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Phosphorylation of Five-Membered Aromatic Heterocycles with Phosphorus Tribromide*

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ABSTRACT

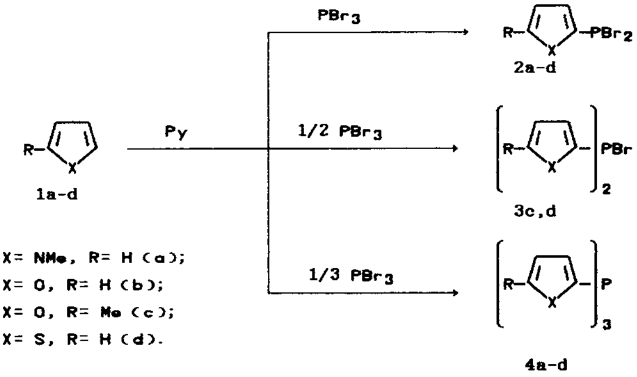
Phosphorus trichloride in a basic medium is a convenient reagent for the direct C-phosphorylation of electron-rich aromatic heterocycles. The compounds obtained can be used for the synthesis of various types of heteroaryl and diheteroaryl derivatives of tri- and pentavalent phosphorus. © 1995 John Wiley & Sons, Inc.

INTRODUCTION

In the series of phosphorylated derivatives of pyrrole, furan, and thiophene, only the latter are well-studied compounds. This is primarily due to the fact that the key compound, 2-thiophenedichlorophosphine, can be easily obtained. A convenient method of synthesizing this compound from thiophene and phosphorus trichloride in the presence of tin tetrachloride has been reported in the literature [2]. The earlier attempts to carry out this reaction with aluminum trichloride as a catalyst were less successful [3]. Since the synthesis of pyrrole- and furandichlorophosphines using Lewis acids is problematical, we tried to find a new general approach to the synthesis of 2-heteroaryldihalophosphines. Previously, we had developed the method of phosphorylation of enamines with trivalent phosphorus halides. It was found in the process that phosphorus tribromide and its derivatives in the presence of pyridine are very active phosphorylation reagents [4]. Taking into account the analogy in the reactivity between enamines and five-membered aromatic heterocycles, we employed this method to obtain heteroarylphosphines.

RESULTS AND DISCUSSION

Phosphorus tribromide readily reacts with *N*-methylpyrrole in the presence of pyridine at 5–10°C with the formation of phosphine **2a**, which is stable only in a solution (δ_p(Py) = 108.9). A similar reaction for *N*-phenylpyrrole proceeds ambiguously, resulting in a 2:3 mixture of phosphines with chemical shifts of δ_P 126.6 and 141.4, irrespective of temperature. Based on the comparison of the ^{31}P NMR spectra for the mixture obtained, phosphine **2a**, and 3-indolephosphines [5], we assume that phosphorylation of *N*-phenylpyrrole leads to a mixture of isomeric 2- and 3-*N*-phenylpyrrolyldibromophosphines. Furan and thiophene undergo reactions with phosphorus tribromide under more severe conditions and maximum yields of dibromophosphines **2b** and **2d** can be obtained only when the reaction is carried out in sealed tubes at 160–180°C.



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*C-Phosphorylated, Electron-Rich Heterocycles, II [1].

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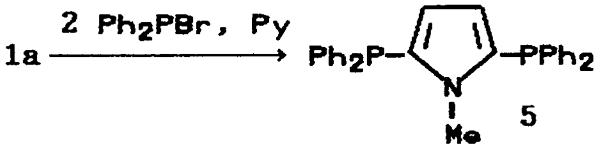
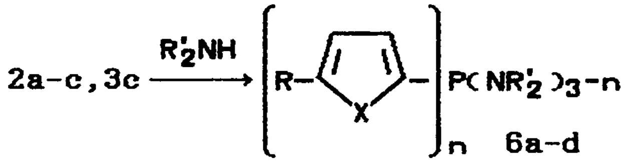
A decrease in the reaction temperature and prolonged heating lead to evident resinification of a mixture and lower yields of dibromophosphines. In contrast to furan, 2-methylfuran reacts with phosphorus tribromide even at 20°C. The reaction is complete after 12 hours and gives nearly a quantitative yield of phosphine **2c**.

