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Reaction of Secondary Phosphine Oxides with Aromatic Aldehydes

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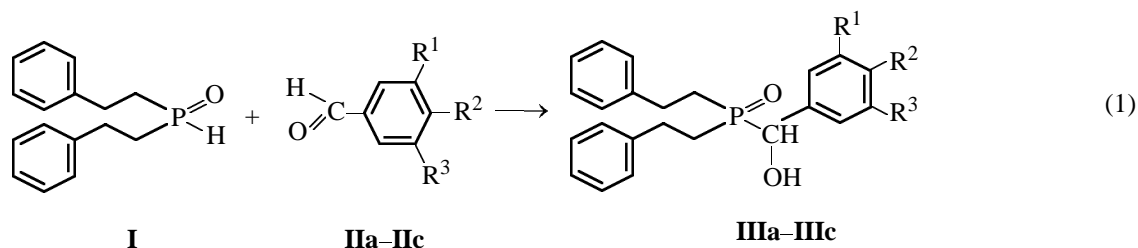
Abstract — Nucleophilic addition of secondary phosphine oxides to aromatic aldehydes proceeds under mild conditions (20–60°C, 10–40 h) and provides [bis(2-organylethyl)](arylhydroxymethyl)phosphine oxides in high yields.

Secondary and tertiary phosphine oxides are readily available by direct reactions of elemental phosphorus with electrophilic agents in the presence of strong bases [1–3]. In the course of systematic reactivity studies on these compounds we showed that diorganylphosphine oxides readily add to heteroaromatic aldehydes, namely, of the imidazole and benzamidazole series, to give in high yields new functionally substituted tertiary phosphine oxides. The latter are known as highly reactive building blocks and intermediate products for designing biologically active compounds and polydentate ligands for metal-complex catalysts, as well as as promising objects for basic research in the area of theoretical coordination chemistry [4–7].

Aiming at gaining further information on the regularities in reactions of secondary phosphine oxides with aldehydes and preparing polyfunctional tertiary phosphine oxides, in the present work we focused on the reactions of the available bis(2-phenylethyl)- and bis[2-(2-pyridyl)ethyl]phosphine oxides [2, 3, 8] with aromatic aldehydes, such as benzaldehyde (**IIa**), vanillin (**IIb**), and syringaldehyde (**IIc**).

The reaction of bis(2-phenylethyl)phosphine oxide (**I**) with aldehydes **IIa**–**IIc** proceeds under mild conditions (20–60°C, dioxane, 10–40 h) and, with equimolar reactant amounts, gives phosphine oxides **IIIa**–**IIIc** in yields of 62–82%.

$$\text{I} + \text{IIa–IIc} \longrightarrow \text{IIIa–IIIc} \tag{1}$$

$R^1 = R^2 = R^3 = H$ (**IIa, IIIa**); $R^1 = H$, $R^2 = OH$, $R^3 = OMe$ (**IIb, IIIb**); $R^1 = R^3 = OMe$, $R^2 =$ (**IIc, IIIc**).

The highest yield (82%) at the lowest temperature and reaction time (20°C, 10 h) was obtained with benzaldehyde.

Reactions (1) with aldehydes **IIb** and **IIc** require higher temperatures and/or more time to occur: 18 h (20–60°C) and 40 h (20°), respectively. Under these conditions, the yields of tertiary phosphine oxides

IIIb and **IIIc** are 62 and 64%, respectively. It should be noted that under the above conditions the starting bis(2-phenylethyl)phosphine oxide is concurrently oxidized to bis(2-phenylethyl)phosphinic acid [9].

Bis[2-(2-pyridyl)ethyl]phosphine oxide (**IV**) reacts with benzaldehyde slightly slower (20°C, 18 h, methanol) than phosphine oxide **I**, providing tertiary phosphine oxide **V** in 73% yield.

