Alkanesulfonyl Chlorides from Alcohols via [2]Betylates (Alkyl 2-Ammonioethanesulfonates)

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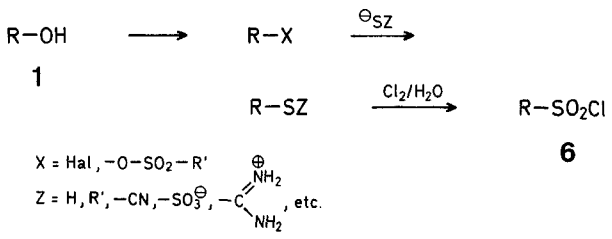
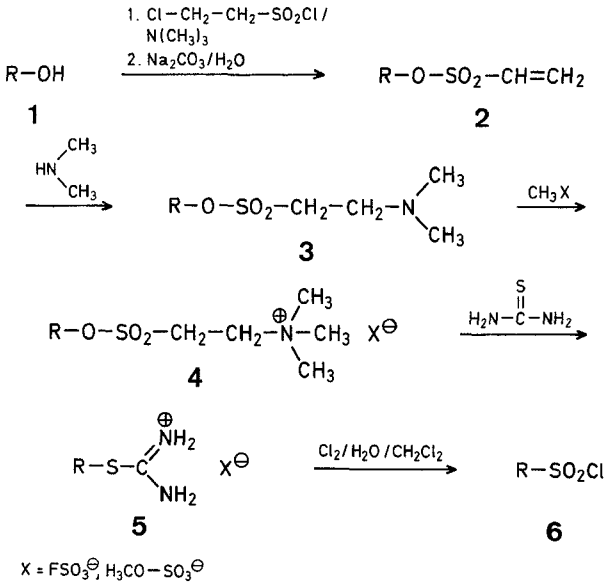
Perhaps the most useful general procedure for converting an alcohol **1** into the corresponding sulfonyl chloride[1] **6** involves (1) transformation of the hydroxy group into a leaving group, (2) replacement of the latter by a divalent sulfur function, followed by (3) aqueous chlorination.



Of the various intermediates, R–SZ, the isothiuronium salt reacts particularly smoothly with aqueous chlorine[2], but unfortunately the procedure for obtaining isothiuronium salts is often inefficient. The reaction of thiourea with alkyl chlorides requires long reaction times (three days and longer refluxing in ethanol), the reaction with alkyl bromides requires an extra step either to remove or replace the bromide ion in order to avoid contamination of the product with the sulfonyl bromide, and procedures for direct reaction of the alcohol with thiourea and hydrochloric acid have the disadvantage of using a large excess of the alcohol. We wish to point to the merits of making isothiuronium salts **5** and thence alkanesulfonyl chlorides **6**, by way of "[2]betylates" **4** (alkyl 2-trimethylammonioethanesulfonates)[3] as in the following scheme.



The conversion of the alcohol **1** to the [2]betylate **4** is readily carried out, requiring typically 1–2 h for 0.5–10 g quantities. We have previously reported that the reaction of [2]betylates with thiourea may be carried out in a two-phase aqueous-organic system[3]. Although this procedure works satisfactorily with primary [2]betylates, those derived from secondary alcohols are readily hydrolyzed, and we find that simple refluxing in dry 1,2-dimethoxyethane for 1–2 h is of more general application. It also has the added benefit that, because the leaving betaine, $(H_3C)_3\overset{\oplus}{N}CH_2CH_2SO_3^{\ominus}$, is insoluble in 1,2-dimethoxyethane, the reaction is easily followed by observing the precipitation of the betaine. When the reaction is complete, removal of the betaine by filtration followed by evaporation of the solvent gives the isothiuronium salt **5**. This material is then taken up directly in dichloromethane/water, chlorinated until the colour of chlorine persists, and worked up forthwith to give the sulfonyl chloride **6**.

Two instances of explosions in connection with the aqueous chlorinolysis of **5** were reported in 1941[10]. In both cases, the reaction mixture had been allowed to stand for extended times (>10 h) before work-up, and it was suggested that explosion was probably caused by nitrogen trichloride which could arise from chlorination of ammonia formed by slow hydrolysis of urea dichloride (chloroformamidinium chloride), the co-product of the initial chlorination[11]. In view of the number of occasions in which this reaction has been carried out without incident (about 20 times in our work alone, for example, see also Ref. [1] and the papers cited therein), it seems likely that this reaction is readily carried out safely *provided the reaction mixture is worked up promptly.* A procedure avoiding the hazard by hydrolyzing **5** to the mercaptan before chlorination, has also been reported[12].

