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OXIDATION OF ALCOHOLS BY "ACTIVATED" DIMETHYL SULFOXIDE. A PREPARATIVE, STERIC AND MECHANISTIC STUDY[1]

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Abstract—The oxidation of primary, secondary, allylic, benzylic, hindered and bicyclic alcohols with dimethyl sulfoxide (DMSO) "activated" by numerous electrophiles was studied; yields of carbonyls, by-products and recovered alcohols were quantitatively determined. Pathways for carbonyl and by-product formation are presented. Generally, yields of carbonyls increase with increased steric hindrance in the alcohols. Steric effects of tertiary amines, used for basification, were also investigated, and the results are consistent with the suggested reaction pathways. Among previously unreported "activators," oxalyl chloride is the most generally effective; yields of carbonyls are typically over 95%. Thionyl chloride is also a satisfactory "activator" although yields of carbonyls are not quite as high. An improved method of preparation of alkyl methylthiomethyl ethers, by-products of the oxidation process, is reported.

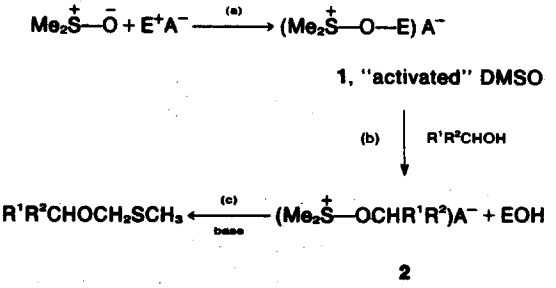
Reaction of dimethyl sulfoxide (DMSO) with electrophilic "activators" has proven highly useful in the mild oxidation of alcohols to carbonyls.[2] Successful use of DMSO as an oxidant for alcohols (Scheme 1) requires (a) "activation" of DMSO by a suitable electrophilic reagent (E^+A^-) below the (Pummerer) rearrangement temperature of the requisite intermediate **1**; (b) facile attack by an alcohol on the electropositive sulfur atom of the intermediate **1** with the departure of a leaving group to form a dimethylalkoxysulfonium salt **2**; (c) reaction of the salt **2** with a base, typically triethylamine (TEA), to form dimethyl sulfide and the carbonyl product; and (d) separation of the carbonyl product from by-products (methylthiomethyl ether of the alcohol, among others).

During studies on the oxidation of alcohols with DMSO "activated" by trifluoroacetic anhydride (TFAA), we noted that the yield of carbonyls increased with increased steric hindrance in the alcohol.[3,4] While the oxidation of various alcohols with DMSO and other "activators" has been explored by other workers,[2] steric effects have not been distinctly recognized, except in oxidations with DMSO-acetic anhydride where a similar trend was observed.[2c] It has also been pointed out that methylthiomethyl ethers are frequently encountered as minimal by-products during the oxidation of relatively nonhindered alcohols with DMSO "activated" by dicyclohexylcarbodiimide.[2c] To ascertain whether steric effects are generally observed, and to learn if the reaction pathways are related to such effects, we studied the scope and limitations of the oxidation of alcohols by DMSO "activated" by previously reported as well as hitherto unreported "activators"; yields of carbonyls and by-products were quantitatively determined. This study also permitted us to assess the relative effectiveness of DMSO "activators" in this oxidation and led to the discovery of oxalyl chloride and thionyl chloride as particularly effective DMSO "activators," especially the former.

RESULTS AND DISCUSSION

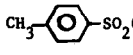
In many literature reports, oxidation with "activated" DMSO has been conducted on complex alcohols. In contrast we selected relatively simple model primary (*n*-decanol, **3**), secondary (2-octanol, **4**) and sterically hindered (isoborneol, **5**, or l-borneol, **6**) alcohols to eliminate or minimize other possible factors, and also to make product analyses readily feasible by GLC. For completeness, allylic and/or benzylic alcohols were also oxidized.

Results of the oxidation of these alcohols with DMSO "activated" by previously reported "activators" are summarized in Table 1. Reactions were carried out according to the procedures described by the original workers. When reactions did not proceed smoothly, the reaction conditions were modified or improved. As expected, oxidations with DMSO and acetic anhydride,



Scheme 1.

Table 1. Oxidation of alcohols to carbonyls by "activated" DMSO

"Activator"	Alcohol (ROH)	Solvent	T, °C	Reaction Time, Hr	Products, %[a] >C=O	ROH	$ROCH_2SCH_3$	R-X
$(CH_3CO)_2O$[b]	n-Decanol (3)	DMSO	25	27	27	1.0	56	6.7 (X = OAc)
	2-Octanol (4)	DMSO	25	30	30	0.8	62	2.9
$Py\cdot SO_3$[c]	3	DMSO	25	0.5	91	0.6	6.3	d
	4	DMSO	25	0.5	93	trace	4.2	d
DMS-NCS[e]	3	Toluene	-25	1.5	94	0.7	2.5	0 (X = Cl)
	4	Toluene	-25	1.5	95	0.7	3.2	0
	3	CH_2Cl_2	-25	1.5	58	21	20	0
	4	CH_2Cl_2	-25	1.5	61	21	19	0
	Isoborneol (5)	CH_2Cl_2	-25	1.5	99	0.3	d	d
$(CH_3SO_2)_2O$[f]	3[g]	HMPA	-15 to -20	0.25	69	16	12	d
	4	HMPA	-15 to -20	0.25	84	8.0	5.1	d
	5	HMPA	-15 to -20	0.25	98	2.1	d	d
Cyanuric Chloride[h]	3	HMPA-CH_2Cl_2	-15 to -20	0.5	73	14	8.5	d
	4	HMPA-CH_2Cl_2	-15 to -20	0.5	82	10	3.2	d
	5	HMPA-CH_2Cl_2	-15 to -20	0.5	99	0.7	d	d
PhCOCl[i]	3[j]	HMPA-CH_2Cl_2	-20	0.25	29	40	26	0.4 (X = OCOPh)
	4	HMPA-CH_2Cl_2	-20	0.25	28	45	22	trace
	5	HMPA-CH_2Cl_2	-20	0.25	90	4.1	d	d
CH_3SO_2Cl[k]	3[l]	HMPA-CH_2Cl_2	18 to 20	0.75	62	2.8	4.5	6.5 (X = Cl)
	4[m]	HMPA-CH_2Cl_2	18 to 20	0.75	77	3.3	2.5	1.3
	3	HMPA-CH_2Cl_2	5	1.25	72	14	10	d
	4[o]	HMPA-CH_2Cl_2	5	1.25	90	2.7	2.2	d
$(CF_3CO)_2O$[p]	3	CH_2Cl_2	-50 to -60	0.5	56	d	8	24 (X = $OCOCF_3$)
	4	CH_2Cl_2	-50 to -60	0.5	78	d	5	14
	5	CH_2Cl_2	-65	0.5	93	d	d	d

