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Phosphorylated aziridinium salts: synthesis and ring opening with nucleophiles

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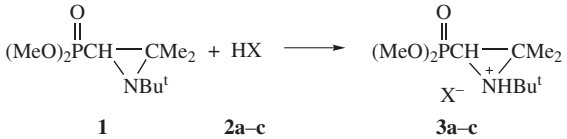
Treatment of 1-*tert*-butyl-2-dimethoxyphosphoryl-3,3-dimethylaziridine with picric, perchloric or fluoboric acid affords the stable corresponding aziridinium salts, which are prone to undergo ring opening on reaction with alcohols, carboxylate and thiocyanate ions.

Phosphorylated aziridines, their salts and ring opening products contain the corresponding pharmacophoric groups and therefore they are potential biologically active substanses. 2-Halogenoalkanamines in alcohol solution are known to form low-stable aziridinium halides which are susceptible of various transformations.[1–3] Aziridinium perchlorates appeared to be stable and can be isolated in pure form.[3,4]

Previously, C-phosphorylated NH-aziridines[5] and their Bu^t-N analogues **1** were documented.[6,7] Obtaining of phosphorylated aziridines **1** by treatment of methanolic solution of 1-*tert*-butylamino-2-chloroalkylphosphonate with amines or sodium methoxide is the evidence of the formation of intermediate phosphorylated aziridinium chloride **3e**.[6–8] The stable salts of compounds **1** were not described in literature.

Herein, we found that treatment of aziridine **1** with acids **2a–c** led to stable salts **3a–c**,[†] which were isolated as individual substances (Scheme 1).

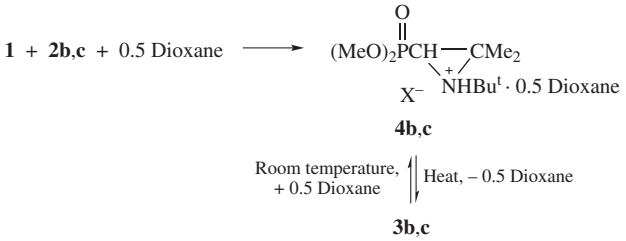


1 **2a–c** **3a–c**

a $X^- = 2,4,6\text{-}(O_2N)_3C_6H_2O^-$
b $X^- = ClO_4$
c $X^- = BF_4$

Scheme 1

When the reactions between compounds **1** and **2b**,**c** were carried out in dioxane, the solvate complexes **4b**,**c**[‡] of the salts **3b**,**c** with dioxane were formed in ratio 2:1. The compounds **4b**,**c** eliminate dioxane on recrystallization from acetone and turn into salts **3b**,**c**. The loss of dioxane by the solvate complexes **4b**,**c** and their decomposition into aziridine **1** at 200 °C was also shown by mass spectrometry.[‡] Solvates **4b**,**c** were also formed on contact of salts **3b**,**c** with dioxane (Scheme 2).



Scheme 2

Aziridinium salts **3** react with nucleophiles to produce polyfunctional organophosphorus derivatives.[§] For example, salt **3a** reacts

† ^{1}H NMR spectra were recorded on a Tesla BS-567A spectrometer (100 MHz, TMS) and ^{31}P NMR spectra – on a CXP-100 spectrometer (36.5 MHz, 85% H_3PO_4). Mass spectra were measured on a DFS instrument (Thermo Electron Corporation, USA) with electron ionization (70 eV). The temperature of the ion source was 280 °C, sample inlet system was used. Processing of the mass spectral data was done using of 'Xcalibur' program. Ion peaks with the most abundant isotops were specified.

