Recent Developments in Preparative Sulfonation and Sulfation

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Recently developed or improved methods for the preparative-scale synthesis of sulfonic acids and their derivatives as well as of alkyl esters of sulfuric acid are reviewed.

This review surveys new or improved sulfonation procedures, mostly developed during the past five years, which appear of practical preparative interest to the laboratory chemist. These are methods which appear fairly general in scope, usually give reasonable yields, and have been studied to an extent sufficient to merit detailed descriptions. Some of the procedures are entirely new in concept, while others represent marked improvements in older methods, or demonstrate their significantly wider utility. A more general review of developments in sulfonation prior to about 1964, as well as a survey of current industrial sulfonation methods, have been made elsewhere by the author.

Definitions of terms and the scope of subjects included are those employed previously. The term sulfonation encompasses all methods for attaching a sulfonic acid group (—SO₂OH), or the corresponding sulfonyl halide or salt moiety, to a carbon atom. Sulfation (the placement of the —SO₂OH on oxygen) is also included. Four general sulfonation methods are recognized:

- treatment of an organic compound with sulfur trioxide, or a material capable of generating it;
- treatment of an organic compound with a compound of sulfur dioxide;
- oxidation of an organic compound already containing sulfur in a lower valence state;
- condensation procedures.

The last approach involves the reaction of an organic compound with another, usually of lower molecular weight and already containing the sulfonate group. A new sulfonate is thus formed with desirably altered properties. When the sulfonate-containing reagent is aliphatic, this method is termed sulfonation. All of these types of procedures are illustrated in the order mentioned by the examples given below.

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3 Ref. 1, pg. 42ff.
5 Ref. 1, pg. 280ff.
A. Sulfonation

1. Sulfonation with Compounds of Sulfur Trioxide

1.1. Aliphatic Compounds (1,3-Sultones from Alkenes)

The fairly recent commercial availability of long-chain 1-alkenes, as well as of sulfur trioxide, has prompted several studies of their interaction. Earlier work had shown\(^3\) that lower alkenes with sulfur trioxide give mixtures of products, and the long-chain alkenes have been found to behave similarly\(^4\).

Although the major portion of the reaction product from long-chain alkenes comprises (after hydrolysis) a mixture of various olefinic and hydroxy 1-sulfonic acids, 1,3-sultones, formed by the following reaction, can be isolated in small yield:

\[
\text{R} - \text{CH}_2 - \text{CH} = \text{CH}_2 + \text{SO}_3 \rightarrow \begin{array}{c}
\text{R} - \text{CH} = \text{CH} - \text{CH} _2 \\
\text{SO}_3
\end{array}
\]

\[
\begin{array}{c}
\text{R} - \text{CH} = \text{CH} - \text{CH}_2 \\
\text{SO}_3
\end{array}
\]

Since these materials, as typified by the parent compound propane-1,2-sultone, are exceptionally versatile and reactive substances\(^3\), a direct method for their preparation is of interest.

Undecane-1,3-sultone\(^6\): A solution of sulfur trioxide (28.3 g; 0.356 mol) in 160 ml liquid sulfur dioxide is added dropwise over 7 minutes at -10° with vigorous stirring to a suspension of 1-undecene (50 g; 0.325 mol) in 100 ml liquid sulfur dioxide. The reaction mixture is then stirred 30 min. at -10°, after which the sulfur dioxide is removed by warming to room-temperature and finally applying vacuum. The oily product is mixed with 11 cold water, and the turbid solution is cooled to 20° to crystallize the suspended crude solid sultone. It is filtered and dried in vacuo over potassium hydroxide. Additional sultone is recovered from the aqueous layer by extraction with ethyl ether, followed by washing with an aqueous suspension of calcium carbonate, drying of the solution over anhydrous sodium sulfate, and evaporation of the solvent. The two portions of sultone are combined and recrystallized from petroleum ether (b. p. 60-80°), yield: 8.5 g (11%); m. p. 45-6°.

Although propane-1,3-sultone itself has not been prepared by this procedure, the method appears fairly general for long-chain 1-alkenes such as 1-dodecene or 1-hexadecene\(^6\). Hexadecane-1,3-sultone has also been made by reacting 1-hexadecene and air/sulfur trioxide vapor in a continuous, moving-film reactor\(^6\). Camphene\(^6\), hexachlorobicyclo[2.2.1]-2.5-heptadiene\(^6\), and a series of γ-branched alkenes\(^9\) likewise yield 1,3-sultones upon treatment with sulfur trioxide or sulfur trioxide/dioxane. Other less direct methods are available for converting 1-alkenes to 1,3-sultones\(^5\), including sulfonation with acetyl sulfate, followed by thermal cyclization\(^10\):

\[
\text{R} - \text{CH}_2 - \text{CH} = \text{CH}_2 + \text{CH}_3\text{COOSO}_3\text{H} \rightarrow \text{R} - \text{CH}_2 - \text{CH} - \text{CH}_2 - \text{SO}_3\text{H} + \text{CH}_3\text{COOH}
\]