[a] Composition was determined by GLC using a column packed with 10% FFAP on Chromosorb P or Apiezon L on Anakrom. In all cases, authentic samples were used for quantitation.

[b] Using alcohol (10 mmol), Ac_2O (10 ml), and DMSO (30 ml), according to the procedure described for the oxidation of p-nitrobenzyl alcohol by Albright.[5b]

[c] Using alcohol (4 mmol), $Py\cdot SO_3$ (13 mmol), DMSO (20 ml) and TEA (58 mmol), according to the procedure described by Parikh and Doering.[6]

[d] Not estimated.

[e] In this case, it is not DMSO but DMS that is "activated" by NCS, using alcohol (8 mmol), NCS (12 mmol), DMS (18 mmol), TEA (14 mmol) and toluene or CH_2Cl_2 (45 ml) under argon, according to the procedure described by Corey and Kim.[7] We find room temperature oxidation to be satisfactory with 4 using alcohol (8 mmol), DMS (20 mmol), NCS (14 mmol), toluene (25 ml) and TEA (22 mmol) at 15°.

[g] Using alcohol (8 mmol), $(CH_3SO_2)_2O$ (16 mmol), DMSO (6 ml), TEA (36 mmol) and HMPA (20 ml), according to Albright's procedure.[8]

[g] Oxidation of 3 for 3 hr instead of 0.25 hr gave virtually identical results.

[h] Using alcohol (8 mmol), cyanuric chloride (16 mmol), DMSO (6 ml), TEA (36 mmol) and CH_2Cl_2-HMPA (13 + 8 ml), according to Albright's procedure.[8]

[i] Using alcohol (8 mmol), PhCOCl (16 mmol), DMSO (6 ml), TEA (36 mmol) and CH_2Cl_2-HMPA (10 + 10 ml), according to Albright's procedure.[8]

[j] Oxidation of 3 for 3 hr instead of 0.25 hr gave virtually identical results.

[k] Using alcohol (8 mmol), CH_3SO_2Cl (16 mmol), DMSO (6 ml), TEA (36 mmol) and CH_2Cl_2-HMPA (10 + 10 ml) according to Albright's procedure[8] except at higher temperature.

[l] The reaction of 3 at -20°C for 5.5 hr (Albright's original conditions) gave no carbonyl; n-decyl methanesulfonate was isolated in 93% yield after work up.

[m] The yield of 2-octanone changed with reaction time in the following way: 19 (5 min), 45 (15 min), 77 (45 min), 67 (1.5 hr) and 34% (6 hr). The reaction at -20°C for 3.5 hr gave traces of carbonyl; 2-octyl methanesulfonate was isolated in 97% yield.

[n] Using alcohol (8 mmol), TsCl (16 mmol), DMSO (6 ml), TEA (36 mmol) and HMPA-CH_2Cl_2 (10 + 10 ml), according to Albright's procedure[8] except at higher temperature.

[o] The yield of 2-octanone reached its maximum in 0.5 to 1.25 hr. Reaction for 5 hr gave 2-octanone (74%), recovery of 4 (16%) and 2-octyl methylthiomethyl ether (5.6%). Oxidation of 4 at -20°C for 3 hr (Albright's original conditions) gave little 2-octanone (15%) and recovery of 4 (67%).

[p] Data from ref. 3 and 4.

originally reported by Albright,[5] at room temperature gave carbonyls in low yields (*ca.* 30%) from the less hindered alcohols 3 and 4. Alkyl methylthiomethyl ethers were the major products (*ca.* 60%), and acetates minor products. DMSO and pyridine–sulfur trioxide complex ($Py\cdot SO_3$), described by Parikh and Doering,[6] oxidized 3 and 4 to carbonyls in high yields (>90%) at room temperature. Oxidation by this method is reported to give negligible formation of methylthiomethyl ethers.[2c,6] We find that 3 and 4 give ethers in 4 to 6% yields.

DMSO–Py·SO_3 oxidizes cinnamyl alcohol and benzhydrol to the corresponding carbonyls in nearly quantitative yields.

Oxidation with dimethyl sulfide (DMS) and *N*-chlorosuccinimide (NCS), as reported by Corey and Kim,[7] was also investigated (Table 1) since it is clearly related to oxidation by "activated" DMSO; the final step is reaction of alkoxysulfonium salts **2** with base. Reaction with this useful oxidant is conducted at −25°C for 1.5–2 h in toluene; **3** and **4** were oxidized to carbonyls very efficiently (*ca.* 95%). In a more polar solvent (methylene chloride) yields of methylthiomethyl ethers and recovered alcohols increase. Isoborneol **5**, however, was quantitatively converted to camphor in that solvent. Oxidation with DMS–NCS can be effected near room temperature in toluene, however, with scarcely any sacrifice in yields of carbonyls provided an excess of DMS and NCS is employed (100–150% excess). At this higher reaction temperature, benzene and toluene give essentially identical results.

Albright[8] recently published a brief communication in which several organic acid halides and anhydrides were shown to be useful "activating" agents for DMSO at −20°C in hexamethylphosphoramide (HMPA) or CH_2Cl_2 with several alcohols. Among those "activators," we chose methanesulfonic anhydride, cyanuric chloride, benzoyl chloride, methanesulfonyl chloride and *p*-toluenesulfonyl chloride for the oxidations of **3**, **4** and **5**.