Some insight into possible pitfalls may be obtained from reactions which might be expected to present difficulties. The formation of the neopentylisothiuronium salt, for example, required modified conditions. Displacement at the primary C-atom was sufficiently slow as to allow extensive side reaction deriving apparently from reversion of **4** to **2**; this was suppressed by addition of *p*-toluenesulfonic acid. Under these conditions, the reaction proceeded slowly and only in mediocre (40%) yield, but even so this method would still seem to be the best available route to neopentanesulfonyl chloride.

S_N2 Reactions at cyclohexyl centres are notoriously inefficient, and in previous work directed at synthesis of equatorial *trans*-2-decalinsulfonyl chloride **(6d)** we had failed to obtain any equatorial product from the tosylate of axial *trans*-2-decalol. We had then devised another procedure requiring a painstaking chromatographic removal of a minor amount of the axial sulfonyl chloride[7]. The yield reported in the Table is almost certainly less than optimal owing to our limited supply of starting material, but this route to the equatorial product **6d**, even though proceeding in poor yield, gives a product uncontaminated by the axial isomer and is distinctly easier than the previous method.

3-Phenylpropyl [2]Betylate Fluorosulfate (4a, X = $FSO_3^{\ominus}$):

3-Phenylpropyl Ethenesulfonate **(2a):** A cold solution of trimethylamine (30 ml) in dichloromethane (50 ml) is added during 10 min to a stirred ice-cooled solution of 3-phenylpropanol (**1a**; 6.8 g, 0.05 mol) and 2-chloroethanesulfonyl chloride (20.2 g, 0.125 mol). The reaction mixture is stirred a further 20 min, and then worked up by washing with cold 10% aqueous sodium carbonate (2 × 100 ml) and then with water. Drying of the organic layer and evaporation of solvent gives a product which is then triturated with dry ether. Filtration and evaporation of the ether gives **2a**; yield: 9.1 g (81%).

3-Phenylpropyl [2]Betylate Fluorosulfate: A portion (4.5 g, 0.02 mol) of compound **2a** is dissolved in dichloromethane (50 ml) and the solution cooled to 0 °C. To this is added dimethylamine (~3 ml), the mixture is stirred for 15 min, and the solvent and excess

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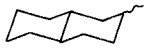
Table. Alkanesulfonyl Chlorides (**6**) from Alcohols (**1**) via [2]Betylate Fluorosulfates (**4**)

6	R	Reaction conditions Temperature [°C]/time [h]		Yield [%]		Refractive index or m.p. of **6**	Characterization
		4 + Thiourea[a]	Chlorination[b]	from **4**	from **1**		
a	$C_6H_5-CH_2-CH_2-CH_2-$	75/0.5	< 20/0.5	84	61	n_D^{20} 1.5385 (Ref. [4], 1.5388)	$R-SO_2NH_2$[g]
b	$H_3C-C(CH_3)_2-CH_2-$	80/72	< 20/1	43	38	n_D^{25} 1.4551 (Ref. [5], 1.4556)	$R-SO_2N(CH_2)_5$[h]
c[d]	$H_3C-(CH_2)_5-CH(CH_3)-$	75/2	< 20/1	(76)[e]	63	n_D^{25} 1.4600 (Ref. [6], 1.4602)	2,4-Dinitrophenyl-S-R[i]
d		80/1	< 20/0.25	18	14	m.p. 25–27.5 °C (Ref. [7], 28–29 °C)	[j]
e	$H_3C-(CH_2)_{14}-CH_2-$	80/2	< 20/1	79	61	m.p. 57–58 °C (Ref. [8], 52–53 °C)	[k]
f	$H_3C-(CH_2)_{20}-CH_2-$	60/24[a]	< 20/1.5	83	58	m.p. 68–71 °C	[l]