$$\text{IV} + \text{IIIa} \rightarrow \text{V} \quad (2)$$
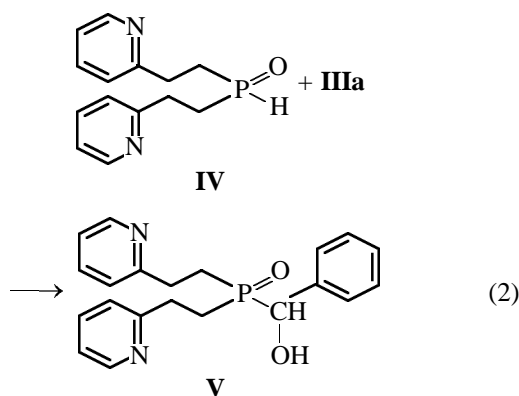
The most characteristic signals in the ^{1}H and ^{13}C NMR spectra of compounds **IIIa–IIIc** and **V** are those of the CH group in the fragment HOCHP=O:a doublet at 5.0–5.1 ppm with the geminal coupling constant ^{31}P–^{1}H of 7–9 Hz (^{1}H NMR) and a doublet near 72 ppm ($^1J_{PC}$ ~60 Hz) (^{13}C NMR). The observed non-equivalence of signals of the two phenyethyl groups in the ^{1}H and ^{13}C NMR spectra for phosphine oxides **IIIa–IIIc** is explained by the presence of a chiral carbon atom in the HOCHP=O fragment.

It can be inferred that reactions (1) and (2) proceed via intermediate **A** and involve nucleophilic attack of the three-coordinate phosphorus atom in the tautomeric forms of phosphine oxides **I** and **IV** on the carbonyl carbon atom of aldehydes **IIa–IIc** with electrophilic assistance from the P–OH proton of the phosphine oxide.

$$\longrightarrow \text{IIIa–IIIc} \quad (3)$$
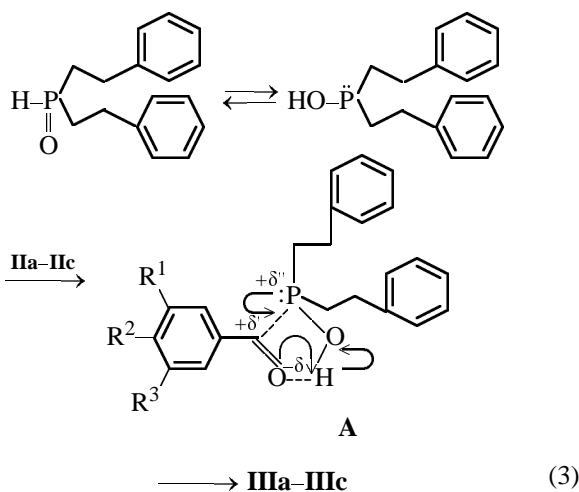
Stability of this intermediate state depends on the electron-acceptor power of the aryl substituent in the aldehyde and should be decreased in the case of aldehydes **IIb** and **IIc** which have electron-donor substituents in their nuclei. This suggestion is consistent with the observation of a higher reactivity of benzaldehyde in the reaction under study. The relatively low

rate of reaction (1) with aldehydes **IIb** and **IIc** can be also associated with steric effects in intermediate **A**: the stronger these effects, the less this intermediate state is favored by energy and, therefore, the harder it to form [10].

The lower reactivity of phosphine oxide **IV** with pyridine substituents as compared with phosphine oxide **I** in the reaction with benzaldehyde can be explained by the fact that the electrophilic assistance of the proton in the first case is suppressed by additional and competing hydrogen bonding (intra- or intermolecular) with the highly basic pyridine nitrogen atom.

Thus, the reaction of secondary phosphine oxides with aromatic aldehydes is a convenient and efficient synthetic route to new polyfunctional tertiary phosphine oxides.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-400 and DPX-250 spectrometers for CDCl$_3$ and CD$_3$OD solutions against internal HMDS. The ^{31}P NMR spectra were obtained on a Bruker DPX-400 spectrometer for the same solutions against external 85% H$_3$PO$_4$. The structure of phosphine oxides **IIIa–IIIc** and **V** was confirmed by means of ^{1}H and ^{31}P NMR spectroscopy, and with compounds **IIIa–IIIc**, ^{1}H–^{13}C HSQC [11] and HMBC [12] correlation techniques were applied.

