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Phosphorylation of 5-Substituted Furfurals

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ABSTRACT: *5-Substituted 2-furaldehyde dimethylhydrazones react regioselectively with P(III) halides to give, after removal of the hydrazone protection, 3-phosphorylated 5-R-2-furaldehydes*. © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9: 559–563, 1998

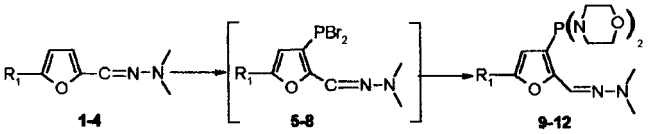
INTRODUCTION

Only a few C-phosphorylated heterocyclic aldehydes have been reported in the literature. Quaternization of triphenylphosphine with 5-bromo-2-furaldehyde derivatives and 5-bromo-thiophene-2-carboxaldehyde, leading to the corresponding phosphonium salts, and cyclization to 5-phosphorylated formylimidazoles have been described [1,2]. In the preceding articles, we reported on the reaction of furfural and 2-thiophenecarboxaldehyde dimethylhydrazones with phosphorus (III) halides and elaborated a simple preparative approach to 5-phosphorylated derivatives of the aldehydes [3]. We have shown also that the dimethylhydrazone group activates the furan and thiophene rings in the phosphorylation reactions.

In this connection, it seemed of interest to study the possible phosphorylation of 5-R-2-furaldehyde dimethylhydrazones at position 3 of the heteroaromatic ring. Such a pathway was not obvious as the trifluoroacetylation of 5-trifluoroacetylfurfural dimethylhydrazone is known to proceed at the exocyclic carbon atom [4], and electrophilic substitution at the position ortho to a dimethylhydrazone group has not yet been described.

RESULTS AND DISCUSSION

We have found that 5-R-2-furaldehyde dimethylhydrazones **1–4** are phosphorylated with PBr_3 at position 3 of the heterocycle to give dibromophosphines **5–8** identified by ^{31}P NMR spectra and the transformation into dimorpholinophosphines **9–12.**



R = Me (1, 5, 9), 4-BrC$_6$H$_4$ (2, 6, 10), P(O)[N(CH$_2$CH$_2$)$_2$O]$_2$ (3, 7, 11), P(S)[N(CH$_2$CH$_2$)$_2$O]$_2$ (4, 8, 12)

The structures of phosphines **9–12** were confirmed by ^1H NMR spectra (Table 2). For hydrazones **1–4,** the reactions could have occurred either at the 3-position of the furan ring or at the exocyclic carbon atom of the CH = N group. The singlet signal of the CH = N proton at δ 7.5–8.0 proves unequivocally the phosphorylation at the 3-C atom. In the other case, two doublets of the furan ring (H^3, H^4) should have been present in the NMR spectra at the regions 6.0–7.0 with the same coupling constant J_{HH}.

The reactivity of the hydrazones is substantially influenced by electronic effects of the substituents at position 5. The electron-acceptor substituents hamper strongly the phosphorylation reaction. Thus, while the reaction of 5-methyl-2-furaldehyde dimethylhydrazone **1** in benzene is complete within 2

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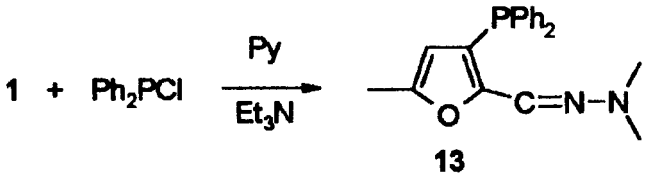
hours, the 5-(4-bromophenyl) analog **2**, under the same conditions, only gives a 50% yield of product after 20 days, and 5-[dimorpholino(thio)phosphinoyl] substituted compounds **3** and **4** are not phosphorylated at all.

