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Aromatic Sulfonation with Sulfur Trioxide in Nitromethane

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Solutions of nitromethane containing about 500 mg of SO_3 pr ml have been used for sulfonation of various aromatic hydrocarbons at 0°C. The separated reaction products have been found to be sulfonic acid anhydrides, and especially with aryl halides this method gives good yields and pure products. The paper describes various anhydrides not previously reported. The exchange reactions $H_2{}^{35}SO_4 + SO_3$ and $Ar^{35}SO_3H + SO_3$ in nitromethane have been qualitatively investigated, and a method for the preparation of pipsan, *p*-iodobenzenesulfonic acid anhydride, labelled with ^{35}S has been developed. The yield of activity has been 60–65 % in the crude product.

In search of a simple method for the preparation of labelled *p*-iodobenzenesulfonic acid anhydride, pipsan, the direct sulfonation of iodobenzene at room temperature, as described by Lukashevich[1], has been investigated. In a previous paper[2] studies on the conditions for the formation of the pipsan in oleum were reported. It was concluded that the optimal conditions correspond to the brutto-equation:

$$3\,SO_3 + 2\,C_6H_5I \rightleftharpoons (IC_6H_4)_2S_2O_5 + H_2SO_4$$

and it was shown that while the amount of free SO_3 (in excess of 100 % H_2SO_4) is critical, the H_2SO_4 appears to act as an inert solvent only.

The present paper describes a new modification in which sulfur trioxide in nitromethane is used as sulfonating agent.

Sulfonations of iodobenzene conducted on a semi-micro scale with varying amounts of SO_3 in nitromethane showed improved yields compared to those obtained with oleum (*cf.* Fig. 1). The optimal range is far broader than that of the previous method. Neither competing crystallization of the sulfonic acid nor tar-formation were observed in these experiments. Further, the low viscosity of the nitromethane solution compared to that of oleum at 0° makes the modification better suited for syntheses in micro and semi-micro scale.

Sulfonation of various aromatic compounds with nitromethane containing sulfur trioxide resulted in many cases in rapid separation of sulfonic acid anhydride, the best yields and purest products having been obtained with the halogen substitutes, *cf.* Table 1.

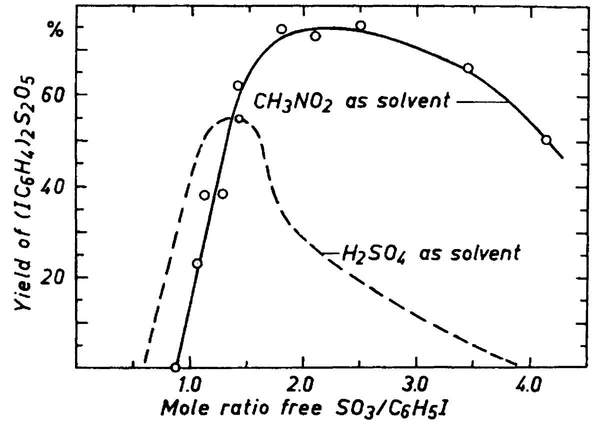

Fig. 1. Yields of iodobenzenesulfonic acid anhydride formed by sulfonation of iodobenzene with 3–5 M solution of sulfur trioxide in nitromethane (full line). Broken line indicates yields obtained with oleum as previously reported[2].

Table 1. Data for sulfonic acid anhydrides.

Sulfonated aromatic compound	Yield %	Solubility in CH_3NO_2. 0°C. mg in 1 g sat. soln.	Neutr. equiv. wt.		M.p. in °C of	
			found	calc. mono-sulf.	anhydrides	amides
Benzene	0	270[a]				
Toluene	20	27[a]	167	163		
m-Xylene	50		135	177		
Diphenyl	85		134	225		
Naphthalene	57		153	199		
Anthracene	0					
Anthraquinone	0					
Chlorobenzene	35	20	190	184	130–141	143–144
Bromobenzene	60	5.0	232	228	178.5–182	166–167
Iodobenzene	70	2.1	279	275	220–221	187–189
p-Dichlorobenzene	0					
p-Diiodobenzene	0					
us-Trichlorobenzene	14		264	253		
o-Chlorotoluene	30	15			148–151[b]	130
m-Chlorotoluene	70	14	195	198	149–150[b]	185
p-Chlorotoluene	90	1.8	199	198	210–211	143
m-Bromotoluene	60		237	242	179.5–180.5	
p-Iodotoluene	36		290	289	215–220	
1-Chloronaphthalene	50		246	234	218.5–219	
1-Bromonaphthalene	60		285	278	217–218	
2-Bromonaphthalene	20		284	278	227–229	

[a] Solubilities of benzene- and toluene sulfonic acid anhydrides were found on samples prepared according to Bernoulli[12] and Fichter[13]

[b] M.p. of mixture from *o*- and *m*- chlorotoluenesulfonic acid anhydrides: 124–126°C.

