On the Route to the N-Phosphoryl Sulfamic Acid

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(Received January 17th, 2000; revised manuscript February 10th, 2000)

Synthesis of the previously unknown N-diethyl phosphorosulfamate 15 was accomplished by direct sulfamation of diethyl phosphoroamidate 4 with sulfur trioxide–DMF complex 14. The acid 15 was isolated in form of benzyl-16 and cyclohexylammonium 17 salts, which were found to be unstable in water solution. The other possible routes to sulfamate 15 were briefly tested.

Key words: sulfamation, SO3–DMF complex, N-diethyl phosphorylsulfamate, N,N'-bis(diethylphosphoro) sulfamide

The chemistry of organic sulfamic acids is widely described [1,2]. Sulfamic acids monosubstituted at nitrogen 1 are frequently used as convenient precursors of highly reactive N-sulfonylamines 2 [3] in the sequence of reactions leading to β–sultams 3 [4] (Scheme 1). We considered it worthwhile to check the possibility of using this sequence and N-phosphoryl sulfamic acids as starting material for the synthesis of N-phosphoryl 1,2-thiazetidine 1,1-dioxide, 3 [R = (alkylO)2P(O)–] [5].

Scheme 1


R = alkyl, aryl, aroyl

In the present work we describe the results of investigations on the development of synthesis of N-phosphoryl sulfamic acids. In contrast to N-substituted N-sulfonyl amines known to date, the ones bearing phosphoryl group on the nitrogen are not on record.

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RESULTS AND DISCUSSION

Our initial attempts to synthesize of \( N \)-phosphoril sulphonyl chloride considered as a convenient precursor of sulfamide 2 \([R = (\text{alkyl } O)_{2}P(O)-]\) by the reaction of sulfuryl chloride with dialkyl phosphoramidate 4 failed [6]. Similarly unsuccessful were also our efforts to synthesize of \( N \)-(diethylphosphoro)sulfamic acid by the direct sulfonation of phosphoroamidate with sulfur trioxide. In both reactions, the unexpectedly facile formation of \( N,N' \)-bis(diethylphosphoryl) sulfamide (5) was observed [6] (Scheme 2).

\[
\begin{align*}
\text{Scheme 2} \quad & \quad 4 \quad \xrightarrow{n\text{SO}_{2}\text{Cl}_{2} \text{ or } n\text{SO}_{3} \quad \text{CCl}_{4}} \quad 5 + \text{other products} \\
\end{align*}
\]

In this situation we turned our attention to the use of silyl protected reagents, \( i.e. \) \( N \)-(trimethylsilyl)-phosphoroamidate 4a and trimethylsilyl chlorosulfonate (6). The corresponding reaction carried out is illustrated in Scheme 3. The sulfonating properties of the trimethylsilyl chlorosulfonate (6) towards different class of organic compounds are well documented [7].

\[
\begin{align*}
\text{Scheme 3} \quad & \quad 4a \quad \xrightarrow{\text{CH}_{2}\text{Cl}_{2} \quad -15^\circ C \quad \text{0°C}} \quad 5 \quad (28\%) + \text{other products} \\
\end{align*}
\]

As revealed by \(^{31}\text{P}\) NMR spectroscopy the chlorosulfonate 6 reacted with amidate 4a in dichloromethane between \(-15^\circ\) to \(0^\circ\)C with the formation of the mixture of organophosphorus compounds resonating at \(\delta\) : \(-3.75\) (53%), \(-5.94\) (28%), \(9.65\) (11%), \(19.72\), \(7.72\), \(-6.3\) and \(-10.35\) (7%). The major signal at \(\delta \approx 3.75\) corresponded most probably to the expected \( N \)-(diethylphosphoryl) trimethylsilyl sulfamate (7), but we were unable to isolate it from the reaction mixture.

One of the common methods of the synthesis of sulfamic acid is the addition of anhydrous sulfuric acid to organic isocyanates, which followed the subsequent evolution of carbon dioxide [8]. It was interesting to check this possibility by using in the reaction the ready available diethyl phosphoroisocyananide (8) and instead of sulfuric acid, the \( n \)-butyl hydrogensulfonate (9). We observed, that the isocyananide 8 reacted with ester 9 in dioxane solution at room temperature and in a slightly exothermic process the formation of only one organophosphorus product resonating at \(\delta \approx 31\text{P} - 1.79\) was observed. This signal was ascribed to the adduct 10. The attempt to isolate this product from the reaction mixture by distillation under high vacuum was unsucces-
ful. As the result the compound characterized by $\delta^{31}\text{P}$ signal at $-12.10$ and identified as diethyl phosphoroisocyanidate (8) was obtained in good yield. The identity of this product was further confirmed by its reaction with benzylamine, which resulted in the expected formation of $N$-diethylphosphoryl-$N^\prime$-benzyleurea (11) (Scheme 4).