Oxidation of these alcohols with DMSO and methanesulfonic anhydride, cyanuric chloride or benzoyl chloride was complete within 15–30 min (Table 1); prolonging the reaction time did not change the product distribution. Oxidation with DMSO–methanesulfonic anhydride (in HMPA) and DMSO–cyanuric chloride (in HMPA–CH_2Cl_2) gave 69–73, 82–84 and 98–99% yields of carbonyls from **3**, **4** and **5**, respectively. The oxidation of **3** and **4** with DMSO–benzoyl chloride (in HMPA–CH_2Cl_2) yielded only about 30% of carbonyls; recovery of the alcohols and formation of methylthiomethyl ethers accounted for the rest of the products. Compound **5** was converted to camphor in high yield (90%) with benzoyl chloride activation of DMSO.

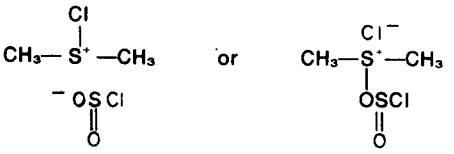
According to Albright, the oxidation of testosterone with DMSO–methanesulfonyl chloride and DMSO–*p*-toluenesulfonyl chloride at −20°C is slower and use of a larger excess of the sulfonyl chlorides is recommended. In fact, "activation" of DMSO by methanesulfonyl chloride in HMPA–CH_2Cl_2 was found to be extremely slow at −20°C. Trace amounts of carbonyls were obtained from **3** or **4** after 3.5 to 5.5 h; methanesulfonate esters of the alcohols were isolated in nearly quantitative yields. Instead of employing a larger amount of the oxidant at −20°C, we therefore attempted the reaction at higher temperature.

Moderate reaction rates were obtained only at about room temperature; carbonyls were obtained in fairly good yields after addition of TEA. There was an optimal reaction time, however, and prolonged reaction resulted in decreased yields of carbonyls, with the formation of several unidentified products. Oxidation of 2-octanol **4** with DMSO–*p*-toluenesulfonyl chloride in HMPA–CH_2Cl_2 at −20° was somewhat faster, yet only 15% of 2-octanone was obtained after 3 h with substantial recovery of **4**. The oxidation was best conducted at *ca.* 5°C for 30 to 75 min, giving carbonyls in good yields (70–90%) from **3** and **4**, but yields slowly decreased with prolonged reaction time.

Although the hindered alcohol **5** was always converted to carbonyl in nearly quantitative yield by DMSO irrespective of its "activator," it was only DMSO–Py·SO_3 and DMS–NCS that afforded carbonyls in greater than 90% yields from the less hindered alcohols **3** and **4**. DMSO "activated" by other "activators" did not give carbonyls in excess of 75% from **3** and 90% from **4**.

The use of these methods is frequently complementary, and even DMS–NCS or DMSO–Py·SO_3 has its own disadvantages.[2,7] It seemed, therefore, desirable to explore new and perhaps more effective "activators." Table 2 summarizes the results of the oxidation of alcohols with DMSO activated by previously unreported "activators," typically inexpensive and common inorganic and carboxylic acid halides. The reactions were conducted basically following the procedure we employed in the oxidation with DMSO–TFAA,[3] using minimal excesses of "activated" DMSO relative to the alcohols, with CH_2Cl_2 as solvent. The proper reaction temperature had to be determined in each case depending on the reactivity of each acid halide toward DMSO.

Reaction of DMSO with thionyl chloride ($SOCl_2$) to form "activated" DMSO was fast at −60°C and oxidation with this reagent gave good yields of carbonyls from **3**, **4** and **5**. 2-Cyclohexen-1-ol (77%), cinnamyl alcohol (85%), benzyl alcohol (100%), and benzhydrol (94%) were also oxidized efficiently under similar conditions. However, marked reduction in the yield of carbonyl from **3** was observed when the oxidation was conducted (1) at higher temperature (−20 to −30°C, reduction from 80 to 50%), (2) using a 100% excess of DMSO–$SOCl_2$ relative to **3** (65%), or (3) in other solvents than CH_2Cl_2 (hexane, toluene or ether). Oxidation of alcohols with DMS–sulfuryl chloride (SO_2Cl_2) in place of DMSO–$SOCl_2$ gave after addition of TEA virtually identical product distributions, indicating that DMSO–$SOCl_2$ and DMS–SO_2Cl_2 produce the same "activated" form of DMSO.



Oxidation with DMSO–phosphorus trichloride (PCl_3) or DMSO–phosphorus oxychloride ($POCl_3$) was best conducted at −30°C. Yields of carbonyls from **3** and **4** were only fair but quite satisfactory with **5**. At −60 or −5°C, yields of carbonyls were usually lower. This suggested that formation of "activated" DMSO **1** is slow at −60°C[a] and intermediate **1** is unstable at −5°C.[b]

Acetyl bromide reacted with DMSO instantaneously at −60°C to form a precipitate, presumably of the intermediate **1**. Oxidation was complete within 15 min and

[a] It is also possible that formation of **1** is fast but reaction with alcohols to form the alkoxysulfonium salt **2** is slow at −60°C. Reaction of **1** with alcohols was considered to be generally fast even at low temperatures, typically, as exemplified later in the oxidation with DMSO–acetyl chloride.

[b] It is possible that **2**, not **1**, is unstable at −5°C, but in general **2** is thermally more stable than **1**. For example, **1** from DMSO and TFAA decomposes above −30°C while **2** (A = CF_3CO_2) is stable for at least several days at room temperature.