1.2. Aromatic Compounds (Hydrocarbons; Nitro- and Halogenated Hydrocarbons)

The sulfonation of aromatic compounds with sulfuric acid, oleum, or sulfur trioxide is usually somewhat inconvenient in the laboratory. A mixture of sulfuric acid and the desired sulfonic acid is always formed from the first two reagents, since the reaction does not go to completion unless special means are employed to remove the water formed:

\[
\text{RH} + \text{H}_2\text{SO}_4 \rightarrow \text{R}-\text{SO}_3\text{H} + \text{H}_2\text{O}
\]

Separation of the sulfonic and sulfuric acids may be laborious. If a sulfonate salt is desired, it must be separated from the inorganic salt. The use of sulfur trioxide usually involves vaporization of the reagent. The two procedures described below, on the other hand, are free of these objections.

1.2.1. With Chlorosulfuric Acid

The first method comprises the addition of slightly more than one molar equivalent of chlorosulfuric acid\(^11\) to the organic compound at 0-30°, usually in the presence of a solvent:

\[
\begin{align*}
\text{RH} + \text{Cl}_2\text{SO}_2\text{H} & \rightarrow \text{R}-\text{SO}_3\text{H} + \text{HCl} \\
\text{R} - \text{SO}_3\text{H} + \text{Cl}_2\text{SO}_2\text{H} & \rightarrow \text{R} - \text{SO}_3\text{Cl} + \text{H}_2\text{SO}_4
\end{align*}
\]

Reaction 4 goes to completion under these conditions with the evolution of hydrogen chloride. (Reaction 5, which occurs only in the presence of excess acid, constitutes a standard procedure for preparing aromatic sulfonyl chlorides\(^12\).) Although reaction 4 has been occasionally used in the past for preparing sulfonic acids, the observation\(^13\) that with the correct reaction solvent, the desired sulfonic acid can crystallize in good purity directly from the reaction mixture, has made this approach decidedly more attractive. A typical procedure follows.

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11 The compound ClSO_2H has in the past been designated chlorosulfuric acid. However, in accordance with the 1967 recommendation of the IUPAC Commission on Nomenclature of Inorganic Chemistry, it is now preferably called chlorosulphuric acid. This nomenclature will be employed herein.
12 Ref. 1, pg. 84 ff.
Biphenyl-4-sulfonic Acid: To a stirred solution of biphenyl (154 g; 1 mol) in 850 ml chloroform is slowly added chlorosulfuric acid (144 g; 1.237 mol) in 125 ml chloroform (the excess acid is used to react with the ethanol present as stabilizer in the chloroform). During the course of the addition, a temperature increase of 15°C is noted. After addition of about 75% of the acid, precipitation of 4-biphenylsulfonic acid begins. The suspension is stirred for 30 min. after completion of the addition of the acid. The precipitate is filtered (sintered glass funnel), washed with chloroform and dried; yield: 187 g (80%); m.p. 138-40°. A second crop (about 15%) of less pure biphenyl-4-sulfonic acid can be obtained from the mother liquor.

The same procedure, with variations in the proportion of solvent, gives yields of the 4'-sulfonic acids as follows from substituted biphenyls: 4-bromo- (97%); 4-nitro- (99%); 4-methyl- (82%). With the 2-bromo- and 4-t-butyl-derivatives, 86 and 91% yields may be obtained by adding hexane to the reaction mixture after sulfonation to reduce the solubility of the product.

Other examples are cited in the following Table. In all of these cases, the sulfonic acids are extracted from the reaction mixture with water. The 3,7-dialkylphenathalenesulfonic acids are isolated by adding just enough water to convert the sulfonic acids to insoluble crystalline hydrates, which are filtered.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Hours</th>
<th>Product</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorobenzene</td>
<td>CICl₄, CH₂Cl₂</td>
<td>10 to 15°</td>
<td>7</td>
<td>4-Sulfonic acid</td>
<td>15</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>CCl₄</td>
<td>0 to 35°</td>
<td>1 to 5</td>
<td>1-Sulfonic acid</td>
<td>16</td>
</tr>
<tr>
<td>1-Nitropthalene</td>
<td>CCl₄</td>
<td>20 to 50°</td>
<td>5 to 10</td>
<td>1-Nitro-4-sulfonic acid</td>
<td>17</td>
</tr>
<tr>
<td>2,6-Dialkynaphthalenes</td>
<td>CICl₄, CH₂Cl₂</td>
<td>25°</td>
<td>2</td>
<td>3,7-Dialkyl-1-sulfonic acids</td>
<td>14</td>
</tr>
<tr>
<td>Alkybenzenes, -napthalenes, -phenols</td>
<td>Nitrobenzene</td>
<td>18°</td>
<td>2</td>
<td>4-Sulfonic acid</td>
<td></td>
</tr>
<tr>
<td>Methylnapthalene</td>
<td>CICl₄, CH₂Cl₂</td>
<td>0°</td>
<td></td>
<td>4-Sulfonic acid</td>
<td></td>
</tr>
<tr>
<td>2-Hexynaphthalene</td>
<td>Nitrobenzene</td>
<td>0°</td>
<td></td>
<td>4-Sulfonic acid</td>
<td></td>
</tr>
<tr>
<td>1,1'-Binaphthyl</td>
<td>Nitrobenzene</td>
<td>0°</td>
<td></td>
<td>4,4'-Disulfonic acid</td>
<td>21</td>
</tr>
</tbody>
</table>
*Yields in nearly all cases were above 75%.

