Synthesis of O-Aryl Phosphonochloridothionates

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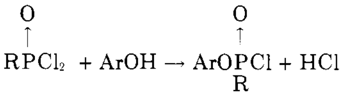
The synthesis of O-aryl phosphonochloridothionates (IV) from alkyl and aryl phosphonothioic dichlorides (III) was investigated. A study of various catalyst systems showed that small amounts of metal or metal salts were promoters for the desired reaction, affording, under optimum conditions, excellent yields of IV. Characterization of IV was accomplished by conversion to crystalline phosphonothionate esters (V).

AN INVESTIGATION of methods of synthesis of *O*-aryl phosphonochloridothionates (IV) was undertaken because of the utility of these compounds as intermediates for the synthesis of phosphonate esters, some of which are known to possess insecticidal activity (*4*).

Usually, *O*-aryl phosphonochloridates (II) are readily prepared by heating phenols with an excess of phosphonic dichloride (I) at 120° to 140° C without the use of a hydrogen halide acceptor or a catalyst (*6*).

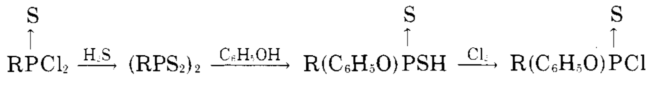


$$R\overset{\overset{O}{\uparrow}}{P}Cl_2 + ArOH \rightarrow ArO\underset{R}{\overset{\overset{O}{\uparrow}}{P}}Cl + HCl$$

I II

An obvious method for preparing *O*-aryl alkylphosphonothionates would be to make the corresponding $RPSCl_2$ react with phenols in the presence of a hydrogen chloride acceptor. This method, employing triethylamine, phenol, and CH_3PSCl_2, gave a 65% yield of IV (see Experimental).

Another method involves converting the phosphonothioic dichloride to the corresponding thionophosphine sulfide (*5*), followed by reaction with phenol and subsequent chlorination (*1*). Although these methods are convenient for laboratory syntheses, they are obviously less attractive for large scale preparations.

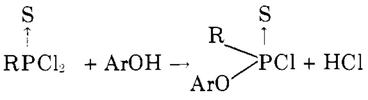


$$R\overset{\overset{S}{\uparrow}}{P}Cl_2 \xrightarrow{H_2S} (RPS_2)_2 \xrightarrow{C_6H_5OH} R(C_6H_5O)\overset{\overset{S}{\uparrow}}{P}SH \xrightarrow{Cl_2} R(C_6H_5O)\overset{\overset{S}{\uparrow}}{P}Cl$$

III IV

It was of interest therefore to study the reaction of phenols with phosphonothioic dichlorides (III) to obtain the desired *O*-aryl phosphonochloridothionates (IV) and to evaluate the reactivity of the chlorine atoms in III qualitatively.

Alkyl and aryl phosphonothioic dichlorides (III) reacted with phenols at moderate temperatures (120° to 140° C) in the presence of catalytic amounts of metals or metal salts to give good yields of IV. Catalysts such as metals and their salts have frequently been used in phosphorus halide displacement reactions (*7*). The reaction proceeds smoothly (4 to 8 hours) with continuous evolution of hydrogen chloride, and the progress of the reaction may be followed by periodic determination of the hydrogen chloride liberated. The physical constants for the compounds prepared by this method are given in Table I.



$$R\overset{\overset{S}{\uparrow}}{P}Cl_2 + ArOH \rightarrow \begin{matrix}R\\ArO\end{matrix}\!>\!\overset{\overset{S}{\uparrow}}{P}Cl + HCl$$

III IV

A study of the effectiveness of several catalyst systems was conducted, in which the product was isolated by distilla-

Table I. O-Aryl Phosphonochloridothionates, $R(ArO)\overset{\overset{S}{\|}}{P}Cl$

Aryl Substituted Phenyl	R	Yield,[a] %	M.P., ° C B.P., ° C/Mm	n_D^{23}	Analysis % P Calcd.	% P Found	% S Calcd.	% S Found	% Cl Calcd.	% Cl Found
H	CH_3	76	97/0.16	1.5726	15.0	14.7	15.5	15.7	17.2	17.1
H	C_6H_5	71	143–45/0.8	1.6199	11.6	11.2	11.9	12.0	13.2	13.8
			110/0.005							
p-CF_3	CH_3	30	70–72/0.3	1.4950	11.3	11.1	11.7	11.6	12.9	12.7
p-NO_2[b]	CH_3	56	67–68.5		12.3	12.1	12.7	12.9	14.1	13.6
p-CH_3S	CH_3	51	97–98/0.008	1.6074	12.3	12.1	25.4	25.5	14.0	13.9
CH_3O	CH_3	61	88–90/0.002	1.5720	13.1	12.5	13.6	14.2	15.0	15.4
2,3-diCl	CH_3	32[c]	130.5–31.5/0.5		11.2	11.0				
p-tert-C_4H_9	CH_3	60	55–57		12.0	11.8	12.4	12.6	13.7	13.5
p-Cl	CH_3	50[c]	96/0.03							
			135–37/1.6		12.9	12.5	13.3	13.5	29.4	29.8

[a] 100% excess of phosphonothioic dichloride used: yield based on phenol. [b] Heated at 130–40° C. [c] Equimolar quantities of reactants and prolonged heating period used.