[Bis(2-phenylethyl)](phenylhydroxymethyl)-phosphine oxide (IIIa). A mixture of 0.24 g of bis-(2-phenylethyl)phosphine oxide (**I**) and 0.11 g of aldehyde **IIa** in 2 ml of dioxane was stirred at room temperature (24–25°C) for 10 h. Precipitate formation was observed. The solvent was distilled off in a vacuum, and the residue was washed with ether and dried in a vacuum (1–2 mm) to obtain 0.31 g (82%) of phosphine oxide **IIIa**, mp 142–144°C (hexane). ^{1}H NMR spectrum (CD$_3$OD), δ, ppm: 7.55 m (2H, H$_r$, PhCHOH), 7.43 m (2H, H$_m$, PhCHOH), 7.38 m (1H, H$_p$, PhCHOH), 7.27 m (4H, H$_m$, PhCH$_2$), 7.25 (2H, H$_r$, PhCH$_2$), 7.20 m (2H, H$_p$, PhCH$_2$), 7.11 m (2H, H$_r$, PhCH$_2$), 5.11 d (1H, CH, $^2J_{PH}$ 8.8 Hz), 4.80 br.s (1H, HH), 2.95 m (2H, CH$_2$Ph), 2.74 m (1H, CH$_2$Ph), 2.53 m (1H, CH$_2$Ph), 2.19 m (2H, CH$_2$P), 1.96 m (2H, CH$_2$P). ^{13}C NMR spectrum (CD$_3$OD), δ$_C$, ppm: 142.68 d (2C, C$_i$, PhCH$_2$, $^3J_{PC}$ 12.7 Hz), 138.71 s (1C, C$_i$, PhCHOH), 129.66 s (2C, C$_m$, PhCH$_2$), 129.61 s (2C, C$_m$, PhCH$_2$), 129.42 s (2C, C$_m$, PhCHOH), 129.25 s (2C, C$_o$, PhCH$_2$), 129.08 s (1C, C$_p$, PhCHOH), 129.08 s (2C, C$_o$, PhCH$_2$), 127.82 s (2C, C$_o$, PhCHOH), 127.43 s (1C, C$_p$, PhCH$_2$), 127.35 s (1C, C$_p$, PhCH$_2$), 72.22 d (1C, CH, $^1J_{PC}$

81.3 Hz), 28.64 d (1C, CH_2P, $^1J_{PC}$ 60.6 Hz), 28.24 s (1C, CH_2Ph), 28.26 s (1C, CH_2Ph), 26.88 d (1C, CH_2P, $^1J_{PC}$ 60.6 Hz). ^{31}P NMR spectrum ($CDCl_3$): δ_P 47.9 ppm. Found, %: C 75.72; H 6.80; P 8.63. $C_{23}H_{25}O_2P$. Calculated, %: C 75.80; H 6.91; P 8.50.

Bis(2-phenylethyl)[hydroxy(4-hydroxy-3-methoxyphenyl)methyl]phosphine oxide (IIIb). A mixture of 0.5 g of phosphine oxide **I** and 0.27 g of 4-hydroxy-3-methoxybenzaldehyde (**IIb**) in 3 ml of dioxane was stirred for 16 h at room temperature, and then for 2 h at 60°C; the solvent was removed in a vacuum, and the residue was washed with ether and dried in a vacuum (1–2 mm) to obtain 0.77 g of a viscous liquid. Its ^{31}P NMR spectrum showed the presence, in addition to the target phosphine oxide **IIIb** (δ_P 49.8 ppm), of bis(2-phenylethyl)phosphine oxide (δ_P 31 ppm) and its oxidation product, bis(2-phenylethyl)phosphonic acid (δ_P 54.3 ppm, identified with a reference sample) in a ratio of 62:13:25. Phosphine oxide **IIIb** was washed out from the starting and by-products with several portions of ether (5 × 0.5 ml) and dried in a vacuum to obtain 0.46 g (62%) of phosphine oxide **IIIb**, mp 148–150°C (hexane). ^1H NMR spectrum (CD_3OD), δ, ppm: 7.25 m (4H, H_m, Ph), 7.22 m (2H, H_o, Ph), 7.12 m (2H, H_p, Ph), 7.11 m (2H, H_o, Ph), 7.11 s (1H, H^2), 6.95 d (1H, H^6, $^3J_{H^5H^6}$ 8.1 Hz), 6.84 d (1H, H^5), 5.01 d (1H, CH, $^2J_{PH}$ 7.1 Hz), 4.83 br.s (2H, OH), 3.84 s (3H, OMe), 2.84 m (3H, CH_2Ph), 2.58 m (1H, CH_2Ph), 2.12 m (2H, CH_2P), 1.98 m (2H, CH_2P). ^{13}C NMR spectrum (CD_3OD), δ_C, ppm: 149.05 s (1C, C^3), 147.72 s (1C, C^4), 142.64 d (2C, C_i, $^3J_{PC}$ 13.0 Hz), 129.69 s (1C, C^1), 129.65 s (4C, C_m), 129.22 s (2C, C_o), 129.09 s (2C, C_o), 127.41 s (1C, C_p), 127.35 s (1C, C_p), 120.69 d (1C, C^6, $^3J_{PC}$ 4.6 Hz), 116.11 s (1C, C^5), 111, 56 d (1C, C^2, $^3J_{PC}$ 3.5 Hz), 72.23 d (1C, CH, $^1J_{PC}$ 82.8 Hz), 56.37 s (1C, OMe), 27.27 d (1C, CH_2P, $^1J_{PC}$ 60.2 Hz), 28.33 s (1C, CH_2Ph), 28.24 s (1C, CH_2Ph), 25.81 d (1C, CH_2P, $^1J_{PC}$ 60.2 Hz). ^{31}P NMR spectrum ($CDCl_3$): δ_P 49.8 ppm. Found, %: C 70.20; H 6.60; P 7.25. $C_{24}H_{27}O_4P$. Calculated, %: C 70.23; H 6.63; P 7.55.