1.2.2. With Sulfuric Acid/Thionyl Chloride

The second method for preparing sulfonic acids involves treatment of the organic compound with sulfuric acid by reaction 3, which is forced to completion by adding thionyl chloride to remove the water by reaction 6:

\[
\text{H}_2\text{O} + \text{SOCl}_2 \rightarrow 2\text{HCl} + \text{SO}_2
\]

Although detailed examples of this procedure are not available, it is stated that treatment of苯 (0.517 mole) at room temperature with 100% sulfuric acid (0.351) and thionyl chloride (0.400 mole) results in complete reaction of the sulfuric acid in 15 minutes and the formation of benzenesulfonic acid in 82% yield. Yields noted with other aromatic compounds are as follows: toluene (93%); o-xylene (99%); p-xylene (92%); ethylbenzene (98%); fluoro-benzene (88%); chlorobenzene (77%); and bromo-benzene (73%). Nitrobenzene, p-nitrotoluene, o-chlorotoluene, p-dichlorobenzene and iodo-benzene gave 28% or less. Sulfones are formed as minor by-products;

\[
\text{R} - \text{SO}_2\text{O} + \text{RH} \xrightarrow{\text{h}_{\text{H}_2\text{O}}} \text{R} - \text{SO}_2\text{R}
\]

with a large excess of thionyl chloride they are the sole products.

The use of sulfuric acid/thionyl chloride for sulfonation is described later.

Styrene-$\beta$-sulfonyl Chloride\textsuperscript{25}: Dimethylformamide (70 g; 0.96 mol, purified by distillation), is cooled to 5° under nitrogen in a laboratory reaction flask, and sulfonyl chloride (110 g; 0.82 mol) is added dropwise with stirring, keeping the temperature below 25°. The mixture is then allowed to warm to room temperature, followed by stirring for 30 minutes. Styrene (50 g; 0.43 mol) is added all at once, and the mixture is heated gradually to 90°, any exothermic reaction being controlled by cooling. The solution is held for 4 hours at 85–90° after which is it cooled to room temperature, and poured on ice. The pale yellow solid is collected, washed with ice water and dried to give crude styrene-$\beta$-sulfonyl chloride (68 g; 71%). Recrystallization from chloroform/light petroleum gives crystals, m.p. 86.5–88.5; after sublimation: m.p. 89–90°.

Yields of sulfonyl chloride obtained similarly from substituted styrenes were as follows: methylstyrene (39%); 2-chlorostyrene (71%); 4-t-butylstyrene (80%\textsuperscript{a}). The sulfonylating agent has been shown to be a complex of the structure\textsuperscript{56}:

\[
\begin{array}{c}
\begin{array}{c}
\text{H}_3\text{C} \\
\text{H}_2\text{C} \\
\text{N} \\
\text{Cl} \\
\text{CH}-\text{O}=\text{SO}_2\text{Cl}
\end{array}
\end{array}
\]

It converts compounds with easily replaceable hydrogen atoms—such as anthracene—to aldehydes; anisole and 2-naphthol undergo ring substitution, yielding sulfonyl chlorides.

2.2. Aromatic Compounds (Preparation of Sulfonyl Halides)

2.2.1. Via the Grignard reaction

Although the conversion of alkyl halides to sulfonyl halides using the Grignard reaction has proved practical for synthesis, past efforts to employ this approach with aromatic halides have given very poor yields. Recent work, however, has shown that aromatic Grignard reagents function satisfactorily, providing the correct solvent mixture is used. The reaction involved is:

\[\text{RMeCl} + \text{SO}_2\text{Cl}_2 \rightarrow \text{R-SO}_2\text{Cl} + \text{MgCl}_2\]

Benzenesulfonyl Chloride\textsuperscript{27}: The Grignard reagent (0.20 mol) prepared from chlorobenzene and magnesium turnings in tetrahydrofuran (100 ml) is added slowly with stirring to a solution of sulfonyl chloride (54 g; 0.40 mol) in hexane (120 ml) at 0°. The mixture is stirred 2 hrs at room temperature, then washed with cold water, dried and distilled; yield: 64%.

