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SULFONATE ESTERS OF HALOGENATED PHENOLS IN GRIGNARD PREPARATIONS (1)

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Berkeley, California

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The work of Gilman and others (2) on reactions of aryl esters of aromatic sulfonic acids with Grignard reagents showed that only slight action took place at 35° C. During the course of work on Grignard preparations, the possibility of obtaining a reaction of magnesium with bromophenyl esters of aromatic sulfonic acids was examined. It was hoped to use these bromo phenol esters as aryl halides and obtain protection of the phenolic group by this esterification.

Some of the bromo esters reacted successfully under entrainment conditions giving about 25% yields of the desired Grignard reagent (viz. $Ar.SO_2.O.C_6H_4.MgX$) whose presence was proved by carbonation and isolation of the corresponding acid. The latter and other reaction products of these Grignards could be hydrolyzed removing the sulfonate group and forming the corresponding hydroxy derivative.

Bromoalkyl esters of aromatic sulfonic acids would not be expected to function as alkyl halides in a similar reaction as these esters have labile alkyl groups.

Para-bromophenol was used in most of the work and its esters with benzene and toluene sulfonic acids were studied. These reacted difficulty or not at all

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(2) Gilman, Beaber, and Myers, J. Am. Chem. Soc., 47 2047 (1925).

with magnesium alone but more facile reaction occurred if the ester-bromide was entrained with excess ethyl bromide. Carbonation and isolation of acids in the usual manner furnished the aryl sulfonic esters of p-hydrobenzoic acid ($Ar.SO_2.O.C_6H_4.COOH$). The tosyl ester was hydrolyzed to p-hydroxybenzoic acid.

This is not a general reaction as esters of several other bromophenols gave little or none of the desired product or unknown substances. Thus, the ester of orthobromophenol yielded a product different from the known desired acid (arylsulfonate ester of salicylic acid) and which was not identified.

As the hydroxy derivatives ultimately desired were organophosphorus acids with a para hydroxy group, the reaction of the ester-Grignards with $POCl_3$ was examined. This reaction was conducted in the reverse manner after Kosolapoff (3) who has demonstrated that phosphinic acids (R_2POOH) can be prepared by this method. The expected product was the bis(arylsulfonate) of di(p-hydroxyphenyl) phosphinic acid. However, the product which was isolated was the sulfonate ester of ethyl-(p-hydroxyphenyl) phosphinic acid, obviously formed by incorporation of the ethyl Grignard entrainer into the reaction product (an excess of ethylmagnesium bromide was present). The acid was hydrolyzed to the parent p-hydroxy acid, $C_2H_5(p\text{-}HO.C_6H_4)POOH$.

An attempt to entrain with butyl bromide and so to include a butyl group in the phosphorus compound gave a poor yield of an acid of this type, probably, though separation from dibutyl phosphinic acid was difficult.

The phenyl ester of p-bromobenzene sulfonic acid, entrained with ethyl bromide and carbonated gave two acids according to conditions. These were not further investigated. No other halogenated phenols were examined as the main object of the work was preparation of p-hydroxy derivatives.

This method of forming p-hydroxy derivatives may serve as a supplement to the method of Gilman (4) involving exchange (interconversion) of butyl lithium

(3) Kosolapoff, J. Am. Chem. Soc., 64 2982 (1942).

(4) Gilman, Arntzen, and Webb, J. Org. Chem., 10 374 (1945).

with p-bromophenol.

EXPERIMENTAL

All melting points are uncorrected.

The aryl esters of aromatic sulfonic acids were prepared according to Slagh and Britton's modification of the Hinsberg method (5). These phenol esters were previously made by Hazlett (6) and by Sekera (7).

Preparation of p-Benzenesulfonyloxy-benzoic acid.- The method used for preparation of the ester-Grignard and its carbonation is illustrated by the synthesis of p-benzenesulfonyloxybenzoic acid.

A solution of 6.55 g. of benzene sulfonic acid p-bromophenyl ester and 2 ml. of ethyl bromide was reacted with a considerable excess of magnesium and when slow, a solution of 16 ml. of ethyl bromide in 50 ml. ether was started in. This was added dropwise at room temperature during 1.5 hours. The solution may be refluxed after the addition but this is not necessary and in some cases is deleterious. The large excess of ethyl bromide enables more of the aryl bromide to be utilized than would otherwise occur, and may possibly be increased still further with advantage. Carbonation with dry ice was as usual. The ether layer of the hydrolysis product was extracted three times with sodium carbonate solution and the combined carbonate extracts acidified to precipitate the acid. Yield 1.59 g. or 24.3%. This was recrystallized several times from ether, m.p. 170-171.5° C. Lit. 170° (8). The non-acidic fraction of the reaction product may be used to recover unreacted bromophenyl ester.

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(5) Slagh and Britton, J. Am. Chem. Soc., 72 2808 (1950).

(6) Hazlett, J. Am. Chem. Soc., 59 287 (1937).

(7) Sekera, J. Am. Chem. Soc., 55 421 (1933).

(8) Frdl 8 155 and B. A. S. F. Ger. Pat. No. 162322. (In Beilstein).