The reaction between heterocyclic compounds and phosphorus tribromide in a 2:1 ratio at 160–180°C in sealed ampules results in diheteroarylbromophosphines of type 3. However, we have managed to isolate only phosphines **3c** and **3d**. In other cases, large amounts of heteroaryldibromo- and triheteroarylphosphines, which cannot be separated, are formed along with the diheteroarylbromophosphine. A 3:1 ratio of reagents under the same conditions gives triheteroarylphosphines **4a–d** in high yields. Phosphine **4a** was previously obtained in a 15% yield by use of 2-lithium-*N*-methylpyrrole [6]. An attempted 2,5-diphosphorylation of heterocycles with phosphorus tribromide failed. However, the reaction of *N*-methylpyrrole with diphenylbromophosphine proceeds easily by use of a 2:1 ratio of reagents with the formation of 2,5-diphosphine 5.

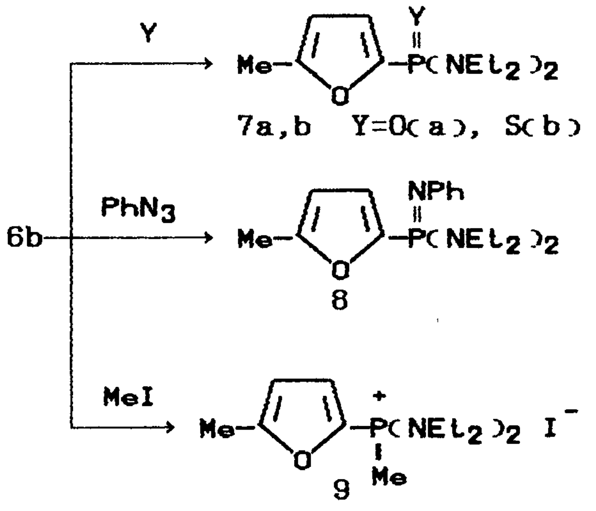


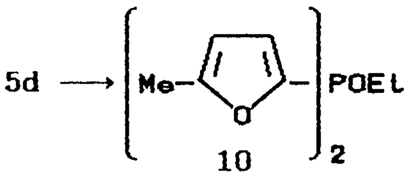
Dibromphosphines **2a–d** and bromophosphines **3c,d** are mobile light-yellow liquids soluble in major organic solvents. Phosphines **2b–d** and **3c,d** are vacuum distillable. Only phosphine **2a** is of low thermal activity and decomposes on heating; thus, it was not obtained in an analytically pure state. Heteroaryldibromophosphines **2a–d** and diheteroarylbromophosphines **3c,d** readily react with secondary amines to form amides **5a–d**.



a: n=1, R=H,X=NMe, R′=Et
b: n=1, R=Me, X=O, R′=Et
c: n=1, R=H, X=S, R′=Me
d: n=2, R=Me, X=O, R′=Me

Compounds **6a–d**, in turn, can be used for the synthesis of various types of heteroaryl and diheteroaryl derivatives of tri- and pentavalent phosphorus, for instance, **7–10**.





The structures of the compounds obtained (**2–10**) were confirmed by the data of ^1H, ^{13}C, and ^{31}P NMR spectra (see Tables 1 through 3). An interesting feature was noted for the PMR and ^{13}C NMR spectra of compounds **2a–6a**, containing an *N*-methylpyrrole residue. The signals for the methyl groups in the spectra of these compounds broaden greatly, and, in the case of compound **4a**, appear as a multiplet in deuteroacetonitrile and as a broadened singlet in deuteriochloroform. Of a similar character are the ^{13}C NMR spectra, and this seems to be associated with a barrier to rotation around the C–P bond.

EXPERIMENTAL

The ^{31}P NMR spectra were obtained with a Bruker WP-200 spectrometer, using 85% H_3PO_4 as the external standard. ^1H and ^{13}C NMR spectra were taken with a Varian Gemini-200 spectrometer, using tetramethylsilane as the internal standard. All measurements were taken in anhydrous solvents.

Furyl-2-dibromophosphine (**2b**). To a solution of furan (0.2 mol) in pyridine (20 mL), phosphorus tribromide (0.2 mol) was added with stirring. The reaction mixture was sealed into a thick-glass ampule and heated for 3 hours at 120°C. The product was extracted with hexane (100 mL), the solvent evaporated in vacuum, and the residue vacuum distilled under argon.

