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Synthesis of 1-Hetarylethylphosphonates

N. S. Gulyukina and I. P. Beletskaya

Faculty of Chemistry, Moscow State University, Vorob'evy gory 1, Moscow, 119992 Russia
e-mail: goulioukina@org.chem.msu.ru

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Abstract—Previously unknown potentially biologically active diethyl 1-(pyridin-3-yl)-, 1-(quinolin-3-yl)-, and 1-(quinolin-6-yl)ethylphosphonates were synthesized by palladium-catalyzed reduction of the corresponding α,β-unsaturated precursors with ammonium formate. The reduction of diethyl 1-(quinolin-6-yl)ethenylphosphonate was accompanied by formation of diethyl 1-(1,2,3,4-tetrahydroquinolin-6-yl)ethylphosphonate as by-product.

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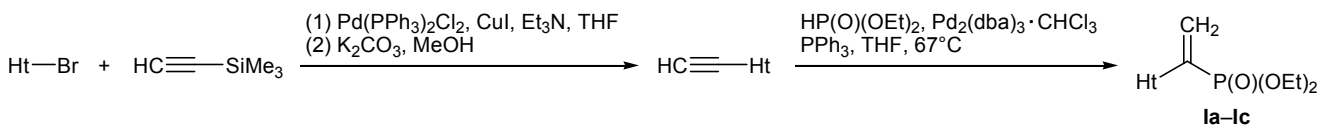
Interest in 1-arylethylphosphonic acids and their esters is determined primarily by their biological activity. 1-Arylethylphosphonates are cyclooxygenase inhibitors [1], Ca^{2+} antagonists [2, 3], neuroprotectors [3], psychotropic [3] and negative inotropic agents [2], and reactive immunization haptens [4, 5]. These compounds may be regarded as phosphorus-containing structural analogs of 2-arylpropionic acids that are widely used in modern medical practice as nonsteroidal analgesic, antiphlogistic, and antipyretic drugs; examples are ibuprofen, naproxen, ketoprofen, flurbiprofen, tiaprofen, etc.

Synthetic applications of 1-arylethylphosphonates are related mainly to their use as reagents in the Horner–Wadsworth–Emmons reactions, which is reflected in numerous patents (see, e.g., [6–9]). It was also shown that vanadyl 1-arylethylphosphonates are characterized by layered structure which makes them promising for the design of functional materials [10]. There are very scanty published data on 1-hetarylethylphosphonates (see, e.g., [11]), though their synthesis and estimation of their biological activity attract undoubted interest. For instance, among the above noted profens, just tiaprofen [(*RS*)-2-(5-benzoylthiophen-2-yl)propionic acid] exhibits the highest selectivity in the inhibition of synthesis of prostaglandin $F_{2\alpha}$. Another example is (*S*)-2-amino-3-[3-hydroxy-5-(pyridin-2-yl)-isoxazol-4-yl]propionic acid which is a considerably more potent AMPA receptor agonist than its 5-phenyl analog [12]. Likewise, replacement of the benzene ring in diethyl 4-(benzothiazol-2-yl)benzylphosphonate (calcium antagonist Fostedil) by pyridine appreciably enhances coronary vasodilating effect [13].

We previously proposed a convenient synthetic approach to 1-arylethylphosphonates, which is based on catalytic reduction of the corresponding α,β-unsaturated precursors. Homogeneous enantioselective hydrogenation of 1-arylethenylphosphonic acids and their esters was performed in the presence of chiral ruthenium [14, 15] and iridium catalysts [16], respectively. This approach was then successfully developed by other authors [17, 18]. A number of racemic 1-arylethylphosphonates containing substituted phenyl and naphthyl groups were synthesized using ammonium formate as reducing agent and carbon-supported palladium as catalyst [14, 15]. The goal of the present study was to synthesize under analogous conditions 1-hetarylethylphosphonates.

As model substrates we selected diethyl 1-(pyridin-3-yl)-, 1-(quinolin-3-yl)-, and 1-(quinolin-6-yl)ethenylphosphonates **Ia**–**Ic** which were prepared by palladium-catalyzed hydrophosphorylation of the correspond-

Scheme 1.



