Chemistry of Heterocyclic Compounds, Vol. 37, No. 9, 2001

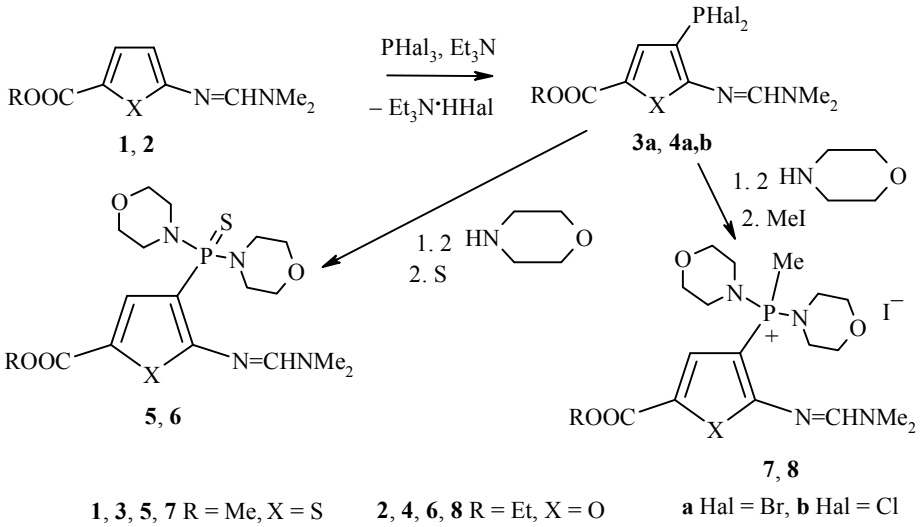
PHOSPHORYLATION OF 2-ALKOXY-CARBONYL-5-(1',3'-DIAZA-1'-BUTENYL-3'-METHYL)THIOPHENES AND 2-ALKOXYCARBONYL-5-(1',3'-DIAZA-1'-BUTENYL-3'-METHYL)FURANS BY TRIVALENT PHOSPHORUS HALIDES

S. A. Kovaleva, S. P. Ivonin, A. M. Pinchuk, and A. A. Tolmachev

Keywords: thiophene, furan, 3-phosphorylated derivatives of furan and thiophene, phosphorylation.

In previous work [1], we have demonstrated the feasibility of using the 3-methyl-1,3-diaza-1-butenyl (N,N-dimethylformamidine) substituent as a protective and activating group in the phosphorylation of 2-aminothiazoles, which permits to prepare phosphorus derivatives of thiazole with a free amino function. The use of this approach for the synthesis of phosphorylated derivatives of other types of amino heterocycles holds considerable preparative interest.

We have found that the electron-donating properties of the N,N-dimethylformamidine substituent permits the regioselective phosphorylation of 5-amino-2-alkoxycarbonylthiophenes and 5-amino-2-alkoxycarbonylfurans by trivalent phosphorus halides under mild conditions at the position $C_{(3)}$ of heterocycle to give 3-dihalophosphines **3a, 4a,** and **4b**, which are valuable reagents for the synthesis of various 3-phosphorylated thiophene and furan derivatives, in particular, **5-8**.



Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kiev 02056, Ukraine, e-mail: hetfos@ukrpack.net. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1285-1287, September, 2001. Original article submitted December 9, 2000.

Unsubstituted thiophene and furan are phosphorylated in the absence of a catalyst by phosphorus tribromide only at 160°C in a sealed ampule to give 2-thienyl- and 2-furyldibromophosphines [2].

The NMR spectra were taken on a Varian 300 spectrometer at 300 MHz using TMS as the internal standard for the ^{1}H NMR spectra and 85% H_3PO_4 as the external standard for the ^{31}P NMR spectra at 121 MHz. All the operations with the phosphorus trihalides were carried out using dry solvents in an argon atmosphere.

Dimorpholino[2-(1',3'-diaza-1'-butenyl-3'-methyl)-5-methoxycarbonyl-3-thienyl] Thiophosphonate (5). A sample of triethylamine (0.011 mol) was added to a solution of thiophene **1** (0.01 mol) in benzene (30 ml). Then, the solution was cooled to 10°C and phosphorus tribromide (0.01 mol) was added dropwise with stirring. The reaction mixture was maintained at 25°C for 12 h. ^{31}P NMR spectrum of thienyldibromophosphine **3a**: 145.5 ppm. After cooling to 10°C, morpholine (0.04 mol) was added. The mixture was stirred for 2 h. Then, sulfur (0.01 mol) was added and the mixture was stirred for 16 h. The precipitate was filtered off and the mother liquor was evaporated. The solid, oily residue was crystallized; mp 169-171°C (2-propanol). Yield of **5** 56%. ^{31}P NMR spectrum (benzene): 65 ppm. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J*, Hz: 3.84 (3H, s, C<u>H</u>$_3$O); 3.13 and 3.15 (6H, s, C<u>H</u>$_3$N); 3.19 (8H, m, C<u>H</u>$_2$N); 3.64 (8H, t, C<u>H</u>$_2$O); 7.68 (1H, s, NC<u>H</u>N); 8.11 (1H, d, $^3J_{HP}$ = 6.3, hetaryl). Found, %: P 6.72, 6.89; N 12.66, 12.52. $C_{17}H_{27}N_4O_4PS_2$. Calculated, %: P 6.94; N 12.55.

