Heteroatom Chemistry
Volume 20, Number 4, 2009

$N \rightarrow C_3$ Migration of Dichlorophosphino Group in the Phosphorylation of N-Unsubstituted Indole with Phosphorus Trichloride

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Received 29 April 2009

ABSTRACT: *A $N \rightarrow C_3$ migration of the dichlorophosphino group has been revealed in the phosphorylation of unsubstituted indole with phosphorus trichloride. Several 3-phosphorylated NH-indole derivatives have thus been obtained and N-acylation of one of the products has been performed.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:235–239, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20540

INTRODUCTION

Design of biologically active substances [1] and metal complex catalysts [2] calls for new synthetic routes to phosphorylated indoles, thus posing an interesting and significant challenge to organophosphorus chemistry. It has been known that direct phosphorylation of unsubstituted indole with phosphorus acid halides proceeds mostly at the nitrogen atom [3,4]. However, when using amidophosphorous esters as phosphorylating agents, initially formed N-phosphorylated derivatives rearrange intramolecularly to C_3-substituted products [5] under the catalytic action of amine hydrochlorides present in the reaction mixture. A similar $N \rightarrow C_3$ sigmatropic rearrangement of phosphorylated indoles occurs in the hydrolysis and alcoholysis of *N*-indolylamidophosphite with respective equimolar amounts of water or alcohol [6]. As previously found by us [7], the phosphorylation of unsubstituted pyrrole with phosphorus trichloride in polar solvents leads to a successive $N \rightarrow C_2 \rightarrow C_3$ migration of the dichlorophosphino group in the pyrrole nucleus. Here we address the same $N \rightarrow C$ rearrangement in unsubstituted indole; it shows much synthetic promise affording 3-indolyldichlorophosphine, a key compound in the preparation of various P- and N-functionalized phosphorylated indoles.

RESULTS AND DISCUSSION

It has been established that the phosphorylation of indole **1** with phosphorus trichloride