Generally a ratio of 1.7 mole SO_3 per mole of aryl was used in these experiments. In some cases improved yields were observed with higher SO_3/ArH-ratios.

The yields have been calculated as per cent of the theoretical from the aromatic compound.

The solubilities of some of the recrystallized samples in nitromethane have been measured at 0°C. The figures given in Table 1 indicate that the yields of the syntheses to some degree depend upon the solubilities of the anhydrides.

The anhydride character of the crude compounds was confirmed by their direct transformation to amides and anilides with ammonia and aniline.

The modification is well suited for the preparation of sulfonic acid anhydride labelled with the radioactive isotope ^{35}S. This aspect has only been investigated with $(I{\cdot}C_6H_4)_2S_2O_5$, but the results will no doubt apply to aromatic sulfonic acid anhydrides in general.

A droplet of concentrated H_2SO_4 containing the radioactive isotope as $^{35}SO_4^{2-}$ was mixed at 0° with the SO_3-nitromethane solution. By sulfonation of iodobenzene with this medium, the anhydride labelled with ^{35}S was formed directly. Assays of activities showed that the original activity had exchanged completely with the sulfur trioxide *.

It was observed that neither the sulfonic acid nor its anhydride would undergo rapid exchange with sulfur trioxide in nitromethane solution, and it could be demonstrated that, with the same amounts of chemicals and activities, the specific activity of the labelled pipsan was increased about 50 % if the sulfonation was conducted in two steps instead of one: the first being the formation of the sulfonic acid by the use of the total activity and only a fraction of the calculated amount of SO_3, the second being the anhydride formation of

Table 2. Syntheses of ^{35}S-labelled pipsan in nitromethane. In each of the experiments were used 245± 10 μC of the activity, 0.02 mmole H_2SO_4 as carrier and 0.59 mmole C_6H_5I, all values referring to one mmole of total SO_3. The activity, carrier and iodobenzene were mixed with the amount of SO_3 given in the second column. To this mixture was subsequently added the quantity given in the third column.

Expt. No.	SO_3 added, mmole per mmole aromatic		Yield of crude pipsan		Spec. activity of pipsan μC/mil. equiv.	Yield of activity in crude products %
	in first step	in second step	% of total SO_3	% of C_6H_5I		
1	1.65	0	40.0	67.9	230± 10	38
2	0.83	0.83	44.5	75.3	330± 15	60
3	0.33	1.33	45.0	76.2	360± 15	66

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* *Added in proof:* It has been observed that also the exchange between SO_3 and Na_2SO_4 in nitromethane is rapid, and the use of Na_2SO_4-carrier instead of conc. H_2SO_4 has proved advantageous in the synthesis of ^{35}S-pipsan.

the labelled sulfonic acid from the first step by the addition of the rest of the SO_3 (*cf.* Table 2). With the latter procedure yields of 60—65 % of the activity have been obtained in the crude pipsan.

EXPERIMENTAL

The nitromethane was from L. Light and Co, boiling range 98—101°. If the amount of free SO_3 had to be known with fair accuracy, the nitromethane was distilled over P_2O_5 prior to use. The solutions of SO_3 in nitromethane were prepared by mixing fibrous SO_3 (from Merck, p.a.) with the nitromethane. The content of SO_3 per ml was determined by weighing of the SO_3 and by assay of specific gravity of the solution. Solutions having a molarity of 7—8 can be prepared. The usual concentrations of the solutions have been 3—5 M. At room temperature the solution will gradually decompose, perhaps due to the process $CH_3NO_2 \rightarrow H_2NOH + CO$, which has been observed by Pfungst[3]. At 0°C the solution can be used for at least 4 h.

