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C-Phosphorylated Pyrrolylcarbaldehydes

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ABSTRACT: *Application of* N,N-*dimethylhydrazone protective group for synthesis of C-phosphorylated aldehydes of the pyrrole series was studied. Removal of the hydrazone protection in monophosphorylated pyrrolylcarbaldehyde hydrazones occurs smoothly, while in biphosphorylated derivatives it results in nitrile formation.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:258–261, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10137

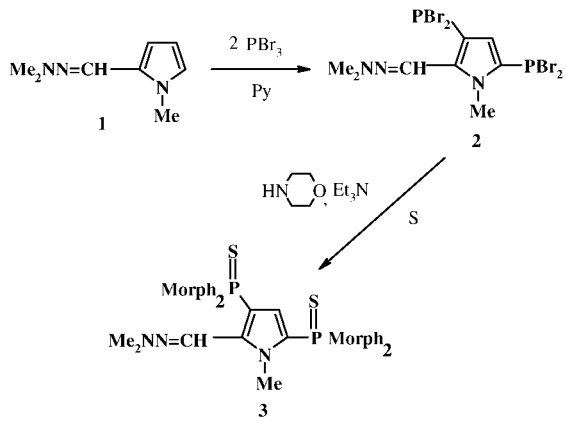
INTRODUCTION

Previously we have shown that the application of *N*,*N*-dimethylhydrazone protective group makes possible the synthesis of C-phosphorylated derivatives of furfurol and 2-thienylcarbaldehyde [1,2]. In the phosphorylation the hydrazone group acts not only as an orienting but also as a strongly activating group. This allowed the synthesis not only of mono- but also of biphosphorylated furfurol derivatives. In the present work we used the method we have developed to obtain the previously unknown C-phosphorylated pyrrolylcarbaldehydes.

RESULTS AND DISCUSSION

Unlike the reaction of phosphorus tribromide with furfurol and 2-thiophene aldehyde hydrazones, the reaction with 2-pyrrolylaldehyde hydrazone (**1**) proceeds not regioselectively but leads to a mixture of products. In the ^{31}P NMR spectra of these mixtures two most intensive signals at $\delta = 106.8$ and 137.7 ppm in 1:6 ratio were observed, indicating that phosphorylation at α and β positions respectively took place. No individual compound could be isolated from the reaction mixture.

Phosphorylation of the hydrazone **1** with two equivalents of phosphorus tribromide in pyridine takes place at positions 2 and 5 of the heterocycle with the formation of bisdibromophosphine (**2**), which can be easily converted into corresponding bisthioamide **3**.



In the ^{1}H NMR spectrum of **3** a triplet at $\delta =$ 6.5 ppm for the proton in the position 4 of the pyrrole ring and a singlet for the CH=N proton at 8.05 ppm can be observed.

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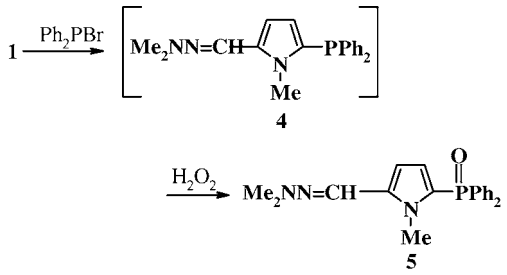
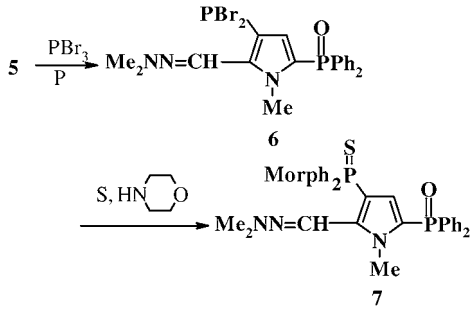
Selective monophosphorylation of **1** was achieved with diphenylbromophosphine in pyridine at room temperature. The resulting phosphine **4** (δ ^{31}P = −18.0 ppm) was converted into the phosphine oxide **5** by hydrogen peroxide in good yield.