2-Methylfuryl-5-dibromophosphine (**2c**). To a solution of 2-methylfuran (0.08 mol) in pyridine (30

TABLE 1 Yields, Analitical, and 31p NMR Spectroscopical Data of **2**–**10**

					Found % (Calcd %)	
No.	*Yield* (%)	*BP (°C/mm)* *MP (°C)*	*Formula*	$\delta\ 31_P\{1_H\}$ (*Solvent*)	*P*	*Br or N*
2b	32	65–66/0.01	$C_4H_3Br_2OP$	103.5 (C_5H_5N)	12.3 (12.0)	61.3 (62.0)
2c	76	80–81/0.01	$C_5H_5Br_2OP$	101.2 (C_5H_5N)	11.2 (11.4)	58.1 (58.8)
2d	59	81–82/0.01	$C_4H_3Br_2PS$	132.7 (C_5H_5N)	11.6 (11.3)	58.1 (58.3)
3c	60	113–114/0.02 60–61	$C_{10}H_{10}BrO_2P$	2.0 (C_5H_5N)	11.5 (11.3)	29.1 (29.3)
3d	21	138–139/0.03	$C_8H_6BrPS_2$	39.3 (C_5H_5N)	11.1 (11.2)	28.7 (28.8)
4a	62	— 117–119	$C_{15}H_{18}N_3P$	−71.7 (C_6H_6)	11.6 (11.4)	15.2 (15.5)
4b	57	63 102–103/0.01	$C_{12}H_9O_3P$	−76.2 (C_5H_5N)	13.2 (13.3)	— —
4c	64	80 149–150/0.03	$C_{15}H_{15}O_3P$	−75.3 (C_5H_5N)	11.4 (11.3)	— —
4d	35	178–179/0.02	$C_{12}H_9PS_3$	−45.8 (C_5H_5N)	11.2 (11.1)	— —
5	78	oil	$C_{29}H_{25}NP_2$	−28.2 (C_5H_5N)	13.7 (13.8)	3.1 (3.1)
6a	74	75–76/0.01	$C_{13}H_{26}N_3P$	80.8 (C_6H_6)	12.3 (12.1)	16.6 (16.5)
6b	87	94–95/0.01	$C_{13}H_{25}N_2OP$	77.9 (C_6H_6)	12.2 (12.1)	10.9 (10.9)
6c	66	77–78/0.03	$C_8H_{15}N_2PS$	92.7 (C_6H_6)	15.2 (15.3)	13.7 (13.9)
6d	53	108–110/0.01	$C_{12}H_{16}NO_2P$	18.1 (C_6H_6)	13.2 (13.1)	5.7 (5.9)
7a	87	110–111/0.05	$C_{13}H_{25}N_2O_2P$	16.0 ($CHCl_3$)	11.2 (11.4)	10.4 (10.3)
7b	93	125–128/0.05	$C_{13}H_{25}N_2OPS$	59.2 (C_6H_6)	10.5 (10.7)	9.9 (9.7)
8	75	158–160/0.06	$C_{19}H_{30}N_3OP$	0.2 (C_6H_{14})	8.7 (8.9)	11.9 (12.1)
9	96	oil	$C_{14}H_{28}IN_2OP$	41.3 ($CHCl_3$)	7.9 (7.8)	7.3 (7.0)
10	93	105–106/0.01	$C_{12}H_{15}PO_3$	56.9 (C_6H_6)	13.1 (13.0)	— —

mL), phosphorus tribromide (0.08 mol) was added with stirring. The mixture was kept for 12 hours at 20°C, and hexane (50 mL) was then added. Pyridinium bromide was filtered off, the filtrate evaporated, and the residue vacuum distilled under argon.

Thienyl-2-dibromophosphine (**2d**). To a solution of thiophene (0.4 mol) in pyridine (150 mL), phosphorus tribromide (0.4 mol) was added with stirring. The reaction mixture was boiled for 48 hours and cooled to 20°C, and hexane (150 mL) was added. Pyridinium bromide was filtered off and the filtrate was evaporated. The oily residue was vacuum distilled under argon.

