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Transformations of Bis(2-chloroethyl) Arylphosphonites in the Presence of Haloacetic Acid Esters

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Abstract—The reaction of aryl(dichloro)phosphines with (2-chloroethoxy)trimethylsilane in the presence of haloacetic acid esters was studied with the goal of developing a new method for the synthesis of ethyl [(2-chloroethoxy)(4-dimethylaminophenyl)phosphoryl]acetate. The effect of various factors, such as substituent in the *para* position of the aromatic ring in the initial aryl(dichloro)phosphine, halogen nature in haloacetic acid ester, and chloro(trimethyl)silane, on the reaction course was analyzed.

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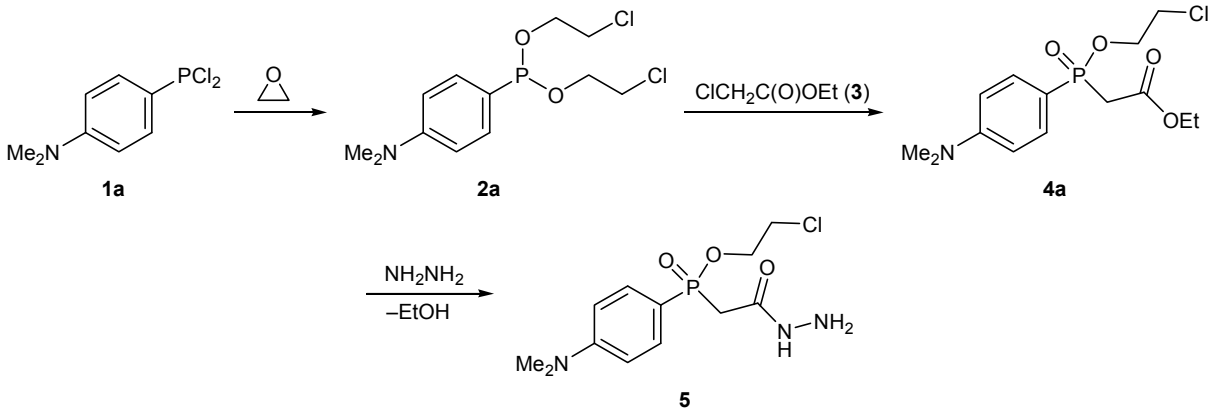
Modern medicine operates with a large number of various drugs for the prophylactics and treatment of neuropsychic disorders. On the other hand, there are increasing demands for medicinal agents improving mental activity, i.e., nootropics. In 1960s, Prof. A.I. Razumov (Kirov Kazan Institute of Chemical Technology) initiated systematic studies of phosphorylated carboxylic acid derivatives, which underlay the design of nootropic agents based thereon [1]. As a result, [(2-chloroethoxy)(4-dimethylaminophenyl)-phosphoryl]acetohydrazide (**5**, CAPAH), was synthesized. Compound **5** is a novel drug for the treatment of neuropsychic disorders; it improves memory and exhibits neuroprotective and antidepressant activity and is characterized by unusual mechanism of action in the treatment of neurodegenerative dementia (including Alzheimer's disease), chronic depression, cerebrovascular insufficiency with impairment of memory and attention; it also improves resistance in immunodeficiency states [2].

It was proposed to synthesize compound **5** according to Scheme 1 which involves the use in the first step of a very toxic, inflammable, and explosive ethylene oxide (oxirane). Therefore, development of a new method for the synthesis of **5** is an important problem. As follows from Scheme 1, they key intermediate product therein is bis(2-chloroethyl) [4-(dimethylamino)phenyl]phosphonite (**2a**) which is obtained by reaction of phosphine **1a** with oxirane. The present study was aimed at modifying the step of synthesis of phosphonite **2a**.