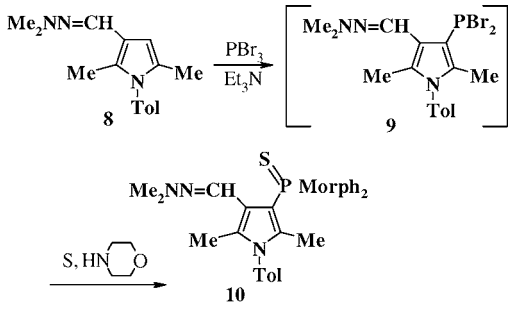


Presence of two doublets of doublets at δ = 6.28 and 5.05 ppm for 4-H and 3-H and a singlet for CH=N at 7.26 ppm in the ^{1}H NMR of **5** indicate that the reaction had occurred at position 5 of the heterocycle.

Phosphine oxide **5** can be regioselectively phosphorylated with phosphorus tribromide at position 3. Dibromophosphine **6** thus obtained (δ ^{31}P = 143 ppm, 15 ppm) was not isolated because of its low stability and was converted into the thioamide **7** in high yield.

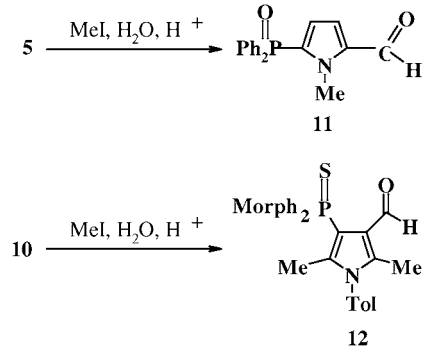


The phosphorylation of hydrazone **8** with phosphorus tribromide yields the dibromophosphine **9** (δ ^{31}P = 141 ppm) which was converted into thioamide **10**.

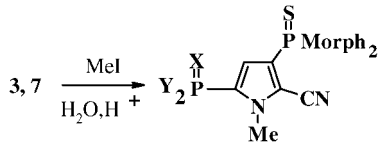


The absence of signals for protons of the heterocyclic system in the ^{1}H NMR spectrum of compound **10** and presence of a signal because of exocyclic proton of hydrazone group at 8.08 ppm indicate that the phosphorylation took place at the ring.

There are several methods of conversion of a hydrazone into an aldehyde group described in the literature [3]. These methods are mostly based on oxidation or hydrolysis of the hydrazone group in strong acid media. We have chosen the method that includes preliminary activation of the C=N bond of the hydrazone by alkylation of the amine nitrogen atom. The subsequent acidic hydrolysis can be then carried out under mild conditions. This method makes it possible to regenerate the carbonyl group despite the well-known low stability of the heterocycles in question in acid media. By alkylation with methyl iodide and subsequent hydrolysis, phosphine oxide **5** and thioamide **10** were converted into the aldehydes **11** and **12** respectively.



The removal of the hydrazone protection in **3** and **7** was made similarly but in this case the nitriles **13** and **14** were obtained.

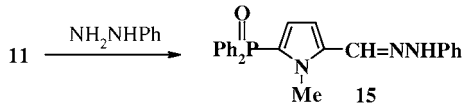


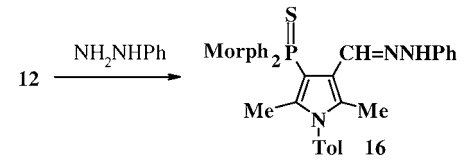
13: X= O Y=Ph **14:** X=S, Y= N O

The structures of **13** and **14** are supported by the absence in the IR spectra of a characteristic absorption band corresponding to the aldehyde group and presence of an absorption band at 2240 cm^{-1} which can be assigned to the nitrile group. In the ^{1}H NMR spectrum of nitriles **13** and **14**, no signals due to proton of the aldehyde group can be observed either.

The formation of nitriles in this reaction is probably caused by the increased acidity of hydrogen atom of hydrazonium group owing to the effect of two electron-withdrawing phosphorous substituents.

The carbonyl group in aldehydes **11** and **12** demonstrates characteristic behavior, e.g. reaction with phenylhydrazine to the corresponding phenylhydrazones **15** and **16**.





