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THE PREPARATION OF ALKANESULFONYL HALIDES

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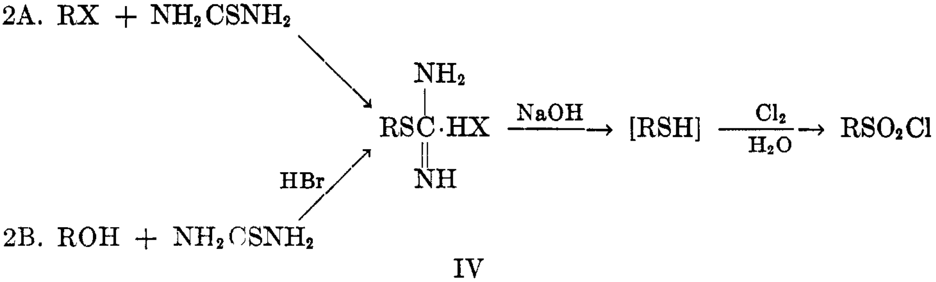
The laboratory preparation of alkanesulfonyl halides through the action of phosphorus trihalide or thionyl chloride upon the sulfonic acids (1) is limited by the relatively small number of sulfonic acids that are available. Also, the use of sulfonic acid salts, although more readily available than the free acids, requires the dry salt and the reaction of these salts with phosphorus pentachloride or thionyl chloride is frequently difficult to carry out in large amounts. The process of sulfochlorination of alkanes through reaction with chlorine and sulfur dioxide (2, 3) may yield a mixture of sulfonyl chlorides and generally is not adaptable to the laboratory preparation of pure alkanesulfonyl chlorides.

The preparation of alkanesulfonyl halides may be accomplished conveniently by the chlorination in aqueous media of alkanethiols or certain of their derivatives, such as I, wherein the Y represents a residue that is readily cleaved during the chlorination process. A number of investigations have shown that alkanesulfonyl chlorides result from the chlorination of thiols (I, Y = H) (4), disulfides (Y = SR) (4, 9), thiocyanates (Y = CN) (3, 4, 10), thiol esters

$$\underset{\text{I}}{\text{RSY}} \xrightarrow[\text{Cl}_2]{\text{H}_2\text{O}} \underset{\text{II}}{\text{RSO}_2\text{Cl}}$$

(Y = R′CO or R′SO$_2$) (4), thiosulfates (Y = SO$_3$Na) (4, 7), and isothiouronium salts (Y = C(=NH)NH$_2$·HX) (5, 6). Of these thiol derivatives, the last two, the sodium alkylthiosulfates (III) and the alkylisothiouronium salts (IV), are the most suitable. These derivatives are easily prepared from the reaction of alkyl halides with sodium thiosulfate (11) and thiourea (5, 6) respectively, and they are usually soluble in water. The present paper reports the extension of this method to a number of alkanesulfonyl halides (Table I) that were required as intermediates for further syntheses.

$$1.\ \text{RX} + \text{Na}_2\text{S}_2\text{O}_3 \rightarrow \text{NaX} + \underset{\text{III}}{\text{RSSO}_3\text{Na}} \xrightarrow[\text{H}_2\text{O}]{\text{Cl}_2} \text{RSO}_2\text{Cl} + \text{RSO}_2\text{X}$$



$$2\text{A}.\ \text{RX} + \text{NH}_2\text{CSNH}_2 \rightarrow \text{RS}\overset{\text{NH}_2}{\underset{\text{NH}}{\text{C}}}\cdot\text{HX} \xrightarrow{\text{NaOH}} [\text{RSH}] \xrightarrow[\text{H}_2\text{O}]{\text{Cl}_2} \text{RSO}_2\text{Cl}$$

$$2\text{B}.\ \text{ROH} + \text{NH}_2\text{CSNH}_2 \xrightarrow{\text{HBr}} \text{RS}\overset{\text{NH}_2}{\underset{\text{NH}}{\text{C}}}\cdot\text{HX}$$