Table 2. Oxidation of alcohols to carbonyls by DMSO "activated" by inorganic and carboxylic acid halides in CH_2Cl_2[a]

"Activator"	Alcohol (ROH)	T, °C	Products, %[b] >C=O	ROH	$ROCH_2SCH_3$	R-X
$SOCl_2$[c]	3[d]	-60	76	12	4.6	trace (X = Cl)[e]
	4	-60	88	4.3	3.2	≤1.5[e]
	1-Borneol (6)	-60	99	0.8	f	f
PCl_3[g]	3[h]	-30	45	18	20-23	trace (X = Cl)
	4	-30	59	22	16	0
	5	-30	98	trace	f	f
$POCl_3$[i]	3	-30	43	24	26	trace (X = Cl)
	4	-30	52	27	19	0
	5	-30	99	trace	f	f
CH_3COBr	3[j]	-60	58	34	7	trace (X = $OCOCH_3$)
	4	-60	70	22	5	5
	6	-60	99	f	f	f
CH_3COCl	4[k]	-20 to -25	40	54	7	f
	6[l]	-20 to -25	57	40	f	f
PhCOCl	3	-60	25	16	1	59 (X = OCOPh)
	3[m]	-60	97	0.3	0.8	2
	3	-20	29	40	26	0
$(COCl)_2$[n]	3	-60	97	1.0	1.8	0 (X = Cl)
	4	-60	98	1.4	0.8	0
	5	-60	99	0.7	f	f

[a] See Experimental for the general procedure. Unless otherwise specified, alcohol (10 mmol), "activator" (11-12 mmol), DMSO (13 mmol), TEA (36-58 mmol) and CH_2Cl_2 (ca. 40 ml) were used. Reaction time, 0.25 hr.

[b] Same as footnote a in Table 1.

[c] Under similar conditions, 2-cyclohexen-1-ol, cinnamyl alcohol, benzyl alcohol and benzhydrol were converted to carbonyls in 77, 85, 100 and 94% yields, respectively.

[d] Reaction for 1 hr instead of 0.25 hr gave essentially the same product distribution.

[e] It is possible that the initial product was the alkyl chlorosulfite (ROSOCl) which could have decomposed in the GLC column to form the alkyl chloride.

[f] Not estimated.

[g] DMSO (35 mmol) was used.

[h] Oxidation of 3 at -5°C and at -60°C gave the aldehyde in 27 and 23% yields, respectively. An even lower yield (7%) of the aldehyde was obtained when 3 was oxidized at -60°C using a smaller amount of DMSO (13 instead of 35 mmol).

[i] DMSO (35 mmol) was used. Oxidation of 3 at -5°C and at -60°C gave the aldehyde in 15 and 12% yields, respectively. Only traces of aldehyde were obtained when 3 was oxidized at -60°C using a smaller amount of DMSO (13 mmol).

[j] Reaction of 3 for 1.5 hr instead of 0.25 hr gave the same results.

[k] Oxidation of 4 at -60°C gave 2-octanone (trace), recovery of 4 (78%), 2-octyl methylthiomethyl ether (0%), and 2-octyl acetate (14%). Oxidation at -5°C gave 2-octanone (10%), recovery of 4 (74%), and 2-octyl methylthiomethyl ether (13%).

[l] Oxidation of 6 at -5°C gave camphor (41%) and recovery of 6 (52%).

[m] DMSO (42 mmol) and PhCOCl (34 mmol) were used. PhCOCl was allowed to react with DMSO for 30 min to build up "activated" DMSO before addition of 3.

[n] DMSO (24 mmol) was used. Oxidation using DMSO (12 mmol) gave similar results.

prolonged reaction times had no effect on the product distribution. In contrast, reaction of acetyl chloride with DMSO was slow at −60°C, and only trace amounts of carbonyls were obtained from 3 and 4. Reaction products consisted of recovered alcohols and their acetates. At −20 to −25°C, the carbonyl was obtained in fair yield (40%) from 4, but unoxidized 4 was still substantial. Recovery of starting alcohol was substantial (40%) even in the oxidation of the hindered alcohol 6. This presumably indicated that not enough "activated" DMSO was present to convert all of the starting alcohols to their alkoxysulfonium salts 2 since, from what we have seen in many examples, the hindered alcohols 5 or 6 are expected to give carbonyls in high to nearly quantitative yield as long as they are completely converted to 2 before addition of TEA.

The following experiment indicated that it is not the reaction of an alcohol with 1 that is slow at −60°C but rather the reaction of DMSO with acetyl chloride to form 1. DMSO and acetyl chloride were mixed in CH_2Cl_2 at −20°C and then rapidly cooled to −60°C after 10 min. 2-Octanol 4 was added followed 15 min later by TEA. Work up gave 2-octanone (41%), 4 (59%) and 2-octyl methylthiomethyl ether (0.3%), a result that closely checked the result obtained when the temperature was maintained at −20°C throughout, except that the yield of the methylthiomethyl ether was very low in this experiment. At 0 to −5°C, destruction of "activated" DMSO

occurs and yields of the carbonyls were only 10 and 40% from **4** and **6**, respectively, with more extensive alcohol recovery. This system was not investigated further although use of a larger excess of DMSO–AcCl would be expected to improve yields of carbonyls. As this example shows, it is important to choose the reaction temperature at which the rate of formation of "activated" DMSO **1** is reasonably high, and at the same time the stability of **1** (which thermally undergoes the Pummerer rearrangement) is adequate.

Benzoyl chloride is the only carboxylic acid halide used previously for "activation" of DMSO. However, we found that yields of carbonyls from the oxidation of the less hindered alcohols **3** and **4** under Albright's conditions were only fair to poor (*ca.* 30%). Benzoyl chloride was between acetyl chloride and acetyl bromide at $-60°C$ in CH_2Cl_2 in reactivity with DMSO. With nearly stoichiometric amounts of DMSO and PhCOCl, an approximately 25% yield of carbonyl was obtained from **3**, but the yield of the benzoate ester and recovery of **3** were substantial (75% in total). At $-20°C$ in CH_2Cl_2, however, yields of aldehyde were poor (30%), and the product distribution closely resembled that obtained from the Albright's procedure utilizing HMPA–CH_2Cl_2 at $-20°C$ (see Table 1). It was assumed that insufficient "activated" DMSO had formed at $-60°C$. Thus, we correctly anticipated that use of a larger excess (200%) of DMSO–PhCOCl would improve the yield of the aldehyde; yields of aldehyde as high as 97% were obtained. Since the least hindered alcohol **3** gave the aldehyde in excellent yields at $-60°C$ with an excess of reagent, it was expected that the more hindered alcohols would be efficiently oxidized as well. Pivaloyl chloride was ineffective in "activating" DMSO at $-60°C$.