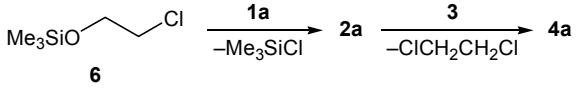
It is well known that phosphonous acid esters can be prepared from phosphonous dichlorides and silyl

Scheme 1.



ethers [3]. When phosphine **1a** reacted with 2-chloroethyl trimethylsilyl ether (**6**) in methylene chloride at –5 to 0°C, the ^{31}P NMR spectrum of the reaction mixture contained only one signal at δ_P 161 ppm corresponding to phosphonite **2a** (Scheme 2). This signal disappeared after keeping for 24 h at room temperature, and two new signals appeared at δ_P 23.3 and 26 ppm (intensity ratio 0.15:1). These findings indicated that phosphonite **2a** is stable at a relatively low temperature and that in undergoes various transformations as the temperature rises. In order to avoid decomposition of **2a**, the first and second steps were combined by reacting **1a** with **6** in the presence of ethyl chloroacetate (**3**). We anticipated that phosphonite **2a** once being formed will react with **3** to give **4a**.

Scheme 2.



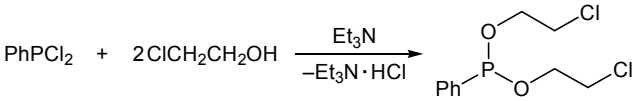
Insofar as phosphine **1a** is insoluble in ester **3**, it was dissolved in methylene chloride, the solution was cooled to 0°C, ether **6** and ester **3** were added in succession, and the mixture was allowed to warm up to room temperature. In the ^{31}P NMR spectrum of the reaction mixture we observed a signal at δ_P 36.8 ppm (**4a**), a very strong signal at δ_P 161.5 ppm (**2a**), and signals at δ_P 27.8 and 22.9 ppm due to by-products. After heating for 3 h at 80–100°C, the signal of **2a** disappeared, while the signal of target ester **4a** increased together with those of the by-products. The formation of by-products may be favored by the effect of the dimethylamino group on the reactivity of the phosphorus atom, which could give rise to inter- and intramolecular Arbuzov reactions; furthermore, the presence of silicon compounds may also affect the reaction course.

In order to elucidate the role of the *para*-substituent in the initial aryl(dichloro)phosphine, model reactions were carried out under analogous conditions with dichloro(phenyl)phosphine (**1b**) and dichloro(4-chlorophenyl)phosphine (**1c**). After heating at 80–100°C, the ^{31}P NMR spectra of the reaction mixtures showed a signal belonging to phosphonite **2b** or **2c** (δ_P 160 or 158.3 ppm), a signal of ester **4b** or **4c** (δ_P 35.2 or 34.5 ppm), and signals at δ_P 24.6 and 18.7 or 26.0 and 19.4 ppm, respectively. Thus, analysis of the ^{31}P NMR spectra of the reaction mixtures obtained in the reactions of phosphines **1a**–**1c** with silyl ether **6** and chloroacetate **3** indicated that the *para*-substituent in the initial arylphosphine does not affect further transformations of **2a**–**2c**.

It is known that Arbuzov reaction is catalyzed by Lewis acids [4, 5]; silicon compounds are also classed with Lewis acids. To exclude the effect of silicon compounds, volatile components were removed from the reaction mixtures by low-temperature evacuation before addition of ethyl chloroacetate (**3**). In fact, the yield of **4** was thus improved to 50%, which confirmed catalytic effect of silicon compounds.

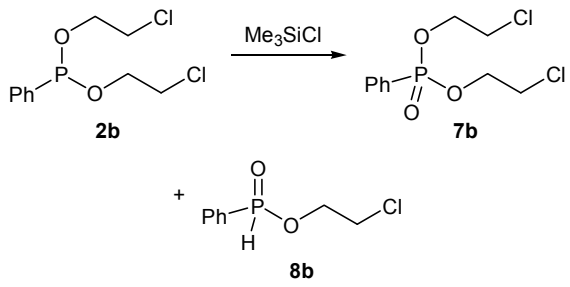
We also examined the stability of intermediate phosphonite **2b** in the absence of silicon compounds. For this purpose, compound **2b** was synthesized in a different way, by reaction of **1b** with 2-chloroethanol in the presence of triethylamine (Scheme 3).

Scheme 3.