IV

TABLE I

ALKANESULFONYL HALIDES, RSO_2X

ALKANE	HALIDE[j]	PROCEDURE	STARTING MATERIAL	YIELD, %		B.P., °C./MM.	n_D^{25}	CHLORINE	
				Crude	Pure[i]			Calc'd	Found
Ethane[a]	Cl, Br	1	RBr	59	—	—	—	—	—
1-Propane[a]	Cl, Br	1	RBr	56	—	—	—	—	—
1-Butane[b]	Cl, Br	1	RBr	56	—	—	—	—	—
2-Methyl-1-propane[a]	Cl, Br	1	RBr	60	—	—	—	—	
1-Pentane[c]	Cl, Br	1	RBr	65	—	—	—	—	—
1-Pentane	Cl	2A	RCl	—	64	75–76/1	—	—	—
1-Pentane	Cl	2B	ROH[g]	—	53	76–80/1	—	—	—
3-Methyl-1-butane[a]	Cl, Br	1	RBr	44	—	—	—	—	—
2-Methyl-1-butane	Cl, Br	1	RBr	50	—	—	—	—	—
2-Methyl-1-butane	Cl	2B	ROH	—	40	85–86/8	1.4535	20.78	20.44
2-Pentane	Cl	2A	RBr	43	30	80–81/7	1.4590	20.78	20.48
3-Pentane	Cl	2A	RBr	—	35	77–78/6	1.4602	20.78	20.78
2-Ethoxy-1-ethane[d]	Cl, Br	1	RBr	55	—	—	—	—	—
2-Ethoxy-1-ethane	Cl	2A	RBr	—	6[k]	75–76/4	1.4552	20.54	20.56
1-Hexane	Cl, Br	1	RBr	73	—	—	—	—	—
1-Hexane	Cl[m]	2A	RBr	—	40	110–112/11	1.4564	19.20	19.01
2-Ethyl-1-butane	Cl, Br	1	RBr	67	—	—	—	—	—
2-Ethyl-1-butane	Cl[n]	2B	ROH	—	20	87–90/5	1.4604	19.20	18.69
4-Methyl-2-pentane	Cl	2A	RBr	—	28	95–96/9	1.4582	19.20	19.17
2-Hexane	Cl	2B	ROH	—	30	94–95/6	1.4610	19.20	18.99
Cyclohexane[b]	Cl	2B	ROH	60	—	—	—	—	—
1-Heptane[a]	Cl, Br	1	RBr	72	—	—	—	—	—
2-Heptane	Cl	2B	ROH	53	41	99–100/5	1.4595	17.84	17.63
4-Heptane	Cl	2B	ROH	—	20	90–92/2	1.4618	—	—
Cyclohexylmethane	Cl	2A	RBr	43	38	112/5	1.4920	18.03	17.87
1-Octane	Cl	2A	RBr	82	20	121–122/4[h]	1.4568	16.67	16.31
2-Octane[b]	Cl	2A	RBr	—	66	94–98/2	1.4600	—	—
2-Cyclohexylethane	Cl, Br	1	RBr	74	—	—	—	—	—
2-Cyclohexylethane	Cl	2A	RBr	67	50	124/3	1.4890	16.83	16.62
Phenylmethane[a, e]	Cl	1	RCl	85–90	—	88–91[p]	—	—	—
4-Nitrophenylmethane[b]	Cl	1	RCl	88	—	90–91[p]	—	—	—
3-Nitrophenylmethane	Cl	1	RCl	86	—	95–100[p]	—	—	—
2-Chlorophenylmethane[e]	Cl	1	RCl	90	—	55–59[p]	—	—	—
4-Chlorophenylmethane[e]	Cl	1	RCl	90	—	90–91[p]	—	—	—
2,4-Dichlorophenylmethane	Cl	1	RCl	90	—	79–81[p]	—	40.98	40.88
3,4-Dichlorophenylmethane	Cl	1	RCl	100	—	67–69[p]	—	40.98	40.50
2-Phenylethane[a]	Cl	1	RCl	73	—	—	—	—	—
2-(4-Nitrophenyl)ethane[f]	Cl	1	RCl	90	—	72–75[p]	—	—	—

[a] Reference (5). [b] Reference (6). [c] Reference (4). [d] Swallen and Boord, *J. Am. Chem. Soc.*, **52**, 651 (1930). [e] Reference (7). [f] Miller, Sprague, Kissinger, and McBurney, *J. Am. Chem. Soc.*, **62**, 2099 (1940). [g] Concentrated hydrochloric acid was used instead of 48% hydrobromic acid in this run. [h] Slight decomposition on distillation was always observed. [i] Distilled to constant refractive index for analysis. [j] When an alkyl bromide was employed in Procedure I, a mixture of alkanesulfonyl chloride and bromide resulted; see discussion. [k] The low yield by Procedure 2A is due to the water-solubility of the intermediate 2-ethoxyethanethiol; this thiol did not separate from the alkaline solution of the isothiouronium salt and was extracted with ether. [m] Also prepared in these laboratories by chlorination of the isothiouronium salt prepared by Procedure 2B from 1-hexanol, thiourea, and hydrogen chloride; yield 70%, n_D^{23} 1.4561, b.p. 92–93° (4–5 mm.). [n] Prepared also by chlorination of the isothiouronium salt from 2-ethylbutanol, thiourea, and hydrogen chloride; yield 55%. b.p. 96–97° (10 mm.). [p] Melting point.