Extension of this procedure gives yields as follows:

2-methoxyphenyl- (53%), 4-(trimethylsilyl)-phenyl- (54%), pentachlorophenyl- (62%).

Use of arylmagnesium bromides, instead of the chlorides in reaction 9 gives mixtures of sulfonyl bromide and chlorides which cannot be separated. The sulfonyl hydrazide procedure described below (equation 10) is therefore better suited to the preparation of arenesulfonyl bromides. In the aliphatic series, the use of reaction 9 has given less satisfactory results than treatment of the Grignard reagent with sulfur dioxide, followed by halogenation of the sulfinate so formed (reaction 11); this concept has apparently not been tried with aromatic compounds.

2.2.2. Via Modified Meerwein Procedures

The method developed by Meerwein and coworkers\textsuperscript{18} for converting aromatic amines to sulfonyl chlorides has proved widely useful. This procedure involves treatment of the diazonium chloride in concentrated hydrochloric acid with sulfur dioxide dissolved in acetic acid, employing cupric ion as catalyst. Recent modification of the original procedure have given improved results. The one found most widely applicable is the following:

**Aromatic Sulfonyl Chlorides\textsuperscript{29}:** The aromatic amine (0.4 mol) in an excess of concentrated (38%) hydrochloric acid (84 ml), is diazotized at 0° with solid sodium nitrite (31 g; 0.45 mol). The solution of diazonium chloride is added with mechanical stirring to a mixture of sulfur dioxide (300 g), benzene (200 ml), copper(I)-chloride (30 g), and potassium chloride (40 g) in dioxane (300 ml), and heated to 40–50°. After the evolution of nitrogen is complete (~30 min.), water (1 l) is added and the sulfonyl chloride extracted with benzene. The benzene extract is washed quickly with 10% aqueous sodium hydroxide (5 x 100 ml), followed by washing with water to neutral reaction. After drying over anhydrous magnesium sulfate, the benzene and chloro compound are removed in that order by distillation under reduced pressure or recrystallized from an appropriate solvent.

This procedure affords eight benzenoid sulfonyl chlorides in 40–70% yield, but that of naphthalene-1-sulfonyl chloride is only 2%. Toluene-4-sulfonyl bromide is prepared in 43% yield, and this apparently constitutes the first preparation of a sulfonyl bromide by the Meerwein procedure.

A second modification involves conducting the diazotization by the addition of solid sodium nitrite with mechanical stirring to a suspension of the mixture of amine (0.4 mol) and concentrated hydrochloric acid (84 ml) in dioxane (75 ml). The subsequent operations are conducted as described above. This modification was used for four benzenoid sulfonyl chlorides.

Both of the above procedures differ from the original Meerwein method mainly in the use of solid sodium nitrite for the diazotization, of dioxane in either or both steps, and of a higher concentration of sulfur dioxide in the second step.

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\textsuperscript{25} J. C. Amelang et al., Ind. Eng. Chem., 45, 204 (1953).
\textsuperscript{26} L. F. Fieser and D. M. Bowen, J. Amer. Soc., 62, 2105 (1940).

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\textsuperscript{29} Ref. 1, pgs. 20, 46, 156.
\textsuperscript{24} German Patent 1,245,940, Farbwerke Hoechst AG. (H. Diery, B. Kieffer); C. A. 67, 90394 (1967).
2.2.3. Via Sulfonyl Hydrazides

The preparation of sulfonyl chlorides has been studied extensively, but that of the corresponding bromides and iodides relatively little. Recently, however, interest in the latter two types has increased with the realization that they undergo certain reactions not shared by the chlorides. An excellent approach to both of the latter species of sulfonyl halides involves the following reactions:\(^{30}\)

\[
\begin{align*}
R - SO_2Cl & \xrightarrow{\text{NH}_2HCl} R - SO_2\text{-NH-NH}_2 \\
2\text{Br}_2(1p) & - \text{N}_2/\text{HBr}(1l) \xrightarrow{} R - SO_2\text{Br}(1l)
\end{align*}
\]

In effect, this method comprises simply an efficient procedure for exchanging chlorine for bromine or iodine.

Arenesulfonyl Hydrazides:\(^{24}\) With rigorous stirring, a solution of 0.1 mol arenesulfonyl chloride, in the form of a concentrated solution in methanol, is added to 0.2 mol hydrazine hydrate cooled to 5°C, the temperature not being allowed to exceed 20°C. The mixture is stirred for further 30 min. at room temperature and is then diluted 1/3 with water. On cooling to 0 to 5°C the arenesulfonyl hydrazide crystallizes. It is filtered, washed, and air-dried. The crude products may be used for preparing sulfonyl bromides; for purification they are recrystallized from methanol/water. Recrystallization is necessary for making the iodides.

