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# Synthesis of 4,5-Dihydroimidazo[5,1-*c*][1,4,2]benzodiazaphosphinines

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ABSTRACT: *Derivatives of a novel phosphorus-containing heterocyclic system, 4,5-dihydroimidazo [5,1-c][1,4,2]benzodiazaphosphinine, have been prepared by the direct phosphorylation of 1-(2-(aroyl/alkyl)aminophenyl)-2-methylthioimidazole with dibromophenylphosphine in a basic medium.* © 2010 Wiley Periodicals, Inc. Heteroatom Chem 22:91–95, 2011; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20658

## *INTRODUCTION*

C-Phosphorylated imidazoles attract a great deal of attention due to their diverse biological activity. In addition, their P(III) derivatives can be prospective ligands for metal complex catalysis [1,2].

Earlier we found a convenient method for the preparation of phosphorylated imidazoles using phosphorus(III) halides in a basic medium [3]. This approach is widely used in a synthetic strategy, allowing synthesis of phosphorus-containing fused heterocyclic systems that are not very accessible by other routes. The approach is based on direct phosphorylation of a substrate containing two nucleophilic centers: electron-rich aryl or heteroaryl C-nucleophilic center and other nucleophilic heteroatom (N, O). Various polycyclic systems based on imidazole, pyrazole, thiophene, and furan were synthesized [4,5,6].

We have shown that phosphorylation of N-alkyl (aryl) substituted imidazoles proceeds at the 2-position. If the second position of the imidazoles is occupied, the phosphorylation is directed at the fifth position [3]. Thus, a series of 5-phosphorylated imidazoles with a trivalent and pentavalent phosphorus atom was synthesized, among which the 5-dichlorophosphino-derivatives of 1,2-disubstitued imidazoles are the most considerable as the first representative of dihalophosphines in the series of imidazoles.

In this paper, we explore a possibility of applying the same strategy for the synthesis of a novel phosphorus-containing heterocyclic system—that is, 4,5-dihydrobenzo[e]imidazo[5,1-*c*][1,4,2]diazaphosphinine. As a substrate, we use the imidazole in which the second position is blocked by a methylthio group and the second N-nucleophilic center is places on the phenyl ring, thus allowing formation of cyclic products with biselectrophiles.

## *RESULTS AND DISCUSSION*

The suitable starting compounds—acylaminophenylimidazole **5** (Scheme 1) and alkylaminophenylimidazole **7** (Scheme 2)—are not described in the literature, so we have synthesized them starting from *o*-nitroaniline. A one-pot two-step treatment of *o*-nitroaniline **1** with thiophosgene in the presence of HCl and 2-aminoacetaldehyde diethylacetal gave imidazole

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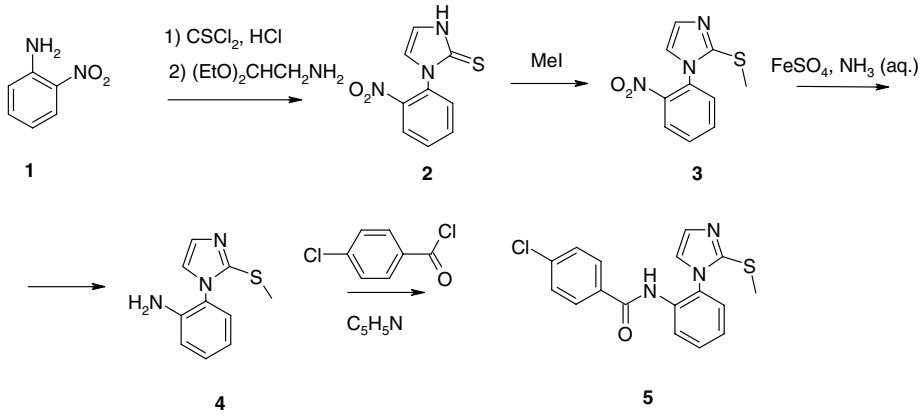
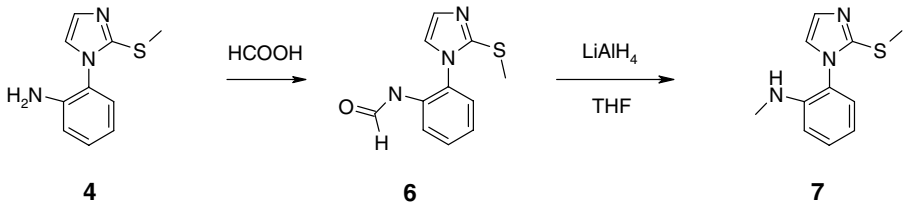



SCHEME 1




SCHEME 2

**2**. Methylation of the SH-group with methyl iodide afforded 2-methylthioimidazole **3**, and its reduction with $FeSO_4$/ammonium hydroxide gave rise to aminophenyl-methylthioimidazole **4**. Acylation of the latter with 4-chlorophenylcarboxylic acid chloride in pyridine afforded derivative **5**.