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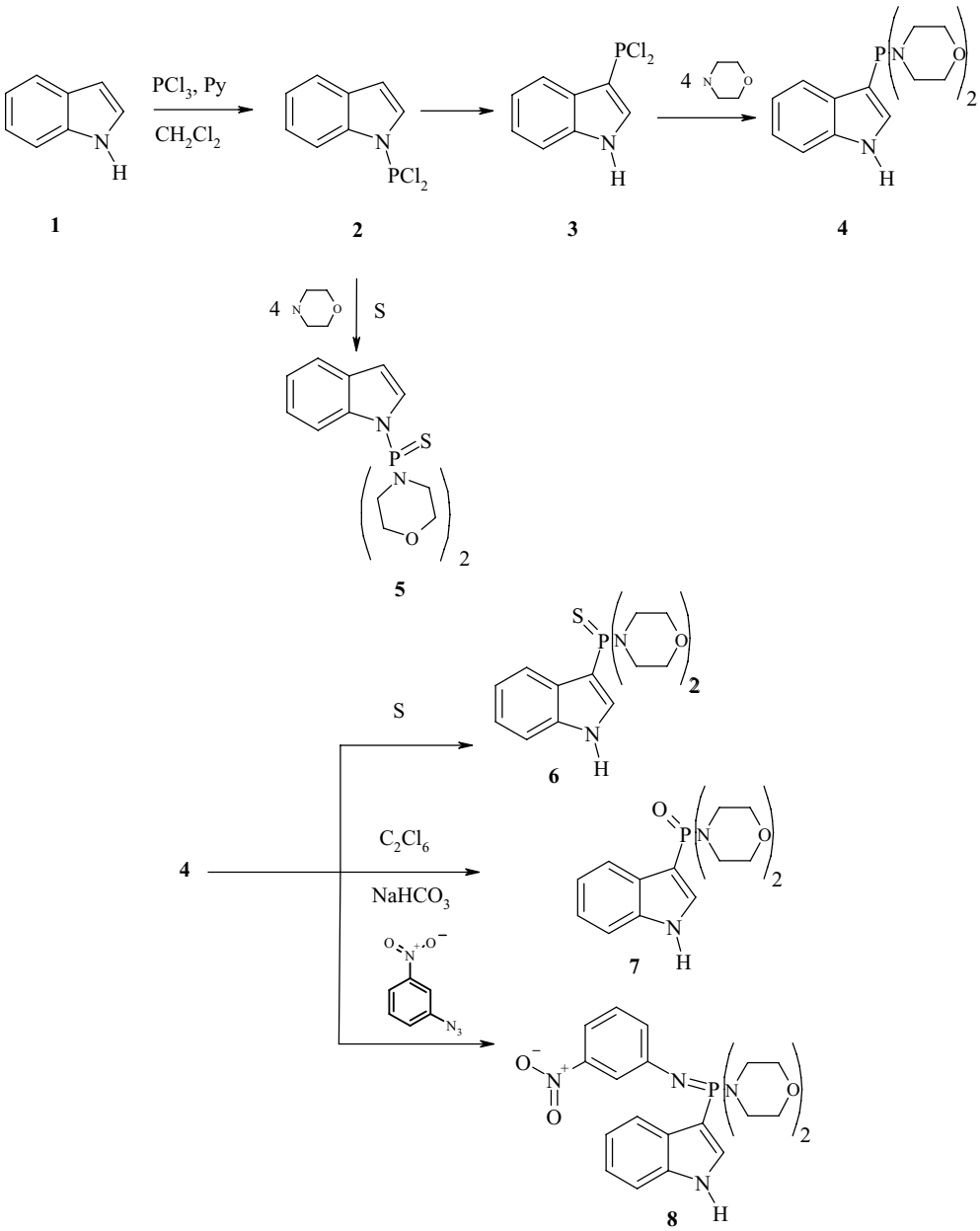
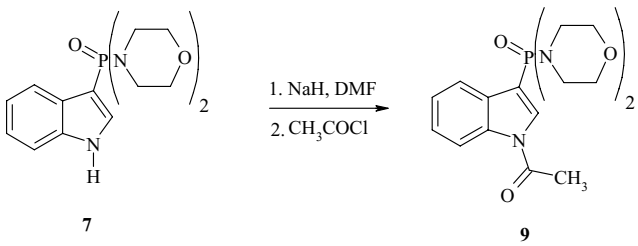


SCHEME 1

in dichloromethane in the presence of 1 equiv of pyridine or triethylamine initially provides the N-phosphorylated product, 1-indolyldichlorophosphine **2**, which rearranges within 2 days to its 3-indolyl isomer **3**. Thus, we have revealed a $N \rightarrow C_3$ migration of the dichlorophosphino group in the indole nucleus (Scheme 1).

^{31}P NMR monitoring of the reaction between indole **1** and phosphorus trichloride in dichloromethane in the presence of 1 equiv of pyridine demonstrates that an hour after the reagents have been mixed, the signal of N-phosphorylated intermediate **2** (143.8 ppm) appears, which is then progressively replaced by that of C_3-phosphorylated product **3** (155.2 ppm). Two days later, the rearrangement is complete and, accordingly, the signal of 3-indolyldichlorophosphine **3** becomes a single one. It should be noted that the migration is significantly slowed down, if conducted in benzene or with triethylamine as base, so that it is possible to obtain 1-indolyldimorpholinophosphine sulfide **5**, a derivative of N-phosphorylated indole **2**.



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SCHEME 2

As previously shown [8], the $C_2 \rightarrow C_3$ migration of the dibromophosphino group in *N*-methylpyrrole occurs due to the catalytic effect of pyridine hydrobromide. Since the $N \rightarrow C_3$ migration of the dichlorophosphino group in indole becomes considerably slower on passing from dichloromethane to benzene, one can assume that this rearrangement is likewise catalyzed by pyridine hydrochloride, which is much less soluble in nonpolar than in polar solvents.

Dichlorophosphines **2** and **3** are highly prone to polymerization and could not be isolated as individual substances; it was, however, possible to isolate amide **4**, a P(III) derivative, which was further converted to P(V) products such as sulfide **6**, oxide **7**, and imino compound **8**.