The preparation and subsequent chlorination of the sodium alkylthiosulfates (III) in dilute acetic acid solution (7) resulted in excellent yields of sulfonyl halides (Procedure I, Table I). The required alkylthiosulfates were formed readily with very reactive alkyl chlorides such as the phenylmethyl chlorides (benzyl chlorides) and the 2-phenylethyl chlorides. However, alkyl chlorides, such as 1-pentyl chloride, failed to react. Primary alkyl bromides, on the other hand, were sufficiently reactive to form the alkylthiosulfates readily. However, secondary alkyl bromides failed to react satisfactorily, possibly due to the tendency for dehydrobromination of the alkyl bromides to the alkenes. The chlorination step was carried out directly upon the mixture from the reaction of the alkyl halide and the sodium thiosulfate; the alkylthiosulfate was not isolated or separated from the sodium halide that was also formed. Therefore, in those cases where an alkyl bromide was employed in the reaction, sodium bromide was present in the chlorination mixture. This resulted in the production of a mixture of alkanesulfonyl chloride and alkanesulfonyl bromide. In those mixtures that were examined the sulfonyl bromides predominated, the mixtures consisting of 80–90% sulfonyl bromides. Similar results were obtained when alkylisothiouronium bromides were chlorinated using comparable conditions (5). Since sulfonyl bromides are difficult to distil without decomposition, in those cases where sulfonyl halide mixtures resulted, the crude products were not purified. They were satisfactory for further use in this form.

The use of alkylisothiouronium salts (Procedure 2) offers several advantages over the thiosulfate method (Procedure 1). The conversion of alkyl halides to alkylisothiouronium salts (IV), through reaction with thiourea, is not limited by the nature of the alkyl group to the extent that was found in reaction with sodium thiosulfate. Alkyl bromides, both primary and secondary, reacted smoothly, and certain alkyl chlorides, such as 1-pentyl chloride, that were inert toward sodium thiosulfate, yielded the isothiouronium chloride satisfactorily. Furthermore, the alkylisothiouronium salts may be prepared directly from the alkanol by reaction with thiourea in the presence of hydrochloric or hydrobromic acid (5). A large number of sulfonyl halides have been prepared by the direct chlorination of these isothiouronium salts in aqueous solution (5, 6). However, this method may be quite hazardous since severe explosions have been reported (8). Since the nitrogen trichloride, that arises from the action of chlorine on the nitrogen-containing portion of the isothiourea structure, appears to be responsible for the explosion hazard an additional step has been employed in the present work in order to avoid the presence of nitrogen-containing compounds during the chlorination. It is well known that isothiouronium salts on treatment with bases yield alkanethiols and that these alkanethiols, as well as the disulfides derived from them, readily yield sulfonyl chlorides on chlorination (4, 9). Therefore, in the isothiouronium method (Procedure 2), the salt IV, that was prepared by either route A from the alkyl halide or route B from the alkanol, was treated with dilute sodium hydroxide and the crude thiol thus formed separated and chlorinated. The introduction of this extra step gives a safe method for the preparation of pure alkanesulfonyl chlorides from alkyl halides in fair over-all yields (Table I) and, furthermore, eliminates the disadvantage of mixed sulfonyl halides that are obtained when alkyl bromides are employed as the starting materials in either the thiosulfate or thiourea route.

In several cases the general methods failed to give sulfonyl halides. 2-Chloromethylthiophene reacted readily with sodium thiosulfate and the reaction product was treated with chlorine in the usual manner at −10°. A solid formed, which, when filtered, decomposed rapidly to an oil, giving off large volumes of sulfur dioxide. *p*-Methoxybenzyl chloride reacted readily with thiourea. The salt was decomposed to the corresponding thiol and oxidized to the known disulfiide. Chlorination of the disulfide in aqueous acetic acid gave an oil that did not have the properties of a sulfonyl chloride. 2-Methyl-1-pentanol and 2-ethyl-1-hexanol and the corresponding alkyl bromides failed to react satisfactorily with sodium thiosulfate or thiourea.