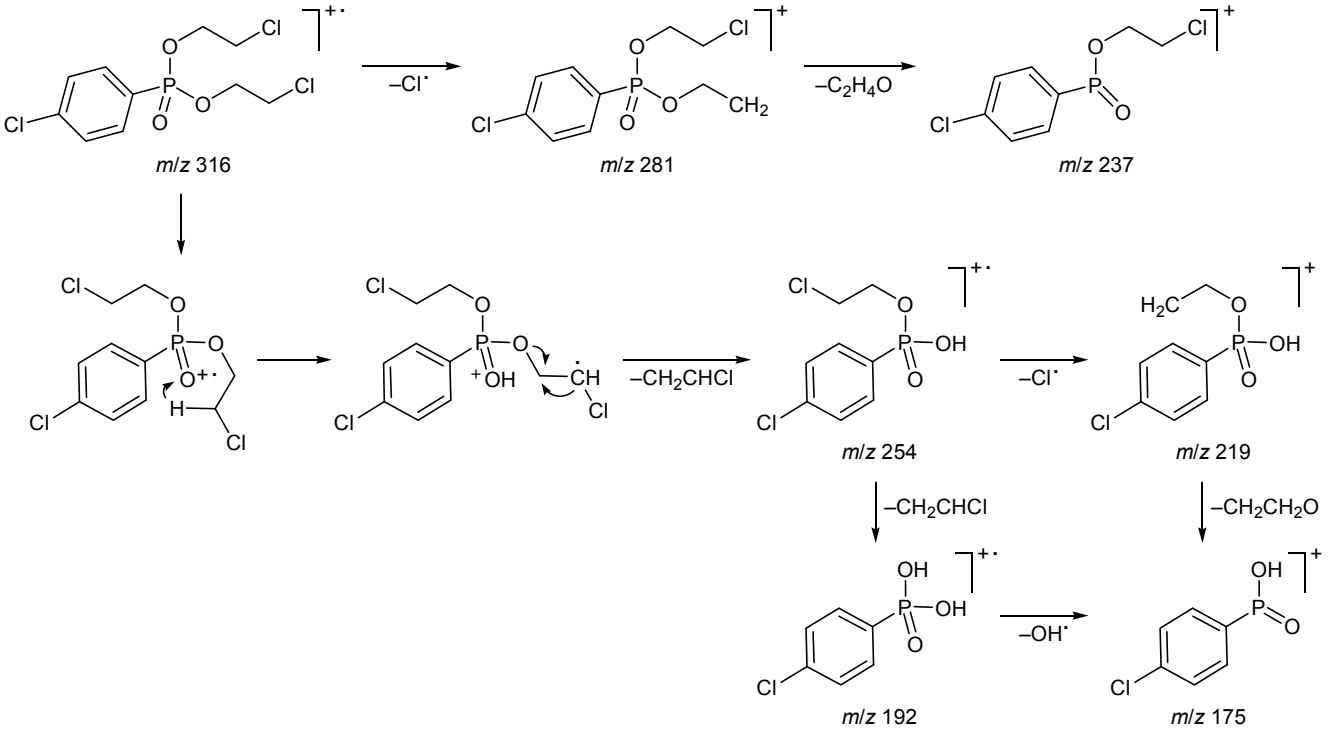
According to the ^{31}P NMR data, the reaction mixture contained target phosphonite **2b** and phosphorus compounds with δ_P 19.4 (11.7%) and 26.3 ppm (27%). The spectral pattern (i.e., the position of signals and their intensity) did not change at room temperature. However, after addition of chloro(trimethyl)silane to the reaction mixture kept at room temperature, the signal of **2b** disappeared while the intensities of the two other signals proportionally increased. By thin-film molecular distillation we isolated two pure compounds which were identified as bis(2-chloroethyl) phenylphosphonate (**7b**) and (2-chloroethyl) phenylphosphinate (**8b**) on the basis of their ^{1}H and ^{31}P NMR spectra and elemental compositions (Scheme 4). This result is fully consistent with published data [6, 7].

Scheme 4.



Additional information on the structure of compounds formed in the reactions of **1a**–**1c** with **6** and **3** was obtained by GC/MS analysis of the reaction mix-

Scheme 5.