These results correspond to the known pattern of thermal decomposition of $N$-phosphoryl urethanes 12 (Scheme 5) [9].

The unsuccessful results of the synthesis of $N$-phosphoryl sulfamic acid in the reactions, shown in Schemes 3 and 4, prompted us to continue our search on reaction between the sulfur trioxide and dialkyl phosphoroamidate 4. We turned our attention to the possibility of using sulfur trioxide complexes with dioxane 13 and with $N,N$-dimethylformamide 14 as sulfonating agents. The reaction between 13 and amidate 4 performed in carbon tetrachloride at room temperature was relatively slow. After 2 hours 44% of the starting amidate 4 ($\delta^{31}\text{P} 10.31$) accompanied by sulfamide 5 $\delta^{31}\text{P} -5.92$ (13%) and two other not identified compounds were found in the reaction mixture. Extending of the reaction time resulted in the formation of a complex mixture of organophosphorus products, which could not be identified. On the other hand, when 4 was reacted with DMF–SO$_3$ complex 14 in dichloromethane solution between $-15^\circ\text{C}$ to $0^\circ\text{C}$, the formation of the major product, $N$-diethylphosphoryl sulfamic acid (15), characterized by a signal at $\delta^{31}\text{P} -1.81$ (83%) together with 17% of the complex of sulfur trioxide with amidate 4 resonating at $\delta$ 11.2, were observed (Scheme 6).
The addition of an excess of benzylamine to this reaction mixture resulted in disappearing of the signal at $\delta$ 11.2 and appearing of a new signal at $\delta^{31}P$ 10.15 characteristic for the amidate 4. Simultaneously, the signal at –1.81 ppm was replaced by a new one at –1.09 ppm due to the transformation of the product 15 ($\delta$ –1.81) into its benzylammonium salt 16. The salt 16 was isolated from the reaction mixture in good yield as a crystalline compound m.p. 223–226°C. In the FAB/MS negative-ion spectrum of the product 16 the presence of the peak at m/z 232 [M–1] characteristic for the anion of N-diethylphosphoryl sulfamic acid (15) was observed. In the positive-ion spectrum the presence of mass m/z 341 and m/z 448 characteristic for the cluster ions 18 and 19, respectively, were observed. In the positive-ion MS/FAB spectrum of the salt 16, to which trace amounts of sodium chloride was added, the peaks m/z 256 and m/z 278 characteristic for the clusters 20 and 21, respectively, were registered. In this spectrum two other peaks ascribed to clusters 22 and 23 formed from sodium ion and benzylamine were also present (Scheme 7).

The synthesized sulfamic acid 15 can be used for further synthetic purposes without isolation. Accordingly, in the reaction of crude 15 with cyclohexylamine, the expected N-diethylphosphoryl cyclohexylammonium sulfamate (17) was obtained in good yield. We have found however, that salts 16 and 17 are relatively easily hydrolyzed in water at room temperature with the formation of diethyl phosphate (24). The transient formation of amidate 4 in this reactions was established by $^{31}P$ NMR spec-
troscopy. Hydrolysis of 17 performed at temperature 50–55°C in acetone–water (10:0.1, vol. ratio) resulted in the formation of the mixture containing amidate 4 and diethylphosphate (24) together with other not identified organophosphorus products (Scheme 8).

Scheme 8

The analogous behaviour characteristic for organic sulfamic acids and some of their derivatives connected with easy hydrolytic cleavage of the amide bond was observed [1].

**EXPERIMENTAL**

The solvents and reagents were purified and dried by standard methods before use. Melting points were determined with a Boetius apparatus and are uncorrected. $^1$H NMR spectra were recorded at 200.13 MHz with a Bruker AC 200 spectrometer using TMS as an internal standard. $^{31}$P NMR spectra were taken on the same spectrometer at 81 MHz. Positive chemical shifts are downfield from 85% H$_3$PO$_4$ used as an external reference. LSIMS spectra were recorded on a Finnigan MAT 95 spectrometer in a glycerol matrix using cesium as the primary ion beam. IR spectra were measured in KBr pellets using the ATI Mattson FT IR spectrometer. The amidates $^4$[10] and $^4a$[11], trimethylsilyl chlorosulfonate ($^6$)[12], sulfur trioxide complexes $^{13}$[13,14] and $^{14}$[15], diethyl phosphoroisocyanidate ($^8$)[16] were synthesized, according to the procedures described. Hydrogensulfonate $^9$ was prepared in situ from the reaction of $^6$ with 1,4-dioxane and n-butanol as a modification of previously described procedure [13].