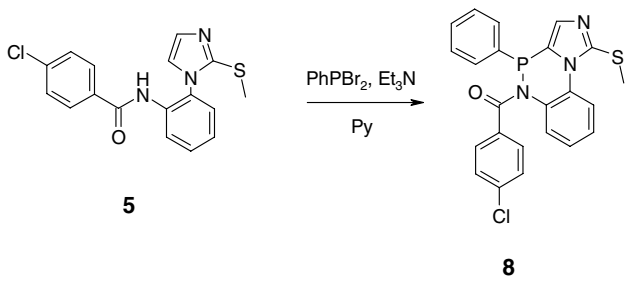
1-(2-Methylaminophenyl)-2-methylthioimidazole **7** was obtained from imidazole **4** by formylation with 85% aqueous formic acid and subsequent reduction with lithium aluminum hydride in THF.

We have found that imidazole derivative **5** reacts with dibromophenylphosphine in pyridine medium in the presence of two equivalents of triethylamine giving rise to diazaphosphinine **8** in high yield (see Scheme 3).

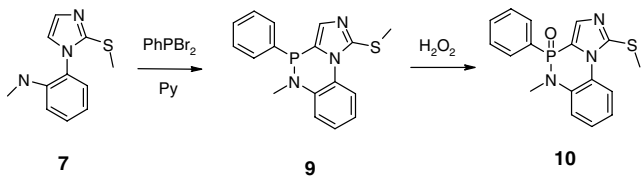
Diazaphosphinine **8** was isolated as white crystals, which are poorly soluble in benzene and diethyl ether.

Synthesis of compound **9** was carried out analogously. As it was impossible to purify the target compound **9** to an analytically pure sample, it was oxidized with hydrogen peroxide to its oxide **10**. Extraction and recrystallization gave product **10** in 33% yield as yellowish air-stable crystals (see Scheme 4).

The cyclization of the starting aminoimidazoles was confirmed by disappearance of signals of C(5)-H and NH-protons of the imidazoles in the $^1H$ NMR spectra.




SCHEME 3




SCHEME 4

## *CONCLUSION*

We have shown that imidazoles **5** and **7** bearing two nucleophilic centers, imidazole C5 carbon atom and NH atom at the phenyl ring, are suitable substrates for phosphorylation with dibromophenylphosphine. A novel phosphorus-containing heterocyclic system, 4,5-dihydroimidazo[5,1-*c*][1,4,2]benzodiazaphosphinine, has been prepared.

## *EXPERIMENTAL*

All the manipulations with air-sensitive compounds were performed under an atmosphere of dry argon using standard Schlenk techniques. Solvents were purified by conventional procedures. Melting points were determined with an electrothermal capillary melting point apparatus and were not corrected.

The $^{31}P$, $^{1}H$, and $^{13}C$ NMR spectra were obtained on a Varian VXR-300 spectrometer (125, 300, and 75 MHz, respectively, if other is not specified). Chemical shifts are reported relative to internal tetramethylsilane ($^{1}H$, $^{13}C$) or external 85% $H_3PO_4$ ($^{31}P$). Mass-spectra were obtained on a MX-1321 instrument (EI, 70 eV) by a direct inlet. LC/MS spectra were recorded using an Agilent 1100 series HPLC equipped with diode-matrix and mass-selective detector Agilent LC\MSD SL. The parameters of chromatography–mass analysis: column, Zorbax SB-C18, 1.8 mm, 4.6 mm × 15 mm; eluent A: MeCN-$H_2O$ with 0.1% of TFA (95:5); eluent B: $H_2O$ with 0.1% of TFA; flow rate, 3 mL/s; volume of injected sample: 1 mL; UV-detectors at 215, 254, and 265 nm; ionization method: chemical ionization under atmospheric pressure (APCI); ionization mode: simultaneous scanning of positive and negative ions in the mass range of 80–1000 *m/z*.