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tion (Table II). To circumvent the necessity of repeated distillation of the product, vapor phase, thin-layer chromatography, and infrared studies were employed for determining the efficiency of the catalysts (Table III).

The necessity of the catalysts was demonstrated by carrying out the reaction under optimum conditions without the catalyst and observing no appreciable evolution of hydrogen chloride. Significant advantages of this method over the others described are that solvents are unnecessary, the yields are higher, and the workup is much simpler.

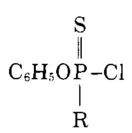
It was determined at this stage that by employing 1% of a metal or metal salt catalyst in the system, a 100% excess of dichloride was necessary to produce acceptable conversions or minimize the formation of tertiary esters. Thus, using a 1% $ZnCl_2$-Cu_2Cl_2 catalyst, equimolar amounts of reactants resulted in only a 59% yield of IV ($R = CH_3$) *vs.* 76% using a 100% excess of dichloride. A 1% copper catalyst gave only a 50% yield using the 2 to 1 mole ratio. However, when copper powder was employed to the extent of 3.5% by weight, excellent yields (ca. 85%) of IV could be obtained, even when approximately equimolar amounts of reactants were charged.

Friedel-Crafts catalysts gave substantial amounts of the tertiary ester. The two free radical initiators, azobisisobutyronitrile and benzoyl peroxide, failed to give substantial amounts of the product, making a free radical process in this reaction unlikely.

The *O*-aryl phosphonochloridothionates were readily converted to tertiary phosphonate esters (V). The physical properties of these compounds are given in Table IV. Some of these compounds exhibit good insecticidal activity (*3*).

$$\underset{\text{IV}}{R(ArO)P(S)Cl} + Ar'OH \xrightarrow{N(C_2H_5)_3} \underset{\text{V}}{R(ArO)P(S)OAr'}$$

Table II. Effect of Catalyst on Yield of O-Phenyl Phosphonochloridothionates



$$C_6H_5O\overset{\overset{S}{\|}}{\underset{\underset{R}{|}}{P}}\text{-}Cl$$

R	Mole Ratio Phenol/ $RP(S)Cl_2$	Catalyst	Yield,[a] %
CH_3	1:2	None	0
CH_3	1:2	Cu_2Cl_2[b]	44
CH_3	1:2	$ZnCl_2$–Cu_2Cl_2[b]	76
CH_3	1:1.1	Cu[c]	84
C_6H_5	1:2	$ZnCl_2$[b]	15
C_6H_5	1:2	Cu_2Cl_2[b]	63
C_6H_5	1:2	$ZnCl_2$–Cu_2Cl_2[b]	71

[a] Distilled yields. [b] 1% by weight based on phenol. [c] 3.5% by weight based on phenol.

Table III. Effect of Catalyst on Yield of O-Phenyl Methylphosphonochloridothionate[a]

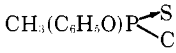
Catalyst	Mole Ratio Phenol/ $MeP(S)Cl_2$	% Yield[b]	
		$CH_3(C_6H_5O)\overset{\overset{S}{\uparrow}}{P}Cl$	$CH_3\overset{\overset{S}{\uparrow}}{P}(-OC_6H_5)_2$
$ZnCl_2$–Cu_2Cl_2	1:2	78	[c]
$AnCl_2$–Cu I	1:2	77	6
$ZnCl_2$	1:2	15	47
$AlCl_3$	1:2	40	26
$TiCl_4$	1:2	56	[d]
$SnCl_4$	1:2	50	[d]
$SbCl_3$	1:2	[e]	[e]
BF_3	1:2	[e]	[e]
$FeCl_3$	1:2	[e]	[e]
Cu	1:2	50	[c]
$COCl_2$	1:2	12	[c]
Azxobisiso-butyronitrile	1:2	2	[c]
Benzoyl peroxide	1:2	3	[e]

[a] All catalysts evaluated using same reaction conditions, 100% excess of methylphosphonothionic dichloride, 6-hour heating period (120–30°), and 1% catalyst by weight, based on phenol. [b] Yields determined by GLC and infrared methods described in experimental section. [c] Less than 3%. [d] Not determined. [e] Incomplete reaction, not determined.

