O-Methylation of a sulfone with methyl fluoride — antimony pentafluoride — sulfur dioxide. Preparation and properties of tetrahydro-1-methoxythiophenium 1-oxide hexafluoroantimonate

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Reaction of sulfolane (tetrahydrothiophene 1,1-dioxide) (1) with methyl fluoride — antimony pentafluoride in liquid sulfur dioxide gives crystalline tetrahydro-1-methoxythiophenium 1-oxide hexafluoroantimonate (2), thereby providing the first characterized example of an alkoxysulfoxonium salt. This salt (2) is also formed, but more slowly, by reaction of methyl fluoride with the crystalline 1:1 complex of sulfolane and antimony pentafluoride. Reaction of 2 with nucleophiles leads to transfer of the methyl group, a facile process even with such weak nucleophiles as nitrobenzene and phenyl N,N-dimethylsulfamate. Spectroscopic evidence has been obtained for O-methylation of other sulfones, either by reaction with MeF•SbF₅•SO₂, or via the sulfone•SbF₅ complex and methyl fluoride, or by transmethylation with 2.


La réaction du sulfolane (tétrahydrothiophènedioxyde-1,1) (1) avec le fluoro de méthyle/pentafluorure d’antimoine dans du dioxyde de soufre liquide donne l’antimoine hexafluoro de tétrahydrométhoxy-1-thiophéniumoxyde-1 (2) cristallin four- nissant ainsi le premier exemple caractérisé d’un sel d’alkoxysulfoxonium. Ce sel (2) se forme également, mais plus lentement, par la réaction du fluoro de méthyle avec le complexe cristallin 1:1 de sulfolane et de pentafluorure d’antimoine. Le composé 2 réagit avec les nucleophiles et conduit à un transfert de méthyle ce qui se produit très facilement même avec des nucleophiles faibles, tels le nitrobenzène et le N,N-diméthylphénylsulfamate. On a obtenu des preuves spectroscopiques pour la O-méthylation d’autres sulfones, soit par réaction avec le MeF•SbF₅•SO₂ ou par l’intermédiaire du complexe sulfone•SbF₅ et du fluoro de méthyle, soit par une trans-méthylation impliquant le composé 2.

[Traduit par le journal]

Sulfones are notoriously weak nucleophiles, being protonated only by very strong acids and forming stable complexes only with powerful Lewis acids (1, 2, and refs. cited). The low reactivity of sulfolane (1) has, in fact, led to its use as a solvent for such powerful alkylation agents as methyl trifluoromethanesulfonate and trimethylsilyl tetrafluoroborate (4, 5). Whiting and co-workers (6) have shown that O-arylation of sulfones to form arylsulfoxonium salts can be effected with aryl diazonium salts, a reaction which apparently proceeds by way of the exceedingly reactive aryl cation. Alkoxysulfoxonium species, formed both by O-alkylation of sulfones (5, 7) and by other pathways (8—11), have been postulated as intermediates on a number of occasions. The only report known to us in which any property of an alkoxysulfoxonium salt has been described, however, is that of Jackman and co-workers (4) who mention briefly in a footnote that “treating anhydrous solutions of silver tetrafluoroborate or silver hexafluoroantimonate in sulfolane with methyl iodide” gives solutions showing a singlet at 4.45 ppm in the ¹Hmr spectrum; the solutions were described as “unstable at room temperature”, decomposing in respectively 1 h and 24 h.

In connection with a collaborative study of the genotoxic effects of powerful alkylation agents, it has been found that sulfolane is an unreactive, water-miscible solvent suitable for the examination of the mutagenic activity of alkylation agents by the Ames test. A particular focus of this study has been the use of very powerful alkylation agents not requiring any kind of potentiation in situ but which are added to the biological system in the form that actually delivers the alkyl group to the biological receptor. It is evident that in any such investigation the product of the alkylation of the solvent holds a unique position, since it is likely to be the most powerful alkylation agent that can reliably be added using the solvent as diluent. Any more potent alkylation agent than this will probably alkylate the solvent in the time taken to make up a solution and introduce it to the biological testing medium. Accordingly, we set out to obtain a very simple O-alkylated derivative of sulfolane, viz. tetrahydro-1-methoxythiophenium 1-oxide hexafluoroantimonate (2). Its preparation and characterization, along with a preliminary study of its reactions with nucleophiles, form the basis of this paper; its behaviour in biological systems will be described elsewhere.