Bis(2-phenylethyl)[hydroxy(4-hydroxy-3,5-dimethoxyphenyl)methyl]phosphine oxide (IIIc). A mixture of 0.31 g of bis(2-phenylethyl)phosphine oxide (**I**) and 0.22 g of 4-hydroxy-3,5-dimethoxybenzaldehyde (**IIc**) in 3 ml of dioxane was stirred at room temperature for 40 h. A precipitate formed. The solvent was distilled off in a vacuum, the residue was washed with ether (5 × 0.5 ml), and dried in a vacuum to obtain 0.34 g (64%) of phosphine oxide **IIIc**, mp 186–188°C (hexane). The ether extract was evaporated in a vacuum. The ^{31}P NMR spectrum of the residue (0.19 g) contained signals of unreacted bis(2-

phenylethyl)phosphine oxide (δ_P 31 ppm) and bis-(2-phenylethyl)phosphinic acid (δ_H 54.3 ppm, identified with a reference sample) in a 65:35 ratio. ^1H NMR spectrum (CD_3OD), δ, ppm: 7.28 m (4H, H_m, Ph), 7.23 m (2H, H_o, Ph), 7.14 m (2H, H_p, Ph), 7.11 m (2H, H_o, Ph), 6.80 s [2H, H^2 (H^6)], 5.03 d (1H, CH, $^2J_{PH}$ 7.3 Hz), 4.80 br.s (1H, OH), 4.61 br.s (1H, OH), 3.84 s (6H, OMe), 2.83 m (3H, CH_2Ph), 2.55 m (1H, CH_2Ph), 2.15 m (2H, CH_2P), 2.00 m (2H, CH_2P). ^{13}C NMR spectrum (CD_3OD), δ_C, ppm: 149.35 s (1C, C^3), 142.66 d (2C, C_i, $^3J_{PC}$ 13.0 Hz), 136.59 s (1C, C^4), 129.62 s (4C, C_m), 129.23 s (2C, C_o), 129.07 s (2C, C_o), 128.96 s (1C, C^1), 127.42 s (2C, C_p), 105.17 d [2C, $C^2(C^6)$, $^3J_{PC}$ 4.5 Hz)], 72.33 d (1C, CH, $^1J_{PC}$ 84.7 Hz), 56.57 s (2C, OMe), 28.50 d (1C, CH_2P, $^1J_{PC}$ 60.2 Hz), 28.29 s (1C, CH_2Ph), 28.24 s (1C, CH_2Ph), 26.97 d (1C, CH_2P, $^1J_{PC}$ 60.2 Hz). ^{31}P NMR spectrum ($CDCl_3$): δ_P 47.3 ppm. Found, %: C 68.13; H 6.74; P 6.99. $C_{25}H_{29}O_5P$. Calculated, %: C 68.17; H 6.64; P 7.03.