EXPERIMENTAL[1]

The following descriptions of specific examples are typical of the numerous preparations that are summarized in Table I. Where mixtures of sulfonyl bromide and sulfonyl chloride were obtained, the yields were calculated on the basis of 100% sulfonyl bromide. In all cases where the sulfonyl chloride alone resulted, the yield of pure product is reported after two distillations; the yield of crude, undistilled material that is satisfactory for most synthetic work was considerably higher than those reported for the pure product.[2]

1-Pentanesulfonyl halides. (*Procedure 1*). A mixture of 302 g. (2 moles) of 1-pentyl bromide, 496 g. (2 moles) of sodium thiosulfate pentahydrate, and a liter of 50% aqueous methanol was refluxed until it became homogeneous. This required about three hours. The solvent then was removed under reduced pressure until the sodium 1-pentylthiosulfate began to crystallize. The resulting suspension was chilled to 10° in an ice-bath and then a kilogram of crushed ice and 500 ml. of glacial acetic acid were added. While the mixture was being stirred vigorously, chlorine was passed in as rapidly as possible. The temperature was maintained below 10° by adding ice to the mixture as necessary. The reaction mixture became orange, then yellow and an oily suspension resulted. Chlorination was continued for 30 minutes longer (about one hour total time). From three-quarters to one pound of chlorine was consumed. The heavy oil layer was extracted with ether. The extract was washed with 5% sodium bisulfite solution until it became colorless, then with cold water and dried over calcium chloride. The extract was filtered and the ether evaporated on the steam-bath. The residual oil was mainly 1-pentanesulfonyl bromide, weighing from 275 to 325 g. (yield 64–75%, calculated as the sulfonyl bromide). It cannot be distilled without extensive decomposition.

Arylalkanesulfonyl chlorides were generally solids that could be filtered from the reaction mixture and recrystallized if necessary.

2-Pentanesulfonyl chloride. (*Procedure 2A*). 2-Pentyl bromide (31.7 g., 0.2 mole), thiourea (15.2 g., 0.2 mole), and 50 ml. of alcohol were refluxed on the steam-bath for eight hours. After this period, no thiourea remained as indicated by the absence of a black precipitate when silver nitrate was added to a sample of the reaction mixture in dilute ammonia. The alcohol was removed under diminished pressure leaving a thick oily residue which did not crystallize. The crude isothiouronium bromide was dissolved in 250 ml. of warm water and 40% sodium hydroxide was added until no more cloudiness developed. The crude 2-pentane-

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[1] Analyses were carried out by Mr. K. B. Streeter and Mrs. Thelma Buchanan.

[2] The sulfonyl halides (Table I) were characterized by conversion to solid derivatives, particularly the anilides derived from the reaction with ethyl *p*-aminobenzoate. These derivatives will be described in another publication.

thiol was separated, washed with water, and dissolved in 50 ml. of acetic acid. About 25 g. of crushed ice was added to the solution and the mixture saturated with chlorine at 0 to 15°. The oily product was extracted with ether. The extract was washed with 5% sodium bisulfite solution, then with water, and dried over calcium chloride. The extract was filtered and the ether evaporated. The residue was distilled rapidly under reduced pressure in order to separate unstable, high-boiling by-products. The sulfonyl chloride then was redistilled. The yield was 10 g. (30%), b.p. 80.5–81° (9 mm.).

2-Heptanesulfonyl chloride (*Procedure 2B*). 2-Heptanol (200 ml.), thiourea (22.5 g., 0.3 mole), and 48% hydrobromic acid (75 ml.) were heated together on the steam-bath for five days. After this time, all of the thiourea had reacted as was shown by a negative test with ammoniacal silver nitrate. About one-half of the excess heptanol was removed under diminished pressure on the steam-bath. Warm water was added and the solution concentrated under reduced pressure on the steam-bath to remove the heptanol completely; this was repeated twice until the residue was completely water-soluble. The residue then was dissolved in 250 ml. of warm water and 40% sodium hydroxide added slowly until no more cloudiness developed. The resulting oil was separated from the aqueous portion and was washed twice with water. The crude 2-heptanethiol then was dissolved in 50 ml. of acetic acid and 25 g. of crushed ice added. The mixture was stirred vigorously and saturated with chlorine while the temperature was maintained at 0 to 15°. The residual oil was extracted with ether, the ether extract washed with 5% sodium bisulfite solution, then with water, and dried over calcium chloride. The extract was filtered and the ether removed on the steam-bath. The residue was first distilled rapidly under reduced pressure by careful heating with a free flame. This was done to remove the sulfonyl chloride from by-products which tend to decompose and give off large volumes of sulfur dioxide. The product was then redistilled. The yield was 30 g. (50%) b.p. 100–101° (5 mm.).

SUMMARY

A number of alkanesulfonyl halides (Table I) have been prepared by the following general procedures: (a) the chlorination of sodium alkylthiosulfates that are derived from the reaction of alkyl bromides and sodium thiosulfate; (b) the chlorination of alkanethiols that are obtained from alkyl isothiouronium salts by treatment with alkali.

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