EXPERIMENTAL

^{1}H and ^{31}P NMR spectra were recorded on Varian VXR 300 using TMS as internal standard for ^{1}H NMR and 85% H_3PO_4 as external standard for ^{31}P NMR spectra. All experiments were carried out in waterfree solvents.

*3,5-Bis(dimorpholinothiophosphonate)-1-methyl-1H-pyrrole-2-carbaldehyde N,N-Dimethylhydrazone (**3**)*

To a solution of 1 mmol of **1** in 50 ml of pyridine a solution of 2 mmol of phosphorus tribromide in 5 ml of pyridine was added at 5°C with stirring. In 48 h, to the reaction mixture a solution of 4 mmol of morpholine and 6 mmol of triethylamine in 150 ml of benzene was added. In 30 min the precipitate was filtered off, to the filtrate 2 mmol of sulphur was added and the resulting mixture was heated over 2 h at 80°C. The solvent was evaporated in vacuo and the product was obtained by crystallization from octane. Yield 54%, m.p. 181–183°C. ^{1}H NMR ($CDCl_3$), δ: 3.02s (6H, N─$(CH_3)_2$); 3.05–3.30m (16H, N─CH_2); 3.50–3.80m (16H, O─CH_2); 4.13s (N─CH_3); 6.51t (1H, Het, J_{PH} = 1.2 Hz), 8.05s (CH═N). ^{31}P NMR ($CDCl_3$), δ: 60.5, 67.8. Found: N, 16.01; P, 10.14. $C_{28}H_{37}N_5O_3P_2S$ (calculated): N, 15.83; P, 10.02.

*5-(Diphenylphosphoryl)-1-methyl-1H-pyrrole-2-carbaldehyde N,N-Dimethylhydrazone (**5**)*

To a solution of 2 mmol of **1** in 10 ml of pyridine a solution of 2 mmol of diphenylbromophosphine in 10 ml of pyridine was added. The reaction mixture was kept for 24 h at room temperature, the precipitate was filtered off, and the solvent was removed from the filtrate in vacuo. The residue was dissolved in 100 ml of chloroform, and 15 ml of 30% hydrogen peroxide was added slowly with stirring in such a way that the temperature of the reaction mixture did not exceed 5°C. Subsequently, the reaction mixture was kept for 2 h at room temperature, the organic layer was separated, neutralized with 5% solution of NaOH, washed with water (3 × 50 ml), dried with sodium sulphate, and the solvent was removed in vacuo. The residue was treated with diethyl ether. Yield 60%, m.p. 136–138°C. ^{1}H NMR ($CDCl_3$), δ: 2.07s (6H, N─CH_3); 3.27s (3H, N─CH_3); 5.05dd (1H, H_3, J_{PH} = 0.9 Hz, J_{HH} = 4.2 Hz); 6.26dd, (1H, H_4, J_{PH} = 1.2 Hz, J_{HH} = 4.2 Hz); 7.26s (1H, CH═N); 7.50–7.80m (10H, Ph). ^{31}P NMR ($CDCl_3$), δ: 18.2. Found: N, 12.01; P, 8.92. $C_{20}H_{22}N_3OP$ (calculated): N, 11.97; P, 8.83.

*3-Dimorpholinothiophosphoryl-5-diphenylphosphoryl-1-methyl-1H-pyrrole-2-carbaldehyde N,N-Dimethylhydrazone (**7**)*

To a solution of 1 mmol of **5** in 20 ml of pyridine a solution of 1 mmol of phosphorus tribromide in 5 ml of pyridine was added. The reaction mixture was kept for 72 h at room temperature. A solution of 2 mmol of morpholine and 3 mmol of triethylamine in 10 ml of benzene was added. In 30 min the 1 mmol of sulphur was added and the resulting mixture was heated over 2 h at 70°C. The precipitate was filtered off, the solvent was evaporated in vacuo, and the residue was treated with diethyl ether. Yield 45%, m.p. 210–211°C. ^{1}H NMR ($CDCl_3$), δ: 2.60–3.20m (14H, $N(CH_3)_2$ + N─CH_2); 3.30–3.50m (8H, O─CH_2); 3.84s (3H, N─CH_3); 6.63t (1H, Het, J_{PH} = 1.0 Hz), 6.90–7.70m (10H, Ph); 7.99s (CH═N). ^{31}P NMR ($CDCl_3$), δ: 18.9, 66.8. Found: N, 12.34; P, 10.76. $C_{28}H_{37}N_5O_3P_2S$ (calculated): N, 12.57; P, 10.92.