We have also succeeded in N-acylating 3-phosphorylated indole **7**, which is unreactive toward acetyl chloride or aryl isocyanates under basic conditions even on long boiling in toluene or acetonitrile. It is only the sodium derivative of **7** that enters into the reaction with acetyl chloride to give compound **9** (Scheme 2).

CONCLUSION

Indole reacts with phosphorus trichloride in the presence of pyridine as a hydrogen chloride acceptor to initially produce a N-phosphorylated derivative that rearranges within 2 days to the C_3-phosphorylated product. Thus, a $N \rightarrow C_3$ migration of the dichlorophosphino group occurs in the indole nucleus. Several 3-phosphorylated NH-indole derivatives have thus been obtained, and one of them has been acylated at the nitrogen atom.

EXPERIMENTAL

^{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 tetramethylsilane as the internal standard for ^{1}H and ^{13}C signals and 85% H_3PO_4 as the external standard for ^{31}P signals. Liquid chromatography–mass spectra were registered on an Agilent 1100 Series LC/MSD instrument. All reactions were performed in dry solvents.

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

To a stirred solution of indole (0.01 mol) and pyridine (0.01 mol) in dichloromethane (40 mL), phosphorus trichloride (0.01 mol) was added in a stream of argon at room temperature. The reaction mixture was allowed to stand at room temperature for 48 h ($\delta_P = 155.2$ ppm), followed by thrice-repeated addition of pentane (100 mL), cooling to 0°C, and separation of the organic layer in a stream of argon. The residue was dissolved in benzene (40 mL), ice-cooled, and treated under stirring with morpholine (0.04 mol). Two hours later ($\delta_P = 86.5$ ppm), the precipitate was filtered off and the filtrate was evaporated. The product appears as a light-colored oil. Yield 90%. ^{31}P NMR ($CDCl_3$): δ 86.5. ^{1}H NMR ($CDCl_3$): δ 2.86 (m, 8H, O—CH_2), 3.61 (m, 8H, N—CH_2), 7.18 (m, 4H, Ar), 8.14 (d, 1H, $J_{CP} = 8.0$ Hz, Ar), 9.44 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 49.67 (s, O—CH_2), 68.22 (d, N—CH_2), 111.22, 116.72 (d, $J_{CP} = 691.0$ Hz, C_3), 121.15 s, 122.02 (d, $J_{CP} = 31.5$ Hz), 123.65 (d, $J_{CP} = 25.5$ Hz), 136.55 (d, $J_{CP} = 78.0$ Hz), 140.42 (d, $J_{CP} = 25.0$ Hz). *m/z* 319 $[M]^+$. Anal. Calcd. for $C_{16}H_{22}N_3O_2P$ (319): C 60.18, H 6.94, P 9.70. Found: C 60.10, H 6.85, P 9.78.

1H-Indol-1-yl[di(4-morpholyl)]phosphine Sulfide **5**

To a stirred, ice-cooled solution of indole (0.01 mol) and pyridine (0.01 mol) in benzene (60 mL), phosphorus trichloride (0.01 mol) was added in a stream of argon. The reaction mixture was allowed to stand at room temperature for 2 h ($\delta_P = 143.8$ ppm), followed by the addition of morpholine (0.04 mol) and elementary sulfur (0.01 mol) with ice cooling. After 0.5 h of boiling and cooling the mixture, the resulting precipitate of salts was filtered off. The filtrate was evaporated and the residue was recrystallized from ethanol. Yield 81%. mp 70–71°C. ^{31}P NMR (DMSO): δ 63.3. ^{1}H NMR (DMSO-d_6): δ 3.13 (m, 8H, O—CH_2), 3.54 (m, 8H, N—CH_2), 6.66 (br s, 1H, H_3), 7.16 (t, 1H, $J_{CP} = 7.6$ Hz, Ar), 7.23 (t, 1H, $J_{CP} = 7.6$ Hz, Ar), 7.57 (br s, 2H, Ar), 8.15 (d, 1H, $J_{CP} = 8.0$ Hz, H_2). ^{13}C NMR (DMSO-d_6): δ 45.13 (s, O—CH_2), 65.92 (d, $J_{CP} = 3.0$ Hz, N—CH_2), 105.88 (d, $J_{CP} = 6.0$ Hz, C_3), 114.53 s, 120.45 s, 122.30 s, 127.78 s, 129.17 (d, $J_{CP} = 5.0$ Hz, C_2), 131.22 (d, $J_{CP} = 7.5$ Hz), 136.26 (d, $J_{CP} = 5.0$ Hz). *m/z* 351 $[M]^+$. Anal. Calcd. for $C_{16}H_{22}N_3O_2PS$ (351): C 54.69, H 6.31, P 8.83. Found: C 54.38, H 6.45, P 9.02.

