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Catalytic Synthesis of α-Hydroxyphosphonates

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Abstract—Reactions of carbonyl compounds of aliphatic, aromatic, and heteroaromatic series with dialkyl phosphites in the presence of DBN were studied under microwave irradiation.

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The reaction of dialkyl phosphites (Abramov reaction) leading to the formation of hydroxyphosphonates is commonly known. Although the reaction has been discovered at the beginning of nineteen fifties [1], it still attracts the interest of chemists [2, 3], evidently due firsts of all to the practical applications of α-hydroxyphosphonates.

Among the functionally substituted phosphonic acids α-hydroxyphosphonic acids and their esters possess a special place for they are endowed with a wide range of biological action: from antibacterial, neuroactive , and anticancer drugs to enzymes inhibitors and pesticides [4–8]. The biological activity of this class of organophosphorus compounds originates from their structural analogy to α-hydroxycarboxylic acids; they exhibit a wide inhibitor effect with respect to enzymes and receptors that usually bind the natural α-hydroxycarboxylic acids [9].

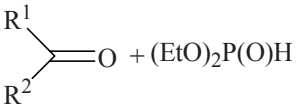
The reactions of dialkyl phosphates with carbonyl compounds are commonly carried out in the presence of a basic catalyst that displaces the tautomeric equilibrium of the dialkyl phosphite to the three-coordinated form. The usually applied catalysts are metal alcoholates, tertiary amines, or inorganic bases taken in equimolar amounts or in excess. However the reaction in the presence of a large quantity of bases is often accompanied by the partial decomposition of the obtained α-hydroxyphosphonates (retro-Abramov reaction) [10, 11], or by the formation of the corresponding phosphates [12]. In this connection the search for new active catalysts and optimum conditions for performance of Abramov reaction is still topical nowadays.

Aiming at the optimization of the preparation conditions for α-hydroxyphosphonates we investigated the reaction of dialkyl phosphates with carbonyl compounds of aliphatic, aromatic, and heteroaromatic series in the presence of 1,5-diazabicyclo-[4.3.0.]non-5-ene (DBN) under the microwave irradiation. The application of microwave irradiation (MW) for acceleration of organic, and in particular, organophosphorus, processes is well known [13–17].

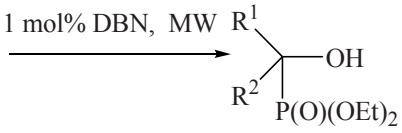
The combination of catalysis by DBN and MW assistance made it possible to obtain α-hydroxyphosphonates quickly (in several minutes) and in high yields.

The reaction of carbonyl compounds of aliphatic, aromatic, and heteroaromatic series **Ia–Ij** with dialkyl phosphates was carried out under the action of the microwave irradiation without solvent in the presence of 1 mol% of DBN. The monitoring of the reaction progress was performed by ^{31}P NMR, IR spectroscopy, and also by TLC (Silufol plates, eluent chloroform–methanol, 10:1). As show the data of ^{31}P NMR spectroscopy, the reactions of aldehydes and ketones **Ia–Ih** with diethyl phosphite under these conditions proceed materially quantitatively.

At the use of aldehydes the yield of the final products is insignificantly affected by the aldehyde structure whereas with ketones the reaction under study occurs easily only with cyclohexanone (**Ih**), yet with cyclopentanone (**Ii**) and methyl ethyl ketone (**Ij**) even at longer heating the corresponding α-hydroxyphosphonates are formed only in ~40% yield.



Ia–Ij



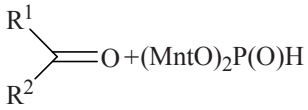
IIa–IIj

R^1 = H, R^2 = Et (**a**), *i*-Pr (**b**), Ph (**c**), *m*-$NO_2C_6H_4$ (**d**), *p*-ClC_6H_4 (**e**), 2-Fur (**f**), 2-Pyr (**g**); R^1,R^2 = *cyclo*-C_6H_{10} (**h**), *cyclo*-C_5H_8 (**i**), R^1 = Me, R^2 = Et (**j**).

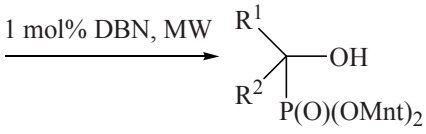
The application of 1 mol% of DBN combined with MW assistance not only provided high yields of hydroxyphosphonates, but also prevented the side processes. The addition of a larger amount of the catalyst (2 mol% and more) at MW irradiation resulted in the reduced product yield due to the phosphate formation by the phosphonate-phosphate rearrangement.

The reaction at room temperature on at heating (40–45°C) proceeded considerably slower. For instance, the reaction of benzaldehyde with diethyl phosphite in the presence of 1 mol% of DBN proceeded at heating for 6 h, and α-hydroxyphosphonate **IIc** formed in 44% yield.

The addition of chiral dialkyl phosphites (dimenthyl phosphite) to aromatic and aliphatic aldehydes at the catalysis with DBN and microwave irradiation led to the formation of α-hydroxyphosphonate (according to ^{31}P NMR data) with a slight stereoselectivity (the diastereomers ratio ~1:1.2). The yields of the corresponding final compounds in these cases are virtually quantitative.



