A New Method for the Preparation of Ifosfamide and Cyclophosphamide


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Dedicated to Professor Dr. med. Dr. h. c. Norbert Brock on the occasion of his 85th birthday

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The reaction of 2-chloro-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorin-2-oxide 1 and 2-chloro-tetrahydro-2H-1,3,2-oxazaphosphorin-2-oxide 2 with 2-(trimethylsiloxy)ethylamine 3 and bis-[2-(trimethylsiloxy)ethyl]amine 4, respectively, yielded the trimethylsilylated compounds 5 and 6, analogous to ifosfamide and cyclophosphamide. The reaction of 5 and 6 with 2-chloro-1,3,5-trimethyl-1,3,5-triaza-2-phosphorin-4,6-dione 7 led to the diphosphorus compounds 8 and 9 which could be transformed to ifosfamide 11 and cyclophosphamide 12 by treatment with sulfuryl chloride. This synthesis shows that the alkylating agents 2-chloroethylammonium chloride and bis-(2-chloroethyl)ammonium chloride can be avoided and the chlorine atom can be introduced in the final reaction step of the synthesis of 11 and 12.

Introduction

Ifosfamide 11 and cyclophosphamide 12 are two clinically widely used alkylating agents in the treatment of many types of human cancers [1, 2]. 2-Chloroethylammonium chloride and bis-(2-chloroethyl)ammonium chloride (nitrogen mustard HCl-salt) are important educts for the synthesis of 11 [3, 4] and 12 [5, 6], respectively. In order to avoid the use of these alkylating agents we developed a new synthesis in which chlorine is introduced in the final reaction step.

Results and Discussion

The substitution of chlorine in 1 and 2 by 2-(trimethylsiloxy)ethylamine 3 and bis-[2-(trimethylsiloxy)ethyl]amine 4, respectively, yielded the products 5 and 6 in nearly quantitative yield. Hydrolysis of these silylated compounds led to the corresponding hydroxy compound only in the case of 5. Its direct chlorination with thionyl chloride gave 11 in low yield. Having in mind that 2-alkoxy-1,3,5-trimethyl-1,3,5-triaza-2-phosphorin-4,6-diones react with sulfuryl chloride with formation of 2-chloro-1,3,5-trimethyl-1,3,5-triaza-2-phosphorin-4,6-dion-2-oxide 10 and the corresponding alkyl chloride [7], the silylated compounds 5 and 6, consequently, were allowed to react with 7 to form the \( \sigma^4 \lambda^5 / \sigma^3 \lambda^3 \)-diphosphorus species 8 and 9. Treatment of 8 and 9 with sulfuryl chloride led to ifosfamide 11 and cyclophosphamide 12, respectively, but the compounds were not stable in the reaction mixture. A \( ^{31} \text{P} \) NMR spectrum, recorded after half an hour of reaction time, showed a yield of ca. 75%. On recrystallisation of the product mixtures from diethyl ether only 2-chloro-1,3,5-trimethyl-1,3,5-triaza-2-phosphorin-4,6-dion-2-oxide 10 crystallized in a pure state. Ifosfamide 11 and cyclophosphamide 12, could be separated by column chromatography of the ethereal mother liquor; the yield after recrystallisation amounted to 10 - 15%.

The previously known methods for the synthesis of ifosfamide and cyclophosphamide do not require chromatographic separation of the products. Our work has demonstrated an alternative synthesis of compounds 11 and 12, avoiding the use of the alkylating agents, 2-chloroethylammonium chloride and bis(2-chloroethyl)ammonium chloride, as starting compounds.

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Experimental

All experiments were carried out with exclusion of air and moisture; solvents were purified and dried according to the usual methods [8]. “In vacuo” (i. v.) refers to a pressure of 0.1 mm Hg at 25°C. NMR spectra were recorded on a Bruker AC 200 spectrometer at 200.1 MHz ($^1$H), 50.3 MHz ($^{13}$C), and 81.0 MHz ($^{31}$P). Chemical shifts δ are given relative to Si(CH$_3$)$_4$ (TMS) ($^1$H, $^{13}$C); 85% H$_3$PO$_4$ ($^{31}$P). High-field shifts were given negative, low-field shifts positive signs. - MS: Finnigan MAT 8430. - Elemental analyses: Analytisches Laboratorium des Instituts für Anorganische und Analytische Chemie der Technischen Universität, Braunschweig. - Precursor compounds: 2-chloro-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorin-2-oxide (1) [9], 2-chloro-tetrahydro-2H-1,3,2-oxazaphosphorin-2-oxide (2) [10], 2-(trimethylsiloxy)ethylamine (3) [11], bis-[2-(trimethylsiloxy)ethyl]amine (4) [11], 2-chloro-1,3,5-trimethyl-1,3,5-triaza-2-phosphorin-4,6-dione (7) [12].