1H-Indol-3-yl[di(4-morpholyl)]phosphine Sulfide **6**

To a solution of compound **4** (0.01 mol) in benzene (50 mL), elementary sulfur (0.01 mol) was added, followed by 0.5 h of boiling and evaporation of the reaction mixture. The residue was recrystallized from acetonitrile. Yield 85%. mp 129–130°C. ^{31}P NMR (DMSO): δ 69.0. ^{1}H NMR (DMSO-d_6): δ 2.99 (m, 8H, O—CH_2), 3.56 (m, 8H, N—CH_2), 7.13 (m, 2H, Ar), 7.47 (d, 1H, $J_{HH} = 7.5$ Hz, Ar), 7.80 (br s, 1H, Ar), 7.92 (d, 1H, $J_{HH} = 9.0$ Hz, Ar), 11.84 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 47.53 (d, $J_{CP} = 18.0$ Hz, O—C), 67.28 (d, $J_{CP} = 25.0$ Hz, N—C), 95.00, 100.82 (d, $J_{CP} = 133.5$ Hz, C_3), 113.25 s, 121.08 s, 122.09 s, 122.86 s, 125.82 (d, $J_{CP} = 25.0$ Hz), 142.38 (d, $J_{CP} = 46.5$ Hz), 142.83 (d, $J_{CP} = 25.0$ Hz). *m/z* 351 $[M]^+$. Anal. Calcd. for $C_{16}H_{22}N_3O_2PS$ (351): C 54.69, H 6.31, P 8.81. Found: C 54.65, H 6.30, P 8.79.

1H-Indol-3-yl[di(4-morpholyl)]phosphine Oxide **7**

To a stirred solution of compound **4** (0.01 mol) in benzene (30 mL), hexachloroethane (0.01 mol) was added at room temperature, followed by stirring the reaction mixture for 3 h. The resulting precipitate was filtered off, dissolved in dichloroethane (30 mL), and treated with a 10% aqueous solution of sodium hydrogen carbonate (30 mL). The organic layer was separated and evaporated, and the residue was recrystallized from diethyl ether. Yield 90%. mp 203–205°C. ^{31}P NMR (DMSO): δ 22.9. ^{1}H NMR (DMSO-d_6): δ 3.01 (br s, 8H, O—CH_2), 3.52 (br s, 8H, N—CH_2), 7.07 (t, 1H, $J_{HP} = 7.5$ Hz, Ar), 7.14 (t, 1H, $J_{HP} = 7.5$ Hz, Ar), 7.44 (d, 1H, $J_{HP} = 8.0$ Hz, Ar), 7.66 (br s, 1H, H_2), 7.75 (d, 1H, $J_{HP} = 8.0$ Hz, Ar), 11.76 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 43.97 (s, O—C), 66.35 (s, N—C), 101.79, 100.36 (d, $J_{CP} = 180.0$ Hz, C_3), 111.7 s, 119.88 (d, $J_{CP} = 29.0$ Hz), 121.49 s, 127.49 (d, $J_{CP} = 11.0$ Hz), 127.99 s, 133.92 (d, $J_{CP} = 20.0$ Hz), 137.16 (d, $J_{CP} = 12.5$ Hz). *m/z* 335 $[M]^+$. Anal. Calcd. for $C_{16}H_{22}N_3O_3P$ (335): C 57.31, H 6.61, P 9.24. Found: C 57.0, H 6.60, P 9.20.

