

# Reaction of (2-methoxyprop-2-yl)diphenylphosphine oxide with alkyl bromides

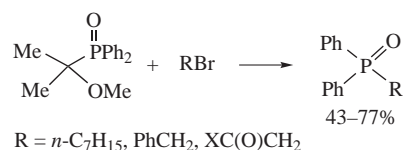
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**Treatment of (2-methoxyprop-2-yl)diphenylphosphine oxide with alkyl bromides affords alkyl(diphenyl)phosphine oxides in good yields.**



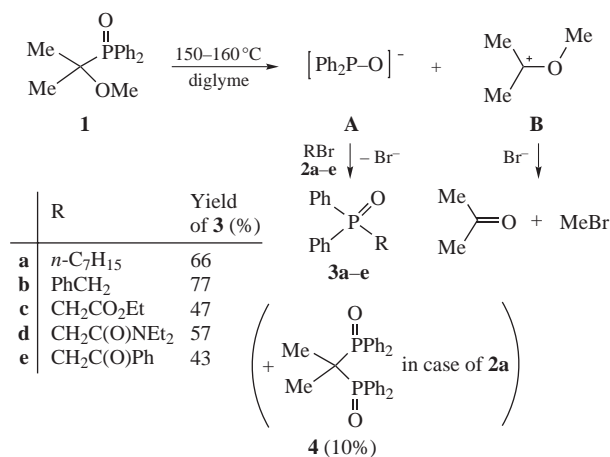
The Michaelis–Arbuzov and Michaelis–Becker reactions are widely used in the synthesis of organophosphorus compounds.<sup>1</sup> However, the Michaelis–Arbuzov reaction requires the use of trivalent phosphorus derivatives sensitive to hydrolysis and oxidation,<sup>1(a),(b)</sup> whereas the Michaelis–Becker reaction comprises application of strong bases.<sup>1(c)</sup> Therefore, the search for alternative methods to form P–C bond remains urgent. We found previously<sup>2</sup> that trimethylsilyl diphenylphosphinite, a potentially valuable precursor for the Michaelis–Arbuzov reaction, can be prepared quickly and in high yield by silylation of stable (2-hydroxyprop-2-yl)diphenylphosphine oxide in 1,4-dioxane at 100 °C. The use of (2-hydroxyprop-2-yl)diphenylphosphine oxide in the syntheses provided higher yields of the products compared with similar syntheses based on ethyl diphenylphosphinite.<sup>3</sup>

Therefore, it was of interest to test methyl ether of the above-mentioned (2-hydroxyprop-2-yl)diphenylphosphine oxide, namely, (2-methoxyprop-2-yl)diphenylphosphine oxide **1**.<sup>4</sup> We found that compound **1** did not react with silylating agents such as hexamethyldisilazane, *N,N*-diethyl-*N*-(trimethylsilyl)amine, and bis(trimethylsilyl)acetamide at 100–130 °C. However, phosphine oxide **1** reacted at 150–160 °C in diglyme with *n*-heptyl bromide **2a** and benzyl bromide **2b** to furnish heptyl(diphenyl)phosphine oxide **3a** and benzyl(diphenyl)phosphine oxide **3b**, respectively (Scheme 1).<sup>†</sup> In case of *n*-heptyl bromide **2a**, 2,2-bis(diphenylphosphoryl)propane **4** isolated in 10% yield was also formed as a by-product.

The observed reactivity of compound **1** can be explained by its propensity to thermal cleavage of the phosphorus–carbon bond to give diphenylphosphinite anion **A** [similarly to diphenyl-

(dialkoxymethyl)phosphine oxides upon their lithiation<sup>5</sup>] along with 2-methoxyprop-2-enium cation **B** (see Scheme 1). Phosphinite anion **A** reacts further with alkyl halides **2** to form phosphine oxides **3**. In case of less reactive *n*-heptyl bromide **2a**, replacement of methoxy group in compound **1** also occurs to afford bis-phosphine dioxide **4**.