3-(2-Chloroethyl)-2-[2-(trimethylsiloxy)ethylamino]-tetrahydro-2H-1,3,2-oxazaphosphorin-2-oxide (5)

A solution of 1 (2.00 g, 15 mmol) and of triethylamine (1.52 g, 15 mmol) in 30 ml of dichloromethane was added dropwise during 15 min. After stirring the reaction mixture for 5 h at -15°C the solvent and all volatile components were removed i. v. The residue was extracted with 50 ml of diethyl ether, and triethylammonium chloride was filtered off. After removing the diethyl ether i. v. 5 was left as a colourless oil; yield: 4.48 g (94.9%); b.p.: >200°C (1 mm Hg).

$^1$H NMR (CDCl$_3$, 200.1 MHz): δ = 0.79 (s, 9 H, Si(CH$_3$)$_3$), 1.83-1.95 (m, 2 H, CH$_2$CH$_2$), 2.90-3.65 (m, 11 H, 3xNCH$_2$, 2xNCH,CH$_2$, NH), 4.13-4.37 (m, 2 H, POCH$_3$). - $^{13}$C NMR (CDCl$_3$, 50.3 MHz): δ = -0.63 (s, Si(CH$_3$)$_3$), 26.41 (d, $^3$J(PC) = 4.6 Hz, PNCH$_2$CH$_2$CH$_2$), 42.01 (d, $^3$J(PO) = 4.0 Hz, PNCH$_2$CH$_2$CH$_2$), 43.22; 62.56 (s; d, 6.4 Hz, PNCH$_2$CH$_2$OSi), 47.73 (s, CH$_3$Cl), 50.15 (d, $^3$J(PO) = 2.7 Hz, PNCH$_2$CH$_2$Cl), 67.01 (d, $^3$J(PO) = 6.8 Hz, POCH$_2$CH$_2$CH$_2$). - $^{31}$P NMR (CDCl$_3$, 110.0 MHz): δ = 13.23 (s) - Ei-MS: m/z (%) = 314 (4) [M$^+$], 299 (24) [M$^+$ CH$_3$], 211 (100) [M$^+$ - CH$_2$OSi(CH$_3$)$_3$], 182 (28) [M$^+$ - NHCH$_2$OSi(CH$_3$)$_3$].

Calcd C 38.15 H 7.68 N 8.90%  
Found C 36.88 H 7.45 N 9.28%.  

The experimental C-value deviates from the calculated value, presumably because of the formation of SiC.
A solution of 2 (5.80 g, 37mmol) and of triethylamine (3.77 g, 37 mmol) in 50 ml of dichloromethane was cooled to 0°C. A solution of bis-[2-(trimethylsiloxy)ethyl]amine 4 (9.30 g, 37 mmol) in 50 ml of dichloromethane was added dropwise during 1 h. After stirring the reaction mixture for 18 h at r.t., the solvent and all volatile components were removed i. v. The residue was extracted with 100 ml of diethyl ether, and triethylammonium chloride was filtered off. After removing the diethyl ether i. v. 6 was left as a colourless oil; yield: 12.08 g (88.7%); b.p.: >200°C (1 mm Hg).

1H NMR (CDCl3, 200.1 MHz); δ = 0.05 (s, 18 H, Si(CH3)3), 1.62-1.94 (m, 2 H, CH2CH2CH2), 2.87-2.96 (br., 1 H, NH), 3.02-3.45 (m, 6 H, 3xNCH2), 3.60 (t, 4 H, J(HH) = 6.2 Hz, NCH2CH2OSi), 4.05-4.46 (m, 2 H, 2 POCH2), - 13C NMR (CDCl3, 50.3 MHz); δ = -0.89 (s, SiCH3), 25.86 (d, 3J(PC) = 6.4 Hz, PNCH2CH2), 49.92 (d, 3J(PC) = 2.6 Hz, PN(CH2CH20 -)2), 67.07 (d, 3J(PC) = 36.3 Hz, P(NCH3)2), 41.60; 41.87; 63.98 (3d, 3J(PC) = 4.2 Hz; 4.6 Hz; 4.8 Hz, POCH2CH2CH2, PNHCH2CH2, PNHCH2CH2OP), 47.40 (s, CH2Cl), 40.90 (d, 3J(PC) = 2.8 Hz, PNCH2CH2CH2), 48.17 (d, 3J(PC) = 4.1 Hz, PN(CH2CH2OSi)2), 60.91 (d, 3J(PC) = 11.6 Hz, PNCH2CH2CH2), 1.62-1.94 (m, 2 H, CH2CH2), 2.87-2.96 (m, 11 H, 3xNCH2, 3xNCH2, 3xNCH2, 3xNCH2), 194 (13) [M+- CH2CH2OSi(CH3)3]_2-NHCH2CH2CH2].