1H-Indol-3-yl[di(4-morpholyl)](N-phenyl)-phosphine Imide **8**

To a stirred solution of compound **4** (0.01 mol) in benzene (30 mL), *m*-nitrophenyl azide (0.01 mol) was added at room temperature, followed by stirring the reaction mixture for 12 h ($\delta_P = 37.14$ ppm). Then, the mixture was boiled for 5 h and evaporated; the residue was recrystallized from methanol. Yield 85%. mp 140–142°C. ^{31}P NMR (DMSO-d_6): δ 14.7. ^{1}H NMR (DMSO-d_6): δ 3.11 (br s, 8H, O—CH_2), 3.57 (br s, 8H, N—CH_2), 7.20 (m, 3H, Ar), 7.34 (br s, 1H, Ar), 7.69 (br s, 1H, Ar), 7.86 (br s, 1H, Ar), 7.93 (m, 2H, Ar), 8.02 (d, 1H, $J_{HP} = 15.0$ Hz, Ar), 11.97 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 44.89 (s, O—C), 66.29 (s, N—C), 99.34, 97.87 (d, $J_{CP} = 185.0$ Hz, C_3), 113.79 s, 115.67 (d, $J_{CP} = 18.5$ Hz), 119.52 s, 120.63 (d, $J_{CP} = 12.5$ Hz), 122.05 s, 125.59 s, 127.53 (d, $J_{CP} = 11.5$ Hz), 129.27 (d, $J_{CP} = 25.0$ Hz), 131.09 s, 135.15 (d, $J_{CP} = 18.5$ Hz), 137.37 (d, $J_{CP} = 14.0$ Hz), 141.22 s, 148.60 (d, $J_{CP} = 16.0$ Hz). *m/z* 457 $[M]^+$. Anal. Calcd. for $C_{22}H_{28}N_5O_4P$ (457): C 57.76, H 6.17, P 6.77. Found: C 57.74, H 6.15, P 6.75.

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

To a stirred solution of compound **7** (0.01 mol) in DMF (10 mL), a 60% mineral oil suspension of sodium hydride (0.012 mol) was added, followed by stirring the reaction mixture at room temperature for 12 h. After the addition of acetyl chloride (0.01 mol), the mixture was stirred at 40°C for another 8 h, poured into water, and extracted with dichloromethane (3 × 20 mL). The organic layer was separated and dried over sodium sulfate, and the solvent was evaporated in vacuo. The residue was recrystallized from acetonitrile. Yield 80%. mp 200–201°C. ^{31}P NMR (DMSO-d_6): δ 19.7. ^{1}H NMR (DMSO-d_6): δ 2.67 (s, 3H, CH_3), 3.17 (m, 8H, O—CH_2), 3.65 (m, 8H, N—CH_2) 7.26 (br s, 1H, H_2), 7.67 (m, 2H, Ar), 8.04 (d, 1H, $J_{HH} = 5.4$ Hz, Ar), 8.50 (d, $J_{HP} = 8.1$ Hz 1H, Ar). ^{13}C NMR (DMSO-d_6): δ 24.65 (s, CH_3), 44.91 (s, O—C), 67.20 (s, N—C), 106.45, 100.86 (d, $J_{CP} = 222.0$ Hz, C_3), 111.70 s, 124.57 (d, $J_{CP} = 10.0$ Hz), 125.08 s, 125.60 s, 126.21 (d, $J_{CP} = 8.0$ Hz), 134.13 (d, $J_{CP} = 16.0$ Hz), 139.50 (d, $J_{CP} = 8.0$ Hz), 166.42 s. *m/z* 378 $[M]^+$. Anal. Calcd. for $C_{18}H_{24}N_3O_4P$ (377): C 57.29, H 6.41, P 8.21. Found: C 57.25, H 6.38, P 8.20.

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