IIIa, IIIb



IVa, IVb

Mnt = (–)-menthyl; R^1 = H, R^2 = *i*-Pr (**a**), Ph (**b**).

Thus we showed that the performance of the reaction of carbonyl compounds with dialkyl phosphates under the catalysis with DBN and with microwave irradiation provided a possibility to obtain α-hydroxyphosphonates of versatile structure quickly and in high yields.

EXPERIMENTAL

^1H, ^{13}C, and ^{31}P NMR spectra were registered on a spectrometer Bruker Avance-400 (at operating frequencies 400, 100.6, 161.9 MHz respectively). The chloroform signal was used as internal reference (δ_H 7.24, δ_C 77.10 ppm). The melting points were measured on an Electrothermal 9100 instrument. The reaction progress was monitored and the purity of chemical compounds was checked by TLC (Silufol UV-254). The preparative column chromatography was carried out using silica gel Merck (40/60).

Synthesis of α-hydroxyphosphonates under the microwave assistance. *General procedure.* To 0.01 mol of O,O-dialkyl phosphite was added in succession 0.0001 mol of 1,5-diazabicyclo[4.3.0.]non-5-ene (DBN) and 0.01 mol of carbonyl compound **Ia–Ij**, **IIIa**, and **IIIb**. The reaction was performed at microwave irradiation (400 W, 180°C). The reaction mixture was distilled in a vacuum. In event of formation of solid compounds the α-hydroxyphosphonate was isolated by column chromatography (silica gel, eluent chloroform–methanol, 10:1).

Diethyl (1-hydroxypropyl)phosphonate (IIa). Reaction time 1 min. Yield 1.9 g (95%), bp 92–95°C (2 mm Hg). ^{31}P NMR spectrum ($CDCl_3$): δ 25.6 ppm [1].

Diethyl (1-hydroxy-2-methylpropyl)phosphonate (IIb). Reaction time 1.5 min. Yield 2.1 g (98%), bp 115–118°C (3 mm Hg). ^{31}P NMR spectrum ($CDCl_3$): δ 25.3 ppm [18].

Diethyl [hydroxy(phenyl)methyl]phosphonate (IIc). Reaction time 3 min. Yield 2.1 g (86%), mp 82–84°C. ^{31}P NMR spectrum ($CDCl_3$): δ 21.7 ppm [1].

Diethyl [hydroxy(3-nitrophenyl)methyl]phosphonate (IId). Reaction time 3.5 min. Yield 2.4 g (85%), mp 93–95°C. ^{31}P NMR spectrum ($CDCl_3$): δ 20.1 ppm [19].

Diethyl [hydroxy(4-chlorophenyl)methyl]phosphonate (IIe). Reaction time 9 min. Yield 2.2 g (82%). Oily substance. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.24 t (3H, OCH_2CH_3, ^2J 7.1 Hz), 1.30 t (3H, OCH_2CH_3, ^2J 7.1 Hz), 4.14 m (4H, OCH_2CH_3), 5.01 d (1H, CHP, ^2J 13.4 Hz), 7.55 t (1H, CHCHCH, ^2J 7.7 Hz), 6.36 t [2H, CHCHC(CHOH), ^2J 7.7 Hz], 6.50 d (2H,

ClCCHCHCH, ^2J 7.7 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.24 s (OCH_2CH_3), 63.00 s, 63.43 s (OCH_2CH_3), 69.81 s (PCN, $^1J_{CP}$ 162.2 Hz), 128.15 s, 128.41 s, 128.49 s, 131.35 s, 133.59 s, 135.57 s (C_6H_5). ^{31}P NMR spectrum ($CDCl_3$): δ 21.2 ppm.

Diethyl [hydroxy(2-furyl)methyl]phosphonate (IIf). Reaction time 1.5 min. Yield 2.4 g (95%), bp 182–185°C (3 mm Hg). ^{31}P NMR spectrum ($CDCl_3$): δ 19.6 ppm [20].

Diethyl [hydroxy(2-pyridyl)methyl]phosphonate (IIg). Reaction time 5 min. Yield 2.0 g (82%), mp 59–61°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.26 t (3H, OCH_2CH_3, ^2J 6.6 Hz), 1.35 t (3H, OCH_2CH_3, ^2J 6.6 Hz), 4.23 d (2H, OCH_2CH_3, ^2J 7.3 Hz), 4.29 d (2H, OCH_2CH_3, ^2J 7.3 Hz), 5.91 d (1H, CHP, ^2J 17.9 Hz), 7.86–8.95 m (4H, C_5H_4N). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.42 s (OCH_2CH_3), 64.37 s (OCH_2CH_3), 67.33 d (PCN, $^1J_{CP}$ 164.7 Hz), 125.47 s, 125.92 s, 141.55 s, 144.88 C, 154.02 s (C_5H_4N). ^{31}P NMR spectrum ($CDCl_3$): δ 15.7 ppm.