Oxalyl chloride [$(COCl)_2$] reacts vigorously with DMSO even at $-60°C$; it was found to be the most effective DMSO "activator" examined by us. As Table 2 shows, yields of carbonyls are essentially quantitative (>95%) at $-60°C$, irrespective of steric factors in the alcohols. Especially significant is the minor dependence of carbonyl yield on the reaction temperature up to $-20°C$ (97% yield of 2-octanone from **4** reduced to 94% at $-20°C$, for example). Above that temperature, with a stoichiometric quantity of DMSO–$(COCl)_2$, yields dropped; at 0°C an 86% yield of 2-octanone was obtained (recovery of **4**, 11%; 2-octyl methylthiomethyl ether, 1.4%), and at 20°C, 95% of alcohol **4** was recovered (no octanone). The intermediate **1** clearly is not stable above 0°C; vigorous evolution of hydrogen chloride occurred when DMSO is mixed with $(COCl)_2$ in CH_2Cl_2 at 20°C. If an excess (100%) of DMSO–$(COCl)_2$ to the alcohol is used, however, operation at 0°C is possible (96% yield of 2-octanone). The yield of 2-octyl methyl thiomethyl ether remains low (0.8–1.4%), regardless of reaction temperature. It is also notable that the reaction can be conducted in more polar media; oxidation of **3** and **4** with DMSO–$(COCl)_2$ in DMSO–CH_2Cl_2 (1:1.3) at $-30°C$ gave the carbonyls in 90 and 93% yields, respectively. In addition, unlike DMSO–PhCOCl, DMSO–$(COCl)_2$ oxidized **3** and **4** to the carbonyls in excellent yields (92 and 96%, respectively) in HMPA–CH_2Cl_2 (1:1.3) at -10 to $-20°C$ under Albright's reaction conditions.[6] Oxidation with DMSO–$(COCl)_2$ was complete within 15 min regardless of the reaction conditions.

Only one of the acyl halide functions of $(COCl)_2$ undergoes displacement by DMSO at $-60°C$ in CH_2Cl_2. With a molar ratio of $(COCl)_2$: DMSO : 2-octanol **4** of 1:2:2, only a 50% yield of carbonyl was obtained; 50% of **4** was recovered. When the molar ratio was 1:2:1 or 1:1:1, the yield of 2-octanone was >95%. That only one chlorine is displaced was confirmed by the observation that the exothermic reaction between DMSO and $(COCl)_2$ ceased after 1 mol of DMSO had been added to 1 mol of $(COCl)_2$ in CH_2Cl_2 at $-60°C$.

Benzhydrol was converted to benzophenone (98%) by DMSO–$(COCl)_2$ at $-60°C$ in CH_2Cl_2, but at $-20°C$ for 30 min, however, only 34% conversion to the ketone was obtained. The remainder of the alcohol was accounted for as benzhydryl chloride. In a similar experiment at $-20°C$, addition of TEA was omitted and the benzhydrol reaction mixture was allowed to warm to room temperature; the chloride was isolated as the exclusive product (100%). This result is consistent with the frequently observed thermal instability of dimethylalkoxysulfonium salt **2** from benzylic and allylic alcohols,[3,7,8] and suggests (although it does not prove) that the alkoxysulfonium salt intermediate is **7** and not **8**.[9,c]

7 **8**

To explore the range of utility of DMSO–$(COCl)_2$, various alcohols were oxidized similarly with DMSO–$(COCl)_2$ in CH_2Cl_2 at $-60°C$. As Table 3 shows, carbonyls were obtained in high to quantitative yields (GLC) from primary, secondary, hindered, benzylic and allylic alcohols. Carbonyls could also be readily isolated in excellent yields. 2-Cyclohexen-1-ol gave a slightly lower yield (87% by GLC) of carbonyl than expected. Even more exceptional was the oxidation of 2-phenylethanol which gave only a 23% yield of phenylacetaldehyde (unoxidized alcohol, 39%; 2-phenylethyl methylthiomethyl ether, 3% and other unidentified products), while the closely related alcohols (benzyl alcohol and 3-phenyl-1-propanol) were oxidized cleanly to carbonyls. We have no explanation for this anomalous result.

Steric effect of alcohols. As amply supported by the results shown above and our previous paper,[4] increasing the bulk of the substituent(s) attached to the carbinol group results in increased yields of carbonyls, regardless of the "activators" used for DMSO or of the oxidation conditions. In most cases, yields of carbonyls increased in the order: **3** < **4** < **5** or **6**. Some systems (DMS–NCS in CH_2Cl_2, DMSO–PhCOCl (Table 1), DMSO–Ac_2O) were less sensitive to steric factors in the alcohols, and virtually identical yields of carbonyls were obtained from **3** and **4**. Even in such cases, the more hindered alcohol (**5** or **6**) was converted to carbonyl in distinctly higher yields. In oxidations with DMS–NCS in toluene, DMSO–Py·SO_3 or DMSO–$(COCl)_2$, yields of carbonyl were so high (>90%) even from the least hindered alcohol **3** that such a steric effect could not be observed.

In addition to the frequently encountered by-product, alkyl methylthiomethyl ether, recovery of alcohol was

[c] Likewise, the reaction of cinnamyl alcohol with DMSO–TsCl (at *ca.* 5°C) or DMSO–$SOCl_2$ (at $-60°C$) resulted in the isolation of cinnamyl chloride in quantitative yields when addition of TEA was omitted.