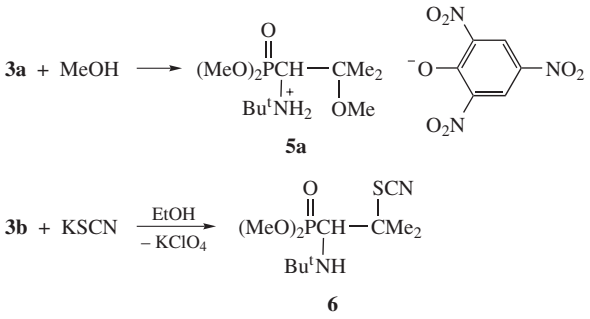
1-tert-*Butyl-2-dimethoxyphosphoryl-3,3-dimethylaziridinium 2,4,6-trinitrophenoxide* **3a**. A solution of 0.6 g (0.02 mol) of picric acid **2a** in 2 ml of diethyl ether was added dropwise to a stirred solution of 0.47 g (0.02 mol) of aziridine **1** in 2 ml of diethyl ether under argon atmosphere. A slight warming-up of the reaction mixture was observed. The mixture was left at room temperature for 24 h. The crystals precipitated were filtered off, recrystallized from ethyl acetate and dried *in vacuo* to afford 0.9 g of aziridinium picrate **3a**, yield 97%, mp 120 °C. ^{1}H NMR (acetone-d_6) δ: 1.68 (s, 9H, CMe_3), 1.88 and 2.00 (s and d, 6H, CMe_2, $^3J_{PH}$ 0 and 3 Hz), 3.79 (d, 1H, PCH, $^2J_{PH}$ 4 Hz), 3.94 and 3.98 (2d, 6H, 2POMe, $^3J_{PH}$ 12 Hz), 5.15 (br. s, 1H, NH), 8.73 (s, 2H, Ar). ^{31}P NMR (acetone-d_6) δ: 15.4. Found (%): C, 41.38; H, 5.39; N, 12.07; P, 6.68. Calc. for $C_{16}H_{25}N_4PO_{10}$ (%): C, 41.17; H, 5.25; N, 12.20; P, 6.84.

‡ *1*-tert-*Butyl-2-dimethoxyphosphoryl-3,3-dimethylaziridinium perchlorate* **3b** *and its solvate with dioxane* **4b**. Under argon atmosphere 0.99 g (0.098 mol) of 67.5% perchloric acid **2b** was added dropwise to 2.3 g (0.098 mol) of aziridine **1** in 15 ml of dioxane with stirring at 13 °C. A slight warming-up of the reaction mixture was observed. The solvate complex with dioxane **4b** was isolated by precipitation with diethyl ether from dioxane, yield 3.21 g (86%), mp 119 °C. ^{1}H NMR (CD_3OD) δ: 1.52 (s, 9H, CMe_3), 1.82 and 1.86 (2s, 6H, CMe_2), 3.67 (s, 4H, dioxane), 3.78 (d, 1H, PCH, $^2J_{PH}$ 2.2 Hz), 3.97 and 3.95 (2d, 6H, 2POMe, $^3J_{PH}$ 11.4 Hz), 7.05 (br. s, 1H, $^+$NH). ^{31}P NMR (CD_3OD) δ: 15.6. MS, *m*/*z* (%): 235 (1.5) $[M_1]^+$, 220 (5.2) $[M - Me]^+$, 178 (17.0) $[M - Bu^t]^+$, 152 (100) $[C_4H_{11}NO_3P]^+$, 150 (20.4) $[C_4H_9NO_3P]^+$, 125 (10.7) $[C_8H_{15}N]^+$, 110 (52.5) $[C_7H_{12}N]^+$, 88 (35.4) $[M_2]^+$, 79 (36.4) $[C_2H_7P]^+$, 57 (42.9) $[Bu^t]^+$. Found (%): C, 37.94; H, 7.11; N, 3.69; P, 8.17; Cl, 9.35. Calc. for $C_{12}H_{27}NPO_5Cl$ (%): C, 37.51; H, 7.01; N, 4.10; P, 8.25; Cl, 9.03.

