Simplified Preparation of Some Trisubstituted Phosphine Oxides

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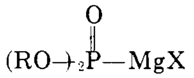
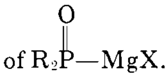
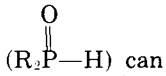
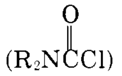
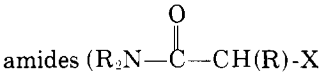
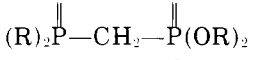
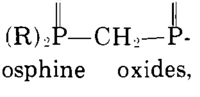
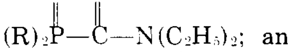
A variety of trisubstituted phosphine oxides were prepared in a two-step reaction, without work-up between steps, by a technique previously reported by Richard and Banks.

RICHARD and Banks (*4*) showed that methyldiphenyl- and methyldihexylphosphine oxides could be produced conveniently in good yield by adding methyl bromide to the complex formed when a dialkyl phosphonate is added to the appropriate Grignard reagent. This success led to an investigation of the general application of this simple technique to the preparation of substituted phosphine oxides. Further reason to expect that such a technique might be extended is found in the work by Gawron and coworkers (*1*) in which addition reactions attributable to  $(RO)_2\overset{O}{\overset{\|}{P}}—MgX$ were obtained. Also, Pudovik (*3*) obtained coupling reactions attributable to  $(RO)_2\overset{O}{\overset{\|}{P}}—MgX$ and postulated the presence of  $R_2\overset{O}{\overset{\|}{P}}—MgX$.

The comparative convenience of such an application is illustrated by the complicated alternatives that are available. For example, dialkylphosphine oxides  $(R_2\overset{O}{\overset{\|}{P}}—H)$ can be made to undergo the Michaelis reaction with *N,N*-dialkylcarbamyl chlorides  $(R_2N\overset{O}{\overset{\|}{C}}Cl)$ and *N,N*-dialkyl α-haloamides  $(R_2N—\overset{O}{\overset{\|}{C}}—CH(R)\text{-}X)$. However, it is first necessary to prepare and isolate the dialkylphosphine oxide and then to perform the Michaelis reaction. It is especially difficult to handle the di-*n*-alkylphosphine oxides since they are solids and because of their low solubility and the even lower solubility of their sodium derivatives. An extension of this technique might make possible the preparation of compounds that are not easily accessible by other methods. For example, a number of unsuccessful efforts have been made in this laboratory to prepare tri-2-butyl-phosphine oxide by adding $POCl_3$ to the Grignard reagent of 2-butyl halide.

RESULTS AND DISCUSSION

A variety of trialkylphosphine oxides, $(R)_3P=O$ and $(R)_2(R')P=O$; dialkylphosphonomethylenedialkylphosphine oxides,  $(R)_2\overset{O}{\overset{\|}{P}}—CH_2—\overset{O}{\overset{\|}{P}}(OR)_2$ and  $(R)_2\overset{O}{\overset{\|}{P}}—CH_2—\overset{O}{\overset{\|}{P}}\text{-}(OR')_2$: dialkyl-*N,N*-diethylcarbamylphosphine oxides,  $(R)_2\overset{O}{\overset{\|}{P}}—\overset{O}{\overset{\|}{C}}—N(C_2H_5)_2$; and miscellaneous triaryl-, alkyldiaryl-, and dialkylarylphosphine oxides were synthesized by applying the technique of Richard and Banks (*4*). Yields were generally fair to good (Table I). For example, tri-2-butyl-phosphine oxide was obtained in 70% yield. This technique has very wide utility.

A typical preparative procedure is illustrated by the preparation of *n*-butyl di-2-butylphosphine oxide. Diethyl phosphonate (0.25 mole) was added, at a rate to give steady reflux, to 1.0 mole (nominal) of 2-butyl-MgBr in about 250 ml. of ethyl ether. The resulting slurry was stirred overnight at room temperature. The 0.3 mole of *n*-butyl bromide was added. The mixture was refluxed overnight, hydrolyzed by pouring over an ice-HCl mixture, and then washed successively with water, 10% sodium carbonate solution, and water. Ether was removed under vacuum, and the product was distilled at about 0.3 mm. Forty grams of material boiling in the range of 90° to 100° C. was obtained; this material was redistilled at 0.3 mm. through a 1-foot Vigreaux column to yield 29 grams of product (50% yield calculated from diethyl phosphonate) boiling at about 100° C.