Table 3. Oxidation of alcohols to carbonyls by DMSO–$(COCl)_2$ in CH_2Cl_2 at −60°C[a]

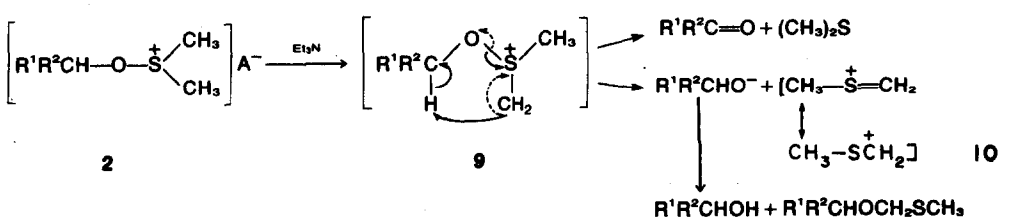
Alcohol	Yield of Carbonyl, %: GLC[b]	Isolation (mp, °C)
n-Decanol (3)	97	94 (as 2,4-DNP)(98-100)
n-Octanol	95	93 (as 2,4-DNP)(100-101.5)
1-Adamantylmethanol	--	99 (as 2,4-DNP)(225-227, dec)
Phenethyl Alcohol[c]	23	--
3-Phenyl-1-propanol	--	96 (as 2,4-DNP)(152-153)
2-Octanol (4)	98	--
Cyclopentanol	99	93 (as 2,4-DNP)(144-145)
Cyclohexanol	97	94 (as 2,4-DNP)(159-161)
Cyclododecanol[d]	97	100 (58-61.5[e])
2-Methylcyclohexanol (cis & trans)	100	100
3,3-Dimethyl-2-butanol	100	76 (bp, 106-107)[f]
Norborneol	97	--
Isoborneol (5)	99	98 (170-176)
trans-2-Hexen-1-ol	100	94 (as 2,4-DNP)(138-142)
Cinnamyl Alcohol	97	100
2-Cyclohexen-1-ol	87	80 (as 2,4-DNP)(157-162)
Benzyl Alcohol	100	98 (as 2,4-DNP)(239-241)
sec-Phenethyl Alcohol	99	100
Benzhydrol	98	100 (46-50)[g]

[a]See Experimental for details. [b]Same as footnote a in Table 1. Approximately 0-1% of unoxidized alcohol and 0-2% of alkyl methylthiomethyl ether were also detected in some cases. [c]Recovered alcohol, 39% and phenethyl methylthiomethyl ether, 3%. [d]Reaction time 0.5 hr. [e]Mp 61-62°C, after one recrystallization from methanol. [f]Isolated by fractional distillation. [g]Mp 48-50°C, after one recrystallization from ethanol.

almost always found.[d] There are two explanations for recovery of alcohol: (1) not all of the alcohol was converted to its alkoxysulfonium salt **2** before addition of TEA, or (2) all the alcohol was converted to the salt **2** but alcohol was partly "reformed" from **2** after addition of TEA. In most cases it seems clear that **3** and **4** are "reformed" by the latter process since (1) under similar conditions, the hindered alcohol **5** or **6** is quantitatively converted to carbonyl; (2) prolonged reaction did not reduce the amount of recovered **3** or **4**, or increase the yields of the other products (carbonyl and methylthiomethyl ether); (3) it was confirmed on several occasions that recovery of alcohol could not be reduced or eliminated by employing a larger excess of "activated" DMSO; and (4) such recovery of alcohol could be reduced or increased by using a different amine base rather than TEA, as described later. Roughly speaking, a parallelism exists between methylthiomethyl ether formation and alcohol recovery; when ether formation is substantial, recovery of alcohol is also relatively large.[e] In all cases, however, as yields of carbonyls increase

[d]Alcohol was occasionally recovered as its ester. For example, in oxidations with DMSO–TFAA, trifluoroacetates of **3** or **4** were found (Table 1). Alcohol can be formed from the reaction of the alkoxysulfonium salt **2** with TEA, and is further converted to its trifluoroacetate by reaction with methylthiomethyl trifluoroacetate in the presence of TEA.[3]

[e]In oxidations with DMSO–Ac_2O, yields of methylthiomethyl ethers from **3** and **4** were as high as *ca.* 60%, while these alcohols were recovered in only trace amounts (Table 1). These reactions are carried out under such conditions that alcohol formed from the reaction of the salt **2** with the *in situ* base (acetate anion) can be once again attacked by "activated" DMSO followed by base; all of the starting alcohol is eventually consumed, and only carbonyl and methylthiomethyl ether are found. A similar argument may be made for the oxidations with DMSO–Py·SO_3.



Scheme 2.

with increasing steric hindrance, yields of thioethers and alcohols decrease.

Reaction pathways. The mechanism of formation of carbonyls from the reaction of the alkoxysulfonium salt **2** with base is well established.[2] Base removes proton from the methyl group of the salt **2** to form the methylcarbanion or ylide **9** which then collapses to carbonyl and DMS by an intramolecular hydrogen transfer (solid arrows). However, ylide **9** may also collapse to methyl methylenesulfonium ion **10** and alkoxide ion (dotted arrows). Alkoxide ion can either remove proton from the system to form alcohol, or recombine with **10** to form alkyl methylthiomethyl ether (Scheme 2).[f]

The steric effect of alcohols is best rationalized by assuming that base (TEA) has two sites it can attack (Scheme 3): it either removes a proton from the methyl group of the salt **2** (Path a), or attacks the sulfur atom (Path b). Carbonyl is the exclusive product arising via Path a and methylthiomethyl ether and alcohol are formed via Path b.

Ample precedent exists in the literature for nucleophilic attack on sulfonium sulfur by primary[12] and secondary[13] amines; we have extended the concept to include tertiary amines. As R^1 and R^2 increase in size, Path b becomes less operative as the sulfur atom becomes less accessible to nucleophilic attack by the amine; proton removal to yield carbonyl (Path a) becomes the predominant process.[g]

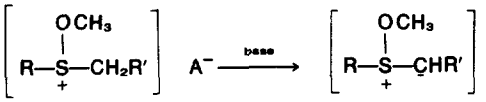
Steric effect of bases. Among amines used for basification in the oxidation, TEA has been the base of choice in many cases. If Path b, Scheme 3, is a feasible reaction pathway, then increasing the size of the alkyl groups in the amine should also result in preferential proton removal (Path a) rather than attack on sulfur (Path b). In fact, during the continued study on the oxidation of alcohols with DMSO–TFAA, it was recently found by us,[14] that basification with diisopropylethylamine (DIPEA), a more hindered base than TEA, always gives higher yields of carbonyls than with TEA. To establish the generality of the steric effect of amine bases, oxidations of **3** with DMSO–methanesulfonic anhydride and DMSO–cyanuric chloride, and of **4** with DMS–NCS in CH_2Cl_2, were conducted using tertiary amines of similar base strength but with different steric hindrance [DIPEA, diethylcyclohexylamine (DECA), TEA, diethylmethylamine (DEMA)]. Results are shown in Table 4.