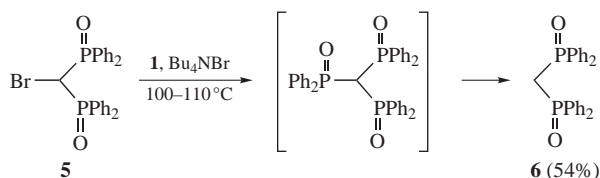
To increase the reactivity of anion **A** by the separation the ion pair **A** and **B**, tetrabutylammonium bromide (10 mol%) was added



Scheme 1

(2-Methoxyprop-2-yl)diphenylphosphine oxide **1**. 2,2-Dimethoxypropane (5.18 g, 49.81 mmol, 10% excess) was added to diphenylphosphinous chloride (5 g, 45.35 mmol) in heptane (20 ml) with stirring. After 2–3 min, an exothermic reaction began with gas evolution. With the external cooling, the temperature of the reaction medium was maintained at 25–30 °C. After another 10–15 min, product **1** began to precipitate, and after 1 h gas evolution almost ceased. The reaction mixture was left at 20 °C for 18 h. The precipitate **1** was filtered off and washed with heptane (2×5 ml). Drying in air and then in a desiccator at 14 Torr afforded 5.84 g (94%) of compound **1** as colourless needles, mp 151–152 °C (lit.,<sup>4(b)</sup> mp 151–153 °C). <sup>31</sup>P NMR, δ: 32.14 (s). <sup>1</sup>H NMR, δ: 7.97–7.92 (m, 4H, *o*-H, 2Ph), 7.37–7.28 (m, 6H, *m,p*-H, 2Ph), 3.13 (s, 3H, OMe), 1.30 (d, 6H, 2Me, <sup>3</sup>J<sub>PH</sub> 14.1 Hz). Found (%): C, 69.94; H, 7.20; P, 11.26. Calc. for C<sub>16</sub>H<sub>19</sub>O<sub>2</sub>P (%): C, 70.06; H, 6.98; P, 11.29.

<sup>†</sup> <sup>1</sup>H and <sup>31</sup>P NMR (δ/ppm) spectra were recorded in CDCl<sub>3</sub> on a Bruker Avance 400 spectrometer operating at 400.13 and 161.98 MHz, respectively. Chloroform-*d* was distilled over P<sub>2</sub>O<sub>5</sub> and stored over K<sub>2</sub>CO<sub>3</sub> at 0 °C in the dark. All syntheses were performed in inert atmosphere. Alkyl bromides **2a–d** were used after distillation; phenacyl bromide **2e** was recrystallized from heptane; bis(diphenylphosphoryl)bromomethane **5** was used as received. Column chromatography was carried out on silica gel 0.060–0.200 mm, 60 Å (Acros Organics). The mass spectra were measured on a Finnigan Polaris Q spectrometer with an ion trap (EI, 70 eV). We failed to obtain molecular ion for 2,2-bis(diphenylphosphoryl)propane **4**, therefore we performed elemental C, H, P analysis for this compound.



Scheme 2

to the reaction system (*cf.* ref. 6). The use of  $\text{Bu}_4\text{NBr}$  additive allowed us to decrease reaction temperature to 100–110 °C and to involve  $\alpha$ -functionalized alkyl bromides **2c–e** into the reaction (see Scheme 1). In this manner, functional derivatives **3c–e** were accessed.<sup>‡</sup> On moving to bis(diphenylphosphoryl)bromomethane

**Compounds 3a and 4 (general procedure).** *n*-Heptyl bromide **2a** (0.78 g, 4.36 mmol, 20% excess) was added to compound **1** (1 g, 3.65 mmol) in diglyme (4 ml). The mixture was heated at 150–160 °C for 2 h, with evolved acetone being distilled off. The mixture was cooled to 20 °C, diluted with  $\text{CH}_2\text{Cl}_2$  (10 ml), washed with water (2 × 10 ml), and dried with  $\text{MgSO}_4$ . The drying agent was separated by filtration, washed with  $\text{CH}_2\text{Cl}_2$  (2 × 5 ml), and the filtrate was concentrated. Column chromatography on silica gel in chloroform–acetone eluent (10:1 and next 5:1) gave products **3a** and **4** in yields of 0.72 g (66%) and 0.15 g (10%), respectively.

