ORTHO-PHOSPHORYLATED PHENOLS AND THEIR METHOXYMETHYL ETHERS, PHOSPHINES, AND PHOSPHINE OXIDES

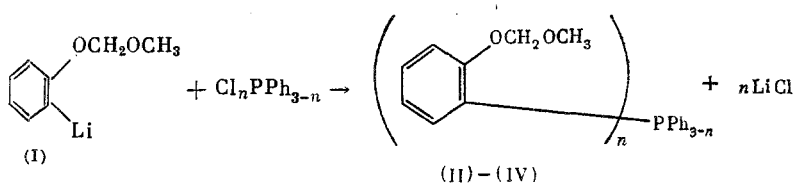
E. N. Tsvetkov, V. Kh. Syundyukova, and V. E. Baulin

UDC 542.91:547.562.4'118

o-Phosphorylated phenols, effective complexating agents for metal cations [1-4], are also of interest as starting materials for obtaining phosphorus-containing macrocyclic compounds and their acyclic analogs [5, 6]. Usually o-phosphorus-containing phenols are synthesized from derivatives of the relatively inaccessible o-bromophenol [1, 3-6]. Direct o-metallation of phenol ether derivatives would seem more practical, which have been widely used recently in synthesis [7].

In this work we describe the synthesis of methoxymethyl ethers of o-phosphino- and o-phosphinyl substituted phenols by reaction of phosphorous-containing acid chlorides with o-methoxymethoxyphenyllithium (I) obtained by direct metallation of phenol methoxymethyl ether with butyllithium. Metallation is carried out by the action of butyllithium on the phenol ether in a mixture of tetrahydrofuran (THF) with hexane in the absence of N,N,N'-N'-tetramethylethylene diamine (TMEDA) which is usually used in similar syntheses [2, 8, 9].

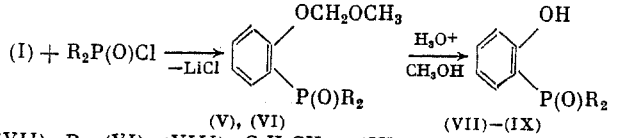
Tertiary o-methoxymethoxyphenyl phosphines (II)-(IV) were obtained by reaction of (I) with acid chlorides of trivalent phosphorus



(I) (II)-(IV)

$n = 1$ (II) [2], 2 (III), 3 (IV).

o-Phosphinyl phenols (VII)-(IX) were obtained by reaction of substituted phenyllithium (I) with chlorides of phosphinic acids in THF followed by removal of the methoxymethyl protecting group by acidic hydrolysis. It should be noted that the above phosphorus-containing phenols can be prepared without isolation of the intermediate methoxymethyl ethers (V), (VI)



(V), (VI) (VII)-(IX)

R = Ph (V), (VII); Bu (VI), (VIII); $C_6H_4CH_3$-*p* (IX).

Phenol methoxymethyl ethers of the general formula $RC_6H_4OCH_2OCH_3$ (R = H, o-Br, p-Br, o-Cl, p-Cl, m-CH_3, p-NO_2) were synthesized by alkylation of phenols with monochlorodimethyl ether in a two-phase system in the presence of a phase transfer catalyst. This method is more convenient than the known methods for synthesis of phenol methoxymethyl ethers which require use of sodium ethoxide [6, 10], sodium hydride [8], or dimethylaniline as base [11]. The characteristics of the obtained compounds are shown in Table 1.

EXPERIMENTAL

PMR spectra were taken on a Bruker CXP-200 spectrometer with TMS as standard and DMSO and CCl_4 solvents. Melting points were measured on a Boetius-PHMK instrument.

Institute of Physiologically Active Substances, Academy of Sciences of the USSR, Chernogolovka. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 1, pp. 147-150, January, 1989. Original article submitted June 22, 1987.