Sulfonyl Bromides from the Hydrazides:\(^{30}\): To a suspension of 0.01 mol crude hydrazide in 20 ml chloroform are added a few pieces of ice, followed by 0.02 mol bromine, introduced portionwise with vigorous stirring. Immediately after addition of the first portions of bromine, the solution becomes colorless and the temperature rises. It is necessary to keep the temperature below 10 to 15°C by the periodic introduction of ice. The addition of bromine is continued until the chloroform layer has acquired a permanent orange color, which requires 10 to 30 minutes. The chloroform layer is separated, water-washed, dried, and the solvent removed in vacuo. The solid residue is transferred to a filter, washed free of bromine with water and dried. The crude sulfonyl bromides are recrystallized from carbon tetrachloride or petroleum ether/benzene 1:1.

Ten benzenoid sulfonyl bromides were thus prepared in yields of 90% or higher. Others were made in yields as follows: 2-nitrobenzene- (55%), 4-nitrobenzene- (83%), naphthalene-1- and 2-sulfonyl bromide (both 80%).

The yields in the above procedure remained unchanged, even upon fifty-fold scaleup. They rose somewhat with use of recrystallized hydrazides. The same conditions were employed when not using chloroform, except that six moles of solid sodium acetate were added and the reaction time was increased somewhat. This modification gave the 4-nitro compound in poor yield, however.

This procedure was discovered independently by others,\(^{31}\) who dissolved the hydrazide in 25% hydrochloric acid and generated the bromine "in situ" by adding a bromide/bromate solution. Several mono- and disulfonyl bromides were thus obtained in excellent yields.

As noted in a preceding section, sulfonyl bromides are known to be accessible by the Meerwein reaction which might be a more efficient approach than the hydrazide method if the required aromatic amine is available.

Sulfanyl Iodides from the Hydrazides:\(^{26}\): To a suspension of 0.02 mol recrystallized hydrazide in 20 ml chloroform is added 0.12 mol sodium acetate dissolved in 40 ml water. The calculated amount of a 20% solution of iodine in a 20% aqueous solution of potassium iodide, or a 10% solution of iodine in methanol, is added slowly (10 to 30 min.), dropwise, and with vigorous stirring. An excess of iodine must be avoided. After completion of the reaction, the chloroform layer is washed and the solvent is removed in vacuo. The solid crude sulfonyl iodide is transferred to a filter, washed with water, and dried between sheets of filter paper. All operations must be conducted rapidly, since the arenesulfonyl iodides are rather unstable, and even in a sealed tube they decompose after only a few days, especially when exposed to light. They are recrystallized from hexane.

The following sulfonyl iodides were thus prepared in the yields given: benzene- (52%), 4-toluene- (80%); 2-naphthalene- (70%), 4-chlorobenzene- (84%).

3. Sulfonation by Oxidative Procedures (Aliphatic Sulfonyl Chlorides and Bromides from Sulfinates)

The halogenation of sulfinate salts appears a promising method for preparing alkanesulfonyl halides\(^{12}\) starting from alkyl halides. The reactions involved are:

\[
\begin{align*}
1. Mg \\
2. SO_2 \\
R - X & \xrightarrow{} R - SO_2MgX \\
x_2 & \xrightarrow{} R - SO_2X \\
X = Cl, Br, I
\end{align*}
\]

This procedure yields sulfonyl chlorides, bromides or iodides starting from primary, secondary, or tertiary alkyl halides. The approach is therefore not only versatile, but as recognized recently - is the only known method for preparing tertiary alkanesulfonyl halides. The following example is typical.

2-Methylpropane-2-sulfonyl Chloride:\(^{22}\): A Grignard solution is prepared from t-butyl chloride (370 g; 4.0 mol) and magnesium turnings (106 g; 4.4 g-atom) in 2 l absolute ether. The flask is cooled with methanol/dry ice to -15 to -20°C bath temperature, and with efficient stirring sulfur dioxide is admitted over the surface of the solution at a maximum temperature of 5°C. The solution turns into a thick slurry as the desired sulfinate separates, the end of the reaction being indicated by a drop in temperature.


\(^{28}\) Ref. 1, pg 171.


\(^{30}\) L. M. Litvinenkov et al., J. Gen. Chem. (USSR), 34, 3730 (1964); C. A. 62, 6420 (1965).


\(^{32}\) Ref. 1, pg 214.

Distillation of the ether yields 685 g magnesium (2-methyl-propane-2-sulfinate) chloride. It is dissolved in water at 50°C, and the solution is decanted from unreacted magnesium. The solution is then chlorinated with efficient stirring at −3°C, the sulfonyl chloride separates as a colorless solid; yield: 440 g (70%). Recrystallization from methanol/water gives m.p. 97°C.