Bis(2-methyl-5-furyl)bromophosphine (**3c**). To a solution of 2-methylfuran (0.2 mol) in pyridine (30 mL), phosphorus tribromide (0.2 mol) was added with stirring and kept for 12 hours at 20°C. To the reaction mixture, 2-methylfuran (0.2 mol) was added, and the mixture was refluxed for 15 hours. The reaction mixture was cooled to 20°C and hexane (100 mL) was then added. Pyridinium bromide was filtered off, the filtrate evaporated, and the oily residue vacuum distilled under argon with use of a deflegmator. The first fraction was dibromophosphine **2c**, and the second fraction was bromophosphine **3c**.

Bis(thienyl-2)bromophosphine (**3d**). To a solution of thiophene (0.2 mol) in pyridine (25 mL), phosphorus tribromide (0.1 mol) was added with stirring. The reaction mixture was sealed into a

TABLE 2 ^{1}H NMR Data of the Heterocycles **2–10**, δ, (Multiplicity), J(Hz), ($CDCl_3$)

No.	*3-H*	*4-H*	*5-H*	*5-Me*	*Others*		
	7.05 (**dd**)	6.42 (**dt**)	7.71 (**d**)				
2b	1.5, 3.5	1.5, 3.0	1.5				
	6.49 (**dd**)	5.49 (**t**)					
2c	2.9, 3.4	2.9	—	1.79 (**s**)			
	7.48 (**dd**)	6.98 (**dt**)	7.69 (**dd**)				
2d	1.1, 5.8	1.1, 5.0	1.1, 4.7				
	6.84 (**dd**)	5.98 (**t**)					
3c	1.0, 3.2	1.0	—	2.29 (**s**)			
	7.15 (**dd**)	6.50 (**dt**)	6.99 (**dd**)				
3d	1.2, 6.2	1.2, 4.8	1.2, 4.8				
	6.70 (**dd**)	5.95 (**dt**)	6.11 (**dd**)				
4a	1.8, 3.5	1.8, 2.6	1.8, 2.6	3.59 (**s**)			
4a[a]	6.72 (**m**)	5.88 (**m**)	6.04 (**m**)	3.46–3.57 (**m**)			
	6.72 (**dd**)	6.32 (**dt**)	7.57 (**d**)				
4b	1.5, 3.4	1.5, 3.0	1.5				
	6.80 (**dd**)	5.74 (**t**)					
4c	1.5, 3.2	1.5	—	1.89 (**s**)			
	7.26 (**dd**)	6.72 (**dt**)	7.08 (**dd**)				
4d	1.0, 4.7	1.0, 3.5	1.0, 3.0				
5	5.82 (**s**)	5.82 (**s**)	—3.60 (**s**)	6.68–7.74 (**m**)		Ph	
6a[b]	6.37 (**s**)	6.22 (**s**)	6.50 (**s**)	3.19 (**s**)	0.83–0.92 (**m**),	2.80–3.10 (**m**)	Net$_2$
	6.48 (**t**)	5.9 (**d**)					
6b	2.7	2.7	—	2.07 (**s**)	0.98–1.06 (**m**),	3.02–3.19 (**m**)	NEt$_2$
	7.14 (**dd**)	7.03 (**t**)	7.31 (**dd**)				
6c	1.8, 3.6	1.8	1.8, 4.7			NMe$_2$	
	6.67 (**dd**)	5.81 (**dd**)					
6d	1.2, 3.0	1.2, 3.1	—	2.01 (**s**)	2.68 (**d**)	10.3	NMe$_2$
	6.94 (**dd**)	6.04 (**dd**)					
7a	1.6, 2.6	1.6, 2.6	—	2.33 (**s**)	0.97–1.11 (**m**),	3.00–3.25 (**m**)	NEt$_2$
	7.05 (**dd**)	6.03 (**dd**)					
7b	2.0, 2.6	2.0, 2.6	—	2.33 (**s**)	0.97–1.12 (**m**),	2.90–3.20 (**m**)	NEt$_2$
					0.89–1.02 (**m**),		NEt$_2$
8[b]	6.84 (**s**)	5.70 (**s**)	—	1.96 (**s**)	7.00–7.28 (**m**)	3.00–3.20 (**m**)	Ph
	7.51 (**dd**)	6.35 (**dd**)			1.14–1.30 (**m**),		NEt$_2$
9	1.2, 2.8	1.2, 1.6	—	2.45 (**s**)	2.50 (**d**) 12.0	3.10–3.35 (**m**)	PMe
	6.83 (**dd**)	5.79 (**dd**)					
10	1.0, 2.6	1.0, 2.0	—	1.97 (**s**)	0.96—1.09 (**m**),	3.74–3.93 (**m**)	OEt

[a] CD_3CN

[b] Broad signals

thick-glass ampule and heated for 24 hours at 180°C. The ampule was opened, the product extracted with benzene (100 mL) and filtered. The filtrate was evaporated, and oily residue was vacuum distilled under argon.