*4-Dimorpholinothiophosphoryl-1-(p-tolyl)-2,5-dimethyl-1H-pyrrole-2-carbaldehyde N,N-Dimethylhydrazone (**10**)*

To a solution of 1 mmol of **8** and 1 mmol of triethylamine in 20 ml of benzene a solution of 1 mmol of phosphorus tribromide in 5 ml of benzene was added. The reaction mixture was kept for 2 h at room temperature and a solution of 2 mmol of morpholine and 2 mmol of triethylamine in 10 ml of benzene was added. In 30 min to the reaction mixture 1 mmol of sulphur was added and the mixture was heated at 70°C for 2 h. The precipitate was filtered off and the solvent from the filtrate was removed in vacuo. The product was obtained by crystallization from ethanol. Yield 60%, m.p. 181–183°C. ^{1}H NMR ($CDCl_3$), δ: 2.13s (3H, C─CH_3); 2.28s (3H, C─CH_3); 2.44s (3H, C─CH_3); 2.90s (6H, N─CH_3); 3.18m (8H,

N—CH_2); 3.67m (8H, O—CH_2); 7.02d (2H, o-H, J_{HH} = 8.4 Hz); 7.29d (2H, m-H, J_{HH} = 8.4 Hz); 8.08s (1H; CH=N). ^{31}P NMR ($CDCl_3$), δ: 67.5. Found: N, 14.21; P, 6.32. $C_{24}H_{36}N_5O_2PS$ (calculated): N, 14.30; P, 6.33.

*5-(Diphenylphosphoryl)-1-methyl-1H-pyrrole-2-carbaldehyde (***11***)*

To 5 mmol of **5**, 5 ml of ethyliodide was added, the mixture was boiled for 4 h, and then the solvent was removed in vacuo. The residue was dissolved in 50 ml of 3% hydrochloric acid solution and was heated for 10 h at 80–85°C. The reaction mixture underwent extraction with chloroform several times; afterwards chloroform was removed in vacuo and the product was obtained by crystallization from heptane. Yield 30%, m.p. 64–65°C. ^{1}H NMR ($CDCl_3$), δ: 4.00s (3H, N—CH_3); 6.07dd (1H, H_3, J_{PH} = 1.0 Hz, J_{HH} = 1.5 Hz); 7.03dd (1H, H_4, J_{PH} = 1.3 Hz, J_{HH} = 1.5 Hz); 7.50–8.10m (10H, Ph); 9.75s (1H, CH=O). ^{31}P NMR ($CDCl_3$), δ: 18.4. Found: N, 4.31; P, 9.96. $C_{18}H_{16}NO_2P$ (calculated): N, 4.53; P, 10.03.

*4-Dimorpholinothiophosphoryl-1-(p-tolyl)-2,5-dimethyl-1H-pyrrole-2-carbaldehyde (***12***)*

A solution of 10 mmol of **10** in 20 ml of methyl iodide was boiled for 5 h. The precipitate was filtered off and dissolved in 10 ml of 1% solution of hydrochloric acid. The reaction mixture was boiled for 3 h. The product was extracted with methylene chloride (2 × 20 ml). The organic layer was separated, dried with sodium sulphate, and the solvent was removed in vacuo. The product was obtained by crystallization from ethanol. Yield 40%, m.p. 214–215°C. ^{1}H NMR ($CDCl_3$), δ: 2.29s (3H, C—CH_3); 2.32s (3H, C—CH_3); 2.45s (3H, C—CH_3); 3.17m (8H, N—CH_2); 3.69m (8H, O—CH_2); 7.00d (2H, o-H, J_{HH} = 8.7 Hz); 7.34d (2H, m-H, J_{HH} = 8.7 Hz); 10.65s (1H; CH=O). NMR ^{31}P ($CDCl_3$), δ: 66.2. Found: N, 9.41; P, 6.83. $C_{22}H_{30}N_3O_3PS$ (calculated): N, 9.39; P, 6.92.