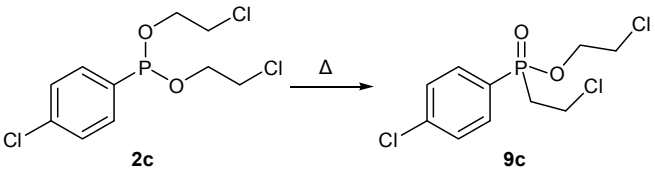


tures [8]. The reaction mixtures were found to contain three structurally related components.

The first (minor) component of the reaction mixture obtained from **1c** showed the molecular ion peak corresponding to bis(2-chloroethyl) (4-chlorophenyl)-phosphonate and $[M - Cl]^+$ ion peak with *m*/*z* 281. Cleavage of one P–O bond in the molecular ion gives $[M - C_2H_4OCl]^+$ ion with *m*/*z* 237. The ion with *m*/*z* 219 is likely to be formed as a result of McLafferty rearrangement followed by elimination of chlorine atom. Therefore, the presence of a ion peak with *m*/*z* 254 might be expected. However, its relative intensity was as low as 4%. Presumably, this ion undergoes subsequent rearrangement to ion with *m*/*z* 192 which loses hydroxy group to give a fragment ion with *m*/*z* 175. The fragmentation pattern of bis(2-chloroethyl) (4-chlorophenyl)phosphonate is shown in Scheme 5.

The second component was characterized by a low-abundance molecular ion corresponding to 2-chloroethyl (2-chloroethyl)(4-chlorophenyl)phosphinate (Scheme 6). Analogous isomerization of P(III) esters was reported in [9]. The peak with *m*/*z* 265 was assigned to $[M - Cl]^+$. Cleavage of the P–C bond in the molecular ion gives $[M - C_2H_4Cl]^+$ with *m*/*z* 237. The base peak in the mass spectrum of the second component was that with *m*/*z* 175 due to (4-chlorophenyl)-hydroxyoxophosphonium ion; in addition, $[M - C_8H_9Cl_2P]^+$ (*m*/*z* 63), $[M - C_4H_8Cl_2O_2P]^+$ (*m*/*z* 111), and other ion peaks were present. These findings suggest similarity of the fragmentation patterns of 2-chloroethyl (2-chloroethyl)(4-chlorophenyl)phosphinate and bis(2-chloroethyl) (4-chlorophenyl)phosphonate.

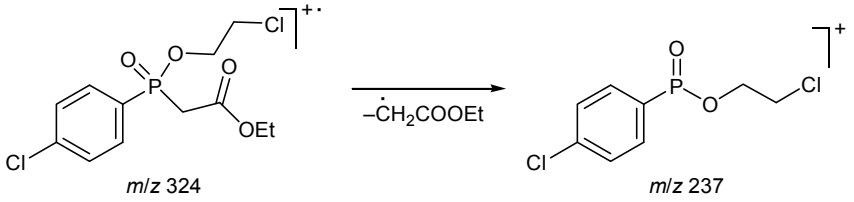
Scheme 6.



The third component was ethyl 2-[(2-chloroethoxy)-(4-chlorophenyl)phosphoryl]acetate which displayed in the mass spectrum $[M - Cl]^+$ ion peak with *m*/*z* 289. Unlike the first two components, its decomposition under electron impact involved elimination of the CH_2COOEt fragment with formation of ion with *m*/*z* 237 (Scheme 7).

The molecular ion peaks derived from compounds with Ar = 4-ClC_6H_4 had low intensity, compounds with Ar = Ph showed no molecular ion at all, while the molecular ions of those with Ar = 4-$Me_2NC_6H_4$ were the most abundant.

Scheme 7.