Tris(1-methylpyrrolyl-2)phosphine (**4a**). To a mixture of *N*-methylpyrrole (0.3 mol) and pyridine (100 mL), a solution of phosphorus tribromide (0.1 mol) in pyridine (20 mL) was added with stirring at 5°C. The reaction mixture was kept for 14 hours, and hexane (100 mL) was then added. The precipitated solid was separated, the filtrate evaporated in vacuum, and the residual oil mixed with water. The product was crystallized from octane after treatment with activated carbon.

Tris(furyl-2)phosphine (**4b**). To a solution of furan (0.2 mol) in pyridine (20 mL), phosphorus tribromide (0.06 mol) was introduced with stirring. The mixture was sealed in a thick-glass ampule and heated for 12 hours at 180°C. The ampule was opened, the product extracted with benzene (100 mL), and filtered. The filtrate was washed with 10% NaOH solution (50 mL) and two portions of water (50 mL each), and then dried over Na_2SO_4. After filtration, the solvent was evaporated in a vacuum. The phosphine was crystallized from the oily residue with hexane, after treatment with activated carbon. Complete crystallization required a freezing-out process.

Tris(2-methyl-5-furyl)phosphine (**4c**). To a solution of 2-methylfuran (0.2 mol) in pyridine (30 mL), phosphorus tribromide (0.06 mol) was added with stirring. The mixture was sealed in a thick-glass ampule and heated for 10 hours at 180°C. The

TABLE 3 $^{13}C(^{1}H)$ NMR Data of the Heterocycles **2–6**, δ, (Multiplicity), J(Hz), ($CDCl_3$)

No.	*1-C*	*2-C*	*3-C*	*4-C*	*Me*
2b	147.0 (**d**) 76.7	119.9 (**d**) 34.6	109.5 (**d**) 5.9	148.2 (**d**) 2.9	
2c	145.3 (**d**) 77.3	121.9 (**d**) 38.0	106.3 (**d**) 7.0	159.5 (**d**) 2.7	11.4 (**s**)
2d	138.0 (**d**) 81.4	134.6 (**d**) 1.6	133.1 (**s**)	134.0 (**s**)	
3c	145.9 (**d**) 35.1	123.1 (**d**) 30.3	106.3 (**d**) 6.4	158.0 (**d**) 4.2	11.5 (**s**)
3d	137.4 (**d**) 50.6	135.3 (**s**)	132.7 (**s**)	134.6 (**s**)	
4a[a]	124.3 (**s**)	112.0 (**s**)	106.9 (**s**)	116.5 (**s**)	32.9 (**s**)
4a[b]	124.4 (**s**)	112.1 (**s**)	106.8 (**s**)	121.0 (**s**)	32.6, 32.9, 33.3 (**s**)
4c	146.6 (**s**)	120.7 (**d**) 23.4	105.8 (**d**) 5.7	155.8 (**d**) 8.5	11.6 (**s**)
4d	135.2 (**d**) 10.8	134.4 (**d**) 12.5	126.7 (**d**) 3.5	132.7 (**d**) 5.5	
5	136.4 (**d**) 3.7	118.1 (**s**)	118.1 (**s**)	136.4 (**d**) 3.7	33.6 (**s**)[a]
6a	130.2 (**d**) 7.2	113.8 (**d**) 6.2	106.3 (**d**) 1.7	123.8 (**d**) 4.0	37.5 (**s**)[a]
6b	153.6 (**d**) 8.7	115.5 (**d**) 15.3	105.3 (**s**)	153.0 (**d**) 4.1	11.6 (**s**)
6c	142.3 (**d**) 6.2	129.4 (**d**) 14.6	126.5 (**d**) 2.8	128.2 (**s**)	
6d	151.5 (**d**) 8.7	119.2 (**d**) 20.7	105.2 (**d**) 4.2	154.8 (**d**) 7.4	11.6 (**s**)

[a] Broad signals
[b] CD_3CN

ampule was opened, the product extracted with benzene (100 mL), and the mixture filtered. The filtrate was evaporated in vacuum, leaving an oily residue. The phosphine was induced to crystallize from this oil by addition of octane (activated carbon). Complete crystallization require a freezing-out process.

