$ = 154.6 Hz), 62.45 s and 62.49 s (**C**H_2OPNH), 63.12 s and 63.16 s (**C**H_2OPCH); 126.21 s, 127.01 s, 133.15 s, 133.95 s, 142.03 s (C_6H_4); 149.87 s (C^p). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 6.28 d and 20.56 d ($^3J_{PP}$ = 41.4 Hz). Found, %: C 42.46; H 6.18; N 6.60. $C_{15}H_{26}N_2O_8P_2$. Calculated, %: C 41.98; H 6.01; N 6.61.

The ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded from solutions in $CDCl_3$ on a Bruker Avance-400 spectrometer at 400, 100.6, and 161.9 MHz, respectively, using the solvent signals as reference (δ 7.28 ppm, δ_C 77.10 ppm). The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using chloroform–methanol (50 : 1) as eluent. Preparative column chromatography was performed on silica gel (40–60 μm, Merck).

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REFERENCES

1. Skropeta, D., Schwörer, R., and Schmidt, R.R., *Bioorg. Med. Chem. Lett*., 2003, vol. 13, p. 3351.
2. Cui, Z., Zhang, J., Wang, F., Wang, Y., Miao, Z., and Chen, R., *Carbohydr. Res*., 2008, vol. 343, p. 2530.
3. Hammerschmidt, F. and Hanbauer, M., *J. Org. Chem*., 2000, vol. 65, p. 6121.