Results and discussion

Methyl fluoride — antimony pentafluoride in sulfur dioxide is an extremely powerful methylating agent which has been

1Part 25 in the series Organic Sulfur Mechanisms; for part 24, see ref. 23.

2In this paper we use the trivial name “sulfolane” in preference to the clumsier alternatives “tetramethylene sulfone” and “tetrahydrothiophene 1,1-dioxide”; the last is preferred by Chemical Abstracts, but the first — in its overseas form, “sulpholane” — is the entry name in the most recent edition of the Dictionary of Organic Compounds (3).

3J. E. Cummins, K. Rochefort, J. D. Lock, and J. F. King. Unpublished observations.

4As we have noted elsewhere (12), failure to take account of this possibility can give highly misleading results.
shown to contain MeOSO\(^+\) Sb\(_2\)F\(_{5+}\) (13-15). The reaction of sulfolane (1) with this methylating agent appeared, from preliminary experiments in conventional round-bottomed flasks, to lead to the O-methylated product (2). The \(^1H\)mr spectrum showed a sharp peak around 4.5 ppm along with complex signals centred around 3.9 and 2.6 ppm. This procedure generally gave the product as a yellowish syrup, though on one occasion white crystals were obtained; in all cases, however, the nmr spectrum of the product showed unreacted sulfolane. Use of dry box - vacuum line techniques with the apparatus shown in Fig. 1, as described in detail in the experimental section, led to a procedure in which premixed Me\(\)F-Sb\(_2\)F\(_5\)·SO\(_2\) was added to a slight excess of 1 in SO\(_2\), and which consistently gave 2 as a white crystalline solid. The identity of this material was established by elemental analysis, nmr spectroscopy, and its chemical reactions. The \(^13C\)mr spectrum of 2 (in liquid sulfur dioxide) showed resonances at \(\delta\) 61.4, 50.4, and 22.7; sulfolane (1) itself under these conditions shows signals at 51.5 and 22.8 ppm. Comparison of the \(^13C\)mr spectrum of 2 with that of 1 and with those of other methylated sulfones (see below) allows the assignment of the signal at 61.4 ppm in the spectrum of 2 to the \(\text{SO}-\text{OME}\) group. The \(^1H\)mr spectrum of 2 (in CD\(_2\)Cl\(_2\)) consisted of a sharp singlet at 4.49 ppm and a pair of multiplets in the ranges 3.6 to 4.2 and 2.5 to 2.7 ppm; on decoupling (by irradiating at 2.6 and 3.9 ppm, respectively) the latter signals were in turn transformed into an AB quartet (\(\delta\) 4.04 and 3.81, \(J_{AB}\) 15 Hz) and an apparent singlet (\(\delta\) 2.58 ppm).

The \(^1H\)mr spectrum of a mixture of 1 and 2, in CD\(_2\)Cl\(_2\) or in neat 1, is simply a superimposition of the spectra of 1 and 2. When 2 is dissolved in sulfolane-\(d_4\) (about 10 equiv.) and the spectrum run as soon as possible (<10 min), the multiplets around 3.9 and 2.6 ppm almost disappear, the strong signals at 3.0 and 2.2 ppm characteristic of sulfolane (1) appear, while the singlet at 4.49 ppm is unaltered; the spectrum remains unchanged on standing for at least one week. These observations clearly indicate that under our conditions the transfer of the methyl group from 2 to 1 is fast on the chemical time-scale (\(t_{1/2} < 2\) min), but slow on the nmr time-scale (\(t_{1/2} > 0.025\) s), as shown by the absence of coalescence of the methylene signals of 1 and 2 in CD\(_2\)Cl\(_2\) or neat 1).