The most reactive hydrazone **1** readily reacts even with such a weak phosphorylating agent as chlorodiphenylphosphine to yield phosphine **13.**



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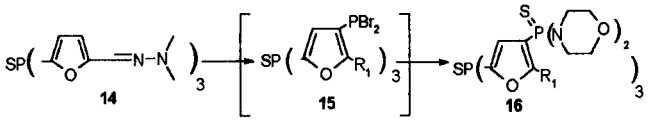
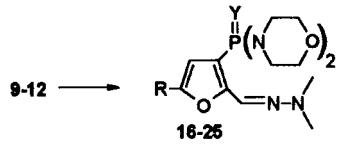
Thus, the phosphorylation of 5-R-2-furaldehyde dimethylhydrazones, in contrast to trifluoroacetylation, proceeds regioselectively at the 3-C atom. The reaction follows this pathway also in the case of more complex substrates, for example, phosphine sulfide **14.** Product **15** was not isolated because of its instability. It was characterized in the form of derivative **16.** Similar to phosphines **9–12,** compound **16** exhibits in its ^{1}H NMR spectrum the singlet of the CH = N proton at δ 7.8, indicating substitution at the 3-C atom (Table 2).



R^1 = CH=N-NMe$_2$

In order to prepare 3-phosphorylated furfurals with a free aldehyde function, phosphines **9–12** were converted to the P(V) derivatives **17–25.**

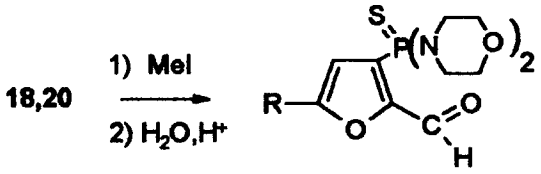


16-25

N	17	18	19	20	21	22	23
R	Me	Me	Br-C6H4	Br-C6H4	Br-C6H4	P(O)(N O)2	P(O)(N O)2
Y	O	S	O	S	=N-C6H4-Me	S	=N-C6H4-Me

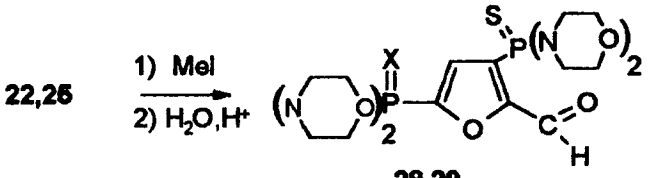
24	25
P(S)(N O)2	P(S)(N O)2
O	S

The protecting dimethylhydrazino group was removed by a reported procedure [5] through alkylation of its amine N atom with methyl iodide followed by acid hydrolysis of the intermediate salt.



26,27

R = Me (26), 4-BrC$_6$H$_4$ (27)

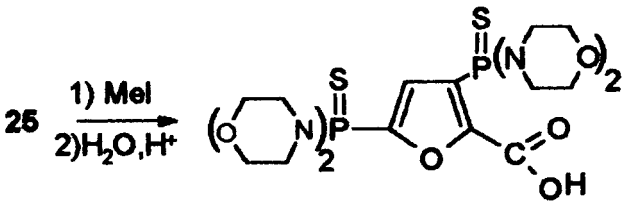


28,29

X = O (28), S (29)

The last step was successfully realized only in the case of thione derivatives **18, 20, 22,** and **25.** Judging by ^{31}P NMR spectra, the hydrolysis of other hydrazonium salts gives a mixture of different products due to cleavage of the C–P bond and the furan ring. The proton signals of CH = N (δ 7.5–8.0) and NMe$_2$ (δ 3.0–3.5) groups observed in the starting hydrazones **18, 20, 22,** and **25** disappear in the deprotected products **26–29** to give rise to the singlet of the CHO group at δ 10.1–10.5 (see Table 2).

Heteroaromatic aldehydes with electron-accepting substituents are known to undergo oxidation readily. Indeed, aldehyde **29** can be obtained only under an inert atmosphere. In the presence of oxygen, the end product is the bisphosphorylated 2-furoic acid **30.**



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EXPERIMENTAL

A Varian Gemini- 200 spectrometer was used to determine the ^{1}H NMR spectra, which were registered with reference to the internal standard, tetramethylsilane.