A similar preparation of the tosylate of p-hydroxybenzoic acid gave a 28.3% yield of the acid. This, after several recrystallizations from ether, also melted 170-171.5° C. Lit. 168-170° C. (8).

Hydrolysis of p-Tosyloxybenzoic acid.- This substance was hydrolyzed quantitatively by 3 hours boiling with 10% sodium hydroxide solution. Acidification and several ether extractions removed the p-hydroxybenzoic acid. This was recrystallized from water and from ether-petroleum ether, m.p. 209-211° C.

Preparation of Ethyl(p-toluenesulfonyloxy-phenyl) phosphinic acid.- A solution of 5 g. p-bromophenyl tosylate and 5 ml. ethyl bromide in 100 ml. ether was reacted with excess magnesium and when nearly quiet a solution of 17 ml. ethyl bromide in 50 ml. ether was started in dropwise. This was added in one hour and then left one-half hour in the cold. It was transferred to a separatory funnel along with any gum which may form (using benzene). The solution was added during one hour to 30 ml. $POCl_3$ in 200 ml. benzene at an average temperature of 30° C. Cooling was used to moderate reaction heat. Twenty minutes after addition was complete, the product was hydrolyzed by ice-hydrochloric acid. The mixture was shaken thoroughly to decompose any excess $POCl_3$. The washed organic layer was extracted twice with sodium carbonate solution to extract the acid, which was obtained on acidifying. A partly gummy product was precipitated but this crystallized and solidified on cooling and standing. Ice-cooling caused separation of a further crop. The weight of washed and dried crude acid was 1.105 g. or 21.25%.

The acid is best recrystallized by solution in acetone and dilution with water and then boiling off the organic solvent. The acid is isolated by ice-cooling. Too long boiling with water causes some decomposition. It was recrystallized as above several times. The analytical sample was then recrystallized from ether-petroleum ether and again from acetone-water, m.p. 153-153.5° C. It forms a white powder.

Anal.:

Calcd for $C_{15}H_{17}PSO_5$

	C	52.94	H	5.00
Found (I)		52.85		5.18
(II)		52.77		5.12

Preparation of Ethyl(p-hydroxyphenyl) phosphinic acid.- This was obtained by hydrolysis of the preceding acid. A mixture of 1.52 g. of this substance and 10 g. of sodium hydroxide dissolved in 50 ml. of water was heated for 4 hours on the steam bath. The solution was cooled, diluted, and acidified with excess hydrochloric acid. It was filtered, concentrated by boiling, and filtered again to eliminate some resin. The water soluble acid could then be recovered by repeated extraction with ether (10 times or more) or by evaporation and repeated and thorough extraction of the dry residue with ether and acetone. The acid was obtained in crude yield of 580 mg. or 69.7%. It was purified by continued recrystallization from benzene-acetone (10:1). Finally it was recrystallized from benzene alone by boiling out acetone from the mixed solvent solution. The powder was washed with ether and air dried. The highest melting point observed was 160-161° C.

Anal.:

Calcd for $C_8H_{11}PO_3$

	C	51.61	H	5.91
Found		51.35		5.91

The reaction of orthobromophenol p-toluenesulfonate (3.7 g.) entrained with 25 ml. of ethyl bromide as before and the mixture carbonated gave 830 mg. of a white acid m.p. 216-217° C. after ether recrystallization. This is not the desired tosylate of salicylic acid (m.p. 154-156° C.) (8). An authentic sample of this compound made by acylation of salicylic acid had m.p. 158-159° C. after recrystallization from water (depressed when mixed with salicylic acid which itself has m.p. 158° C.).

Entrainment of the phenyl ester of p-bromobenzene sulfonic acid with ethyl bromide and carbonation gave an acid m.p. 206° C. if the solution was not refluxed after ethyl bromide addition, while when refluxed one-half hour and then carbonated, an acid m.p. above 260° C. resulted. One of these (most probably the first) may be the expected $p\text{-}C_6H_5O.SO_2.C_6H_4.COOH$.

Entrainment of p-Bromophenyl Tosylate with Butyl Bromide and Reaction with Phosphoryl Chloride.- This was analogous to the reaction with ethyl bromide except that butyl bromide was used. The reaction gave a mediocre yield of acid which was difficult to purify. It was recrystallized a number of times from ether and from ether-petroleum ether but was not obtained quite free from dibutyl phosphinic acid. The highest melting point observed was 141-142.5° C.

Anal.:

Calcd for $C_{17}H_{21}PSO_5$, butyl(p-tosyloxy-phenyl) phosphinic acid

C	55.43	H	5.71
Found	54.77		5.44

Preliminary work indicates that the phenolic group in halophenols may also be protected by esterification with diphenyl phosphoryl chloride, $(C_6H_5O)_2POCl$. Thus, the compound diphenyl p-bromophenyl phosphate, $(C_6H_5O)_2PO.OC_6H_4Br$, can be made to react with magnesium by ethyl bromide entrainment and the resulting solution used in a similar manner as an arylmagnesium halide.

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