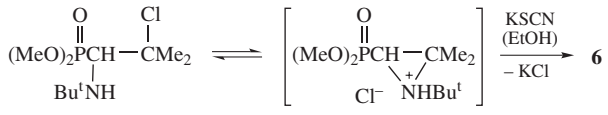
After recrystallization from acetone, the product was proved to be compound **3b**, mp 126 °C. ^{1}H NMR (CD_3OD) δ: 1.52 (s, 9H, CMe_3), 1.82 and 1.86 (2s, 6H, CMe_2), 3.78 (d, 1H, PCH, $^2J_{PH}$ 3.1 Hz), 3.93 and 3.97 (2d, 6H, 2POMe, $^3J_{PH}$ 11.3 Hz), 7.05 (br. s, 1H, $^+$NH). ^{31}P NMR (MeCN) δ: 13.55. MS, *m*/*z* (%): 235 (1.3) $[M_1]^+$, 220 (5.3) $[M - Me]^+$, 178 (14.3) $[M - Bu^t]^+$, 152 (100) $[C_4H_{11}NO_3P]^+$, 150 (28.3) $[C_4H_9NO_3P]^+$, 125 (10.8) $[C_8H_{15}N]^+$, 110 (79.7) $[C_7H_{12}N]^+$, 79 (15.6) $[C_2H_7P]^+$, 57 (43.3) $[Bu^t]^+$.

with methanol and **3b** reacts with potassium thiocyanate affording the corresponding ring opening products **5a** and **6** (Scheme 3).

Compound **6** was also obtained on treatment of dimethyl (1-*tert*-butylamino-2-chloro-2-methylpropyl)phosphonate **7** with potassium thiocyanate in ethanol. The reaction probably proceeds through the intermediate formation of aziridinium salt **3e** (Scheme 4).



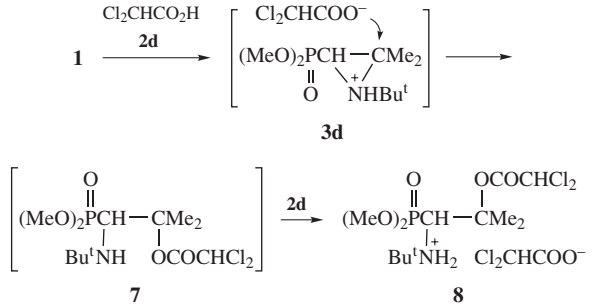
Scheme 3



Scheme 4

In the case of dichloroacetic acid **2d** (Scheme 5) salt **3d** was found to be unstable and it was converted into the salt of (1-*tert*-butylamino-2-dichloroacetoxy-2-methylpropyl)phosphonate **8**¶ by reacting with the second carboxylate species. Apparently the dichloroacetate anion in salt **3d** acts as a nucleophile attacking the carbon atom of the aziridinium ring and causing ring opening. Amine **7** formed is protonated by the second molecule of acid **2d** giving salt **8**.

In conclusion, for the first time the stable phosphorylated aziridinium salts and their solvates with dioxane were synthesized.



Scheme 5

Dioxane (3 ml) was added to 0.5 g (0.0015 mol) of compound **3b** with stirring at room temperature under argon atmosphere. The mixture was left for 24 h. After removal of the solvent the residue was found to be the solvate complex **4b**, yield 86%.

1-tert-*Butyl-2-dimethoxyphosphoryl-3,3-dimethylaziridinium tetrafluoroborate* **3c** *and its solvate with dioxane* **4c**. In a similar manner, 7.2 g (0.0306 mol) of aziridine **1** in 35 ml of dioxane and 16.73 g (0.0306 mol) of 40% fluoboric acid **2c** gave 10.36 g of the solvate complex with dioxane **4c**, yield 92%, mp 115–117 °C. ^{1}H NMR (CD_3OD) δ: 1.64 (s, 9H, CMe_3), 1.97 and 2.01 (2s, 6H, CMe_2), 3.59 (s, 4H, dioxane), 4.01 and 4.05 (2d, 6H, 2POMe, ^3J 11.4 Hz), 4.34 (d, 1H, PCH, $^2J_{PH}$ 17.6 Hz), 6.65 (br. s, 1H, $^+$NH). ^{31}P NMR (CD_3OD) δ: 14.42. MS, *m/z* (%): 235 (1.4) $[M_1]^+$, 220 (5.5) $[M - Me]^+$, 178 (20.2) $[M - Bu^t]^+$, 152 (71.5) $[C_4H_{11}NO_3P]^+$, 150 (15.5) $[C_4H_9NO_3P]^+$, 125 (7.8) $[C_8H_{15}N]^+$, 110 (100) $[C_7H_{12}N]^+$, 88 (12.2) $[M_2]^+$, 79 (29.0) $[C_2H_7P]^+$, 57 (45.6) $[Bu^t]^+$.