[a] In 1,2-dimethoxyethane except for R = docosyl which was carried out in aqueous acetone (see experimental part).
[b] In dichloromethane/water.
[c] Except as indicated otherwise, refers to $CHCl_3$ solutions in NaCl cells.
[d] A chiral sample of the alcohol gave **6c** with complete inversion of configuration[9].
[e] Yield from 2-octyl ethenesulfonate (**2c**).
[f] The axial alcohol gave equatorial **6d** (with no sign of any axial **6d**).
[g] m.p. 60–60.5 °C (Ref. [4], m.p. 60–60.5 °C); M^+: calc. 199.0667, found 199.0669.
[h] m.p. 91–92 °C (Ref. [5], m.p. 90–91 °C); M^+: calc. 219.1293, found 219.1290.
[i] m.p. 49–50 °C (Ref. [6], m.p. 49.5–50 °C); M^+: calc. 312.1144, found 312.1140.
[j] Comparison of I.R.- and ^{1}H-N.M.R. spectra with those of the original authentic specimen[7].
[k] $C_{16}H_{33}ClO_2S$ (324.9) calc. C 59.14 H 10.24 Cl 10.91 S 9.87; found 58.97 10.18 11.01 9.91
[l] $C_{22}H_{45}ClO_2S$ (409.0) calc. C 64.59 H 11.09 Cl 8.67 S 7.84; found 64.51 11.14 8.73 7.88

amine are evaporated. The residual **3a** is dissolved in dichloromethane (50 ml), the solution is cooled to 0 °C, and methyl fluorosulfate (1.77 ml, 0.02 mol) is added. After 15 min, anhydrous ether (20 ml) is added and the precipitated betylate isolated by filtration; yield: 6.9 g (89% from **2a**; 73% from **1a**).

3-Phenylpropanesulfonyl Chloride (6a):
A solution of betylate **4a** (6.8 g, 17.6 mmol) and thiourea (6.7 g, 88 mmol) in dry 1,2-dimethoxyethane (200 ml) is heated at 75 °C for 30 min. The betaine is removed by filtration and the solvent evaporated to give solid **5a**, which is then dissolved in water (50 ml). Dichloromethane (50 ml) is added and chlorine bubbled into the mixture for 30 min while the temperature of the mixture is kept below 20 °C. The dichloromethane layer is then separated, washed successively with cold dilute sodium hydrogen sulfite solution (2 × 50 ml), sodium hydrogen carbonate solution (50 ml), and water (50 ml), and dried with magnesium sulfate. The solvent is evaporated to give **6a**; yield: 3.2 g (84%); [distillation did not alter the ^{1}H-N.M.R. spectrum].

Modifications:

(a) In the reaction of neopentyl betylate (**4b**; 2.8 g, 8.3 mmol) with thiourea (3.1 g, 41.5 mmol) in 1,2-dimethoxyethane (150 ml), *p*-toluenesulfonic acid (0.4 g) is added to the reaction mixture.

(b) Following reaction of the *trans*-decalyl betylate **4d** with thiourea, non-polar materials are removed by washing the aqueous solution of **5d** with pentane just prior to addition of dichloromethane and chlorination.

(c) The docosyl betylate (**4f**; 7.5 g, 13 mmol) is dissolved in warm acetone (150 ml) and mixed with a solution of thiourea (9.8 g, 130 mmol) in water (150 ml) which has been adjusted to pH 4 with sulfuric acid. The isothiuronium salt (**5f**) is obtained by filtration; this material is suspended in cold water/dichloromethane and the mixture stirred while chlorine is bubbled in for 1.5 h.

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I.R. of **6** ν [cm^{-1}][c]	^{1}H-N.M.R. ($CDCl_3$) of **6** δ [ppm]
1602 (m), 1495 (s), 1455 (s), 1370 (vs), 1165 (vs), 745 (s), 695 (s) (neat sample)	7.3 (m, 5H); 3.62 (t, 2H); 2.82 (t, 2H); 2.35 (quin, 2H)
1475 (m), 1370 (vs), 1165 (vs)	3.80 (s, 2H); 1.25 (s, 9H)
1465 (m), 1465 (vs), 1160 (vs)	3.6 (br m, 1H); 2.17 (m, 2H); 1.58 (d, 3H, J=7 Hz); 1.2–1.4 (br, 8H); 0.88 (t, 3H)
1450 (s), 1370 (vs), 1165 (vs), 610 (s), 600 (s), 555 (s), 545 (s) (CH_2Cl_2 in KBr cells)	3.58 (tt, 1H); 2.4 (brt, 2H); 0.7–2.1 (br, 14H)
1465 (m), 1380 (vs), 1165 (vs), 590 (m)	3.67 (t, 2H); 2.05 (quin, 2H); 1.27 (br, s, 26H); 0.88 (t, 3H)
1465 (m), 1380 (vs), 1165 (vs)	3.67 (t, 2H); 2.05 (quin, 2H); 1.27 (br s, 38H); 0.88 (t, 3H)

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