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Phosphorylation of *N*-Silylpyrroles with Phosphorus Tribromide

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ABSTRACT: *Phosphorylation of N-trimethylsilyl- and N-dimethyl-tert-butylsilylpyrroles with phosphorus tribromide in pyridine proceeds selectively at position 3 of the pyrrole ring. Removal of the trialkylsilyl protecting group has furnished the first representatives of N-unsubstituted 3-phosphorylated pyrroles.*
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INTRODUCTION

C-Phosphorylation of N-substituted pyrroles with P(III) halides in pyridine provides the most general synthetic route to dihalogeno, halogeno, and tertiary pyrrolylphosphines, regarded as promising reagents in the development of new types of organophosphorus compounds [1,2]. However, C-phosphorylated pyrroles containing the NH group are hard to access and scantily studied; only a few compounds of this kind, with the phosphorus-containing substituent at the C2 ring atom, have been reported to date, among them tertiary phosphines, phosphine oxides, phosphonium salts, and pyrrolyl phosphonates obtained by the reaction of P(III) and P(V) halides with *N*-pyrrolylmagnesium bromide [1].

One might expect that C-phosphorylated N-unsubstituted pyrroles could result from the reaction of *N*-silylated pyrroles with P(III) halides in pyridine followed by the removal of the silyl-protecting group. At the same time, the literature evidence refers only to phosphorylation of *N*-trimethylsilylpyrrole with fluorophosphoranes [3] or dimethylamidodichlorophosphite [4] that involves the pyrrole nitrogen atom and is accompanied by the trimethylsilyl halide elimination.

RESULTS AND DISCUSSION

We have found that *N*-trialkylsilylpyrroles **1** and **4** are phosphorylated with phosphorus tribromide in pyridine at position 3 of the pyrrole ring. Phosphorylation selectivity is caused by bulky trialkylsilyl substituents, as was the case with *N-tert*-butylpyrrole [5].

^{31}P and ^{29}Si NMR monitoring of the reaction of compound **1** demonstrates that phosphorylation rapidly proceeds at position 3 of the pyrrole ring, with the N—Si bond remaining intact. Already within 30–40 min, the signal from phosphorus tribromide completely vanishes, the peaks from dibromophosphine **2** ($\delta^{31}P = 145.00$ ppm and $\delta^{29}Si = 15.21$ ppm) appear instead. The action of pyridine hydrobromide causes a gradual cleavage of the N—Si bond in

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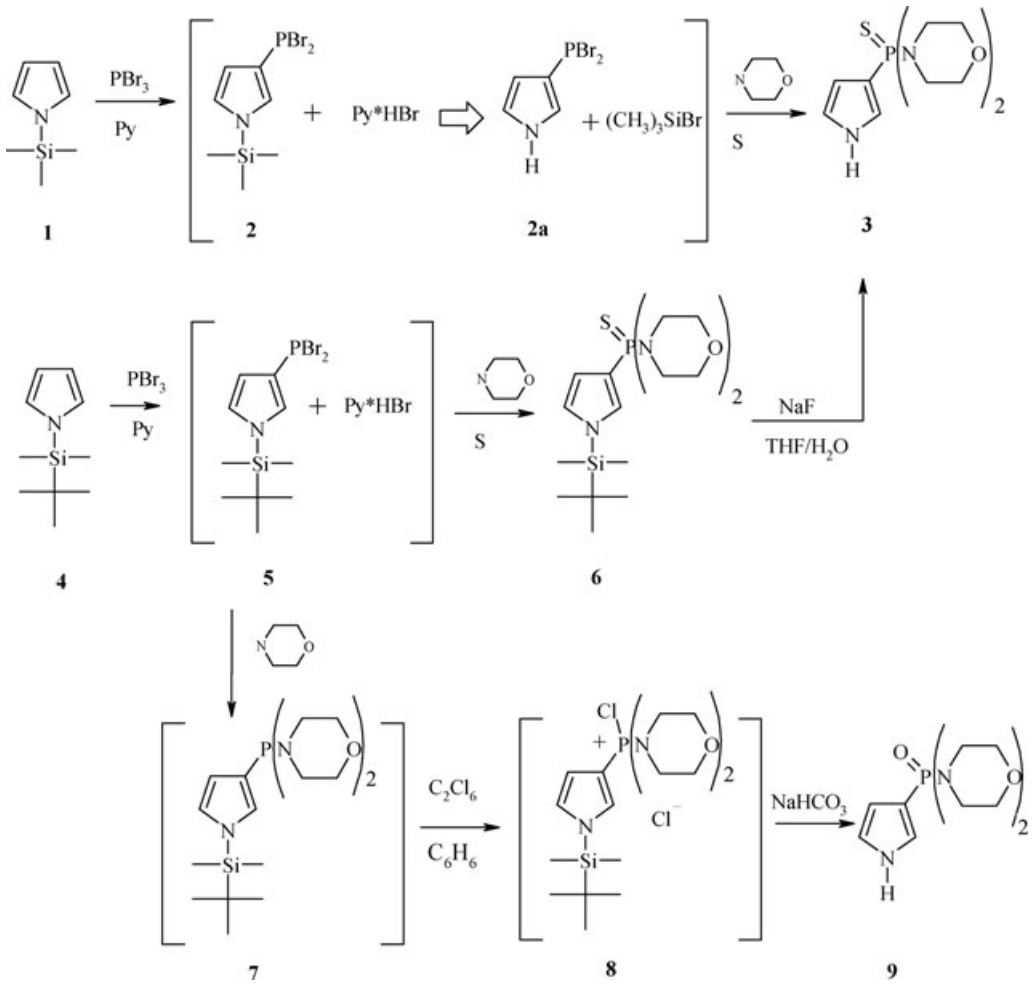

