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METHOD OF PREPARING ORGANIC PHOSPHONATES BY TRANSESTERIFICATION
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This invention pertains to a method of preparing esters of phosphonic acids. In particular, the invention is concerned with the preparation of mixed alkyl aryl phosphonates.

As heretofore practiced, the production of mixed phosphonates has entailed a two-fold operation in which each esterifying alcohol is separately introduced into the phosphonic acid molecule. In a typical synthesis, a phosphonic dichloride is first treated with the requisite alcohol in the presence of a base whereby one of the chlorine atoms is replaced by the alkoxy function provided by the particular esterifying alcohol. From this reaction there is obtained an intermediate phosphonochloridate which, after being isolated, is once more subjected to esterification as above described and the remaining chlorine replaced by a second and different alkoxylic function.

Although the two-stage esterification of phosphonic dichloride appears to offer a general synthetic route for the production of mixed phosphonate esters, the reaction is subject to a considerable degree of variation. This is especially true with respect to yields of final product. Such a variation in yield stems primarily from the difficulties encountered in isolating the intermediate phosphonochloridate, a factor which has been found to differ markedly in individual cases. In this connection, it is interesting to refer to a rather recent article in the JACS, 80, 3948 (1958), in which the authors report the preparation of O-isopropyl ethylphosphonochloridate by the stepwise reaction of a phosphonic chloride with alcohols. Even after several attempts making use of different reaction conditions, the highest yield reported amounted to only 12.5%.

Manifestly, the organophosphorus art would be extended and benefitted if mixed phosphonate esters could be obtained in higher yields and with greater reliability than is realizable by the presently known methods.

It has now been discovered that mixed phosphonates wherein one of the esterifying moieties is aryl and the other alkyl are realizable by a process which does away with the step-wise reaction of alcohol with a phosphonic dichloride thereby eliminating the difficulties attendant the isolation of an intermediate phosphonochloridate. In accordance with the present invention, excellent yields of mixed aryl alkyl phosphonates can be achieved by subjecting under anhydrous conditions a diaryl phosphonate to a transesterification reaction in the presence of an alkali metal salt of a weak acid which functions as a catalyst, whereby one of the aryl groups is replaced by an alkyl radical derived from the esterifying alcohol. The reaction which is of general applicability can be schematically depicted by the following chemical equation:

\[
R-Ar + ROH \rightarrow R-PO(OAr) \rightarrow R-P(OAr) + HOAr
\]

wherein \( R \) and \( R' \) represent alkyl radicals of from 1 to 20 carbon atoms, e.g., methyl, ethyl, n-propyl, isopropyl, sec-butyl, tert.-butyl, n-amyl, tert.-amyl, sec.-emyl, n-hexyl, iso-hexyl, iso-cyctyl, n-nonyl, n-decyl, n-tridecyl, n-tetradecyl, penta-decyl, hexadecyl, octadecyl, etc., \( X \) is a chalcojen such as sulfur or oxygen, and \( Ar \) represents an aromatic hydrocarbon residue of the benzene and naphthalene series.

In preparing the mixed aryl alkyl phosphonates in accordance with the transesterification reaction as contemplated herein, it has been ascertained that a high degree of reproducibility accompanied by superior yields results by heating in the presence of an alkali metal alkoxide catalyst a diaryl phosphonate with an aliphatic alcohol having an alkyl radical identical to the alkyl group of the desired aryl alkyl phosphonate. A convenient and simple procedure consists in refluxing the diaryl phosphonate in the aliphatic alcohol containing a catalytic quantity of sodium alkoxide derived from the particular alcohol utilized in the transesterification. After removing the phenolic by-product of the transesterification, the so-obtained mixed aryl alkyl phosphonate is separated and isolated by means of techniques commonly employed in the organic chemistry art, such as crystallization, sublimation, distillation and the like.

The diarylphosphonates, which serve as intermediates for the transesterification process of the invention, are known chemical entities, the preparation and description of which can be found in the technical literature and various chemical brochures and textbooks. Normally such materials are formed by reacting under basic conditions about one mole of a phosphonic dichloride with at least two moles of a phenolic reactant. For a more detailed account of the synthesis of diarylphosphonates, reference is made to the well known treatise, "Organophosphorus Compounds," by G. H. Kosolapoff.

Reference is now made to the following examples which are presented for the purpose of illustration only since variations in practicing the invention without departing from the spirit or scope thereof will be apparent to those skilled in the art to which the said invention pertains.

**Example I**

![Chemical Structure](image)

- **O-isopropyl 0.2-chloro-4-nitrophenyl ethylphosphonothioate**
  - 122 g. (0.28 M) of O,O-bis(2-chloro-4-nitrophenyl) ethylphosphonothioate was mixed with 300 ml. of isopropanol—previously reacted with 2 g. of sodium—and the resulting mixture refluxed for a period of 56 hours, during which interval the initially insoluble starting material underwent gradual dissolution. After distilling off the isopropanol, the residue was taken up in 250 ml. of benzene, the organic solution washed with 600 ml. of 2% sodium hydroxide, then with water and the organic layer dried over anhydrous magnesium sulfate and the solvent removed by distillation. There was obtained 72 g. (80%) of a light brown residue having a refractive index of...
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1.5582. On cooling and inoculation, the product solidified, and after crystallization from hexane melted at 48° C. The analysis of the purified product was in consonance with the above depicted structure.