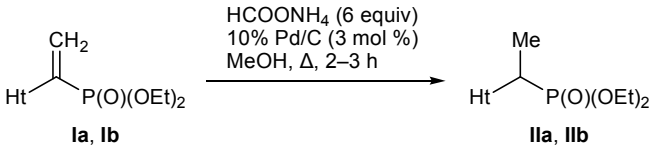
Ia–Ic

Ht = pyridin-3-yl (**a**), quinolin-3-yl (**b**), quinolin-6-yl (**c**).

ing hetarylacetylenes. The latter were synthesized in turn by cross-coupling of trimethylsilylacetylene with hetaryl bromides according to Sonogashira, followed by removal of trimethylsilyl protection under basic conditions [19] (Scheme 1).

1-Hetarylethenylphosphonates **Ia**–**Ic** were reduced with 6 equiv of ammonium formate in boiling methanol in the presence of 10% Pd/C (3 mol %). The progress of reactions was monitored by ^{31}P NMR spectroscopy following disappearance of the signal of initial compound **Ia**–**Ic** (δ_P 15.5–16.3 ppm) from the ^{31}P NMR spectrum of the reaction mixture. We found that the reduction of phosphonates **Ia** and **Ib** is complete in 2–3 h, leading exclusively to the corresponding 1-hetarylethylphosphonates **IIa** and **IIb** (Scheme 2); no other products were detected by ^{31}P NMR spectroscopy. Compounds **IIa** and **IIb** were isolated in 84 and 90% yield, respectively; their structure was confirmed by elemental analyses and spectral data. The presence of a characteristic set of signals in the aromatic region of the ^{1}H NMR spectra of phosphonates **IIa** and **IIb** indicated conservation of the heteroaromatic fragment. According to [11], reduction of structurally related systems with hydrogen in the presence of Pd/C is generally accompanied by hydrogenation of heteroaromatic ring.

Scheme 2.



Ia, **Ib** **IIa**, **IIb**

Ht = pyridin-3-yl (**a**), quinolin-3-yl (**b**).

In the reduction of diethyl 1-(quinolin-6-yl)ethenylphosphonate (**Ic**) with ammonium formate the complete conversion was achieved in 3 h, and the reaction mixture contained two reduction products at a ratio of 7:3. In this case, the reduction of the exocyclic double C=C bond was accompanied by hydrogenation of the pyridine fragment. The products, phosphonate **IIc** and diethyl 1-(1,2,3,4-tetrahydroquinolin-6-yl)ethylphosphonate, were isolated by chromatography (Silufol, EtOAc) in 60 and 27% yield, respectively, and were characterized by spectral data. The structure of the by-product was confirmed by ^{1}H NMR spectroscopy. The carbocyclic fragment retains its aromaticity, as follows from the multiplicity of signal from the CH proton, which appears as a doublet of quartets at δ 3.01 ppm ($^3J_{HH}$ = 7.2, $^2J_{HP}$ = 22.4 Hz), and from the presence of a one-proton doublet ($^3J_{HH}$ = 8.4 Hz) and a two-proton multiplet in the aromatic region (δ 6.43 and 6.92 ppm, respectively). Methylene protons in the heterocyclic fragment resonated as three two-proton multiplets at δ 1.93, 2.75, and 3.28 ppm.

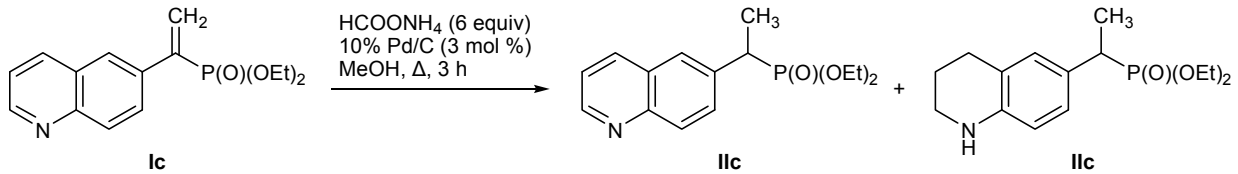
Selective reduction of the heteroaromatic ring in substituted quinolines, isoquinolines, and indoles by the action of formic acid salts in the presence of carbon-supported palladium was reported in [20–22]; this procedure was successfully used for the preparation of 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, and dihydroindole derivatives. Comparison of our results in the reduction of substrates **Ib** and **Ic** shows that the ability of quinoline ring to undergo partial hydrogenation strongly depends on the substitution pattern.