### *1-(2-Nitrophenyl)-1H-imidazole-2-thiol (**2**)*

o-Nitroaniline **1** (25.0 g, 0.18 mol) was added to hydrochloric acid (500 mL, 20%). The resulted mixture was heated at 50°C until all *o*-nitroaniline was dissolved. Then, $CSCl_2$ (22.6 g, 0.2 mol) was added and the reaction mixture was stirred at 20°C for 4 h. The precipitate was filtered and added to the solution of 2-aminoacetaldehyde diethylacetal (24.0 g, 0.18 mol) in ethanol (200 mL). The reaction mixture was refluxed for 30 min, then ethanol was evaporated. The residue was refluxed for 1 h with hydrochloric acid (200 mL, 10%). The precipitated solid was filtered and crystallized from ethanol. Yield: 41.0 g (28%), mp 202–205°C. $^{1}H$ NMR (DMSO-$d_6$/TMS, 500 MHz): $\delta$ (ppm) 7.11 (s, 1H, H-5 Im), 7.31 (s, 1H, H-4 Im), 7.60 (d, $J$ = 8.5 Hz, 1H, H-6 Ph), 7.73 (t, $J$ = 7 Hz, 1H, H-4 Ph), 7.88 (t, $J$ = 9 Hz, 1H, H-5 Ph), 8.16 (d, $J$ = 7.5 Hz, 1H, H-3 Ph), 12.43 (br-s, 1H, SH). $^{13}C$ NMR (DMSO-$d_6$/TMS): $\delta$ (ppm) 116.24, 116.39, 120.11, 125.75, 130.63, 130.88, 131.44, 135.11, 146.23, 163.15. NMR spectrum is consistent with the literature data [7].

### *1-(2-Nitrophenyl)-2-methylthioimidazole (**3**)*

Compound **2** (19.1 g, 87.0 mmol) and NaOH (4.0 g, 0.1 mol) were dissolved in methanol (100 mL). Methyl iodide (5.4 mL, 87.0 mmol) was added to the solution. After stirring for 2 h at 20°C, the reaction mixture was evaporated and the residue was extracted with hot benzene (100 mL). The precipitated solid was filtered off; the filtrate was evaporated. The residue was recrystallized from ethanol. Yield: 18.3 g (90.1%). $^{1}H$ NMR ($CDCl_3$/TMS): $\delta$ (ppm) 2.57 (s, 3H, SMe), 7.06 (d, $J$ = 1.2 Hz, 1H, H-5 Im), 7.25 (d, $J$ = 1.5 Hz, 1H, H-4 Im), 7.49 (dd, $J$ = 7.8 Hz, $J$ = 1.5 Hz, 1H, H-6 Ph), 7.68 (td, $J$ = 7.8 Hz, $J$ = 1.5 Hz, 1H, H-4 Ph), 7.80 (td, $J$ = 6 Hz, $J$ = 1.5 Hz, 1H, H-5 Ph), 8.13 (dd, $J$ = 8 Hz, $J$ = 1.2 Hz, 1H, H-3 Ph). MS (APCI) $m/z$(%) = 236 [M].

### *1-(2-Aminophenyl)-2-methylthioimidazole (**4**)*

Aqueous $NH_3$ (20%, 450 mL) was added to methylthioimidazole **3** (9.0 g, 0.04 mol). A solution of $FeSO_4 \cdot 7H_2O$ (65.0 g) in water (80 mL) was added to the mixture with stirring at 50°C. The reaction mixture was refluxed for 2 h. Then, water was evaporated and the residue was extracted with dichloromethane. Combined extracts were washed with water; the organic layer was separated, dried, and evaporated. Yield: 6.0 g (77%). $^{1}H$ NMR (DMSO-$d_6$/TMS): $\delta$ (ppm) 2.46 (s, 3H, SMe), 4.85 (br-s, 2H, $NH_2$), 6.62 (td, $J$ = 7.5, $J$ = 1.4, 1H, H-5 Ph), 6.84 (dd, $J$ = 8.1 Hz, $J$ = 1.2 Hz, 1H, H-3 Ph), 6.97 (dd, $J$ = 6.3 Hz, $J$ = 1.4 Hz, 1H, H-6 Ph), 7.12 (dd, $J$ = 1.2 Hz, 1H, H-5 Im), 7.16 (td, $J$ = 7.2 Hz, $J$ = 1.4 Hz, 1H, H-4 Ph), 7.23 (d, $J$ = 1.4 Hz, 1H, H-4 Im). MS (70 eV) $m/z$ (%): 205 (82.11, $M^+$), 158 (100), 132 (43.25), 131 (45.50), 106 (56.51).