Sulfonyl chlorides were prepared similarly from 1-, 2-, and 3-chloroheptanes, except that the chlorination step was conducted in anhydrous ether. Treatment of the Grignard reagent with sulfur chloride, instead of chlorine, gave only 11% of 2-methylpropane-2-sulfonyl chloride.

Sulfinate salts have also been prepared by treating aluminum trialkyls with sulfur dioxide; aqueous chlorination gave octane-1-sulfonyl chloride in excellent yield:

\[
\text{R}_2\text{Al} \rightarrow \text{SO}_2 \rightarrow (\text{R-SO}_2)\text{Al} \rightarrow \text{Cl} \rightarrow 3 \text{R-SOCl} + \text{AlCl}_3
\]

In using this method for making hexane-1-sulfonyl bromide, the bromide was withdrawn as formed to prevent loss by hydrolysis.

Sulfinate salts can also be prepared by a standard method from sulfonil halides as follows:

\[
\text{R-SO}_2\text{X} + \text{Na}_2\text{SO}_3 + 2\text{NaOH} \rightarrow \text{R-SO}_2\text{Na} + \text{NaX} + \text{Na}_2\text{SO}_4 + \text{H}_2\text{O}
\]

Treatment of the sulfinate with a different halogen yields a new sulfonil halide. This halogen exchange procedure has been employed to convert perfluoro-octanesulfonil fluoride to the chloride and bromide, and to convert trichloromethanesulfonil chloride to the bromide.

4. Condensation Methods (Sulfoxalkylation with Ethanethiosulfonic Acid Derivatives)

The esters of ethanethiosulfonic acid are remarkable for their high reactivity with many diverse substrates. They are also readily available, and they yield sulfonates without the formation of secondary inorganic products, which is an objectionable feature of other sulfoxalkylating agents. The esters are prepared as follows from commercially available 2-mercaptoethanol:

\[
\text{HO-CH}_2-\text{CH}_2-\text{SH} + 3\text{Cl}_2 + \text{H}_2\text{O} \rightarrow \text{Cl-CH}_2-\text{CH}_2-\text{SOCl} + 4\text{HCl}
\]

\[
\text{Cl-CH}_2-\text{CH}_2-\text{SOCl} + 2\text{RONa} \rightarrow \text{H}_2\text{C}=\text{CH-} + \text{SO}_2\text{OR} + 2\text{NaCl} + \text{ROH}
\]

2-Chloroethanesulfonil Chloride: In a laboratory reaction flask are placed 166 g (2.0 mol) of technical (95%) 2-mercaptoethanol and 300 g 1,2-dichloroethane. With cooling and stirring, 455 g (6.4 mol) chlorine gas is bubbled into the flask at 0 to 10°C. After the addition of about 150 g chlorine, the dropwise addition of water (40 g; 2.2 mol) is begun. Unreacted chlorine is finally removed by sweeping with nitrogen. The solution is then distilled at 1 mm pressure to recover the product boiling at 80°C; yield: 306 g (94% of theory).

Methyl Ethanethiosulfonate: 2-Chloroethanesulfonil chloride (326 g; 2 mol) is placed in a laboratory reaction flask and cooled to 0°C. An approximately 30% methanolic solution (710 g) of sodium methoxide is added dropwise over a period of two hours, the mixture being maintained at about 0°C. The addition is stopped when the pH reaches a value of 5. (The solution must under no circumstances be allowed to become alkaline.) After warming for 1 hour to about 30°C, sodium chloride is filtered and the solvent removed in vacuo. The gel-like residue is washed with about 100 ml ice water. After drying, the ester is distilled at 0.2–0.4 mm pressure; yield: 210 g (86%); b.p. 54–60°C.

Warning: Esters of ethanethiosulfonic acid are irritants and vesicants; the methyl ester is in addition a powerful alkylating agent with toxicity resembling that of dimethyl sulfate.

The esters of ethanethiosulfonic acid smoothly sulfoethylate many compounds containing active hydrogen:

\[
\text{HA} + \text{H}_2\text{C}=\text{CH-} = \text{A-CH}_2-\text{CH}_2-\text{SO}_2\text{OR}
\]

Included are phenols, alcohols, amines, sulfonic acids, sodium bisulfite, thiols and compounds of the structure (RO)_2PSSH, “active methylene” compounds (i.e. nitroaraffins, esters of dichloroacetic, malonic, acetoacetic and benzylacetic acids), α-olefins, amides, sulfonamides, imides, amines, thioureas and oximes. In addition, the esters add diazonium salts, or halogens, and undergo the Diels-Alder reaction. When R is aliphatic, these derivatives can be hydrolyzed to the salts:

\[
\text{A-CH}_2-\text{CH}_2-\text{SO}_2\text{OR} + \text{NaOH} \rightarrow \text{A-CH}_2-\text{CH}_2-\text{SO}_2\text{Na}
\]

The following example typifies both of these reactions.