After recrystallization from acetone the product was proved to be compound **3c**, mp 117 °C. ^{1}H NMR (CD_3OD) δ: 1.64 (s, 9H, CMe_3), 1.97 and 1.98 (2s, 6H, CMe_2), 3.90 (d, 1H, PCH, $^2J_{PH}$ 16 Hz), 3.96 and 3.94 (2d, 6H, 2POMe, ^3J 11.4 Hz), 7.06 (br. s, 1H, $^+$NH). ^{31}P NMR (CD_3OD) δ: 13.5. MS, *m/z* (%): 235 (16.0) $[M_1]^+$, 220 (66.1) $[M - Me]^+$, 178 (88.6) $[M - Bu^t]^+$, 152 (100) $[C_4H_{11}NO_3P]^+$, 125 (83.2) $[C_8H_{15}N]^+$, 110 (100) $[C_7H_{12}N]^+$, 79 (86.9) $[C_2H_7P]^+$, 57 (94.8) $[Bu^t]^+$.

Dioxane (3 ml) was added to 0.5 g (0.0015 mol) of compound **3c** with stirring at room temperature under argon atmosphere. The mixture was left for 24 h. After removal of the solvent the residue was found to be the solvate complex **4c**, yield 89%.

§ *Interaction of aziridinium salts with nucleophiles.*

N-tert-*Butyl*-N-*(1-dimethoxyphosphoryl-2-methoxy-2-methylpropyl)-ammonium 2,4,6-trinitrophenoxide* **5a**. Aziridinium picrate **3a** (0.9 g, 0.019 mol) was dissolved with stirring in 3 ml of methanol under argon atmosphere. The mixture was left for 2–3 days. After removal of the solvent product **5a** was obtained, yield 95%, mp 115–117 °C. ^{1}H NMR ($CDCl_3$) δ: 1.57 and 1.66 (2s, 9H, CMe_3), 1.62 (s, 6H, CMe_2), 3.38 (d, 1H, PCH, $^2J_{PH}$ 15.5 Hz), 4.02 (d, 6H, 2POMe, $^3J_{PH}$ 11 Hz), 8.70 (br. s, 2H, $^+NH_2$), 8.97 (s, 2H, Ar). ^{31}P NMR ($CDCl_3$) δ: 20.7. Found (%): C, 41.13; H, 5.85; N, 11.29; P, 6.25. Calc. for $C_{17}H_{29}N_4PO_{11}$ (%): C, 41.01; H, 5.78; N, 11.34; P, 6.47.

Reaction between aziridine **1** *and 2,4,6-trinitrophenol* **2a** *in methanol*. *Method A*. A solution of 4.21 g (0.179 mol) of aziridine **1** in 10 ml of methanol was added dropwise to a stirred solution of 4.10 g (0.179 mol) of picric acid **2a** in 25 ml of methanol under argon atmosphere. A slight warming-up of the reaction mixture was observed. The mixture was left at room temperature for 24 h. The precipitated crystals were filtered off and dried *in vacuo* to give 10.2 g of the mixture of aziridinium picrate **3a** and the product of its ring opening **5a** in 1:1 ratio, yield 60%. ^{31}P NMR (CD_3OD) δ: 16.6 and 20.7.

Method B. A solution of 2.00 g (0.085 mol) of aziridine **1** in 2 ml of methanol was added dropwise to a stirred solution of 1.95 g (0.085 mol) of picric acid **2a** in 2 ml of methanol under argon atmosphere. A slight warming-up of the reaction mixture was observed. The mixture was left at room temperature for 2–3 days. The crystals precipitated were filtered off, recrystallized from ethyl acetate and dried *in vacuo* to afford 2.84 g of the product **5a**, yield 67%.