phosphine **2**, which is independently corroborated by reacting compound **1** with pyridine hydrobromide. Within 3 weeks, the ^{29}Si resonance of dibromophosphine **2** (at 15.21 ppm) completely disappears and that of trimethylbromosilane (at 28.03 ppm) is only observable for the reaction mixture. It is noteworthy that the ^{31}P NMR spectrum exhibits the only peak at 145.00 ppm, thus implying rather close positions of the phosphorus atom signals for dibromophosphines **2** and **2a**. Instead of isolating compound **2a**, we have directly converted it into stable thiophosphonic diamide **3**.

A dimethyl-*tert*-butylsilyl protecting group is known to be much more resistant to solvolysis in protic media than a trimethylsilyl group [6]. Thus, it was possible to isolate, as an individual compound, *N*-silylated thiophosphonic diamide **6** derived from *N*-dimethyl-*tert*-butylsilylpyrrole **4** and then to hydrolyze it to compound **3** in aqueous tetrahydrofuran in the presence of sodium fluoride. However, the conditions of phosphonous diamide **7** oxidation and the action of hydroxide anions in the hydrolysis of phosphonium salt **8** lead to the cleavage of the N—Si bond and the formation of phosphonic diamide **9**.

Since trialkylsilyl groups are stronger electron acceptors than alkyl substituents, they significantly hinder phosphorylation. To exemplify, *N*-trimethylsilylpyrrole is practically unreactive toward phosphorus halides in benzene, in contrast to *N*-*tert*-butylpyrrole that is readily phosphorylated with phosphorus tribromide in benzene, so that the reaction goes to completion within 12 h [5]. *N*-Trialkylsilylpyrroles are much more difficult to phosphorylate with phosphorus trichloride, a weaker electrophile as compared to phosphorus tribromide. For instance, *N*-trimethylsilylpyrrole is phosphorylated with PCl_3 in pyridine to a degree of 20% after a 24-h reaction time, whereas the phosphorylation of *N*-*tert*-butylpyrrole under the same conditions goes to completion within this period [5].

The nature of the solvent also causes a notable effect on the *N*-trialkylsilylpyrrole phosphorylation selectivity. As an example, the reaction between *N*-trimethylsilylpyrrole and phosphorus tribromide

becomes completely unselective, if conducted in dichloromethane: after 12 h of the reaction time, ^{31}P MNR spectra exhibit the signals from 2-, 3-, and *N*-phosphorylated pyrrole nucleus at 113.3 (21%), 142.9 (33%), and 145.4 ppm (46%), respectively.

CONCLUSION

As shown, phosphorylation of *N*-trialkylsilylpyrroles with phosphorus tribromide in pyridine proceeds selectively at position 3 of the pyrrole ring, whereas this reaction does not take place in benzene in the presence of bases and becomes unselective in dichloromethane to give 2-, 3-, and *N*-phosphorylated pyrroles. 3-Phosphorylated *N*-unsubstituted pyrroles have been obtained for the first time.

EXPERIMENTAL

The ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Varian VXR-300 spectrometer (at 300, 75, and 121 MHz, respectively, 25°C), with TMS as internal standard for ^{1}H and ^{13}C signals, and 85% H_3PO_4 as an external standard for ^{31}P signals. The chromato mass spectra were registered on an Agilent 1100 series LC/MSD instrument.

1H-Pyrrol-3-yl[di(4-morpholyl)]phosphine Sulfide **3**

Method A. To a solution of pyrrole **1** (0.51 g, 0.0036 mol) in dry pyridine (20 mL), phosphorus tribromide (0.996 g, 0.0036 mol) was added under dry argon. The reaction mixture was allowed to stand at room temperature for 2 h, followed by adding elementary sulfur (0.11 g, 0.0039 mol) and morpholine (1.27 g, 0.014 mol). After keeping the reaction mixture for 12 h, the solvent was evaporated under vacuum, and the residue was treated with water (3 × 25 mL), dissolved in the mixture acetone:dichloromethane (5:1), and chromatographed on a silica gel column, with the mixture acetone:dichloromethane (5:1) used as eluent. The solvent was evaporated under vacuum. Yield 0.11 g (10%); mp 127–128°C. ^{31}P NMR (DMSO-d_6): δ 68.96. ^{1}H NMR (DMSO-d_6): δ 3.04 (m, 8H, O-CH_2); 3.54 (m, 8H, N-CH_2); 6,24 (br s, 1H, H_4); 6.85 (br s, 1H, H_5); 7.14 (br s, 1H, H_2); 11,39 (br s, 1H, N—H). ^{13}C NMR (DMSO-d_6): δ 44, 98 (s, O—C); 66.77 (s, N—C); 110,76 (d, J_{CP} = 10.06 Hz, C_4); 112.91; 111.79 (d, J_{CP} = 145.87 Hz, C_3); 120.37 (d, J_{CP} = 13.83 Hz, C_5); 127.52 (d,J_{CP} = 23.89 Hz C_2). *m/z* 302 $[M]^+$. Anal. Calcd for $C_{12}H_{20}N_3O_2PS$ (301.35): N 13.94, P 10.28. Found: N 13.74, P 10.03.