Sodium 2-dodecylthio-ethanesulfonate: 1-Dodecanethiol (202 g; 1 mol) and n-butyl ethanesulfonate (164 g; 1 mol) are dissolved in 450 g ethanol, and a 6% solution of sodium hydroxide in ethanol is added slowly at room temperature with agitation at pH 7.5–8. Stirring is continued for one day at room temperature, and the mixture is then added to 3000 g ice water. The oily layer is separated and the aqueous layer extracted with ether. The organic layers are combined and dried over anhydrous sodium sulfate. The solvent is removed by distillation in vacuo to give 342 g (94%) of n-butyl 2-dodecylthio-ethanesulfonate as a colorless oil. To effect hydrolysis to the sodium salt, the ester is added to powdered sodium hydroxide (38 g; 0.95 mol) dissolved in 400 g ethanol, and the mixture is refluxed with stirring for two days. Upon cooling, the desired sodium salt separates as fine crystals, which are filtered and washed with a little ethanol.

37. U.S. Patent 3,326,928, J. K. MATTSON.
Salts of this type can also be prepared in some cases as follows\(^{42}\):

\[
18 \quad \text{HA} + \text{H}_2\text{C}=\text{CH}-\text{SO}_3\text{Na} \rightarrow \text{A}-\text{CH}_2-\text{CH}_2-\text{SO}_3\text{Na}
\]

This approach is more direct than that involving the ester, since sodium ethanesulphonate is commercially available\(^{43}\). However, the ability of the salts to undergo such reactions has been studied in only a few cases, and they may be less widely applicable than the esters.

**B. Sulfation of Alcohols**

1. With Sulfuric Acid

Alcohols sulfate reversibly with sulfuric acid, as follows:

\[
19 \quad \text{ROH} + \text{H}_2\text{SO}_4 \rightleftharpoons \text{ROSO}_2\text{H} + \text{H}_2\text{O}
\]

Although sulfuric acid is a desirably mild reagent, even under the most favorable conditions at an equimolar ratio of acid to alcohol, reaction 19 is only 65\% complete. The use of excess acid favors sulfate formation, but increases the difficulty of product isolation and enhances the likelihood of injurious side reactions, such as disulfation, dehydration, or oxidation. If a chemical acceptor for water is added, however, reaction 19 is driven to the right and good yields of sulfate are obtained. This principle underlies the two new sulfation procedures described below.

1.1. Using Dicyclohexylcarbodiimide as Acceptor for Water

Although dicyclohexylcarbodiimide has been employed in the past as an acceptor for water to promote the formation of esters and amides, its use for the sulfation of alcohols is novel. The dicyclohexylurea formed during the reaction is relatively insoluble and precipitates from the reaction mixture:

\[
20 \quad \text{R}^1\text{CH}-\text{OH} + \text{H}_2\text{SO}_4 \rightarrow \text{R}^1\text{HN}=\text{C}=\text{N}\text{SO}_2\text{H} + \text{H}_2\text{O}
\]

**Potassium Cholesteryl Sulfate**\(^{44}\): Cholesterol (5.05 mmol), dissolved in 3.5 ml dimethylformamide, is added to 24.4 mmol dicyclohexylcarbodiimide dissolved in 3 ml dimethylformamide in a 50 ml Erlemeyer flask. A solution of sulfuric acid (5.55 mmol) in 1 ml dimethylformamide, containing 0.2\(\mu\)C\(\text{C}^{35}\text{SO}_3\text{H}\)\(^{45}\) to permit monitoring of the reaction, is added dropwise with stirring and cooling at a maximum temperature of 25°. After 30 minutes the precipitated dicyclohexylurea is filtered, and washed with 5 ml dimethylformamide. The combined filtrates are neutralized with potassium hydroxide, and this solution is transferred to a 250 ml separatory funnel. 100 ml each of water and chloroform are added to the funnel and the mixture is shaken. The insoluble cholesteryl sulfate collects at the interface between the two layers. The chloroform and water layers are removed and the insoluble sulfate ester is washed again with these two solvents. The interfacial layer is then filtered, yielding crude potassium cholesteryl sulfate, which is recrystallized from ethanol; yield: 74\%; m. p. 274-248°\(^{46}\).

This general procedure may also be followed to sulfate other alcohols, with yields as given: 1-octadecanol (74\%) 1-decanol (72\%); testosterone (71\%). In these cases, the product is soluble in the aqueous layer and is extracted from it with butanol, which is then distilled at not above room temperature to give the solid product. In order to obtain good yields, it is necessary to use excess acid and carbodiimide, and to employ the stated order of addition. Since 35\%-sulfuric acid, unlike labelled chlorosulfuric acid or sulfur trioxide, is available, this procedure is convenient for the preparation of radiolabelled sulfates.