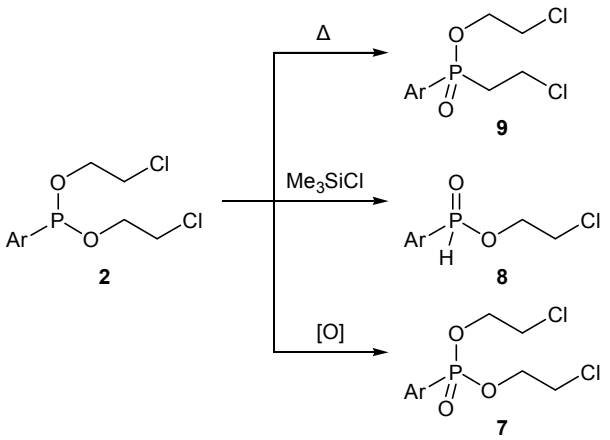


m/*z* 324 *m*/*z* 237

Obviously, the product ratio may be changed in favor of ester **4** by increasing the rate of the main reaction. It is known that the reactivity series of halogen derivatives looks like RI > RBr > RCl, other conditions being equal. [10]. Therefore, apart from ethyl chloroacetate (**3**), we tried methyl bromoacetate and ethyl iodoacetate; the latter was generated in situ from **3** and potassium iodide. In the reactions with methyl bromoacetate, the signal intensity ratio in the ^{31}P NMR spectra of the reaction mixtures was almost the same as in the reactions with **3**, and the target ester was formed as minor product. The reaction with ethyl iodoacetate gave an intractable mixture of numerous products, in agreement with published data [11].

Thus, the reaction of aryl(dichloro)phosphines with (2-chloroethoxy)trimethylsilane and haloacetic acid esters leads to a mixture of target ethyl [aryl(2-chloroethoxy)phosphoryl]acetate and bis(2-chloroethyl) arylphosphonate, (2-chloroethyl) arylphosphinate, and 2-chloroethyl aryl(2-chloroethyl)phosphinate as by-products (Scheme 8).

Scheme 8.



EXPERIMENTAL

The ^{1}H and ^{31}P NMR spectra were recorded on a Bruker MSL-400 spectrometer at 400 and 166 MHz, respectively, relative to tetramethylsilane (^{1}H) or 85% H_3PO_4 (^{31}P). Gas chromatographic–mass spectrometric analyses were obtained on a Thermo Electron DFS instrument (electron impact, 70 eV; ion source temperature 290°C; ID-BPX5 capillary column, 50 m×0.32 mm; carrier gas helium).

All solvents used were preliminarily dried and purified. Initial aryl(dichloro)phosphines **1a**–**1c** and silyl ether **6** were synthesized according to the procedures described in [12, 13]. Final products were not isolated, and their concentrations were determined by ^{31}P NMR.

Bis(2-chloroethyl) [4-(dimethylamino)phenyl]-phosphonite (2a). A solution of 1.5 g (6.75 mmol) of dichloro[4-(dimethylamino)phenyl]phosphine (**1a**) in 6 mL of methylene chloride was added at –5°C under argon to a solution of 2.21 g (14.5 mmol) of (2-chloroethoxy)trimethylsilane (**6**) in 3 mL of methylene chloride, and the mixture was stirred for 30 min at –5 to 0°C. ^{31}P NMR spectrum (CH_2Cl_2): δ_P 161 ppm.

Reaction of aryl(dichloro)phosphines 1a–1c with (2-chloroethoxy)trimethylsilane (6) in the presence of haloacetic acid esters (*general procedure***).** A solution of 7 mmol of phosphine **1a**–**1c** and 10 mmol of haloacetic acid ester in 8 mL of methylene chloride was cooled to –5°C, 15 mmol of silane **6** was added, and the mixture was stirred for 30 min at –5 to 0°C and then for 3 h at 80–100°C with simultaneous removal of volatile components by distillation.

Reaction of dichloro[4-(dimethylamino)phenyl]-phosphine (1a) with (2-chloroethoxy)trimethylsilane (6) in the presence of ethyl chloroacetate (3). The reaction mixture was stirred for 30 min at 20–22°C. ^{31}P NMR spectrum, δ_P, ppm: 161 (72%), 36.8 (5%), 27.8 (18%), 22.9 (5%). The mixture was then heated for 3 h at 80–100°C. ^{31}P NMR spectrum, δ_P, ppm: 36.6 (25%), 27.3 (61%), 22.9 (15%).