**Heptyl(diphenylphosphine) oxide 3a**, mp 61–62 °C, (*lit.*,<sup>7(a)</sup> 61–62 °C). <sup>31</sup>P NMR,  $\delta$ : 32.57 (s). <sup>1</sup>H NMR,  $\delta$ : 7.82–7.67 (m, 4H, *o*-H<sub>Ph</sub>), 7.49–7.40 (m, 6H, *m,p*-H<sub>Ph</sub>), 2.25–2.12 (m, 2H, P-C<sup>1</sup>H<sub>2</sub>), 1.63–1.53 (m, 2H, C<sup>2</sup>H<sub>2</sub>), 1.38–1.31 (m, 2H, C<sup>3</sup>H<sub>2</sub>), 1.24–1.15 (m, 6H, C<sup>4</sup>H<sub>2</sub> + C<sup>5</sup>H<sub>2</sub> + C<sup>6</sup>H<sub>2</sub>), 0.81 (t, 3H, Me, <sup>3</sup>J<sub>H,H</sub> 7.0 Hz) [*cf.* ref. 7(b)]. MS, *m/z*: 300 [M]<sup>+</sup>.

**2,2-Bis(diphenylphosphoryl)propane 4, semihydrate**, mp 265–267 °C, (*lit.*,<sup>8</sup> mp 270–271 °C for anhydrous form). <sup>31</sup>P NMR,  $\delta$ : 29.97 (s). <sup>1</sup>H NMR,  $\delta$ : 7.73–7.77 (m, 8H, *o*-H<sub>Ph</sub>), 7.52–7.42 (m, 12H, *m,p*-H<sub>Ph</sub>), 2.14 (s, 1H, 0.5H<sub>2</sub>O), 2.00 (d, 6H, 2Me, <sup>3</sup>J<sub>P,H</sub> 13.0 Hz). Found (%): C, 71.60; H, 6.32; P, 13.35. Calc. for  $\text{C}_{27}\text{H}_{26}\text{P}_2\text{O}_2 \cdot 0.5\text{H}_2\text{O}$  (%): C, 71.51; H, 6.00; P, 13.66.

**Benzyl(diphenylphosphine) oxide 3b** was obtained similarly, the eluent was chloroform–acetone, 10:1. Yield 77%, mp 191–193 °C (*lit.*,<sup>9(b)</sup> mp 192–193 °C). <sup>31</sup>P NMR,  $\delta$ : 29.31 (s) (*cf.* ref. 9). <sup>1</sup>H NMR,  $\delta$ : 7.69–7.65 (m, 4H, *o*-H, 2PhP), 7.51–7.47 (m, 2H, *p*-H, 2PhP), 7.44–7.39 (m, 4H, *m*-H, PhP), 7.18–7.15 (m, 3H, *m,p*-H, CH<sub>2</sub>Ph), 7.10–7.07 (m, 2H, *o*-H, CH<sub>2</sub>Ph), 3.64 (t, 2H, CH<sub>2</sub>Ph, <sup>2</sup>J<sub>P,H</sub> 13.8 Hz) (*cf.* ref. 9). MS, *m/z*: 292 [M]<sup>+</sup>.

<sup>‡</sup> Compounds **3c–e** were synthesized according to the general procedure at 100–110 °C in the presence of  $\text{Bu}_4\text{NBr}$  (0.1 g) from reactants **1** and **2c–e**. Chromatography was carried out using chloroform–acetone (5:1) mixture as an eluent.

**Ethyl 2-(diphenylphosphoryl)acetate 3c**. Yield 47%, mp 73–76 °C, (*lit.*,<sup>2</sup> mp 75–77 °C). <sup>31</sup>P NMR,  $\delta$ : 24.64 (s). <sup>1</sup>H NMR,  $\delta$ : 7.77–7.52 (m, 4H, *o*-H<sub>Ph</sub>), 7.50–7.42 (m, 6H, *m,p*-H<sub>Ph</sub>), 3.94 (q, 4H, OCH<sub>2</sub>Me, <sup>3</sup>J<sub>H,H</sub> 5.3 Hz), 3.44 (d, 2H, PCH<sub>2</sub>, <sup>2</sup>J<sub>P,H</sub> 11.3 Hz), 0.97 (t, 3H, OCH<sub>2</sub>Me, <sup>3</sup>J<sub>H,H</sub> 5.3 Hz) (*cf.* refs. 2, 10). MS, *m/z*: 288 [M]<sup>+</sup>.