EXPERIMENTAL

Methods for Analysis of Reaction Mixtures. GAS-LIQUID CHROMATOGRAPHY. The analyses were performed on an F and M 500 programmed temperature gas chromatograph with a hot filament detector. Resolution of methylphosphonothioic dichloride, *O*-phenyl methylphosphonochloridothionate, and *O,O*-diphenyl methylphosphonothionate and unknowns in a 3-μl sample was obtained by programming the temperature from 30° to 325° C at 21° C per minute on a 2 foot × 1/4 inch o.d. column packed with 10% silicone gum rubber on 60–80-mesh firebrick. The other conditions of analysis were: flow rate, 60 ml of He per minute (35 psig); injection block temperature, –275° C; detector block temperature, –400° C; and filament current, 95 ma.

INFRARED ANALYSIS. The method described by Hawkes (*2*) was adapted for the analyses of the reaction mixtures. The wavelengths selected for quantitative evaluation are:



$CH_3(C_6H_5O)P\genfrac{}{}{0pt}{}{\nearrow S}{\searrow Cl}$	14.6 and 15.6 microns
$CH_3P(S)Cl_2$	14.93 microns
$CH_3P(S)(OC_6H_5)_2$	14.6 microns

Since *O,O*-diphenyl methylphosphonothionate absorbs only at 14.6 microns and with much greater intensity than IV, the procedure referred to above may be conveniently employed to analyze the reaction mixture. Conditions: 3.5% solution in carbon disulfide; cell length 0.200 mm. The instrument was a Beckman IR5.

THIN-LAYER CHROMATOGRAPHY. Thin-layer chromatography was found to be well suited to follow the course of the reaction. The components of the reaction mixture, with the exception of the $CH_3P(S)Cl_2$, could be resolved by applying 5 μl of a 10% solution in benzene to a 250-micron layer of silicic acid on glass. The chromatograms were developed by the ascending technique, using a mixture of 30% *n*-pentane in benzene. When the solvent had traveled the predetermined distance, the plate was removed and dried. To visualize the chromatogram, the plate was sprayed with a 10% solution of KOH in methanol and dried at 115° C for 5 minutes. After cooling to room temperature, the plate was sprayed with a freshly prepared mixture of 1% sulfanilic acid and 1% sodium nitrite in water. Phenol had the lowest R_f value, *O,O*-diphenyl methylphosphonothionate was intermediate, while IV exhibited the highest value.

O-Phenyl Methylphosphonochloridothionate. TRIETHYLAMINE METHOD. To a solution of 14.9 grams (0.1 mole) of methylphosphonothionic dichloride and 9.4 grams (0.1 mole) of phenol in 100 ml of benzene was added dropwise a solution of 10.1 grams (0.1 mole) of triethylamine in 100 ml of benzene with stirring at 0° to 5° C. After the addition was complete, the reaction mixture was stirred

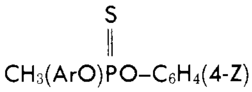


Table IV. *O*-Aryl Methylphosphonothionates $\mathrm{CH_3(ArO)}\overset{\overset{S}{\|}}{\mathrm{P}}\mathrm{O{-}C_6H_4(4\text{-}Z)}$

Substituted Phenyl or Aryl	Z	M.P., ° C.	%P Calcd.	%P Found	%S Calcd.	%S Found	%N Calcd.	%N Found	%Cl Calcd.	%Cl Found	Yield, %
H	NO_2	80–81	10.0	9.9	10.3	10.1					95
o-C_2H_5	NO_2	64–66	9.2	9.0	9.5	9.2	4.2	4.3			64
2-Naphthyl	NO_2	93–95	8.6	8.2	8.9	8.5	3.8	3.5			74
p-tert-C_4H_9	NO_2	83	8.5	8.3	8.8	8.3	3.8	3.7			90
p-CF_3	NO_2	75–77	8.2	8.2	8.5	8.8	3.7	3.9			74
1-Naphthyl	NO_2	104–06	8.6	8.3	8.9	8.6	3.9	3.8			51
p-Cl[a]	NO_2	111–13	9.0	9.0			4.1	4.0	10.3	10.2	77
H	CN	73–74	10.7	10.6	11.1	10.7					74
p-CH_3	NO_2	107–08	9.6	9.5	9.9	9.2					70
p-CH_3O	NO_2	105.5–06	9.5	9.1	9.8	9.8					80
m-CH_3	NO_2	57–59	9.6	9.3	9.9	9.8	4.3	4.2			76
o-CH_3	NO_2	71–71.5	9.6	9.4	9.9	9.7					80
p-NO_2[b]	NO_2	148–49	8.8	8.4	9.1	8.4	7.9	7.6			90
2,4-di-Cl	NO_2	84.5–85.0	8.2	8.2			3.7	3.9	18.8	18.5	76
m-Cl[a]	NO_2	75–77	9.03	9.0			4.1	4.0	10.4	10.2	85
o-Br[a]	NO_2	71–73	7.97	8.0			3.6	3.6	Br 20.6	Br 20.5	78
o-Cl[a]	NO_2	84–86	9.03	8.9			4.1	4.2	10.4	10.2	81