To conclude, we have shown that palladium-catalyzed reduction of 1-hetarylethenylphosphonates with ammonium formate leads to the formation of the corresponding diethyl 1-(pyridin-3-yl)- and 1-(quinolin-3-yl)ethylphosphonates in nearly quantitative yields. Under analogous conditions, the yield of diethyl 1-(quinolin-6-yl)ethylphosphonate appreciably decreases due to side formation of diethyl 1-(1,2,3,4-tetrahydroquinolin-6-yl)ethylphosphonate. The results of biological tests on diethyl 1-hetarylethylphosphonates **IIa**–**IIc** will be reported elsewhere.

EXPERIMENTAL

The ^{1}H and ^{31}P–{^{1}H} NMR spectra were recorded on a Bruker Avance-400 spectrometer at 400 and 162 MHz, respectively. The chemical shifts were determined relative to 85% H_3PO_4 (external reference, ^{31}P) or tetramethylsilane (internal reference, ^{1}H). The IR spectra were measured on an Ikar spectrometer with Fourier transform (*Mikrotekh* Ltd., Russia). The ele-

Scheme 3.



Ic **IIc** **IIc**

mental compositions were determined on a Carlo Erba automatic analyzer. Methanol was heated under reflux over magnesium methoxide and then distilled. Ammonium formate of pure grade was dried under reduced pressure over P_2O_5. Carbon-supported palladium (10% Pd/C) was commercial product (from Aldrich).

Diethyl 1-(pyridin-3-yl)ethylphosphonate (IIa). A mixture of 0.55 g (2.3 mmol) of diethyl 1-(pyridin-3-yl)ethenylphosphonate (**Ia**), 0.88 g (14.0 mmol, 6 equiv) of ammonium formate, and 0.07 g of 10% Pd/C (3 mol % of Pd) in 34 ml of anhydrous methanol was heated for 2 h with stirring under reflux in a stream of dry argon. The mixture was filtered from the catalyst through a small layer of silica gel, the solvent was distilled off from the filtrate on a rotary evaporator, and the residue was treated with diethyl ether. The ether extracts were combined, washed with a small amount of water, dried over $MgSO_4$, and evaporated, and the residue was subjected to chromatography on silica gel using ethyl acetate as eluent. Yield 0.46 g (84%), yellow oily substance, R_f 0.15 (Silufol, EtOAc). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.18 t and 1.29 t (3H each, $CH_2C\mathbf{H}_3$, $^3J_{HH}$ = 7.1 Hz), 1.60 d.d (3H, $CHC\mathbf{H}_3$, $^3J_{HH}$ = 7.4, $^3J_{HP}$ = 18.4 Hz), 3.84–4.02 m (2H, CH_2), 3.21 d.q (1H, CH, $^3J_{HH}$ = 7.4, $^2J_{HP}$ = 22.6 Hz), 4.07 m (2H, CH_2), 7.30 d.d (1H, 5-H, $^3J_{HH}$ = 8.0, $^3J_{HH}$ = 4.6 Hz), 7.76 br.d (1H, 4-H, $^3J_{HH}$ = 8.0 Hz), 8.51 m (1H, 6-H), 8.54 br.s (1H, 2-H). ^{31}P NMR spectrum (CD_3OH): δ_P 32.6 ppm. Found, %: C 54.77; H 7.23; N 6.02. $C_9H_{14}NO_3P$. Calculated, %: C 54.32; H 7.46; N 5.76.

Diethyl 1-(quinolin-3-yl)ethylphosphonate (IIb) was synthesized in a similar way by reduction of 0.97 g (3.3 mmol) of diethyl 1-(quinolin-3-yl)ethenylphosphonate (**Ib**) with 1.27 g (20.1 mol) of ammonium formate in 50 ml of methanol in the presence of 0.11 g of 10% Pd/C (3 mol % of Pd); Reaction time 3 h. Yield 0.88 g (90%), yellow oily substance, R_f 0.25 (Silufol, EtOAc). IR spectrum (film), ν, cm^{-1}: 2920, 2850, 1464, 1252 (P=O), 1163, 1055, 1024 (O–C), 962 (OC–C), 789, 756, 730. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.16 t and 1.29 t (3H each, $CH_2C\mathbf{H}_3$, $^3J_{HH}$ = 7.0 Hz), 1.70 d.d (3H, $CHC\mathbf{H}_3$, $^3J_{HH}$ = 7.4, $^3J_{HP}$ = 18.0 Hz), 3.84–4.02 m (2H, CH_2), 3.39 d.q (1H, $C\mathbf{H}CH_3$, J_{HH} = 7.4, $^2J_{HP}$ = 22.8 Hz), 4.10 m (2H, CH_2), 7.54 m (1H, 6-H), 7.69 m (1H, 7-H), 7.81 d (1H, 5-H, $^3J_{HH}$ = 8.0 Hz), 8.10 d (1H, 8-H, $^3J_{HH}$ = 8.8 Hz), 8.16 m (1H, 4-H), 8.87 br.s (1H, 2-H). ^{31}P NMR spectrum (CD_3OH): δ_P 32.7 ppm. Found, %: C 61.30; H 6.91; N 5.03. $C_{13}H_{16}NO_3P$. Calculated, %: C 61.43; H 6.87; N 4.78.