0568-5230/89/3801-0135$12.50

TABLE 1. Yields, Constants, and Analytical Data for o-Phosphorus-Substituted Phenols and Their Ethers

Compound	Yield, %	Mp (solvent for recrystallization) or bp, °C (p, mm Hg)	Found, %			Molecular formula	Calculated, %		
			C	H	P		C	H	P
(II)	54	126–127* (MeOH – CH_2Cl_2)	–	–	–	–	–	–	–
(III)	89	129–131 (C_6H_6 – hexane)	68,9	6,4	7,6	$C_{22}H_{23}O_4P$	69,1	6,1	8,1
(IV)	55	130–131,5 (C_6H_6 – hexane)	65,1	6,1	6,9	$C_{24}H_{27}O_6P$	65,1	6,2	7,0
(V)	70	106–108 (C_6H_6 – hexane)	71,4	5,6	8,6	$C_{20}H_{19}O_3P$	71,0	6,7	9,1
(VI)	56	165–167(1)	64,5	9,0	10,6	$C_{16}H_{27}O_3P$	64,4	9,1	10,4
(VII)	91	232–234† DMF	–	–	–	–	–	–	–
(VIII)	72	108,5–109,5 (Et_2O – hexane)	66,1	9,1	12,3	$C_{14}H_{23}O_2P$	66,1	9,1	12,2
(IX)	56	196–198 (chromatographic purification on SiO_2)	70,0	5,5	9,6	$C_{20}H_{19}O_2P$	74,5	5,9	9,6

*See [2].
†See [1, 5, 15, 16].

All operations were carried out in an argon atmosphere.

Phenol Methoxymethyl Ether. A solution of 128.8 g of monochlorodimethyl ether in 100 ml of benzene was added dropwise with stirring at 35-40°C to a mixture of 94.0 g phenol in 400 ml of benzene, 68.8 g of NaOH in 170 ml water, and 16.2 g of Bu_4NBr. The mixture was refluxed for 4 h, the organic layer was separated, washed twice with water, and dried with $MgSO_4$. The residue was distilled. The yield was 69%, bp 71-72°C (9 mm), d_4^{20} 1.0475, n_D^{20} 1.5050. Literature data [11]: bp 63-65°C (8 mm), d_4^{20} 1.0489, n_D^{20} 1.5027.

Other ethers ($RC_6H_4OCH_2OCH_3$) (R = o-Cl, p-Cl, m-CH_3, p-Br) were obtained analogously. Compounds with R = p-NO_2, o-Br, and o-Cl were synthesized using methylene chloride as solvent. The characteristics of the obtained compounds correspond with the literature [6, 10-13].

o-Methoxymethoxyphenyldiphenylphosphine (II). 14.5 ml of a 2.12 N solution of butyl lithium in hexane was added dropwise with stirring to 4.1 g of phenol methoxymethyl ether in 50 ml of THF freshly distilled from $LiAlH_4$. The mixture was kept 4 h at −5°C and then allowed to warm to 20°C over 1 h. The resultant solution of o-methoxymethoxyphenyllithium (I) was gradually added at 0°C to 5.3 g of diphenylchlorophosphine in 10 ml of THF. The mixture was stirred for 3 h at 20-25°C, 1 h at 60°C, and evaporated under vacuum. The residue was dissolved in methylene chloride, the solution washed with 1 M NaH_2PO_4, water, dried with $MgSO_4$, and evaporated under vacuum. After recrystallization of the residue there was obtained 4.3 g of (II). PMR spectrum ($CDCl_3$, δ, ppm): 3.23 s (3H, OCH_3), 5.06 s (2H, OCH_2O), 6.75 m (2H, arom.), 6.99 m (10H, arom.), 7.34 m (2H, arom.). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): −27.31.