In a sealed tube the alkoxysulfonylum salt (2) keeps indefinitely as the crystalline solid or a solution in liquid sulfur dioxide; solutions of 2 in sulfolane showed no significant decomposition in one week but gradually turned brown over longer periods. As noted above, however, Jackman and co-workers (4) reported that 2 in sulfolane decomposes to methyl fluoride and Sb\(_2\)F\(_5\) in 24 h. It seems likely from the absorption they observed at 4.45 ppm in the \(^1H\)mr spectrum that they indeed had 2 in the solution, and in the absence of further information we ascribe the relatively rapid decomposition of their sample to the action of impurities.

We have also looked into the possibility of making 2 by reacting a preformed sulfolane-Sb\(_2\)F\(_5\) complex with methyl fluoride in the hope that, once formed, handling an easily prepared, stable isolable complex might avoid some of the experimental difficulties attendant upon frequent quantitative transfer of antimony pentafluoride. Sulfolane and Sb\(_2\)F\(_5\) gave a solid product which gave correct elemental analyses for a 1:1 complex and which showed \(^1H\)mr multiplets centered at 2.1 and 3.3 ppm and \(^13C\)mr lines at 53.3 and 22.6 ppm. Reaction of this complex with excess Me\(\)F in liquid SO\(_2\) in an nmr tube showed a clean conversion to 2 which required, however, a number of hours at room temperature to go to completion.

Methylene chloride-\(d_2\) solutions of 2, though sufficiently stable for the determination of nmr spectra, gradually decompose \((t_{1/2} \sim 5\) h) with formation of sulfolane and a peak at 3.0 ppm ascribed to methyl chloride; the same peak appears, but more slowly, with chloroform-\(d\). These observations point to the following scheme involving initial formation of a dialkylechloronium ion (16) which then cleaves to methyl chloride and the unstable halocarbenium species (17).

\[
2 + \text{ClCD}_2\text{C}_3\text{Cl}_{3-n} 
\rightarrow \left[\text{CH}_3\text{Cl} - \text{Cl} - \text{CD}_2\text{C}_3\text{Cl}_{3-n}\right] 
\rightarrow \text{CH}_3\text{Cl} + \left[\text{CD}_2\text{C}_3\text{Cl}_{3-n}\right]
\]

These observations, of course, imply that 2 is a very powerful methylating agent, and we have carried out some preliminary experiments using nmr to make a brief survey of its methylating capabilities. As expected, 2 reacts instantly with water, the \(^1H\)mr spectrum (in D\(_2\)O) showing a methanol resonance at 3.35 ppm and the two multiplets of sulfolane at 2.2 and 3.1 ppm. Table 1 summarizes a number of nmr experiments, which show that 2 rapidly methylates sulfides, difenyl sulfide, and sulfones, and reacts rather more slowly with nitrobenzene and phenyl N,N-dimethylsulfamate. This last reaction allows a very rough comparison of 2 with methyl fluorosulfate. Whereas the reaction with 2 in CD\(_2\)Cl\(_2\) solution (\(\sim 0.1\) M in substrate and \(\sim 0.05\) M in 2) was about two-thirds complete after about 40 min at room temperature, even neat methyl fluorosulfate was unreacted after 12 h at room temperature and required heating at 50°C for several hours to achieve the same extent of methylation (18); one may thus conservatively estimate that 2 is at least three orders of magnitude more reactive than methyl fluorosulfate. The reactions of 2 with diethyl and diethyl sulfones were, like that with sulfolane-\(d_4\), complete in less than the time required to observe the nmr spectrum. The spectra showed peaks appropriate to equilibrium mixtures (in CD\(_2\)Cl\(_2\)) with equilibrium constants, \(K\), of roughly 0.3 and 0.6, respectively.

\[
R_3\text{SO}_2 + 2 \rightleftharpoons R_3\text{S} + \text{SbF}_5^- + 1
\]

\[
R_3\text{OMe} + 2 \rightleftharpoons R_3\text{O} + \text{SbF}_5^- + 1
\]
We have also explored the preparation of other O-methylated sulfones by reaction of the sulfone with SbF₅·MeF·SO₂. The ³¹Cmr spectrum of the product from dimethyl sulfone showed peaks at 60.9 and 39.9 ppm along with a signal for the unreacted sulfone (at 42.8 ppm). Upon washing with Freon 21 we were unable to remove the remaining sulfone. The peaks at 60.9 and 39.9 ppm also appeared when dimethyl sulfone was mixed with 2 in liquid SO₂, with the signal amplitudes corresponding to K₁. Reaction of the solid Me₂SO-OMe and Me₂SO₂, which showed no impurity by 'Hmr spectroscopy; they were used as received, as were sulfolane-d₈ (Merck Sharp and Dohme Canada Ltd.). Diethyl sulfone was prepared by oxidation of diethyl sulfide with hydrogen peroxide — acetic acid; mp 73°C (lit. (20) mp 70°C).