3-Dimorpholinophosphino-5-methyl-2-furaldehyde Dimethylhydrazone 9

To a stirred solution of hydrazone **1** (10 mmol) and pyridine (10 mmol) in dry benzene (20 mL) was

TABLE 1 Yields, Analytical Data of **9–30**

			Found, %			Calcd, %	
No.	*Yield, %*	*M.P., °C*	*N*	*P*	*Formula*	*N*	*P*
9	76	122–123	24.04	13.21	$C_{16}H_{26}N_4O_3P$	24.03	13.30
10	72	145–146	11.33	6.31	$C_{21}H_{28}N_4O_3PBr$	11.36	6.29
11	82	175–176	14.91	11.32	$C_{23}H_{40}N_6O_6P_2$	15.05	11.47
12	85	146–147	15.01	10.86	$C_{23}H_{40}N_6O_5P_2S$	18.55	8.21
13	61	99–100	8.52	9.37	$C_{20}H_{21}N_2P$	8.33	9.23
16	75	235–236	14.35	10.43	$C_{45}H_{72}N_{12}O_9P_4S_4$	14.27	10.54
17	70	105–107	7.23	8.41	$C_{16}H_{27}N_4O_3PO$	7.348	8.362
18	77	110–111	14.64	8.09	$C_{16}H_{27}N_4O_3PS$	14.51	8.03
19	61	146–147	10.83	5.97	$C_{21}H_{28}N_4O_4PBr$	10.96	6.07
20	68	175–176	10.71	5.94	$C_{21}H_{28}N_4O_3PSBr$	10.63	5.88
21	65	159–160	11.72	5.08	$C_{28}H_{35}N_5O_3PBr$	11.86	5.20
22	81	155–156	14.19	10.42	$C_{23}H_{40}N_6O_6P_2S$	14.24	10.25
23	75	211–213	14.87	9.82	$C_{30}H_{47}N_7O_6P_2$	14.78	9.65
24	78	162–163	14.17	10.78	$C_{23}H_{40}N_6O_6P_2S$	14.24	10.58
25	85	170–171	14.02	10.29	$C_{23}H_{40}N_6O_5P_2S_2$	13.86	10.23
26	61	123–124	8.41	9.37	$C_{14}H_{21}N_2O_4PS$	8.38	9.28
27	60	170–171	6.73	7.78	$C_{19}H_{22}N_2O_4PS$	6.91	7.65
28	65	198–199	10.35	11.87	$C_{21}H_{34}N_4O_6P_2S$	10.53	12.03
29	40	183–185	10.11	9.98	$C_{21}H_{34}N_4O_6P_2S_2$	9.923	10.97
30	75	200–201	9.47	11.21	$C_{21}H_{34}N_4O_7P_2S_2$	9.67	11.03

added dropwise at 5°C, in 5 minutes, a solution of PBr_3 (10 mmol) in the same solvent (10 mL). After 2 hours, a solution of morpholine (20 mmol) and triethylamine (30 mmol) in dry benzene (10 mL) was slowly added with stirring to the reaction mixture. Three hours later, the mixture was filtered and the filtrate was evaporated in vacuo. The remaining product was purified by crystallization from hexane.

5-(4-Bromophenyl)-3-dimorpholinophosphino-2-furaldehyde Dimethylhydrazone **10**

Phosphorus tribromide (10 mmol) in dry pyridine (10 mL) was added dropwise to a stirred solution of hydrazone **2** (10 mmol) in the same solvent (30 mL) and, within 12 hours, the mixture was treated at 10°C with a solution of morpholine (20 mmol) and triethylamine (30 mmol) in 10 mL of dry benzene. After 3 hours, the reaction mixture was filtered and the filtrate was evaporated in vacuo to leave the crude product that was crystallized from hexane.

3-Dimorpholinophosphino-5-dimorpholinophosphinoyl-2-furaldehyde Dimethylhydrazone **11**

Phosphorus tribromide (9 mmol) in dry pyridine was added to a solution of hydrazone **3** (9 mmol) in the same solvent, and within 48 hours, the mixture was treated at 10°C with a solution of morpholine (20 mmol) and triethylamine (30 mmol) in dry benzene (10 mL). After the mixture had been stirred for a further 3 hours, the solids were filtered off and the filtrate was evaporated in vacuo. The product was crystallized from octane.

3-Dimorpholinophosphino-5-dimorpholinothiophosphinoyl-2-furaldehyde Dimethylhydrazone **12**

The product was prepared as described for **11.**

3-Diphenylphosphino-5-methyl-2-furaldehyde Dimethylhydrazone **13**

Hydrazone **1** (10 mmol) dissolved in dry pyridine (10 mL) was added to a solution of chlorodiphenylphosphine (10 mmol) in the same solvent (10 mL). After two months, the reaction mixture was diluted with dry heptane and filtered. The filtrate was evaporated in vacuo to leave the product that was crystallized from ethanol.