**Reaction of amidate $^4a$ with the chlorosulfonate $^6$:** Into the stirred solution of 0.6 g (2.6 mmol) of amidate $^4a$ in 15 ml CH$_2$Cl$_2$ was added 0.69 g (3.2 mmol) of the chlorosulfonate $^6$ in 15 ml of dry dichloromethane at –15°C. The stirring was continued for 4 hours at 0°C, the solvent was removed in vacuo and the composition of residual liquid was studied by $^{31}$P NMR. The two major products resonating at $\delta$–3.75 (53%) and $\delta$–5.94 (28%) (sulfamide $^5$) together with 12% of substrate $^4a$ were found. The residual was then treated at 20°C with 0.38 g (5.1 mmol) of dry n-butanol in 15 ml of CH$_2$Cl$_2$. The solution was stirred at 35°C for 2 hrs and after this time was shown by $^{31}$P NMR spectroscopy to contain two major products resonating at $\delta$–5.92 (48%) and $\delta$ 0.1 (23%). The reaction mixture was evacuated for 1 h at room temperature under pressure 1–5 mmHg and to the residual liquid was added 0.56 g (6.0 mmol) of dry aniline in 10 ml of CH$_2$Cl$_2$. In the $^{31}$P NMR spectrum of this reaction solution the presence of signals at $\delta$ 0.16 (35%) and $\delta$–1.0 (52%) was registered. The signal at $\delta$–0.16 was not identified and the another one at $\delta$–1.0 was ascribed as a characteristic for the phenylammonium salt of $^5$.

**Reaction of phosphoryl isocyanidate $^8$ with the hydrogensulfonate $^9$:** Trimethylsilyl chlorosulfonate ($^6$) 1.88 g (10 mmol) was added to dry 1,4-dioxane (20 ml) at room temperature. After stirring, the TMSCl was removed in vacuo (20–25 mmHg) over 20 min., next of 0.74 g (10 mmol) of dry n-butanol was added slowly at temperature 15–18°C. The reaction mixture was stirred at this temperature for 2 hrs and 1.8 g (10 mmol) of isocyanidate $^8$ was added dropwise. The temperature of a slightly exothermic reaction was kept at 18–20°C and after the addition of $^8$ the solution was stirred at room temperature for further 2 hrs. The solvent was distilled off (10–15°C, 1–2 mmHg) and the residual liquid was found by $^{31}$P NMR spectroscopy to contain mainly product 10 resonating at $\delta$–1.79 (90%). Attempted isolation of this product by distillation gave only 1.57 g (83%) of its decomposition product phosphoroisocyanidate $^8$, b.p. 40–42°C (bath temp. 85–90°C), $^{31}$P NMR (CDCl$_3$): $\delta$–15.9; IR (film, cm$^{-1}$), 603(m), 776(m,sh), 925(s), 1032(vs),...
1196(s), 1284(s) (P=O), 1398(s), 1736(w), 2281(vs) (–NCO), 2877(w), 2967(m).

Reaction of amidate 4 with complexe 13: To a stirred suspension of 0.36 g (2.1 mmol) of the freshly prepared 13 in 20 ml of dry carbon tetrachloride was added dropwise of 0.33 g (2.1 mmol) of amidate 4 in 10 ml CHCl3 at temperature 15–20°C. After 2 hours of stirring at this temperature the reaction mixture was checked by 31P NMR spectroscopy and the presence of product characterized by signals at δ 10.31 (48%), amidate 4, δ 1.51 (38%), –5.92 (13%, sulfamide 5) and –12.75 (5%) was revealed. The 31P NMR spectrum recorded after next 12 hours of stirring the reaction solution showed the presence of a complex mixture of products, which were not separated from the solution.