The reaction vessel for the reactions with methyl fluoride — antimony pentfluoride (Fig. 1) consisted of three 18-mm od glass tubes, A, B, and C, each with constriction, as shown, and of roughly medium sinter; the A-B and B-C connections were mutually at right angles. Tube B, the principal reaction vessel, contained a Teflon-covered magnetic stirrer bar. The dimensions of the apparatus were determined in large part by the necessity of having it pass through the 30-cm diameter port of the glove box (see below).

The apparatus was baked out at 140°C (50°C for the Teflon stopcock) and then transferred to an N₂-filled dry box in which the dry atmosphere was maintained by circulation through liquid nitrogen cooled copper coils.

### Experimental

Sulfolane (tetramethylene sulfone; Aldrich Chemical Co.) was purified as described in the literature (19) and stored over 3 Å molecular sieves at 40°C. Antimony pentafluoride (PCR Research Chemicals, Inc.) was distilled twice in a dry nitrogen atmosphere before use, then stored in a sealed container in a dry box. Sulfur dioxide (Canadian Liquid Air Ltd; anhydrous grade) and dichlorofluoromethane (Freon 21; Matheson of Canada Ltd.) were allowed to stand over 3 Å molecular sieves, in the gas and liquid phases, respectively, for at least 12 h before use. Neither methyl fluoride (Pfaltz and Bauer, Inc.) nor dimethyl sulfone (Aldrich Chemical Co.) showed any significant impurity by 'Hmr spectroscopy; they were used as received, as were diethyl sulfide (Aldrich), which showed no impurity by ¹³Cmr nmr, and sulfolane-d₈ (Merek Sharp and Dohme Canada Ltd.). Diethyl sulfone was prepared by oxidation of diethyl sulfide with hydrogen peroxide — acetic acid; mp 73°C (lit. (20) mp 70°C).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>'Hmr peaks¹</th>
<th>Assignment</th>
<th>Reaction extent and time</th>
</tr>
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<tbody>
<tr>
<td>PhNO₂</td>
<td>4.84(s), 7.8–8.8.0(m), 8.6–8.7(“d”)</td>
<td>Ph-N=O+      OMe</td>
<td>&gt;60% in 40 min</td>
</tr>
<tr>
<td>Ph₃S</td>
<td>3.58(s), 7.8(s)</td>
<td>Ph₃SMe</td>
<td>Complete in &lt;10 min</td>
</tr>
<tr>
<td>Me₂SO₂</td>
<td>3.31(s), 4.15(s)</td>
<td>Me₂S—OMe²</td>
<td>Complete in &lt;10 min</td>
</tr>
<tr>
<td>Ph₄SO</td>
<td>4.30(s), 7.86(“s”)</td>
<td>Ph₄SOMe</td>
<td>Complete in &lt;10 min</td>
</tr>
<tr>
<td>Me₄SO₂</td>
<td>3.86(s), 4.45(s)</td>
<td>Equilibrium mixture (see text)</td>
<td>Complete in &lt;10 min</td>
</tr>
<tr>
<td>Et₂SO₂</td>
<td>1.58(t), 3.90(q), 4.42(s)</td>
<td>Equilibrium mixture (see text)</td>
<td>Complete in &lt;10 min</td>
</tr>
<tr>
<td>PhOSO₂NMe₂</td>
<td>3.71(s), 7.4–7.6(m)</td>
<td>PhOSO₂NMe²</td>
<td>&gt;70% in 40 min</td>
</tr>
<tr>
<td></td>
<td>4.66(s), 3.76(s), 3.56(s), 2.7–3.5(m), 2.0–2.5(m)</td>
<td>*OMe·Me'</td>
<td>Complete in &lt;10 min</td>
</tr>
</tbody>
</table>

¹In CD₃Cl₃ at room temperature.
²XL-100 spectra.
³Reported: 4.65 and 7.6–8.2 ppm in liquid SO₂ (16).
⁴J. D. Lock (unpublished observations in this laboratory) found 3.23 and 4.02 ppm (in CD₃CN).
⁵Reported: 3.70 and 7.56 ppm (in CD₃CN) (18).
⁶Reported: 4.86, 3.18, 2.24 ppm (in CD₃CN) (16).