C13H32N2O8P2S (368.56)
Calcd C 42.37 H 9.02 N 7.60%.
Found C 41.39 H 9.03 N 7.71%.

The experimental C-value deviates from the calculated value, presumably because of the formation of SiC.

3-(2-Chloroethyl)-2-[2-(1,3,5-trimethyl-1,3,5,2-triaza-phosphorin-4,6-dion-2-yloxy)ethylamino]-tetrahydro-2H-1,3,2-oxazaphosphorin-2-oxide (8)

To a solution of 3.15 g (10 mmol) of 5 in 50 ml of dichloromethane was added. After stirring the reaction mixture for 1 h at r.t., the solvent and all volatile components were removed i. v. The residue was washed with 50 ml of n-hexane and dried i. v.; yield: 3.60 g (86.5%); m.p.: 54°C.

1H NMR (CDCl3, 200.1 MHz); δ = 1.86-1.91 (m, 2 H, CH2CH2CH2), 2.99-3.62 (m, 11 H, 3xNCH2, 2xNCH2CH2, NH), 3.08 (d, 6 H, J(PH) = 11.7 Hz, P(NCH2)), 3.24 (s, 3 H, [C(O)2]NCH2), 4.08-4.33 (m, 2 H, PO(O)CH2), - 13C NMR (CDCl3, 50.3 MHz); δ = 26.32 (d, 3J(PC) = 4.4 Hz, PNCH2CH2CH2), 30.20 (s, [C(O)2]NCH2), 33.43 (d, 3J(PC) = 36.3 Hz, P(NCH2)), 41.60; 41.87; 63.98 (3d, 3J(PC) = 4.2 Hz; 4.6 Hz; 4.8 Hz, POCH2CH2CH2, PNHCH2CH2, PNHCH2CH2OP), 47.40 (s, CH2Cl), 49.92 (d, 3J(PC) = 2.6 Hz, PNCH2CH2Cl), 67.07 (d, 3J(PC) = 6.8 Hz, POCH2CH2CH2), 153.27 (d, 3J(PC) = 9.9 Hz, P(NCH2C(O)2)), - 31P NMR (CDCl3, 81.0 MHz); δ = 90.93 (s), 13.06 (s). - EI-MS: m/z (%) = 415 (2) [M+], 380 (10) [M+- Cl], 366 (5) [M+- CH2Cl], 225 (100) [M+- OP{NCH2C(O)2}NCH2Cl], 211 (42) [M+- CH2OP{NCH2C(O)2}NCH2Cl].

C13H32N2O8P2S (368.56)
Calcd C 35.95 H 6.28 N 19.33%.
Found C 35.95 H 6.28 N 19.33%.

3-(2-Chloroethyl)-2-[2-(chlooroethyl)amino]-tetrahydro-2H-1,3,2-oxazaphosphorin-2-oxide (Ifosfamide) (11) and 2-bis-[2-chloroethyl)amino]-tetrahydro-2H-1,3,2-oxazaphosphorin-2-oxide (Cyclophosphamide) (12)

To solutions of 2.49 g (6 mmol) of 8 and of 3.42 g (6 mmol) of 9, respectively, in 50 ml of dichloromethane sulfuryl chloride (0.81 g, 6 mmol) was added at 0°C. After stirring the solutions for 1 h at 0°C, the solvent and all volatile components were removed i. v. The residues were dissolved in 30 ml of diethyl ether each and kept overnight at -20°C. Pure 2-chloro-1,3,5-trimethyl-1,3,5-triaza-phosphorin-4,6-dion-2-oxide 10 crystallized from both
solutions, while ifosfamide 11, cyclophosphamide 12 and other by-products remained in solution. After filtration, both 11 and 12 were separated by column chromatography on silica gel (CH2Cl2/n-hexane, 5:2) of the ethereal mother liquor and recrystallized from 5 ml of diethyl ether each at -20°C. The identity of 10, of ifosfamide 11 and of cyclophosphamide 12 was established by 1H- and 31P NMR-spectroscopy [4, 6, 12]; yield: 11: 0.24 g (14.8%); 12: 0.17 g (10.9%).

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