[a] Prepared from *O*-*p*-nitrophenyl methylphosphonochloridothionate. [b] Prepared directly from methylphosphonothioic dichloride.

at 10° C for an additional hour. The mixture was allowed to warm to room temperature and filtered, and the solvent was removed under reduced pressure. Fractionation of the residue gave 13.3 grams (65%) of a water-white liquid (b.p. 100–03° C per 1.0 mm, n_D^{25}, 1.5726). The infrared spectrum and physical properties were consistent with those of an authentic sample.

VIA CHLORINATION OF *O*-PHENYL METHYLPHOSPHONODITHIOIC ACID. The method employed here was essentially that given by Chupp and Newallis (*1*).

To a solution of 110 grams (0.54 mole) of *O*-phenyl methylphosphonodithioic acid in 250 ml of benzene was added dropwise with stirring 65.6 grams (0.49 mole) of sulfuryl chloride at 50° to 60° C. After cooling, the benzene was removed by distillation under reduced pressure. Fractionation of the residue gave 73.0 grams (60% yield) of a pale yellow liquid (b.p. 92° per 0.3 mm).

Analysis. Calculated for C_7H_8ClOPS: P, 15.0; S, 15.5; Cl, 17.2. Found: P, 14.6; S, 15.9; Cl, 17.4.

CATALYTIC METHODS. Cu_2Cl_2–$ZnCl_2$. The generalized procedure for the preparation of *O*-phenyl methylphosphonochloridothionate using a zinc chloride–cuprous chloride mixture as the catalyst is typical for this method.

To 9.4 grams (0.1 mole) of phenol and 29.8 grams (0.2 mole) of methylphosphonothioic dichloride were added 0.05 gram of anhydrous zinc chloride and 0.05 gram of cuprous chloride and the reaction mixture was heated to 120° to 130° until evolution of hydrogen chloride ceased (normally ca. 6 hours). After cooling, the solids were filtered and the residue was fractionated. A water-white liquid (16.0 grams, 77%) was obtained which distilled at 90–93° per 0.3 mm.

Analysis. Calculated for C_7H_8ClOPS: Cl, 17.2. Found: 17.4.

Metallic Copper. To 94 grams (1.0 mole) of phenol and 164 grams (1.1 mole) of methylphosphonothioic dichloride was added 3.4 grams of copper powder and the reaction mixture was heated to 130–35°. When the evolution of hydrogen chloride ceased and thin-layer chromatography indicated the absence of phenol (ca. 8 hours), the reaction mass was fractionated. The main fraction (172 grams, 84%) distilled at 105–07° per 4 mm. The crystallizing point was 28°. Assay by VPC was 98.5%.

O-p-Nitrophenyl O-Phenyl Methylphosphonothionate. The preparation of this compound is typical of those given in Table IV.

To a solution of 6.95 grams (0.05 mole) of *p*-nitrophenol in 100 ml of benzene was added all at once with stirring and cooling 6.1 grams (0.06 mole) of triethylamine. A solution of 10.35 grams (0.05 mole) of *O*-phenyl methylphosphonochloridothionate in 50 ml of benzene was then added dropwise and the reaction mixture was heated under reflux for 5 hours. After cooling, approximately 200 ml of water was added to dissolve the amine hydrochloride and the benzene was removed from the organic phase by distillation under reduced pressure. A white solid (14.8 grams, 95%) was formed, which when recrystallized from *n*-hexane melted at 80–81° C.

O,O-Diphenyl Methylphosphonothionate. To a solution of 18.8 grams (0.2 mole) of phenol in 300 ml of benzene was added with cooling and stirring 20.2 grams (0.2 mole) of triethylamine. Methylphosphonothioic dichloride (14.9 grams, 0.1 mole) in 100 ml of benzene was added dropwise, at a temperature maintained below 30° C. After the addition was complete, the reaction mixture was heated under reflux for 8 hours, cooled, and quenched with cold water. The organic phase was then washed with dilute sodium carbonate solution, followed by water. Distillation of the solvent under reduced pressure left 15.2 grams (58% yield) of yellow oil as residue, which crystallized on cooling (m.p. 20–22° C).

Analysis. Calculated for $C_{13}H_{13}O_2PS$: P, 11.7; S, 12.1. Found: P, 11.8; S, 12.4.

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