### *1-(2-(4-Chlorobenzylamino)phenyl)-2-methylthioimidazole (**5**)*

4-Chlorobenzoylchloride (4.2 g, 0.025 mol) was dissolved in dry pyridine (50 mL), and the mixture was cooled to −10°C. 5.0 g (25.0 mmol) of compound **4** was added after precipitation of colorless complex. The reaction mixture was stirred for 4 h at 20°C. Then the solution was poured onto ice, the crystals were filtrated, crystallized from benzene. Yield: 4.3 g

(51%). $^1$H NMR (DMSO-$d_6$/TMS): $\delta$ (ppm) 2.43 (s, 3H, SMe), 6.99 (s, 1H, H-5 Im), 7.25 (s, 1H, H-4 Im), 7.41 (d, $J$ = 4 Hz, 2H, H-6, H-3 Ph), 7.53 (m, 3H, H-5 Ph + *meta*-Cl-$C_6H_4$-CO), 7.61 (m, 1H, H-4 Ph), 7.76 (d, $J$ = 8 Hz, 2H, *ortho*-Cl-$C_6H_4$-CO), 9.97 (br-s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$/TMS): $\delta$ (ppm) 15.64, 122.85, 126.83, 127.84, 127.91, 127.95, 128.40, 128.71, 129.19, 129.42, 129.55, 132.35, 132.40, 132.83, 132.88, 133.39, 133.53, 136.47, 142.53, 164.41, 164.51. MS (70 eV) *m/z* (%): 343 (16.95, $M^+$), 141 (32.33), 139 (100), 132 (20.23), 111 (40.75).

### *1 - (2 - Formylaminophenyl) - 2 - methylthioimidazole (**6**)*

Imidazole **4** (3.0 g, 14.6 mmol) was added to an aqueous solution of formic acid (20 mL 85%, 0.44 mol). The reaction mixture was refluxed for 0,5 h. After cooling to r.t., the solution was evaporated and the residue was crystallized from MeOH-$H_2O$ (1:1). Yield: 2.3 g (68%). $^1$H NMR ($CDCl_3$): $\delta$ (ppm) 2.52 (s, 3H, SMe), 7.01 (d, 1H, H-4 Im, $J$ = 1,2 Hz), 7.13 (d, 1H, H-5 Im, $J$ = 1,5 Hz), 7.25 (br m, 2H, H-3,5 Ph), 7.50 (br m, 1H, H-4 Ph), 8.15 (br s, 1H, NH), 8.46 (d, 1H, H-6 Ph, $J$ = 1,7 Hz), 8.52 (d, 1H, C(O)H, $J$ = 8.4 Hz), $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) 15.33, 119.77, 122.00, 122.57, 124.76, 125.94, 128.06, 130.57, 133.90, 145.24, 159.42. MS (70 eV) *m/z* (%): 233 (100, $M^+$), 186 (78.19), 158 (83.00), 131 (87.02), 106 (86.02). mp 170–175°C.

### *1 - (2 - Methylaminophenyl) - 2 - methylthioimidazole (**7**)*

Lithium aluminum hydride (1.14 g, 0.03 mol) was added to THF (25 mL), then 2.3 g (9.6 mmol) of compound **6** was added to the reaction mixture. It was stirred for 2 h and was quenched with water. The solution obtained was filtered, the filtrate was evaporated, and the residue was twice recrystallized from heptane. The product was dried in vacuum. Yield: 1.6 g (77%). $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ (ppm) 2.59 (s, 3H, SMe), 2.84 (d, 3H, NH-Me, $J$ = 5 Hz), 3,53 (br s, 1H, NH), 6.78 (d, 2H, H-5.6 Ph), 7.02 (d, 1H, H-5 Im, $J$ = 0.5 Hz), 7.10 (d, 1H, H-3 Ph, $J$ = 7.5 Hz), 7.24 (d, 1H, H-4 Im, $J$ = 1 Hz), 7.38 (t, 1H, H-4 Ph, $J$ = 7.5 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) 15.30, 29.99, 111.26, 116.47, 122.07, 122.11, 128.19, 130.03, 130.57, 145.16, 144.96. MS (70 eV) *m/z* (%): 219 (23.72, $M^+$), 172 (100.00), 157 (21.81), 145 (23.26), 131 (15.76). mp 137–140°C.