As expected, oxidation of **3** with DMSO–methanesulfonic anhydride gave a better yield of carbonyl when basification was conducted with the more hindered amines. Thus, the yield of carbonyl from the least hindered alcohol **3** was improved from 68 to 94% by using DIPEA in place of TEA. In contrast, both the yield of methylthiomethyl ether and recovery of alcohol declined with increasing steric hindrance in base. In addition, the ratio, alcohol recovery/methylthiomethyl ether, remained approximately constant regardless of choice of base. These facts are consistent with Scheme 3. A similar effect of base was observed in the oxidation of **3** with DMSO–cyanuric chloride. The oxidation of **4** with DMS–NCS in CH_2Cl_2 was rather insensitive to size of amine, and basification with DIPEA, DECA and TEA gave virtually identical results. This system was also relatively insensitive to small changes in steric hindrance in the alcohols (Table 1).

Other factors that can affect the site of attack on dimethylalkoxysulfonium salts **2** by base (Path a or Path b) include solvent polarity, temperature at which the alkoxysulfonium salt **2** reacts with base, nature of the counter anion (A^-) of the alkoxysulfonium salt, nature of the acidic leaving product (EOH, Scheme 1) formed from "activated" DMSO **1** after displacement by alcohol, and base strength.

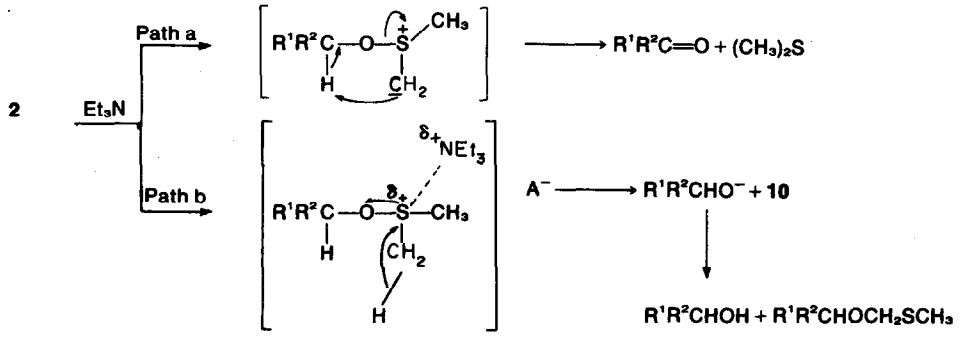
Assessment of "activators". Oxalyl chloride is the most generally satisfactory DMSO "activator" we have examined, based on yields of carbonyls, speed and ease of manipulation, general applicability to virtually all types of alcohols, cost per equivalent, relative insensitivity to reaction time and temperature, and high reactivity between −60° and −20°C in various solvents without side reactions. The DMSO–SO_3–pyridine oxidation system of Parikh and Doering[6] and the dimethyl sulfide-*N*-chlorosuccinimide (toluene solvent) system of Corey and Kim[7] also give consistently high yields of carbonyls with a wide range of alcohols. The former method is operative at room temperature and the latter, at 0° to −25°C.

[f] Johnson and Phillips[10] have investigated the reaction of the alkoxysulfonium salts of type **11** (R = phenyl or isopropyl; R′ = H) with acetate ion as base, and concluded that thioacetals are formed only via attack of base on the sulfur of **11**, not via ylide of the type **12**; **12** can collapse only to carbonyl and sulfide (analogous to Scheme 3). They have also shown that thioacetals, however, can be formed via ylide **12** when R′ is a substituent that can contribute to stabilization of a carbonium ion[11] (analogous to Scheme 2).



11 **12**

[g] Occasional reports suggest that oxidation of extremely hindered alcohols results in recovery of alcohols. Perhaps they are so hindered that they have no access to "activated" DMSO to form alkoxysulfonium salts **2**.[2]



Scheme 3.

Table 4. Steric effect of the amine bases on the oxidation of alcohols with "activated" DMSO

Oxidant	Alcohol (ROH)	Base	Products, %[a] >C=O	ROH	$ROCH_2SCH_3$	Ratio: $ROH/ROCH_2SCH_3$
DMSO-$(CH_3SO_2)_2O$[b]	3	Diethylmethylamine (DEMA)	45	28	24	1.2
		Triethylamine (TEA)	68	18	13	1.4
		Diethylcyclohexylamine (DECA)	92	3.1	2.5	1.2
		Diisopropylethylamine (DIPEA)	94	2.1	1.7	1.2
DMSO-Cyanuric Chloride[c]	3	DEMA	47	32	18	1.8
		TEA	80	11	7.9	1.4
		DECA	93	4.9	2.6	1.9
		DIPEA	95	2.8	1.3	2.2
DMS-NCS[d] (in CH_2Cl_2)	4	DEMA	55-56	28-31	15-16	1.8-2.1
		TEA	59	23	18	1.3
		DECA	60	23	17	1.4
		DIPEA	60	23	18	1.3

[a] Same as footnote a in Table 1. [b] n-Decanol (3) (8 mmol), $(CH_3SO_2)_2O$ (16 mmol), DMSO (6 ml), base (36-37 mmol) and HMPA (20 ml); reaction temperature, -15°C; reaction time, 0.5 hr. The reaction was carried out according to Albright's procedure.[8] [c] n-Decanol (3) (8 mmol), cyanuric chloride (9 mmol), DMSO (6 ml), base (36-37 mmol) and CH_2Cl_2-HMPA (13 + 10 ml); reaction temperature, -15°C; reaction time, 0.5 hr. The reaction was carried out according to Albright's procedure.[8] [d] 2-Octanol (4) (8 mmol), NCS (12 mmol), DMS (18 mmol), base (14 mmol) and CH_2Cl_2 (50 ml); reaction temperature, -20°C; reaction time, 1.5 hr, according to the procedure by Corey and Kim.[7]

Thionyl chloride and acetyl bromide are also good "activators", the former being generally superior. All the other reagents studied are less efficient and do not convert primary alcohols to aldehydes in greater than about 50–80% yields, unless a large excess of DMSO and activators are used.