1-tert-*Butylamino-1-dimethoxyphosphoryl-2-methylprop-2-yl thiocyanate* **6**. *Method A*. Under argon atmosphere 1.93 g (0.0575 mol) of aziridinium perchlorate **3b** was added to a solution of 0.67 g (0.0575 mol) of finely powdered KSCN in 5 ml of ethanol with stirring at 13 °C. A slight warming-up of the reaction mixture was observed. The mixture was left at room temperature for 24 h. The precipitated crystals of $KClO_4$ (0.43 g) were filtered off, the reaction mixture was treated with diethyl ether. The solvent was evaporated from the ether layer *in vacuo*. The residue was recrystallized from Et_2O–hexane and dried *in vacuo*, giving 0.6 g of compound **6**, yield 35%, mp 82–83 °C. ^{1}H NMR ($CDCl_3$) δ: 1.14 (s, 9H, CMe_3), 1.62 and 1.84 (2s, 6H, CMe_2), 1.71–1.87 (br. s, 1H, NH), 3.18 and 3.20 (2d, 1H, PCH, $^2J_{PH}$ 16 Hz), 3.78 (d, 6H, 2POMe, $^3J_{PH}$ 11 Hz). ^{31}P NMR ($CDCl_3$) δ: 26.5. Found (%): C, 48.80; H, 7.85; N, 9.50; P, 10.49, S, 10.68. Calc. for $C_{12}H_{23}N_2PO_3S$ (%): C, 48.60; H, 8.00; N, 9.05; P, 10.66; S, 10.90.

Method B. Dimethyl (1-*tert*-butylamino-2-chloro-2-methylpropyl)phosphonate **7** (5.0 g, 0.184 mol) was added to a solution of finely powdered KSCN (1.79 g, 0.184 mol) in 20 ml of ethanol with stirring under argon atmosphere. A slight warming-up of the reaction mixture was observed. The mixture was left at room temperature for 24 h. The precipitated crystals of KCl (1.14 g) were filtered off, the reaction mixture was treated with diethyl ether. The solvent was evaporated from the ether layer *in vacuo*. The residue was recrystallized from Et_2O–hexane and dried *in vacuo* to provide 3.42 g of product **6**, yield 63%, which was identical to that obtained by method A.

¶ N-tert-*Butyl*-N-*(2-dichloroacetoxy-1-dimethoxyphosphoryl-2-methylpropyl)ammonium dichloroacetate* **8**. A solution of 3.29 g (0.256 mol) of dichloroacetic acid **2d** in 2 ml of diethyl ether was added dropwise to a stirred solution of 3.0 g (0.128 mol) of aziridine **1** in 25 ml of diethyl ether at 0 °C under argon atmosphere. A slight warming-up of the reaction mixture was observed. The mixture was left at room temperature for 48 h. After removal of Et_2O *in vacuo* the precipitated crystals were filtered off, recrystallized from benzene and dried *in vacuo* to give 5.66 g of product **8**, yield 90%, mp 87–88 °C. ^{1}H NMR ($CDCl_3$) δ: 1.16 (s, 9H, CMe_3), 1.58 and 1.66 (2s, 6H, CMe_2), 3.85 (d, 6H, 2POMe, $^3J_{PH}$ 11 Hz), 3.91 (d, 1H, PCH, $^2J_{PH}$ 18 Hz), 6.41 and 6.47 (2s, 1H, $CHCl_2$), 8.6 (br. s, 2H, $^+NH_2$). ^{31}P NMR ($CDCl_3$) δ: 27.3. Found (%): N, 2.84; P, 6.29; Cl, 28.80. Calc. for $C_{14}H_{26}NPO_7Cl_4$ (%): N, 2.86; P, 6.33; Cl, 28.99.

The salts undergo ring opening on reaction with methanol, carboxylate and thiocyanate ions. Perchlorate **3b** displayed bactericidal activity with regard to such microorganisms as *Staphylococcus aureus* and *E. coli*.

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