### Table 1. Methylation with tetrahydro-1-methoxythiophenium 1-oxide hexafluorantimonate (2)

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<td>4.30(s), 7.86(“s”)</td>
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<td>*OMe·Me'</td>
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</tr>
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plus unidentified material

We have also explored the preparation of other O-methylated sulfones by reaction of the sulfone with SbF₅·MeF·SO₂. The ³¹Cmr spectrum of the product from dimethyl sulfone showed peaks at 60.9 and 39.9 ppm along with a signal for the unreacted sulfone (at 42.8 ppm). Upon washing with Freon 21 we obtained a solid material which appeared to be a 60:40 mixture of Me₂SO—OMe SbF₅⁻ and Me₂SO₂, but we were unable to remove the remaining sulfone. The peaks at 60.9 and 39.9 ppm also appeared when dimethyl sulfone was mixed with 2 in liquid SO₂, with the signal amplitudes corresponding to K₁~0.4. Reaction of the solid Me₂SO₂·SbF₅ complex with methyl fluoride in liquid SO₂, overnight at room temperature, gave a material which showed strong ³¹Cmr resonances at 60.7 and 39.8 ppm (from Me₂SO₂Me and Me₂SO₂Me respectively) with only a weak signal (at 42.6 ppm) due to unreacted Me₂SO₂, thereby evidently providing the cleanest specimen of Me₂SO—OMe SbF₅⁻ that we have observed to date.

Attempts to methylate diethyl sulfone with MeF·SbF₅·SO₂ gave only intractable oily products, while transmethylolation with 2 in liquid SO₂ gave a mixture showing ³¹Cmr lines due to unreacted diethyl sulfone (δC = 46.6 and 5.4 ppm), reacted ₂, and the expected Et₂SO₂Me (δC = 61.0, 46.6, and 5.4 ppm); we estimate K~0.8 in liquid SO₂. Similar reactions of diphenyl sulfone showed largely unreacted starting materials with small peaks at 62.3, 129.2, 132.0, and 139.3 ppm, reasonably attributable to Ph₅SO—OMe SbF₅⁻ (K<0.1).

This study shows that alkoxysulfoxonium salts are stable, isolable materials with interesting potential as alkylating agents. We hope to exploit this potential in future work.
Methyl fluoride (25 mmol) was similarly condensed into tube B, allowing to cool and a similar amount was condensed onto the sulfolane. The apparatus was moved from the vacuum line and allowed to warm to room temperature (with care! the vessel being under ca. 3 atm pressure).

The mixture of SbF₅ and CH₂F in SO₂ was stirred for 15 min at room temperature, then poured into the sulfolane solution in tube A; the addition was noticeably exothermic and was accompanied by the appearance of a yellow solution. The total reaction mixture was returned to tube B and stirred for a further 15 min. Excess CH₂F and SO₂ were removed by slow cooling of tube A over a few hours. Finally A was frozen in liquid nitrogen cooling. The apparatus was once more removed from the vacuum line and allowed to warm to room temperature. The Freon—product mixture was stirred for 5–10 min before decanting the upper (Freon) layer (which contains unreacted sulfolane) from B into C. The Freon was returned to tube B by cooling and this washing process repeated twice. Finally, the apparatus was frozen in liquid nitrogen and the heterogeneous mixture of the product with Freon was sublimed in an ice bath for about 30 min. During this time, white crystals of the product formed. The mother liquor was decanted into C and the product washed twice with Freon before cooling C in liquid N₂ and flame sealing at F.