Tris(2-dimethylhydrazonomethyl-3-dimorpholinothiophosphinoyl-5-furyl)phosphine Sulfide **16**

Phosphorus tribromide (3 mmol) in dry pyridine (5 mL) was added dropwise to a stirred solution of

TABLE 2 The NMR Spectra Data

		I^1, Het		
No.	*SOLV*	δ	J_{HP}	*Other groups*
9	C_6D_6	5.84	—	2.30 s (3H, Het–Me); 3.02 m (14H, NCH_2, NMe_2); 3.62 m (8H, O–CH_2); 7.95 s (1H, CH = N).
10	C_6D_6	6.54 d	2.2	3.0–3.3 m (14H, NCH_2, NMe_2); 3.67 m (8H, O–CH_2); 7.53 d J = 8.7 Hz (2H, O–Ph); 7.61 d J = 8.7 Hz (2H, O–Ph); 7.74 s (1H, CH = N).
11	C_6D_6	7.19	—	2.7–3.1 m (22H, NCH_2, NMe_2); 3.4–3.5 m (16H, O–CH_2); 7.75 s (1H, CH = N).
12	C_6D_6	7.15	—	3.0–3.3 m (22H, NCH_2, NMe_2); 3.5–3.7 m (16H, O–CH_2); 7.9 s (1H, CH = N).
13	$CDCl_3$	5.72	—	2.29 s (3H, Het–Me); 2.92 (6H, NMe_2); 7.2–7.4 m (11H; Ph + CH = N).
16	$CDCl_3$	7.27 d	7.2	2.8–3.2 m (3H, Het–Me); (58H, NCH_2, NMe_2); 3.58–3.71 m (24H, O–CH_2); 7.8 s (CH = N).
17	$CDCl_3$	6.12	—	2.38 s (3H, Het–Me); 3.06 m (14H, NCH_2, NMe_2); 3.66 (8H, O–CH_2); 8.09 s (1H, CH = N).
18	$CDCl_3$	6.07	—	2.35 s (3H, Het–Me); 3.06 m (14H, NCH_2, NMe_2); 3.66 (8H, O–CH_2); 8.04 s (1H, CH = N).
19	$CDCl_3$	6.74 d	2.2	3.13 m (14H, NCH_2, NMe_2); 3.68 m (8H, O–CH_2); 7.53 d J = 8.7 Hz (2H, O–Ph); 7.61 d J = 8.7 Hz (2H, O–Ph); 7.96 s (1H, CH = N).
20	$CDCl_3$	6.74 d	3.0	3.1–3.2 m (14H, NCH_2, NMe_2); 3.6–3.7 m (8H, O–CH_2); 7.51 d J = 8.7 Hz (2H, O–Ph); 7.59 d J = 8.7 Hz (2H, O–Ph); 7.96 s (1H, CH = N).
21	$CDCl_3$	6.98 d	2.5	2.24 s (3H, Me); 3.0–3.24 m (14H, NCH_2, NMe_2); 3.6–3.7 m (8H, O–CH_2); 7.40–7.63 m (9H, Ar, −CH–N).
22	$CDCl_3$	7.17	—	3.04–3.12 m (22H, NCH_2, NMe_2); 3.13–3.22 m (16H, O–CH_2); 7.95 s (1H, CN = N).
23	$CDCl_3$	7.12	—	2.5 s (3H, Me); 3.0–3.2 m (22H, NCH_2, NMe_2); 3.6–3.8 m (16H, O–CH_2); 6.74 d J = 7.3 Hz (2H, Ar); 6.94 d J = 7.3 Hz (2H, Ar); 8.04 s (1H, CH = N).
24	$CDCl_3$	7.15	—	2.8–3.2 m (22H, NCH_2, NMe_2); 3.2–3.8 m (16H, O–CH_2); 7.8 s (1H, CH = N).
25	$CDCl_3$	7.19 d	2.3	3.0–3.3 m (22H, NCH_2, NMe_2); 3.5–3.7 m (16H, O–CH_2); 7.9 s (1H, CH = N).
26	$CDCl_3$	6.39	—	2.44 s (3H, Het–Me); 3.10 m (8H, NCH_2); 3.70 m (8H, O–CH_2); 10.14 (1H).
27	$CDCl_3$	6.88 d	—	3.15 m (8H, NCH_2); 3.74 m (8H, NCH_2); 7.62 d J = 8.7 Hz (2H, m-Ph) 7.70 d J = 8, 7 Hz (2H, o-Ph) 10.25 s (1H).
28	$CDCl_3$	7.30	—	3.18 m (16H, O–CH_2); 3.69 m (8H, NCH_2); 10.29 s (1H).
29	$CDCl_3$	7.62	—	3.00–3.20 m (16H, NCH_2); 3.50–3.70 m (16H, O–CH_2).
30	$CDCl_3$	7.51	—	3.0–3.22 m (16H, NCH_2); 3.6–3.81 m (16H, O–CH_2).