The aromatic compounds were pure preparations from Fluka and British Drug Houses. Weighed amounts of these compounds (around 0.5 g) were dissolved in 0.5—2.0 g of nitromethane in 10 ml centrifuge tubes placed in ice-water. The sulfonation mixture, which had been prepared shortly before and stored at 0°, was added with micropipettes.

In most cases the precipitation started immediately after the mixing of the components and was apparently complete after a few minutes, but occasionally, especially with the unsubstituted hydrocarbons, the precipitation did not start until several minutes after the mixing.

After one hour the precipitate was washed, dried and weighed as crude products as described previously[2], the only exception being the use of nitromethane instead of acetic anhydride as washing agent.

The melting points given in Table 1 are corrected. Since prolonged heating lowers the melting points of the anhydrides, the capillary tubes with these compounds have been immersed in the oil bath 10—20°C before the expected melting points. The rate of heating in this range was 2°C per minute.

The melting ranges of the sulfonic acid anhydrides are often fairly broad. Although the sulfonic anhydrides generally are insoluble in cold water and only slowly decomposed by hot water, they appear to be quickly hydrolysed by humid atmosphere. Therefore anhydrous conditions are necessary in order to obtain sharp melting points of these compounds.

By hydrolysis and evaporation of crude pipsan and subsequent boiling with thionylchloride and recrystallization from anhydrous chloroform-pentane, a pure product is consistently obtained with melting point 220—221°C. This melting point has previously been observed on the pure *p*-iodobenzenesulfonic acid anhydride[4]. In our laboratory the same melting point has sometimes been observed on products recrystallized from anhydrous chloroform or nitromethane, but quite as often this procedure results in products melting only at 200—210°. On the other hand the crude pipsan may sometimes melt as high as 218—219°.

An accelerated hydrolysis of the anhydrides is conveniently carried out by exposure to steam. The hydrolysates of the crude products have in all cases been found to be completely soluble in water indicating absence of sulfone. The neutr. equiv. weights were determined by titration with 0.1 N NaOH on crude products.

Sulfonyl chlorides were prepared from the crude sulfonic anhydrides of the mono halogen benzenes by steam hydrolysis, treating the acid with excess of PCl_5 in $POCl_3$, destruction of the excess with ice-water, extraction with benzene and finally sublimation. The following m.p's. were found: chloro- 51.5°, bromo- 75.0°, and iodo- 82.5—83.5°C. All three correspond to the *p*-halogeno-benzenesulfonyl chlorides.

The *sulfonic amides* were prepared from the crude sulfonic anhydrides by dissolving in chloroform and treating with aqueous ammonia. By evaporation of the chloroform phase and acidifying the aqueous solution, the amides separated in 60—70 % yields. The melting points in Table 1 were determined on samples recrystallized from alcohol.

In order to obtain chlorobenzenesulfoneamide it was necessary to apply a dry NH_3-$CHCl_3$ solution.

The *anilides* of the monohalogeno-benzene sulfonic acids were prepared in a similar way, the melting points being: chloro- 93.5—96.0°, bromo- 117—118°, and iodo- 142—144°C.

The pure anhydrous *sulfonic acids* are difficult to isolate by classical sulfonation. By the present method these difficulties are overcome, as the sulfonic acids are obtained merely by hydrolysis of the recrystallized sulfonic anhydride and drying. The anhydrous acids are apparently even more hydroscopic than the anhydrides. The sulfonic acids of the halogeno-benzene prepared according to this method were dried for three days over P_2O_5 *in vacuo*, and the samples in the capillary tubes intended for determination of melting points were dried for one day more in the same way. The following melting ranges were observed: chloro- 89—99°, bromo- 90—92°, and iodo- 75—77.5°C.

The *solubilities* in nitromethane at 0° of various sulfonic anhydrides were determined by shaking recrystallized samples in closed 5 ml bottles for 6 h. Samples of clear supernatants were taken at intervals to check equilibrium.