EXPERIMENTAL

Most of the reactants were obtained commercially and used without further purification. The diethyl and dibutyl phosphonates were distilled under vacuum before use, as were the chloromethylphosphonic dichloride and dibutyl chloromethylphosphonate. Dihexyl and di-2-amyl chloromethylphosphonate were prepared by conventional esterification with the alcohol in the presence of pyridine, and they were then purified by washing followed by vacuum distillation. Di-2-amyl-phosphine oxide was prepared by the method that Kosolapoff (*2*) used as a route to phosphinic acids, and was then distilled under vacuum.

Diethyl and dibutyl phosphonates were used interchangeably with no apparent effect on yields. Generally a larger amount of product was obtained when only 0.25 mole of phosphonate, rather than 0.33 mole was used per nominal mole of Grignard reagent. There appears to be a definite advantage in adding up to about 50% excess of the third reactant. In some experiments, the mixture of phosphonate and Grignard reagent was allowed to stand overnight before the third reactant was added. There is probably no advantage in this delay, and immediate addition of a third reactant may be preferable. It is often possible to avoid slurries that are difficult to stir if the third reactant is added immediately after the dialkyl phosphonate. It appears to be generally unnecessary to stir after addition of the third reactant is complete, and no difficulty results if a hard mass forms. Addition of THF after adding the third reactant usually serves to lossen up such masses, but with little or no effect on yield. Generally more stirrable mixtures were obtained when the original Grignard reagent was a bromide rather than a chloride.

Purity and identification of all preparations were checked by infrared spectra, and preparations, of one or more of each class were also examined by proton magnetic resonance.

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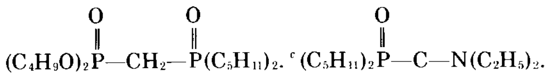
Table I. List of Compounds and Their Properties

Compound	% Yield	Approximate B.P., ° C., Pressure, Mm. Hg[a]	Density, 25° C.	Refractive Index, 25° C.	Theory				Analysis				Notes, Description, M.P. (Uncorrected), ° C.
					% C	% H	% P	% N	% C	% H	% P	% N	
n-Butyldi-2-butylphosphine oxide	50	100, 0.3	0.913	1.4663	66.0	12.5	14.2	. . .	65.4	12.6	14.3	. . .	Colorless liquid
n-Octyldicyclopentylphosphine oxide	60	170, 0.3	. . .	. . .	72.4	11.8	10.4	. . .	71.9	12.0	10.5	. . .	White solid, too hygroscopic for accurate m.p.
2-Ethylhexyldi-2-propylphosphine oxide	25	105, 0.3	0.902	1.4650	68.3	12.7	12.5	. . .	68.1	12.7	12.6	. . .	Colorless liquid
n-Octyldi-2-propylphosphine oxide	65	125, 0.3	0.889	1.4631	68.3	12.7	12.5	. . .	68.7	12.9	12.8	. . .	Colorless liquid
n-Butyldicyclohexylphosphine oxide	55	145, 0.3	. . .	. . .	70.1	11.5	11.5	. . .	70.1	11.5	12.2	. . .	White, hygroscopic solid, m.p. 58
Tri-2-butylphosphine oxide	70	105–110, 0.3	0.922	1.4598	66.0	12.5	14.2	. . .	65.6	12.6	14.0	. . .	Colorless liquid
Dibutylphosphonomethylenediamylphosphine oxide[b]	40	165–180, 1×10^{-4}	0.993	1.4598	57.6	10.6	15.7	. . .	58.0	10.8	15.0	. . .	Colorless liquid
Dihexylphosphonomethylenedihexylphosphine oxide	22	195–210, 1×10^{-4}	0.952	1.4554	62.5	11.3	12.9	. . .	63.2	11.7	11.7	. . .	Colorless liquid
Dibutylphosphonomethylenedihexylphosphine oxide	65	190–195, 1×10^{-4}	0.970	1.4617	59.4	10.9	14.6	. . .	59.9	11.0	14.0	. . .	Slightly brownish liquid
Di-2-amylphosphonomethylenediamylphosphine oxide	40	190–195, 1×10^{-4}	0.970	1.4598	59.4	10.9	14.6	. . .	60.5	10.9	14.4	. . .	Slightly brownish liquid
Diamyl-*N*,*N*-diethylcarbamylphosphine oxide[c]	40	145–150, 0.3	0.953	1.4685	62.3	11.1	10.7	4.8	63.0	11.7	10.3	4.4	Colorless liquid
Di-2-amyl-*N*,*N*-diethylcarbamylphosphine oxide	55	145–150, 0.3	0.963	1.4752	62.3	11.1	10.7	4.8	63.3	11.5	10.0	4.8	Colorless liquid
Dicyclopentyl-*N*,*N*-diethylcarbamylphosphine oxide	55	150, 0.3	1.056	1.5023	63.2	9.8	10.9	4.9	62.7	10.1	10.5	4.8	Viscous, colorless liquid
Dihexyl-*N*,*N*-diethylcarbamylphosphine oxide	50	160, 0.3	0.939	1.4682	64.4	11.4	9.8	4.4	63.5	11.3	9.9	4.5	Viscous, colorless liquid
Dicyclohexyl-*N*,*N*-diethylcarbamylphosphine oxide	80	Not distilled	. . .	. . .	65.2	10.2	9.9	4.5	65.0	10.3	9.8	4.5	White solid, m.p. 113 after twice crystallized, from hexane
Diphenylbenzylphosphine oxide	40	Not distilled	. . .	. . .	78.0	5.8	10.6	. . .	78.3	5.7	10.6	. . .	White solid, crystallized 2× acetone, 1× acetone–ethanol, 1× toluene, m.p. 200
Diphenyl-2-propylphosphine oxide	70	Not distilled	. . .	. . .	No analysis performed								Crystallized 2× acetone, m.p. 140, literature m.p. 142
Di-2-propylbenzylphosphine oxide	75	115, 0.3	. . .	. . .	69.6	9.4	13.8	. . .	68.7	9.0	13.6	. . .	White solid, too hygroscopic for accurate m.p.