Reaction of amidate 4 with complex 14: Benzylationnium N-diethylphosphoryl sulfamate: (16): To the stirred suspension of 1.43 g (9.3 mmol) of the complex 14 in 20 ml of dry CH2Cl2 was added at –15°C of 1.43 g (9.3 mmol) of amidate 4 in 10 ml of CH4Cl at –15°C. The reaction mixture was stirred for 2 hrs at 0–5°C and the solution was concentrated under reduced pressure (15 mmHg). In the residual liquid the presence of a major product 15 with δ –1.45 (83%) and of another one with δ 11.2 (17%) were found by 31P NMR. Into 2.17 g sample of this mixture the excess of dry benzylamine (2.1 g, 19.5 mmol) was added in CH2Cl2 (10 ml) at temperature –60°C. The reaction solution was stirred for 2 hrs and the temperature was allowed to rise slowly to –20°C. The solvent was removed in vacuo (15 mmHg) and the residue was further evacuated for 4 h at temperature –20°C to 0°C under reduced pressure (0.1 mmHg) and the presence of product resonating at δ –1.09 (83%), salt 16, together with other, identified as a 4 at δ 10.15 (15%) was registered spectroscopically. The fractional crystallization of the residual solid material from acetonitrile gave 2.44 g (77% yield) of solid m.p. 223–226°C. 31P NMR (CDCl3): δ –1.29. MS/FAB, negative-ion m/z 232 [M–1] anion of acid 15, positive-ion, m/z 341, cluster ion 18; m/z 448 ion 19; MS/FAB (NaCl), positive-ion, m/z 256 ion 20; m/z 278 ion 21; m/z 341 ion 22; m/z 363 ion 23. IR (KBr pellet, cm–1), 578.52(w), 618.60(s), 698.53(m), 749.06(m), 985.49(w), 1067.78(vs), 1080.54(vs), 1151.81(s), 1379.51(w), 1457.57(w), 1619.72(w), 2149.31(w), 2640.89(w), 2852.84(m), 2922.22(s), 3030.34(m), 3437.20(m).

Reaction of salt 16 with water: The sample of 0.02 g (0.05 mole) of benzylamine salt 16 was dissolved in 1 ml of water and the solution was stirred at room temperature for 2 hrs. Water was evaporated in vacuo (10–15 mmHg, temp. 30–35°C) and in the residual material the presence of one product phosphate 24 resonating at δ –0.1 was found by 31P NMR, MS/FAB; negative-ion, m/z 153 [M acid 24 –1], m/z 232 [M+I], positive-ion, m/z 108 [M cyclohexylamine –1].

Reaction of 15 with cyclohexylamine: Cyclohexylaminationium N-diethylphosphoryl sulfamate: (17): To the solution of the crude product of the reaction between 0.71 g (4.6 mmol) of amidate 4 and 0.71 g (4.6 mmol) of complex 14 in 20 ml of dry CH2Cl2, 0.46 g (4.6 mmol) of cyclohexylamine at –40°C was added. The solution was stirred for 1 h and temperature was slowly increased to 10°C. The solvent was evaporated under reduced pressure 0.1 mmHg and 0.94 g (81% yield) of oily liquid salt 17 (δ –1.39) admixed by 19% of amidate 4 (δ 10.79). MS/FAB, negative-ion, m/z 232 [anion salt 17], positive-ion, m/z 100 C6H11NH+, m/z 333 [M salt 17 + cyclohexylamine +1].

Hydrolysis of salt 17.

a. in water–acetone solution: Dissolving of the sample of 17 (mixture of 81% of 17 and 19% of 4) at temperature 50–55°C in aceton containing ca. 1% of water, resulted in the formation of amidate 4 δ 10.98 (62%), 20% of phosphate 24 and 18% of unidentified product δ 6.88, which were found by 31P NMR. The cyclohexylammonium hydrogen sulfate was found in this reaction was separated by crystallization from aceton m.p. 116–117°C [m.p. 117–118°C, ref. 17].

b. with water: The sample of 0.04 g (0.12 mmol) of the crude cyclohexylaminationium salt 17 containing of 19% of amidate 4 was dissolved in 1 ml of water and the solution was stirred for 2 hrs. After this time the solution was concentrated under reduced pressure 10–15 mmHg (temp. 30–35°C). In the obtained liquid the presence of 46% amidate 4 δ 10.2 together with 54% of unexchanged substrate 17 δ –1.54 was found by 31P spectroscopy. The reaction solution was stirred for the next 12 hrs at room temperature and after this time the formation of only one organophosphorus product 24 resonating at 31P NMR (CDCl3); δ –0.1 was observed. MS/FAB, negative -ion, m/z 153 [M acid 24 –1], m/z 195 [M salt 25 –2].
Acknowledgment

Financial support by the Polish State Committee for Scientific Research (grant 3 T09A 032 11) is acknowledged.

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