Diethyl 1-(quinolin-6-yl)ethylphosphonate (IIc) was synthesized in a similar way by reduction of 1.01 g (3.5 mmol) of diethyl 1-(quinolin-6-yl)ethenylphosphonate (**Ic**) with 1.32 g (20.9 mmol) of ammonium formate in 52 ml of methanol in the presence of 0.11 g of 10% Pd/C (3 mol % of Pd); reaction time 3 h. The product was isolated by chromatography on silica gel using ethyl acetate as eluent. Yield 0.61 g (60%), R_f 0.2 (Silufol, EtOAc). IR spectrum (film), ν, cm^{-1}: 2981, 1500, 1456, 1248 (P=O), 1163, 1055, 1022 (O–C), 962 (OC–C), 893, 841, 796, 780, 732. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.14 t and 1.29 t (3H each, $CH_2C\mathbf{H}_3$, $^3J_{HH}$ = 7.1 Hz), 1.69 d.d (3H, $CHC\mathbf{H}_3$, $^3J_{HH}$ = 7.6, $^3J_{HP}$ = 18.2 Hz), 3.39 d.q (1H, CH, $^3J_{HH}$ = 7.6, $^2J_{HP}$ = 22.8 Hz), 3.83 m and 3.94 m (1H each, CH_2), 4.07 m (2H, CH_2), 7.40 d.d (1H, 3-H, $^3J_{HH}$ = 8.0, 4.4 Hz), 7.74 m (1H, 7-H, $^3J_{HH}$ = 8.6 Hz), 7.81 m (1H, 5-H), 8.08 d (1H, 8-H, $^3J_{HH}$ = 8.6 Hz), 8.15 br.d (1H, 4-H, $^3J_{HH}$ = 8.0 Hz), 8.89 br.s (1H, 2-H, $^3J_{HH}$ = 4.4 Hz). ^{31}P NMR spectrum, δ_P, ppm: 33.3 (in CD_3OH), 28.8 (in $CDCl_3$). Found, %: C 61.24; H 6.65; N 4.59. $C_{13}H_{16}NO_3P$. Calculated, %: C 61.43; N 6.87; N 4.78.

In addition, 0.28 g (27%) of diethyl 1-(1,2,3,4-tetrahydroquinolin-6-yl)ethylphosphonate was isolated. R_f 0.4 (Silufol, EtOAc). IR spectrum (film), ν, cm^{-1}: 2956, 2920, 2852, 1463, 1234 (P=O), 1162, 1054, 1024 (O–C), 962 (OC–C), 908, 838, 795, 771, 734. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.17 t and 1.28 t (3H each, $CH_2C\mathbf{H}_3$, $^3J_{HH}$ = 7.2 Hz), 1.51 d.d (3H, $CHC\mathbf{H}_3$, $^3J_{HH}$ = 7.4, $^3J_{HP}$ = 18.8 Hz), 1.92 m and 2.74 m (2H each, CH_2), 3.02 d.q (1H, CH, $^3J_{HH}$ = 7.4, $^2J_{HP}$ = 22.2 Hz), 3.27 m (2H, CH_2), 3.82 m and 3.94 m (1H each, OCH_2), 4.03 m (2H, OCH_2), 6.42 d (1H, 8-H, $^3J_{HH}$ = 8.8 Hz), 6.92 m (2H, 5-H, 7-H). ^{31}P NMR spectrum, δ_P, ppm: 35.1 (in MeOH), 30.4 (in $CDCl_3$). Found, %: C 60.59; H 8.34; N 4.70. $C_{13}H_{20}NO_3P$. Calculated, %: C 60.59; H 8.14; N 4.71.

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