Bis(o-methoxymethoxyphenyl)phenylphosphine (III) was obtained analogously from 10.8 ml of 2.78 N butyllithium solution, 4.1 g of phenol methoxymethyl ether in 50 ml of THF, and 2.2 g of phenyldichlorophosphine in 10 ml of THF. The yield of (III) was 3.4 g. PMR spectrum ($CDCl_3$, δ, ppm): 3.26 s (6H, OCH_3), 5.04 s (4H, OCH_2O), 6.79 m (4H, arom.), 6.99 m (7H, arom.), 7.31 m (2H, arom.). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): −26.98.

Tris(o-methoxymethoxyphenyl)phosphine (IV) was obtained analogously from 35.2 ml of 2.84 N butyllithium solution, 13.8 g of phenol methoxymethyl ether in 120 ml of THF, and 3.76 g of phosphorus trichloride in 10 ml of THF. The yield of (IV) was 6.7 g. PMR spectrum ($CDCl_3$, δ, ppm): 3.30 s (9H, $3OCH_3$), 5.08 s (6H, $3OCH_2O$), 6.84 m (6H, arom.), 7.08 (3H, arom.), 7.30 (3H, arom.). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): −30.33.

o-Methoxymethoxyphenyldiphenylphosphine Oxide (V) was obtained analogously from 10.2 ml of 1.96 N butyllithium solution, 2.8 g phenol methoxymethyl ether in 30 ml of THF, and 5.0 g diphenylphosphinyl chloride in 10 ml of THF. The mixture was stirred for 5 h at 20-25°C and solvent was removed under vacuum. To the residue 20 ml of water and 60 ml of chloro-

form was added, the organic layer was separated, dried over $MgSO_4$, and evaporated under vacuum. By chromatography on brand L SiO_2 (eluent: chloroform–ethanol, 20:1) followed by recrystallization there was isolated 3.8 g of (V). PMR spectrum (DMSO-d_6, δ, ppm): 2.9 s (3H, OCH_3), 5.02 s (2H, OCH_2O), 7.19 m (2H, arom.), 7.60 m (12H, arom.). ^{31}P NMR spectrum (DMSO-d_6, δ, ppm): 26.82.

o-Methoxymethoxyphenyldibutylphosphine Oxide (VI) was obtained analogously from 10.2 ml of 1.96 N butyllithium solution, 2.8 g of phenol methoxymethyl ether in 30 ml of THF, and 3.2 g of dibutylphosphinyl chloride [14]. Yield 2.4 g, n_D^{20} 1.5060, d_4^{20} 1.0540. PMR spectrum (CCl_4, δ, ppm): 0.78 m (6H, $2CH_3$), 1.30 m (4H, $2CH_2$), 1.55 (4H, $2CH_2$), 3.41 s (3H, OCH_3), 5.20 s (2H, OCH_2O), 7.05 (2H, arom.), 7.39 m (1H, arom.), 7.93 m (1H, arom.). ^{31}P NMR spectrum (CCl_4, δ, ppm) 40.05.

o-Diphenylphosphinylphenol (VII). To 1.0 g of o-methoxymethoxyphenyldiphenylphosphine (V) in 10 ml of CH_3OH 1 ml of concentrated HCl was added. After 12 h, o-diphenylphosphinylphenol (VII) was filtered off and washed with water. After recrystallization 0.8 g of (VII) was obtained. PMR spectrum (DMSO-d_6, δ, ppm): 6.95 m (2H, arom.), 7.60 m (12H, arom.), 10.60 s (1H, OH). ^{31}P NMR spectrum (DMSO-d_6, δ, ppm): 27.70.

o-Diphenylphosphinylphenol without Isolation of Methoxymethyl Ether. To the residue after evaporation of chloroform from the extract [see synthesis (V)] 15 ml of CH_3OH and 5 ml of concentrated HCl were added. After 12 h (20-25°C) 2.9 g of (VII) was filtered off.