### *5-(4-Chlorobenzoyl)-1-(methylthio)-4-phenyl-4,5-dihydroimidazo[5,1-c][1,4,2]benzodiazaphosphine (**8**)*

Dibromophenylphosphine (0.80 g, 3.0 mmol) and dry triethylamine (0.63 g, 6.2 mmol) were consequently added to a solution of imidazole **5** (1.0 g, 3.0 mmol) in dry pyridine (10 mL) cooled from −5 to −10°C. After keeping for 30 h at 2 °C, the pyridine was evaporated in vacuo, the residue was treated with hot benzene (20 mL), $Et_3N{\cdot}HCl$ precipitated was filtered under argon, the filtrate was evaporated, and the residue was extracted with hot hexane (60 mL). After decantation from the oil, the extract was evaporated. The residue obtained after evaporation was treated with ether (30 mL), and the solid product was collected by filtration. Yield: 1.2 g (91%), mp 148–149°C. $^1$H NMR ($C_6D_6$/TMS): $\delta$ (ppm) 2.50 (s, 1H, SMe), 6.43 (t, $J$ = 6.3 Hz, 1H, H-5 Ph), 6.58 (t, $J$ = 7.8 Hz, 1H, H-4 Ph), 6.75 (m, 6H, P-Ph + H-6 Ph), 7.21 (m, 4H, Cl–$C_6H_4$–CO), 7.52 (s, 1H, H-4 Im), 7.76 (d, $J$ = 8.4 Hz, 1H, H-3 Ph). $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) 15.66, 120.75, 125.58, 126.14, 126.81, 126.91, 128.48, 128.61, 129.03, 129.56, 130.97, 131.74, 132.94, 135.73, 137.34, 137.68, 137.98, 146.85, 171.41. $^{31}$P NMR ($C_6D_6$): $\delta$ (ppm) 5.50. MS (70 eV) *m/z* (%): 449 (20.17, $M^+$), 325 (37.07), 312 (45,79), 237 (21.33), 139 (100), 111 (48.25).

### *1-Ethyl-5-methyl-4-phenyl-4,5-dihydroimidazo[5,1-c][1,4,2] benzodiazaphosphinine 4-oxide (**10**)*

Compound **7** (0.90 g, 4.0 mmol) was added to a solution of 1.1 g (4 mmol) of dibromophenylphosphine in pyridine (10 mL) to cooled to −30°C. The mixture was allowed to warm to r.t. After a week, the solution was evaporated in vacuum, the residue was treated with hot benzene, and the precipitated material was filtrated. The benzene filtrate was evaporated, and the impurities were extracted by hot hexane. The residue was dissolved in $Et_2O$ and $H_2O_2$ (0.5 mL 35% aq.) was added. The ether solution was evaporated, and the residue was dissolved in dichloromethane and washed with water. The organic layer was evaporated, and the residue was extracted with hot benzene, the benzene was evaporated, and the residue was recrystallized from ether. Yield: 0.46 g (33%) $^1$H NMR ($CDCl_3$): $\delta$ (ppm) 2.82 (s, 3H, SMe), 3.12 (d, 3H, NMe, $J$ = 8.5 Hz), 7.2 (br m, 2H, H-6 Ph, *para*-H P-Ph), 7.38 (br t, 1H, H-5 Ph), 7.45 (br s, 2H, *meta*-H P-Ph), 7.45 (br m, 2H, H-3,4 Ph), 7.69 (br m, 2H, *ortho*-H P-Ph), 8.14 (d, 1H, H-4 Im, $J$ = 8 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm)

16.50, 30.41, 30.89, 116.84, 116.80, 120.24, 121.58, 123.03, 124.23, 125.39, 127.77, 128.72, 128.83, 129.95, 131.06, 131.71, 131.80, 132.73, 132.75, 134.27, 135.56, 135.69. $^{31}$P NMR ($CDCl_3$): $\delta$ (ppm) 9.52. MS (APCI) $m/z$ (%) = 342 [M + 1].

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