Bis[2-(2-pyridyl)ethyl][hydroxy(phenyl)methyl]-phosphine oxide (V). A mixture of 0.18 g of phosphine oxide **IV** and 0.07 g of benzaldehyde (**IIa**) in 2 ml of methanol was stirred at room temperature for 30 h. The solvent was distilled off, the residue was washed with ether (5 × 0.5 ml), and dried in a vacuum to obtain 0.18 g (73%) of phosphine oxide **V** as a yellow oily substance. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.07–2.35 m (4H, HCH_2), 2.55 m, 2.75 m, 2.95 m, 3.25 m (4H, $PyCH_2$), 5.20 d (1H, CH, $^2J_{PH}$ 6.8 Hz), 7.00–7.70 m (11H, pyridine H^3, H^4, and H^5; Ph), 8.05 d (2H, pyridine H^2, $^3J_{H^2H^3}$ 7.2 Hz), 10.00 br.s (1H, OH). ^{31}P NMR spectrum ($CDCl_3$): δ_P 57.4 ppm. Found, %: C 68.37; H 6.29; N 7.69; P 8.23. $C_{21}H_{23}N_2O_2P$. Calculated, %: C 68.84; H 6.33; N 7.65; P 8.45.

REFERENCES

1. Trofimov B.A., Gusarova N.K., and Brandsma L., *Main Group Chem. News,* 1996, vol. 4, no. 1, p. 18.

2. Gusarova, N.K., Malysheva, S.F., Arbuzova, S.N., and Trofimov, B.A., *Izv. Ross. Akad. Nauk, Ser. Khim.,* 1998, no. 9, p. 1695.

3. Trofimov, B.A., Gusarova, N.K., and Arbuzova, S.N., *Usp. Khim.,* 1999, vol. 68, no. 3, p. 240.

4. Ivanova, N.I., Reutskaya, A.M., Arbuzova, S.N., Baikalova, L.V., Afonin, A.V., Gusarova, N.K., and Trofimov, B.A., *Khim. Geterotsikl. Soedin.,* 2000, no. 2, p. 262.

5. Gusarova, N.K., Arbuzova, S.N., Reutskaya, A.M., Ivanova, N.I., Baikalova, L.V., Sinegovskaya, L.M., Ghipanina, N.N., Afonin, A.V., and Zyryanova, I.A., *Khim. Geterotsikl. Soedin.,* 2002, no. 1, p. 71.

6. Reutskaya, A.M., Ivanova, N.I., Baikalova, L.V., Zyryanova, I.A., Arbuzova, S.N., Gusarov, A.V., and Trofimov, B.A., Abstracts of Papers, *I Int. Conf. on Chemistry and Biological Activity of Nitrogen-containing Heterocyles and Alkaloids,* Moscow, 2001, vol. 2, p. 250.

7. Reutskaya, A.M., Zyryanova, I.A., Gusarova, N.K., and Trofimov, B.A., Abstracts of Papers, *Youth Workshop–Conf. on Topical Problems of Organic Chemistry,* Ekaterinburg, 2001, p. 221.

8. Trofimov, B.A., Shaikhudinova, S.I., Dmitriev, V.I., Nepomnyashchii, K.V., Kazantseva, T.I., and Gusarova, N.K., *Zh. Org. Khim.,* 2000, vol. 70, no. 1, p. 43.

9. Malysheva, S.F., Ivanova, N.I., Belogorlova, N.A., Khil'ko, M.Ya., Larina, L.I., Gusarova, N.K., and Trofimov, B.A., *Khim. Geterotsikl. Soedin.,* 1998, no. 9, p. 1195.

10. Sykes, P., *A Guidebook to Mechanisms in Organic Chemistry,* New York: Longmans, 1972. Translated under the title *Mekhanizmy reaktsii v organicheskoi khimii,* Moscow: Khimiya, 1973, p. 319.

11. Bodenhausen, G. and Ruben, D., *J. Chem. Phys. Lett.,* 1980, vol. 69, no. 2, p. 185.

12. Bax, A. and Summers, M.F., *J. Am. Chem. Soc.,* 1986, vol. 108, no. 5, p. 2093.