o-Dibutylphosphinylphenol (VIII) was obtained analogously to (VII). The product was purified by chromatography on SiO_2 (eluent: chloroform–ethanol, 24:1) and by recrystallization. There was obtained 0.6 g of compound (VIII). PMR spectrum (DMSO-d_6, δ, ppm): 0.76 m (6H, $2CH_3$), 1.30 m (4H, $2CH_2$), 1.55 m (4H, $2CH_2$), 1.99 m (4H, $2CH_2$), 7.20 m (2H, arom.), 7.92 m (2H, arom.), 11.80 s (1H, OH). ^{31}P NMR spectrum (δ, ppm): 41.78.

o-Di(p-tolyl)phosphinylphenol (IX) was obtained analogously to (VII) from 10.2 ml of 1.96 N butyllithium solution, 2.8 g of phenol methoxymethyl ether, and 4.2 g of di-p-tolylphosphinyl chloride (bp 205-208°C, 1 mm). To the residue after evaporation of chloroform from the extract 15 ml of CH_3OH and 5 ml of concentrated HCl was added, the mixture was kept for 12 h (20-25°C), and solvent was evaporated under vacuum. The product was crystallized by addition of ether. After chromatographic purification on SiO_2 there was obtained 2.6 g of compound (IX). PMR spectrum (DMSO-d_6, δ, ppm): 2.40 s (6H, 2-CH_3), 7.36 m (12H, arom.), 10.04 s (1H, OH). ^{31}P NMR spectrum (DMSO-d_6, δ, ppm): 25.65.

CONCLUSIONS

1. By reaction of o-methoxymethoxyphenyllithium with P(III) acid chlorides and with phosphinyl chlorides o-methoxymethoxyphenylphosphines and methoxymethyl ethers of o-phosphinyl-substituted phenols were obtained, and by hydrolysis transformed into the corresponding o-phosphinyl-substituted phenols.

2. A method for obtaining phenol methoxymethyl ethers was developed by alkylation of phenols with monochlorodimethyl ether in two steps.

LITERATURE CITED

1. E. G. Amarskii, A. A. Shvets, and O. A. Osipov, Zh. Obshch. Khim., 44, 461 (1974).
2. T. B. Rauchfuss, Inorg. Chem., 16, 2966 (1977).
3. H. D. Empsall, B. L. Shaw, and B. L. Turtle, J. Chem. Soc. Dalton Trans., 1500 (1976).
4. T. B. Rauchfuss, R. T. Patino, and D. M. Roundchill, Inorg. Chem., 14, 652 (1975).
5. A. H. Alberts, K. Timmer, J. G. Noltes, and A. L. Spek, J. Am. Chem. Soc., 101, 3375 (1979).
6. G. B. Bodrin, Yu. M. Polikarpov, T. Ya. Medved', and M. I. Kabachnik, Izv. Akad. Nauk SSSR, Ser. Khim., 1930 (1978).
7. D. W. Slocum and D. I. Sugarman, Adv. Chem. Ser., 130, 222 (1974).
8. H. Christensen, Synth. Commun., 65 (1975).
9. R. C. Ronald, Tetrahedron Lett., 46, 3973 (1975).
10. A. K. Yagoub and G. M. Isakander, J. Chem. Soc. Perkin Trans., 1, 1043 (1975).
11. Sh. Mamedov, Kh. M. Alieva, and M. A. Avanesyan, Zh. Obshch. Khim., 34, 3222 (1964).
12. B. M. Dunn and T. C. Bruice, J. Am. Chem. Soc., 92, 2410 (1970).
13. R. L. Edwards and N. Kole, J. Chem. Soc., 4084 (1964).
14. M. I. Kabachnik and E. N. Tsvetkov, Dokl. Akad. Nauk SSSR, 135, 323 (1960).
15. H. G. Henning and W. Wild, J. Pract. Chem., 318, 69 (1976).
16. K. A. Petrov, S. V. Agafonov, and V. P. Pokatun, Zh. Obshch. Khim., 57, 98 (1987).