*2-Cyano-1-methyl-1H-pyrrole-5-diphenylphosphoryl-3-dimorpholinothiophosphonate (***13***)*

To 1 mmol of **8**, 5 ml of ethyl iodide was added. The mixture was boiled for 7 h and the solvent was removed in vacuo. To the residue thus formed 50 ml of 3% solution of hydrochloric acid was added and the reaction mixture was heated for 96 h at 85°C. The formed precipitate was recrystallized from octane. Yield 37%, m.p 233–234°C. ^{1}H NMR ($CDCl_3$), δ: 2.70–3.10m (8H, N—CH_2); 3.40–3.70m (8H, O—CH_2); 3.80s (3H, N—CH_3); 6.24 br s (1H, Het); 7.50–7.85m (10H, Ph). NMR ^{31}P ($CDCl_3$), δ: 60.5, 67.3. IR: 2240 cm^{-1} band corresponding to —C≡N bond. Found: N, 10.24; P, 11.51. $C_{26}H_{30}N_4O_3P_2S$ (calculated): N, 10.37; P, 11.48.

*2-Cyano-1-methyl-1H-pyrrole-3,5-bis(dimorpholinothiophosphonate) (***14***)*

The product is obtained from **3** using the method similar to the one described above for nitrile **13**. Yield 33%, m.p. 225–226°C. ^{1}H NMR ($CDCl_3$), δ: 2.65–3.07m (16H, N—CH_2); 3.42–3.76m (16H, O—CH_2); 3.76s (3H, N—CH_3); 6.18 br s (1H, Het). ^{31}P NMR ($CDCl_3$), δ: 18.7, 66.3. IR: 2240 cm^{-1} band corresponding to —C≡N bond. Found: N, 16.27; P, 12.15. $C_{22}H_{36}N_6O_4P_2S_2$ (calculated): N, 16.41; P, 12.11.

*5-Diphenylphosphoryl-1-methyl-1H-pyrrole-2-carbaldehyde Phenylhydrazone (***15***)*

To a solution of 1 mmol of **11** in 5 ml of ethanol a solution of 1 mmol of phenylhydrazine in 5 ml of ethanol and catalytic amount of *p*-toluenesulphonic acid were added. The mixture was heated for 2 h at 50°C, and the precipitate thus formed was filtered off. Yield 88%, m.p. 132–133°C. ^{1}H NMR ($CDCl_3$), δ: 3.97s (3H; N—CH_3); 5.97t J = 3.0 Hz (1H; H_3); 6.28t J = 3.0 Hz (1H; H_4); 6.84t J = 9.0 Hz (1H, *p*-Ph); 6.98d J = 9.0 Hz (1H, *o*-Ph); 7.23t J = 9.0 Hz (1H, *m*-Ph); 7.50–7.75m (10H, Ph) 7.95s (1H; CH=N). Found: N, 10.24; P, 7.32. $C_{24}H_{22}N_3OP$ (calculated): N, 10.53; P, 7.77.

*4-Dimorpholinothiophosphoryl-1-(p-tolyl)-2,5-dimethyl-1H-pyrrole-2-carbaldehyde Phenylhydrazone (***16***)*

A solution of 10 mmol of **12** and 10 mmol of phenylhydrazine in 20 ml of ethanol was boiled for 2 h. The solvent from the reaction mixture was evaporated in vacuo and the product was obtained by crystallization from octane. Yield 90%, m.p. 159–160°C. ^{1}H NMR ($CDCl_3$), δ: 2.08s (3H, C—CH_3); 2.27s (3H, C—CH_3); 2.46s (3H, C—CH_3); 2.90s 3.19m, (8H, N—CH_2); 3.68m (8H, O—CH_2); 7.0–7.4m (9H, Ar + Ph); 8.57s (1H; CH=N). Found: N, 12.95; P, 5.82. $C_{28}H_{36}N_5O_2PS$ (calculated): N, 13.03; P, 5.76.

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