phosphine sulfide **14** (1 mmol) in the same solvent (10 mL), and within 48 hours, the mixture was treated with a solution of morpholine (6 mmol) and triethylamine (9 mmol) in dry toluene and, 3 hours later, with sulfur powder (3 mmol). After having been heated at 80°C for 3 hours, the liquid phase was filtered and the filtrate evaporated in vacuo. The solid residue was crystallized from octane.

3-Dimorpholinophosphinoyl-5-methyl-2-furaldehyde Dimethylhydrazone **17**

Hexachloroethane (5 mmol) in dry toluene was added to a solution of hydrazone **9** (5 mmol) in the same solvent (30 mL). After 3 hours, the precipitate was isolated by decantation and dissolved in chloroform. The resulting solution was made alkaline by vigorous stirring with 5–10% aqueous NaOH, and then the chloroform layer was separated, dried over sodium sulfate, and evaporated. The solid residue was crystallized from heptane.

3-Dimorpholinothiophosphinoyl-5-methyl-2-furaldehyde Dimethylhydrazone **18**

Finely powdered sulfur (5 mmol) was added to a solution of hydrazone **9** (5 mmol) in dry toluene (30 mL). The reaction mixture was heated at reflux for 2 hours and evaporated. The product was crystallized from heptane.

5-(4-Bromophenyl)-3-dimorpholinophosphinoyl-2-furaldehyde Dimethylhydrazone **19**

The product was prepared from **10** as described for **17.**

5-(4-Bromophenyl)-3-dimorpholinothiophosphinoyl-2-furaldehyde Dimethylhydrazone **20**

The product was prepared from **10** as described for **18.**

5-(4-Bromophenyl)-3-dimorpholino(4-tolylimino)phosphinoyl-2-furaldehyde Dimethylhydrazone **21**

A mixture of hydrazone **10** (9 mmol) and 4-tolyl azide (9 mmol) in dry toluene (50 mL) was heated at reflux for 3 hours. The solvent was evaporated, and the solid residue was crystallized from heptane.

5-Dimorpholinophosphinoyl-3-dimorpholinothiophosphinoyl-2-furaldehyde Dimethylhydrazone **22**

The product was prepared from **11** as described for **18.**

5-Dimorpholinophosphinoyl-3-dimorpholino(4-tolylimino)phosphinoyl-2-furaldehyde Dimethylhydrazone **23**

The product was prepared from **11** as described for **21.**

5-Dimorpholinothiophosphinoyl-3-dimorpholinophosphinoyl-2-furaldehyde Dimethylhydrazone **24**

The product was prepared from **12** as described for **17.**

3,5-Bis(dimorpholinothiophosphinoyl)-2-furaldehyde Dimethylhydrazone **25**

The product was prepared from **12** as described for **18.**

3-Dimorpholinothiophosphinoyl-5-methyl-2-furaldehyde **26**

A solution of hydrazone **18** (7 mmol) in methyl iodide (15 mL) was heated under reflux for 48 hours. The precipitate that had formed was removed by filtration, dissolved in water, and refluxed with hydrochloric acid (14 mmol) for 3 days. The product was crystallized from heptane.

5-(4-Bromophenyl)-3-dimorpholinothiophosphinoyl-2-furaldehyde **27**

The product was prepared from **20** as described for **26.**

5-Dimorpholinophosphinoyl-3-dimorpholinothiophosphinoyl-2-furaldehyde **28**

The product was prepared from **22** as described for **26.**

3,5-Bis(dimorpholinothiophosphinoyl)-2-furaldehyde **29**

The product was prepared from **25** as described for **26.** The hydrolysis in water solution was conducted under an argon atmosphere.

3,5-Bis(dimorpholinothiophosphinoyl)-2-furoic Acid **30**

The acid was prepared from hydrazone **25** by the procedure used for the synthesis of aldehyde **26.**

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