Dimorpholino[2-(1',3'-diaza-1'-butenyl-3'-methyl)-5-ethoxycarbonyl-3-furyl] Thiophosphonate (6) was synthesized in 60% yield from furan **2** analogously to **5**; mp 188°C (ethanol). ^{31}P NMR spectrum (benzene): 66.6 ppm. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J*, Hz: 1.26 (3H, t, J_{HH} = 7.2, C<u>H</u>$_3$CH$_2$); 4.22 (2H, q, J_{HH} = 7.2, CH$_3$C<u>H</u>$_2$); 3.16 (3H, s, C<u>H</u>$_3$N); 3.05 (11H, m, C<u>H</u>$_2$N + CH$_3$N); 3.52 (8H, br. s, C<u>H</u>$_2$O); 8.25 (1H, s, NC<u>H</u>N); 7.32 (1H, d, $^3J_{HP}$ = 4.8, hetaryl). ^{31}P NMR spectrum of furyldibromophosphine **4a** (pyridine): 140.9 ppm. When phosphorus trichloride was used, the reaction was carried out in benzene with a two-fold excess of the phosphorylating agent. ^{31}P NMR spectrum of furyldichlorophosphine **4b** (benzene): 150.1 ppm. Found, %: P 6.88, 6.91; N 12.71, 12.58. $C_{18}H_{29}N_4O_5PS$. Calculated, %: P 6.97; N 12.60.

Dimorpholino[2-(1',3'-diaza-1'-butenyl-3'-methyl)-5-methoxycarbonyl-3-thienyl]methylphosphonium Iodide (7). Phosphine **3a** was synthesized as in the preparation of **5**. Then, the reaction mixture was cooled to 10°C and phosphorus tribromide (0.01 mol) was added dropwise with stirring. The mixture was maintained for 12 h at 25°C. The ^{31}P NMR spectrum of thienyldibromophosphine **3a**: 145.5 ppm. Then, the mixture was cooled to 10°C and morpholine (0.04 mol) was added with stirring. After 2 h, the precipitate was filtered off and the filtrate was evaporated in vacuum. The oily residue was dissolved in benzene (20 ml) and methyl iodide (0.05 mol) was added. The reaction mixture was maintained for 1 h at room temperature and heated at reflux for 1 h. Benzene was decanted and the residue was crystallized; mp 206-207°C (ethanol–2-propanol). Yield of **7** 40%. ^{31}P NMR spectrum (methanol): 49 ppm. ^{1}H NMR spectrum (CD_3OD), δ, ppm, *J*, Hz: 3.88 (3H, s, C<u>H</u>$_3$O); 3.21 (3H, s, C<u>H</u>$_3$N); 3.33 (11H, m, C<u>H</u>$_2$N + C<u>H</u>$_3$N); 3.80 (8H, t, C<u>H</u>$_2$O); 7.55 (1H, s, NC<u>H</u>N); 7.97 (1H, d, $^3J_{HP}$ = 4.9, hetaryl); 2.67 (3H, d, $^2J_{HP}$ = 11.1, C<u>H</u>$_3$P). Found, %: P 5.52, 5.54; N 9.89, 9.96. $C_{18}H_{30}IN_4O_4PS$. Calculated, %: P 5.57; N 10.07.

Dimorpholino[2-(3'-methyl-1',3'-diaza-1'-butenyl)-5-ethoxycarbonyl-3-furyl]methylphosphonium iodide (8) was synthesized in 42.5% yield analogously to **7** from furan **2**; mp 216-217°C (ethanol). ^{31}P NMR spectrum (methanol): 48.8 ppm. ^{1}H NMR spectrum (CD_3OD), δ, ppm, *J*, Hz: 1.35 (3H, t, J_{HH} = 7.2, C<u>H</u>$_3$CH$_2$); 4.34 (2H, q, J_{HH} = 7.2, CH$_3$C<u>H</u>$_2$); 3.20 (3H, s, C<u>H</u>$_3$N); 3.27 (11H, m, C<u>H</u>$_2$N + C<u>H</u>$_3$N); 3.71 (8H, t, C<u>H</u>$_2$O); 8.48 (1H, s, NC<u>H</u>N); 7.40 (1H, d, $^3J_{HP}$ = 3.6, hetaryl); 2.34 (3H, d, $^2J_{HP}$ = 14.1, C<u>H</u>$_3$P). Found, %: P 5.40, 5.52; N 10.16, 10.24. $C_{19}H_{32}IN_4O_5PS$. Calculated, %: P 5.59; N 10.11.

REFERENCES

1. A. A. Tolmachev, G. V. Oshovsky, A. S. Merkulov, and A. M. Pinchuk, *Khim. Geterotsikl. Soedin.*, 1288 (1996).
2. A. A. Tolmachev, S. P. Ivonin, and A. M. Pinchuk, *Heteroatom Chem.*, **6**, 407 (1995).