***N,N*-Diethyl-2-(diphenylphosphoryl)acetamide 3d**. Yield 57%, mp 172–175 °C (*lit.*,<sup>11</sup> mp 173–175 °C). <sup>31</sup>P NMR,  $\delta$ : 28.30 (s). <sup>1</sup>H NMR,  $\delta$ : 7.88–7.83 (m, 4H, *o*-H, 2Ph), 7.52–7.43 (m, 6H, *m,p*-H, 2Ph), 3.54 (d, 2H, PCH<sub>2</sub>, <sup>2</sup>J<sub>P,H</sub> 15.7 Hz), 3.39 (q, 2H, NCH<sub>2</sub>, <sup>3</sup>J<sub>H,H</sub> 7.1 Hz), 3.23 (q, 2H, NCH<sub>2</sub>, <sup>3</sup>J<sub>H,H</sub> 7.1 Hz), 1.11 (t, 3H, Me, <sup>3</sup>J<sub>H,H</sub> 7.1 Hz), 0.89 (t, 3H, Me, <sup>3</sup>J<sub>H,H</sub> 7.1 Hz) (*cf.* ref. 11). MS, *m/z*: 305 [M]<sup>+</sup>.

**2-Diphenylphosphoryl-1-phenylethan-1-one 3e**. Yield 43%, mp 137–140 °C (*lit.*,<sup>12(a)</sup> mp 138–140 °C). <sup>31</sup>P NMR,  $\delta$ : 27.05 (s). <sup>1</sup>H NMR,  $\delta$ : 7.98–7.96 [m, 2H, *o*-H, PhC(O)], 7.82–7.77 (m, 4H, *o*-H, 2PhP), 7.52–7.49 [m, 3H, *m,p*-H, PhC(O)], 7.47–7.40 (m, 6H, *m,p*-H, 2PhP), 4.13 (d, 2H, CH<sub>2</sub>, <sup>2</sup>J<sub>P,H</sub> 15.4 Hz) [*cf.* ref. 12(b)]. MS, *m/z*: 320 [M]<sup>+</sup>.

**Methylenebis(diphenylphosphine) dioxide 6** was obtained similarly to compounds **3c–e** from compound **1** and bis(diphenylphosphoryl)bromomethane **5**. Yield 54%, mp 180–182 °C (*lit.*,<sup>2</sup> mp 180–182 °C). <sup>31</sup>P NMR,  $\delta$ : 24.69 (s). <sup>1</sup>H NMR,  $\delta$ : 7.77–7.72 (m, 8H, *o*-H, 2Ph), 7.46–7.42 (m, 4H, *p*-H, 2Ph), 7.38–7.34 (m, 8H, *m*-H, 2Ph), 3.54 (t, 2H, CH<sub>2</sub>, <sup>2</sup>J<sub>P,H</sub> 14.8 Hz) (*cf.* refs. 2, 13). MS, *m/z*: 416 [M]<sup>+</sup>.

**5**, we obtained methylenebis(diphenylphosphine) dioxide **6**, a product of degradation of thermally unstable expected tris(diphenylphosphoryl)methane (Scheme 2).<sup>‡</sup> Attempted reactions of alkyl bromides **2c–e** and **5** at 150–160 °C in the absence of  $\text{Bu}_4\text{NBr}$  led to complex mixtures.

In summary, we have proposed a new alternative to the Arbuzov–Michaelis reaction, which enables the one-stage synthesis of alkyl(diphenyl)phosphine oxides from available and stable (2-methoxyprop-2-yl)diphenylphosphine oxide **1**. The results herein obtained allow one to consider compound **1** as a hidden form of diphenylphosphinite anion **A**. The starting compound **1** can be easily synthesized in an analytically pure form by a modified method<sup>4(b)</sup> in 94% yield by the interaction of commercially available 2,2-dimethoxypropane with diphenylphosphinous chloride  $\text{Ph}_2\text{P}(\text{Cl})$ .

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