[a] When pressure was 1×10^{-4} mm., isolation was by molecular distillation.



[b] $(C_4H_9O)_2\overset{O}{\overset{\|}{P}}-CH_2-\overset{O}{\overset{\|}{P}}(C_5H_{11})_2$. [c] $(C_5H_{11})_2\overset{O}{\overset{\|}{P}}-\overset{O}{\overset{\|}{C}}-N(C_2H_5)_2$.

With tri-2-butylphosphine oxide no product was obtained when the ether solution was refluxed overnight before final work-up. However, when ether was displaced with dioxane and the dioxane solution refluxed overnight, a 70% yield of product was obtained.

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Some Substituted Thiophenes and 2,2′-Bithiophenes

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The properties of a number of substituted thiophenes and 2,2′-bithiophenes are reported. Per cent yields and melting or boiling points are given for the reported compounds, which were among those prepared in a study of the synthesis of carboxylic acids.

PREVIOUS work (*1*) by the author on hydrocarbons has now been successfully extended to the preparation of two substituted thiophenes and four substituted 2,2′-bithiophenes. Data are given in Tables I and II. The basic conditions used for the necessary acylations and reductions (*2*) were the same for both thiophene and bithiophene, affording a basis for comparison of yields.

Boiling points were determined during vacuum distillation of the compounds using standard apparatus. Melting points were determined using a Vanderkamp "Melt-Pointer" (Scientific Glass Apparatus Co., Inc., Catalog No. M-1945). Mixed melting points were determined using a 50 to 50 mixture of the synthetic and commercial products. Neutralization equivalents were determined using standard titration methods. Ultimate analyses for carbon, hydrogen, and sulfur were in accord with theory.

Table I. Properties of Substituted Thiophenes and 2,2′-Bithiophenes

				%C		%H		%S	
Compound	Yield	B.P., ° C.	M.P., ° C.	Found	Calcd.	Found	Calcd.	Found	Calcd.
Methyl-5-(2-*n*-butyl-5-thenoyl)valerate	74.0	188–190 (1 mm.)	34–35	63.95	63.79	7.94	7.79	11.11	11.34
6-(2-*n*-Butyl-5-thienyl)-hexanoic acid	85.5	171–174 (0.1 mm.)	...	66.35	66.09	9.09	8.72	12.68	12.60
5-*n*-Butyryl-2,2′-bithiophene	76.0	...	76–77	60.69	60.98	5.08	5.12	26.89	27.14
5-*n*-Butyl-2,2′-bithiophene	65.6	109–113 (1.5 mm.)	...	64.76	64.79	6.42	6.34	28.63	28.84
Methyl 5-[5′-*n*-butyl-5-(2,2′-bithenoyl)]-valerate	48.1	...	68–69	62.57	62.61	6.74	6.64	17.82	17.59
6-[5′-*n*-Butyl-5-(2,2′bithienyl)]-hexanoic acid	76.6	...	60–61	64.22	64.25	7.06	7.19	18.88	19.06

Table II. Properties of Carboxylic Acids

				Neut. Equiv.	
Acid	Yield	M.P., ° C.	Mixed M.P., ° C.	Found	Calcd.
Tetradecanoic	85.2	54.0	54.0	228.0	228.4
Octadecanoic	76.5	69.5	69.5	284.4	284.4

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