Method B. To pyrrole **6** (0.5 g, 0.0012 mol), distilled water (15 mL), tetrahydrofuran (15 mL), and sodium fluoride (0.1 g, 0.0024 mol) were added. The reaction mixture was stirred at room temperature for 24 h, extracted with diethyl ether (3 × 30 mL), evaporated, dissolved in methanol, and chromatographed on a silica gel column; the eluent was evaporated under vacuum. Yield 0.29 g (80%).

1-tert-Butyl(dimethyl)silyl-1H-pyrrol-3-yl[di(4-morpholyl)]phosphine Sulfide **6**

To a solution of pyrrole **4** (0.5 g, 0.0027 mol) in dry pyridine (20 mL), phosphorus tribromide (0.26 ml, 0.74 g, 0.0027 mol) was added under dry argon. The reaction mixture was allowed to stand at room temperature for 2 h, followed by adding elementary sulfur (0.08 g, 0.0029 mol) and morpholine (1.43 g, 0.0162 mol). After keeping the reaction mixture for 12 h, the solvent was evaporated under vacuum and the residue was treated with water (50 mL) and methanol (5 mL). The resulting precipitate was filtered off and recrystallized from aqueous methanol. Yield 0.85 g (75%). mp 101–103°C. ^{31}P NMR (DMSO-d_6): δ 69.00. ^{1}H NMR (DMSO-d_6): δ 0.46 (s, 6H, CH_3—Si), 0.84 (s, 9H, CH_3—Si), 2.92 (m, 8H, O—CH_2), 3.53 (m, 8H, N—CH_2), 6.37 (br s, 1H, H_4), 6.92 (br s, 1H, H_5), 7.14 (br s, 1H, H_2). ^{13}C NMR (DMSO-d_6): δ 17.59 (s, Si—C), 25.32 (s, CH_3), 44.26 (s, O—C), 66.02 (s, N—C), 112.62 (d, J_{CP} = 15.09 Hz, C_4), 115.75; 114.62 (d, J_{CP} = 142.09 Hz, C_3), 125.97 (d, J_{CP} = 15.09 Hz, C_5), 132.82 (d, J_{CP} = 25.15 Hz, C_2), *m/z* 416 $[M]^+$. Anal. Calcd for $C_{18}H_{34}N_3O_2PSSi$ (415.61): N 10.11, P 7.45. Found: N 10.07, P 7.30.

1H-Pyrrol-3-yl[di(4-morpholyl)]phosphine Oxide **9**

To a solution of pyrrole **4** (0.5 g, 0.0027 mol) in dry pyridine (20 mL), phosphorus tribromide (0.26 ml, 0.74 g, 0.0027 mol) was added under dry argon. The reaction mixture was allowed to stand at room temperature for 2 h, followed by adding morpholine (1.43 g, 0.0162 mol) and 30–35 min later hexachloroethane (0.65 g, 0.0027 mol) and dry benzene (20 mL). After 48 h, the resulting gel-like precipitate was filtered off and dissolved in dichloromethane (30 mL); the solution was treated with a 10% aqueous sodium hydrocarbonate (30 mL). After evaporating the water layer and adding acetone (20 mL), the precipitate was filtered off. Yield 0.55 g (70%). mp 155–157°C.^{31}P NMR (DMSO-d_6): δ 23.70. ^{1}H NMR (DMSO-d_6): δ 2.93 (m, 8H, O—CH_2), 3.51 (m, 8H, N—CH_2), 6.19 (br s, 1H, H_4), 6.91 (br s, 1H, H_5), 7.11 (br s, 1H, H_2). ^{13}C NMR (DMSO-d_6): δ 44.06 (s, CH_2—O), 66.53 (s, CH_2—N),

109.33; 107.91 (d, $J_{CP} = 178.56$ Hz, C_3—P), 110.33 (d, $J_{CP} = 11.31$ Hz, C_4), 119.82 (d, $J_{CP} = 13.83$ Hz, C_5), 125.33 (d, $J_{CP} = 20.12$ Hz, C_2). *m/z* 286 $[M]^+$. Anal. Calcd for $C_{12}H_{20}N_3O_3P$ (285.29): C 50.52, H 7.07, P 10.86. Found: C 50.48, H 7.00, P 10.63.

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