Diethyl (1-hydroxycyclohexyl)phosphonate (IIh). Reaction time 4 min. Yield 1.9 g (84%), mp 74–76°C. ^{31}P NMR spectrum ($CDCl_3$): δ 26.8 ppm [1].

Diethyl (1-hydroxycyclopentyl)phosphonate (IIi). Reaction time 15 min. Yield 0.7 g (40%), mp 71–73°C. ^{31}P NMR spectrum ($CDCl_3$): δ 27.2 ppm [1].

Diethyl (1-hydroxy-1-methylpropyl)phosphonate (IIj). Reaction time 21 min. Yield 0.8 g (38%). Oily substance. ^{31}P NMR spectrum ($CDCl_3$): δ 27.8 ppm [21].

Di(–)-menthyl (1-hydroxy-2-methylpropyl)phosphonate (IVa). Reaction time 10 min. Yield 4.0 g (94%). Oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.81–0.83 m (6H, CH_3CCH_3 for two diastereomers), 0.90–0.94 m [12H, $CH(CH_3)_2$ for two diastereomers], 1.05–1.09 m [4H, $CHCH_2CHC(CH_3)_2$], 1.30–1.33 m (6H, CH_3CCH_3 for two diastereomers), 1.65–1.68 m [4H, $CHCH_2CHC(CH_3)_2$], 2.00–2.04 m (8H, $CHCH_2CH$, for two diastereomers), 2.14–2.17 m (4H, CH_2CHCH_2 for two diastereomers), 2.29–2.35 m [4H, $CHCHC(CH_3)_2$ for two diastereomers], 3.50–3.55 m [2H, $CH(CH_3)_2$ for two diastereomers], 4.23–4.26 m (8H, $POCH_2$ for two diastereomers), 5.02–5.06 m (2H, PCHN, for two diastereomers), 5.75–5.82 m [4H, $CCHCHC(CH_3)_2$ for two diastereomers]. ^{13}C NMR spectrum ($CDCl_3$) (for two diastereomers), δ, ppm: 15.58 s, 15.82 s, 17.83 s, 18.03 s [$CH(CH_3)_2$], 20.18 s, 20.28 s, 25.27 s, 25.50 s (CH_3CCH_3), 30.13 s, 30.23 s [$CH_2CHC(CH_3)_2$], 31.55 s, 31.61 s [$CH(CH_3)_2$], 34.05 s, 34.16 s ($CHCH_2CH$), 43.10 s, 42.22 s [$CHCH_2CHC(CH_3)_2$]; 43.72 s, 43.79 s [$CHCHC(CH_3)_2$], 73.62 d, 74.00 d (PCHN, $^1J_{CP}$ 156.7, $^1J_{CP}$ 155.4 Hz), 77.87 s, 78.00 s ($POCH_2$). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 23.69, 23.90 Found, %: C 68.97; H 14.52. $C_{24}H_{39}O_4P$. Calculated, %: C 68.22; H 15.15.

Di(–)-menthyl [hydroxy(phenyl)methyl]phosphonate (IVb). Reaction time 19 min. Yield 4.2 g (92%), mp 95–98°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.74–0.81 m (6H, CH_3CCH_3 for two diastereomers), 1.11–1.15 m [4H, $CHCH_2CHC(CH_3)_2$], 1.28–1.31 m (6H, CH_3CCH_3 for two diastereomers), 1.61–1.66 m [4H, $CHCH_2CHC(CH_3)_2$], 2.00–2.04 m (8H, $CHCH_2CH$, for two diastereomers), 2.24–2.27 m (4H, CH_2CHCH_2 for two diastereomers), 2.70–2.74 m [4H, $CHCHC(CH_3)_2$ for two diastereomers], 4.22– 4.25 m (8H, $POCH_2$ for two diastereomers), 4.94–4.97 m (2H, PCHN, for two diastereomers), 5.35–5.42 m [4H, $CCHCHC(CH_3)_2$ for two diastereomers], 7.36–7.61 m (10H, C_6H_5, for two diastereomers). ^{13}C NMR spectrum ($CDCl_3$) (for two diastereomers), δ, ppm: 21.93 s, 25.27 s (CH_3CCH_3), 31.47 s, 31.59 s [$CH_2CHC(CH_3)_2$], 33.98 s, 34.05 s ($CHCH_2CH$), 42.58 s, 42.82 s [$CHCH_2CHC(CH_3)_2$], 43.69 s, 43.92 s [$CHCHC(CH_3)_2$], 69.01 d, 71.67 d (PCHN, $^1J_{CP}$ 152.8, $^1J_{CP}$ 158.7 Hz), 78.26 s, 78.57 s ($POCH_2$), 127.31 s, 127.41 s [$CCHCHC(CH_3)_2$], 127.16 s, 127.89 s, 128.10 s (C_6H_5). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 19.88, 20.32. Found, %: C 70.87; H 8.23. $C_{27}H_{37}O_4P$. Calculated, %: C 71.03; H 8.17.

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