The 2-chloro-4-nitrophenol formed as a by-product during the transesterification can be recovered from the alkaline aqueous phase by acidification for preparing additional diarylphosphonate for use as starting material in further preparations.

Example 2

O-2-chloro-4-nitrophenyl O-n-butyl ethylphosphonothioate

The procedure for this preparation was patterned after Example 1 but using 50 g. (0.118 M) of \(\text{O,O-bis(2-chloro-4-nitrophenyl) ethylphosphonothioate}\) and 100 ml. of \(\text{n-butanol}\) previously reacted with 0.5 g. of sodium. The mixture was refluxed at 115-120° C. for six hours. The light brown, oily product was obtained in a yield of 85%; the \(\text{N_25 is 1.5422.}\)

Example 3

O-2-chloro-4-nitrophenyl O-isopropyl methylphosphonothioate

Using the procedure set forth in the previous examples, 57 g. of \(\text{O,O-bis(2-chloro-4-nitrophenyl) methylphosphonothioate}\) was refluxed for 77 hours with isopropanol previously reacted with 0.75 g. of sodium. There was obtained in a 77% yield a brown, oily product having a refractive index of 1.5545.

Example 4

O-isopropyl O-2,4,5-trichlorophenyl ethylphosphonothioate

The product of this example was prepared using 48.7 g. of \(\text{O,O-bis(2,4,5-trichlorophenyl) ethylphosphonothioate}\) and 150 ml. of isopropylic alcohol previously reacted with 0.75 g. of sodium. There was obtained 35 g. (94%) of a light yellow, oily product having an \(\text{N_25 of 1.5390.}\)

Example 5

O-isopropyl O-4-nitrophenyl ethylphosphonothioate

The above depicted compound was obtained by refluxing a mixture of 27 g. of \(\text{O,O-bis(2-chloro-4-nitrophenyl) ethylphosphonothioate}\) and 200 ml. of isopropanol previously reacted with 1 g. of metallic sodium. After the mixture was refluxed for 47 hours, there was isolated a light yellow oil, the \(\text{N_25 of which is 1.4555.}\)

Example 6

O-2-chloro-4-nitrophenyl O-sec-butyl ethylphosphonothioate

The above depicted compound was obtained by refluxing for 100 hours a mixture of 43.7 g. of \(\text{O,O-bis(2-chloro-4-nitrophenyl) ethylphosphonothioate}\) and 100 ml. of sec-butanol previously reacted with 1.2 g. of metallic sodium. There was obtained in 76% yield a brown oil exhibiting a refractive index of 1.5487 at 25° C.

Example 7

O-isopropyl O-phenyl phenylphosphonate

The above depicted compound was prepared by refluxing for 32 hours diphenyl phosphonophosphate and isopropyl in accordance with the procedures of the previous examples.

In general, it has been ascertained that any weak acid salt which is capable of forming the phenoxide ion from the liberated phenol is satisfactory as a catalyst. It is the phenoxide ion itself which constitutes the direct and active catalyst in the transesterification system. Particularly suitable for the aforesaid purpose are the alkali metal salts of weak acids, e.g. sodium alkoxides, e.g. sodium methoxide, sodium ethoxide, and the like, sodium carbonate, potassium bicarbonate, sodium hydride, potassium amide, potassium hydride, etc., the tetra-substituted onium type salts of weak acids, e.g. tetramethylammonium hydride, tribenzylmethylammonium hydride, tetrathylammonium alkoxides, triphenylsulfonium hydride and the like.

I claim:

1. The method of preparing a mixed alkyl aryl alkylphosphonate of the following formula:

\[
\begin{align*}
\text{X} & \quad \text{B} \quad \text{OAr} \\
\text{OR'} &
\end{align*}
\]

wherein each of R and R' represents an alkyl radical of from 1 to 18 carbon atoms, Ar represents an aromatic hydrocarbon residue selected from the class consisting of a phenyl radical and a naphthyl radical and X is a chalcogen selected from the class consisting of oxygen and sulfur, which comprises reacting under anhydrous conditions in the presence of an alkali metal salt of a weak acid capable of forming a phenoxide ion with phenol as the catalyst and in approximately equal molar amounts an aliphatic alcohol of the formula R'—OH wherein R' has the significance as above set forth with an alkyl phosphonate of the formula:

\[
\begin{align*}
\text{X} & \quad \text{B} \quad \text{OAr} \\
\text{OR'} &
\end{align*}
\]

wherein R, X, Ar have the values as above defined and separating the resulting mixed alkyl aryl alkylphosphonate from the phenolic by-product.

2. The method according to claim 1 wherein the catalyst is an alkali metal alkoxide.

3. The method according to claim 2 wherein the alkali metal alkoxide is sodium alkoxide.

4. The method according to claim 1 wherein the reaction is carried out in the presence of excess alcohol as solvent.

5. The method according to claim 1 wherein the reaction is carried out under reflux.

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