Tris(2-thienyl)phosphine (**4d**). To a solution of thiophene (0.2 mol) in pyridine (30 mL), phosphorus tribromide (0.06 mol) was added with stirring. The mixture was sealed in a thick-glass ampule and heated for 20 hours at 180°C. The ampule was opened, the product extracted with benzene (100 mL) and the mixture filtered. The filtrate was washed with a 10% solution of NaOH (50 mL) and then with water (2 × 50 mL). The solution was dried over Na_2SO_4 and diethyl ether (70 mL) was then added. The precipitated solid was separated, and the solvent was evaporated in vacuum. The oily residue was vacuum distilled under argon.

2,5-(1-Methylpyrroldiyl) bis(diphenylphosphine) (**5**). To a solution of *N*-methylpyrrole (0.1 mol) in pyridine (50 mL), a solution of diphenylbromophosphine (0.2 mol) in pyridine (50 mL) was added with stirring at 20°C. The mixture was allowed to stand at this temperature for 4 days, and hexane (100 mL) was then added. The oil that formed was dissolved in benzene (100 mL), the precipitated solid was separated and the filtrate was evaporated in vacuum.

Tetraethyldiamide (1-methylpyrrolyl-2) phosphonous acid (**6a**). To a mixture of pyridine (0.2 mol) and *N*-methylpyrrole (0.2 mol) in benzene (100 mL), a solution of phosphorus tribromide (0.2 mol) in benzene (100 mL) was added with stirring at 5°C and kept at this temperature for 1 hour. To the reaction mixture, hexane (100 mL) was added, and the precipitated solid was separated. To the filtrate, a solution of diethylamine (0.8 mol) in hexane (200 mL) was added with stirring at 5°C and the mixture was allowed to stand for 2 hours at 20°C. The precipitated solid was separated, the filtrate was evaporated in vacuum, and the residue was vacuum distilled under argon.

General Procedure for Obtaining Amides (**6a–6d**). To a solution of dibromophosphine **2b–d** (0.15 mol) in hexane (100 mL), a solution of diethylamine (0.7 mol) in hexane (200 mL) was added with stirring at 5°C. After 2 hours the reaction mixture was filtered, the filtrate evaporated in vacuum, and the oily residue vacuum distilled under argon.

Tetraethyldiamide-5-methyl-2-furyl phosphonic acid (**7a**). To a solution of diamide **6b** (0.01 mol) in hexane (50 mL), hexachloroethane (0.011 mol) in hexane (30 mL) was added. The precipitated salt was filtered off and dissolved in chloroform (30 mL). To the solution, 10% NaOH was added until the pH of the aqueous layer was 10. The chloroform layer was dried over sodium sulfate. The solvent was distilled off and the residual oil was vacuum distilled.

Tetraethyldiamide-5-methyl-2-furyl thiophosphonic acid (**7b**). To a solution of diamide **6b** (0.01 mol) in benzene (10 mL), sulfur (0.01 mol) was added with stirring. The reaction mixture was heated to 45°C. After 10 hours, benzene was evaporated, and the oily residue was vacuum distilled.

Tetraethyldiamide-5-methyl-2-furyl phenyliminophosphonic acid (**8**). To a solution of amide **6b** (0.01 mol) in hexane (30 mL), phenylazide (0.01 mol) in hexane (20 mL) was added with stirring. The reaction mixture was refluxed for 1 hour, and hexane was evaporated in vacuum. The residual oil was vacuum distilled.

Methyl-bis(diethylamino)-5-methyl-2-furyl phosphonium iodide (**9**). To a solution of diamide, **6b** (0.01 mol) in hexane (100 mL), methyl iodide (0.02 mol) was added with stirring. After **3d**, the solvent and excess methyl iodide were evaporated in vacuum, and the oil remained.

o-Ethyl-bis(2-methyl-5-furyl)phosphinite (**10**). To a solution of dimethylamide, **6b** (0.03 mol) ethyl alcohol (0.03 mol) was added, and the mixture was refluxed for 4 hours. The oil formed was vacuum distilled under argon.

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