The rest of the apparatus (tube B) containing the pure product was reattached to the vacuum line and pumped for several hours to remove any residual Freon. In the dry box, the apparatus was broken at the constriction. The product (5.8 g, 82% yield) was transferred to a mass glass container and stored in the dry box at room temperature. Under these conditions little deterioration was noticed over a period of several months. Anal. calcd.: for CH₄F₃SbSbF₅: C 16.19, H 2.99, S 8.64, Sb 32.82; found: C 16.05, H 3.09, S 8.66, Sb 33.13.

Preparation of antimony pentfluoride—sulfolane 1:1 adduct

A two-armed H-shaped glass reaction/filtration vessel of a type described earlier (21) was used for this synthesis. In the glove box, antimony pentfluoride (4.0 g, 18 mmol) was added from an all-glass glass container and stored in the dry box at room temperature. Outside the glove box, liquid sulfolane (1.9 mL, 20 mmol) was added to the arm with the stirrer under a flow of dry nitrogen. The apparatus was attached to the vacuum line at the sulfolane side, evacuated, and flame sealed at the unattached outlet. Sulphur dioxide (ca. 75 mmol) was introduced with liquid nitrogen cooling prior to separation from the vacuum line by flame sealing at the 9-mm outlet. With care (see above), the apparatus was allowed to warm to room temperature, some SO₂ was condensed onto the SbF₅ by gentle cooling, and the SbF₅ solution was slowly added to the well-stirred sulfolane solution. Slow reduction of the solution volume by cooling the opposite arm, with the concomitant cooling effect on the product solution, resulted in crystallization of the product which was filtered off, washed with small portions of SO₂, and isolated in the general manner reported previously (21). Anal. calcd.: for C₄H₈O₂SbSbF₅: C 14.26, H 2.39; found: C 14.03, H 2.56.

Nuclear magnetic resonance samples and spectra

Samples for proton nmr spectroscopy, except those involving liquid SO₃ as solvent, were prepared in standard 5-mm od capped nmr tubes. The experiments in Table 1 were carried out by transferring 2 (20 mg, ~0.05 mmol) to the nmr tube in the dry box and adding the substrate (~0.1 mmol), CD₂Cl₂ (1 mL), and TMS. The spectra (XL-100) were run within 5 min, with subsequent spectra to follow the course of slow reactions run on the T-60 at appropriate intervals.

For samples in liquid SO₃ the procedure was as follows: a 5-mm od medium-walled nmr tube sealed onto ca. 8-cm lengths of 9-mm od special-walled glass tubing was baked out at 140°C; under an atmosphere of dry nitrogen (in the dry box for solid materials or a flow of H₂SO₄-dried N₂ for liquids) an appropriate mass of each solid reactant or volume of liquid sulfolane was added to the tube; the tube was attached to the calibrated vacuum line via the 9-mm tubing and 3/8-in. Ultratorr union and evacuated; with liquid N₂ cooling, appropriate amounts of SO₃ and MeF₂ when needed, were metered into the tube before flame sealing at the top of the 5-mm od section. Samples for 13C nmr spectroscopy of SO₃ solutions were made up in an analogous manner in flame-sealed handmade tubes of 10-mm od standard-wall glass tubing.

Samples contained in capped tubes were used immediately. Similarly, the solutions in flame-sealed tubes were used fresh or stored in liquid nitrogen until used.

Proton nmr spectra were measured using a Varian T-60, Varian EM-360, or Varian XL-100-12 spectrometer. All the 1H nmr spectra were obtained at 308 K using the XL-100-12 spectrometer system operating at 25.2 MHz in the FT mode; the 10-mm sample tubes were held coaxially in a 12-mm od standard nmr tube and a 10% (v/v) solution of dioxane in D₂O in the outer annulus was used as an external lock and 13C reference, as described earlier (22). For this reference, δC (TMS in SO₂, int) = δC (dioxane in D₂O, ext) + 67.8 ppm (22). Typically, satisfactory 1H nmr spectra of ca. 0.15 m solutions were obtained in several thousand transients with a 5 kHz spectra window, 3.3 s acquisition time, 3.5 s cycle time, and 38° (8.5 μs) tip angle (pulse width) (28° (7 μs) for samples containing PbSO₄).

Acknowledgments

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