A noteworthy aspect of this approach is the use of dimethylformamide as the reaction medium. Not only is it a solvent for the two organic starting materials, and for the sulfate product, but also for sulfuric acid. Being a weak base, it unquestionably forms complexes with the sulfuric acid as well as with the acid sulfate product; the reaction is thus conducted under the desirably mild condition of low acidity. Sulfur trioxide/dimethylformamide has been in use for several years, but the system cited above appears novel. Undoubtedly it will find other applications where maintenance of mild conditions is essential.

1.2. Using Thionyl Chloride as Acceptor for Water

As indicated earlier, thionyl chloride can be employed to remove the water formed during the sulfonation of aromatic hydrocarbons with sulfuric acid (equations 3 and 4). A recent study\(^{45}\) has shown that it is also suitable for removing the water formed in sulfation (reaction 19).

**1-Dodecyl Acid Sulfate**\(^{47}\): 1-Dodecanol (5.5 g; 0.03 mol) is dissolved in 100 ml dry petroleum ether and the solution is cooled to -15°. With stirring and external cooling, 100% sulfuric acid (2.9 g; 0.03 mol) is added dropwise, after which the mixture is warmed to room temperature. Thionyl chloride (3.5 g; 0.03 mol) is added dropwise with stirring. The solvent is removed in vacuo; yield: 95\%; m. p. 35°:

The same procedure was used to prepare other alcohol sulfates, as follows, the yields given being those of the sodium salts: 1-propyl- (96\%); 1-butyl- (100\%); 2-butyl- (88\%); isobutyl- (90\%); 1-octyl- (88%).

Another recent example of “in situ” generation of sulfur trioxide with sulfuric acid/thionyl chloride and its use for sulfation, is the following:\textsuperscript{46}:

\[(\text{R}_3\text{Si})_2\text{O} \cdot \text{H}_2\text{SO}_4 \cdot \text{SOCl}_2 \rightarrow (\text{R}_3\text{Si})_2\text{SO}_4 \cdot \text{SO}_2 \cdot \text{HCl}\]

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Like the procedure described previously involving dicyclohexylcarbodiimide with dimethylformamide, this method can be employed to prepare radiolabelled sulfates. However, the acidity level of the former method is much lower, which would be advantageous with acid-sensitive alcohols.

2. With Chlorosulfuric Acid/Diethyl Ether

Chlorosulfuric acid is soluble in diethyl ether, forming a complex which is a milder reagent than the free acid. It is excellently suited for low-temperature laboratory sulfation of alcohols, since it gives better yields and fewer side reactions than other reagents\textsuperscript{47}. The reaction involved is the following:

\[\text{ROH} \cdot \text{CISO}_2\text{H} \xrightarrow{\text{ether}} \text{ROSO}_2\text{H} \cdot \text{HCl}\]

Sulfation of Long-Chain Secondary Alcohols\textsuperscript{48}: Chlorosulfuric acid (117 g; 1 mol) is added slowly with stirring to 200 g anhydrous ethyl ether at 0 to 5°. After addition is complete, the alcohol (1 mol of mixed isomers - linear, secondary, C\textsubscript{13} to C\textsubscript{18}), predissolved in 400 g anhydrous ether, is added to the acid-ether complex at 0-5° over 10 minutes with stirring and external cooling with dry ice/acetone. The mixture is stirred and purged with nitrogen for an additional 35 minutes to remove the hydrogen chloride formed. The mixture is then poured with stirring onto to a mixture of 50% sodium hydroxide (1 mol NaOH) and 300 g ice. Additional 50% sodium hydroxide is added as needed to reach pH: 10. The mixture is diluted with 800 ml isopropanol and 500 ml water and extracted with 2 x 500 ml portions of petroleum ether to remove unsulfated materials. The alcohol-water layer is stripped of solvents on a short-path still, and finally on a rotary evaporator. The residue is finally dried in a vacuum oven at 40°. Yields, as reported by others\textsuperscript{49,50}, are quantitative.

Essentially the above approach was employed for sulfating long-chain primary alcohols\textsuperscript{49,50}. It was also used at - 50° for sulfating a series of long-chain secondary alcohols\textsuperscript{51}, a type of alcohol quite susceptible to isomerization by acid reagents, including sulfuric acid. None was noted, however, with chlorosulfuric acid/ether, sulfur trioxide/dioxane, or sulfur trioxide/pyridine; the first reagent was chosen for convenience. Chlorosulfuric acid/ether is suitable for sulfating alcohols, also containing ether, amide, nitro, and thioether groups\textsuperscript{47}. Numerous esters and amides of 12-hydroxyoleic and 12-hydroxystearic acids have also been sulfated with this reagent without attack of the olefinic, ester, or amide moieties\textsuperscript{52}.

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