Reaction of dichloro(phenyl)phosphine (1b) with (2-chloroethoxy)trimethylsilane (6) in the presence of ethyl chloroacetate (3). ^{31}P NMR spectrum of the reaction mixture, δ_P, ppm: 160 (10%), 35.2 (30%), 26 (40%), 19.4 (20%).

Reaction of dichloro(4-chlorophenyl)phosphine (1c) with (2-chloroethoxy)trimethylsilane (6) in the

presence of ethyl chloroacetate (3). ^{31}P NMR spectrum of the reaction mixture, δ_P, ppm: 158.3 (28%), 34.5 (26%), 24.6 (32%), 17.8 (15%).

Reaction of dichloro(phenyl)phosphine (1b) with (2-chloroethoxy)trimethylsilane (6) in the presence of ethyl chloroacetate (3) and potassium iodide. A solution of 1.35 g (11 mmol) of ethyl chloroacetate (**3**) in 5 mL of anhydrous acetone was added to 1.67 g (10 mmol) of finely powdered potassium iodide. The mixture was stirred for 2 h at 20–22°C and cooled to –5°C, 1.8 g (10 mmol) of phosphine **1b** and 3.35 g (22 mmol) of silane **6** were added in succession, and the mixture was heated for 2 h under reflux with stirring. ^{31}P NMR spectrum, δ_P, ppm: 44.9 (63%), 43.4 (12 %), 35.3 (18%), 19.6 (7%).

Reaction of dichloro(phenyl)phosphine (1b) with (2-chloroethoxy)trimethylsilane (6) in the presence of methyl bromoacetate. A solution of 2.9 g (19 mmol) of silane **6** in 4 mL of anhydrous benzene was added at –5°C under argon to a solution of 1.6 g (9 mmol) of phosphine **1b** in 4 mL of benzene. The mixture was stirred for 1 h at –5°C, and 1.35 g (18 mmol) of methyl bromoacetate was added dropwise. ^{31}P NMR spectrum of the reaction mixture, δ_P, ppm: 34.8 (18%), 25.4 (74%), 19.7 (8%).

Reaction of dichloro(phenyl)phosphine (1b) with 2-chloroethanol. Phosphine **1b**, 5 g (30 mmol), was added under argon to a solution of 6.3 g (60 mmol) of triethylamine and 4.5 g (60 mmol) of 2-chloroethanol in 35 mL of anhydrous benzene on cooling to –5°C. The mixture was stirred for 1 h at 40°C, and the precipitate was filtered off. ^{31}P NMR spectrum of the filtrate, δ_P, ppm: 159.7 (61%), 26.3 (12%), 19.4 (27%). Chloro(trimethyl)silane, 0.32 g (3 mmol), was then added, and the mixture was stirred for 1 h at 60°C. ^{31}P NMR spectrum of the reaction mixture, δ_P, ppm: 26 (55%), 19 (45%). Thin-film molecular distillation of the mixture at 135°C (0.1 mm) gave compound **8b** as distillate, and **7b**, as still residue.

Bis(2-chloroethyl) phenylphosphonate (7b). Yield 3.31 g (39%). ^{31}P NMR spectrum: δ_P 19 ppm. ^{1}H NMR spectrum, δ, ppm: 3.6 m (4H, CH_2Cl), 4.2 m (4H, CH_2O), 7.1 m (2H, H_{arom}), 7.5 m (1H, H_{arom}), 7.7 m (2H, H_{arom}). Found, %: Cl 24.21; P 11.12. Calculated, %: Cl 24.05; P 10.94.

2-Chloroethyl phenylphosphinate (8b). Yield 2.76 g (45%). ^{31}P NMR spectrum: δ_P 26 ppm (J = 570 Hz). ^{1}H NMR spectrum, δ, ppm: 3.4 m (2H, CH_2Cl), 3.7 m (2H, CH_2O), 7.56 d (1H, PH, J = 570 Hz), 7.3 m (2H, H_{arom}), 7.4 m (1H, H_{arom}), 7.6 m (2H, H_{arom}). Found, %: Cl 17.42; P 15.23. Calculated, %: Cl 17.33; P 15.14.

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