The ^{35}S-*activity* was prepared on Risø's Isotope Laboratory from KCl irradiated in the reactor DR2. It was obtained as an aqueous solution of $^{35}SO_4^{2-}$. A solution containing about 1 mC ^{35}S and 10 mg of H_2SO_4 per ml was prepared. In each of the experiments referred to in Table 2, 1 ml of this solution was transferred to the test-tubes with a micropipette. The solutions were evaporated at 100°C with a gentle stream of dry nitrogen blowing in the tube. Towards the end of the evaporation the temperature was raised to 120° and kept there for 5 min. The tube with the evaporated sulfuric acid (forming a droplet in the bottom of the tube) was transferred to an ice-bath, and the solutions of SO_3 and C_6H_5I were added with micropipettes in the amount and sequence as indicated in Table 2. The pipsan was isolated, dried and weighed.

Counting was performed with a calibrated end-window Geiger-Müller-tube. The samples for assay of activity were prepared from dilute aqueous solutions by drying 100 μl drops on alumina planchets. The labelled pipsan products were recrystallised from nitromethane prior to weighing, steam hydrolysis, dilution and sampling.

RESULTS AND DISCUSSION

If it may be assumed that the nitromethane does not interfere with the solutes, the exchange reaction between SO_3 and the H_2SO_4 possibly takes place with a polysulfonic compound as intermediate, *e.g.*

$$H_2S^*O_4 + SO_3 \rightleftharpoons H_2SS^*O_7 \rightleftharpoons H_2SO_4 + S^*O_3 \qquad \text{(i)}$$

The exchange is so rapid even at 0° that no kinetic effect can be observed with the described simple technique of synthesis.

The neutr. equiv. of the compounds so far investigated correspond to monosulfonation except for xylene, diphenyl and naphthalene. These three hydrocarbons gave all substantial amounts of precipitate, but the products were amorphous and difficult to obtain dry. By sulfonating naphthalene at 0° with SO_3 in chloroform Courtot *et al.*[5] found products with SO_3-contents varying according to the SO_3/ArH ratio in the sulfonation mixtures. Disulfonation and adducts with SO_3 were observed. An American patent [6] describes the formation of 1-naphthalenesulfonic acid anhydride by sulfonation of naphthalene with SO_3 dissolved in phosphorus oxychloride or dimethylsulfate. Blangey [7] observed formation of long anhydride-chains by sulfonation of naphthalene with oleum.

Toluene and the halogen substituted compounds form anhydrides derived from monosulfonation. The melting points of the derivatives suggest that the conditions of isomerism are identical to those obtained in classical sulfonation.

The variations in melting points from a rather large number of pipsan preparations suggest that the conditions of synthesis are not yet fully controlled. It is possible that slight variations in the temperature during the sulfonation may lead to small variations in the formation of isomers. The importance of anhydrous conditions has been demonstrated by Field[8], who observed that even slight contamination with *p*-toluenesulfonic acid in the corresponding anhydride seriously depressed the melting point. Isomeric impurities present in the starting materials used in our investigation may possibly also contribute to the unsharpness of the m.p.'s.

The observation of increased specific activity with sulfonation starting with low values of SO_3/C_6H_5I-ratios (Table 2) shows that the *p*-iodobenzenesulfonic acid is formed in this range although it is not precipitated as in the investigations with oleum[2]. Probably the sulfonic acid is the primary product with all SO_3/C_6H_5I ratios.

In this connection attention should be paid to a kinetic investigation of aromatic sulfonation carried out by Hinshelwood and co-workers[9,10]. No formation of anhydride was observed in these investigations, probably due to the use of dilute solutions. The sulfonation at room temperature with solutions of SO_3 in nitrobenzene was found to be second order in SO_3, the rate determining reaction possibly being

$$S_2O_6 + ArH \rightarrow ArS_2O_6H \qquad \text{(ii)}$$

Lukashevich[11], assuming a very reactive pyrosulphonic acid as precursor to the anhydride formed by sulfonation with oleum, suggested the following route of reaction:

$$ArS_2O_6H \rightleftharpoons ArSO_3H + SO_3 \qquad \text{(iii)}$$

$$ArS_2O_6H + ArSO_3H \rightleftharpoons Ar_2S_2O_5 + H_2SO_4 \qquad \text{(iv)}$$

The lower yields of pipsan with oleum than with nitromethane may be due to the excess of H_2SO_4 forcing eqn.(iv) from right to left.

The described method has been used for the preparation of ^{35}S-labelled pipsan in charges of 100—200 mC, and with a specific activity of 600 mC/g or more. Products prepared by this method has proved fully applicable in analyses of steroid hormones according to Bojesen[4].

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