TFAA, described by us,[3] is also a highly effective DMSO "activator" but it is not quite in the same class as oxalyl chloride, particularly for the oxidation of primary alcohols, and TFAA is costly and toxic.

An important factor in correctly evaluating the efficiency of DMSO "activators" is the determination of the optimum reaction temperature for formation of the initial intermediate (Scheme 1). If the temperature is too low, the DMSO displacement reaction to obtain the necessary intermediate may not occur and yields of carbonyls will be low. If the temperature is too high (generally above about −20°C) Pummerer rearrangement of the intermediate occurs and again yields of carbonyls will be poor. The reaction of alcohols with "activated" DMSO is extremely fast irrespective of reaction temperature, at least down to −70°C.

Modified procedure for alkyl methylthiomethyl ether formation. Authentic alkyl methylthiomethyl ethers were required as standards for GLC analyses of crude oxidation mixtures. They were prepared using a modification of the DMSO–TEA–alcohol procedure described in our previous publication.[3] Addition of an excess of boron fluoride etherate to the reaction mixture at −50°C prior to addition of TEA[h] results in substantially increased yields of methylthiomethyl ethers (60–70% by GLC). The function of boron fluoride is not clear, but very recently Pojar and Angyal[15] showed that the deliberate addition of acetic acid to a DMSO–acetic anhydride–alcohol reaction mixture at room temperature followed by basification with aqueous sodium carbonate also gave increased yields of methylthiomethyl ethers. No explanation was given for their results. In the DMSO–TFAA–alcohol procedure, however, we find that addition of excess trifluoroacetic acid has only a modest effect on the yield of the ethers (with *n*-decanol, the yield increases from 14 to only 23%). The increased yield with the use of boron trifluoride cannot be due to increased polarity of the reaction medium as we find only minor changes in yield when excess DMSO or HMPA is used to dilute the solvent, CH_2Cl_2.

[h] Omission of TEA results in virtually no methylthiomethyl ether formation.

EXPERIMENTAL

M.ps were determined with a Thomas–Hoover apparatus and are uncorrected. IR spectra were obtained using a Pye Unicam SP 1000 Spectrometer. NMR spectra were obtained with Varian A-60A or XL-100 spectrometers using CCl_4 or $CDCl_3$ as solvent and Me_4Si as internal standard. Gas chromatographic analyses were conducted in most cases with a 6 ft × 0.25 in. column with 10% FFAP on Chromosorb P. Occasionally 12% SE-30 on Chromosorb W or Apiezon L on Anakrom were used; He was the carrier gas. DMSO was distilled from calcium hydride under reduced pressure and the heart cut was stored over Linde Molecular Sieves Type 3A in a sealed brown bottle. Purest grades of alcohols were purchased and purified if necessary; purity exceeded 99% in most cases. Liquid acid halides for "activation" of DMSO were freshly distilled before use; solid "activators" were used as received. Amines were distilled from calcium hydride and the heart cuts were retained and stored over Linde Molecular Sieves Type 4A. Authentic samples of carbonyls and alkyl halides were purchased. Other reference compounds such as esters were prepared by known methods. An improved procedure for preparing alkyl methylthiomethyl ethers is described

below. Solvents were thoroughly dried and purified by conventional methods. Glassware was dried in an oven just before use.

Comparative studies of "activators" (*Table* 1). The reactions were conducted addording to the procedures described by the original workers, and already referred to, using the amounts of reactants and solvents specified in the footnotes to the table.

Oxidations with DMSO "activated" by inorganic and acid halides (*Table* 2)

General Procedure. Oxidation of 2-*Octanol* 4 *with DMSO–*$(COCl)_2$. Oxalyl chloride (11 mmol) dissolved in CH_2Cl_2 (25 ml) was placed in a 4-neck flask equipped with a stirrer, thermometer and two pressure-equalizing addition funnels protected by drying tubes. One addition funnel contained DMSO (24 mmol) dissolved in CH_2Cl_2 (5 ml) and the other 2-octanol 4 (10 mmol) dissolved in CH_2Cl_2 (10 ml). The contents of the flask were cooled to −60°C and the DMSO solution was added dropwise in *ca.* 5 min. Stirring was continued at −60°C for 10 min followed by addition of the alcohol solution in *ca.* 5 min. The reaction mixture was stirred for 15 min, and TEA (50 mmol) was added in *ca.* 5 min with stirring at −60°C. The cooling bath was removed and water (*ca.* 30 ml) was added at room temperature. Stirring was continued for *ca.* 10 min and the organic layer was separated. The aqueous phase was re-extracted with CH_2Cl_2 (20 ml), and the organic layers were combined and evaporated to 25 ml. Composition of the oxidation mixture was determined by GLC (10% FFAP; column temperature, 120°C). Yields are shown in Table 2. Isolation of 2-octanone is described below. In the oxidation of 4 at higher temperatures (see text), DMSO was allowed to react with $(COCl)_2$ for only 3 min before addition of 4 to minimize thermal decomposition of "activated" DMSO (the instantaneous reaction of the two reactants was indicated by its exothermicity even at −60°C). In the oxidation of *n*-decanol 3 with DMSO(42 mmol)–PhCOCl(34 mmol) at −60°C, DMSO was allowed to react with PhCOCl for 30 min instead of the usual 10 min before addition of 3.

Oxidation of alcohols to carbonyls by DMSO–$(COCl)_2$ (*Table* 3). The oxidation of structurally varied alcohols with DMSO–$(COCl)_2$ in CH_2Cl_2 at −60°C was performed as described for 2-octanol 4. After GLC analysis the CH_2Cl_2 solution was either (1) washed successively with dilute HCl, water, dilute Na_2CO_3 and water, and evaporated to dryness to give a slightly colored crude carbonyl without further purification; IR and NMR spectra of the product were identical with those of authentic samples of the carbonyl, or (2) condensed to a smaller volume (*ca.* 10 ml) and treated with 0.1 M 2,4-dinitrophenylhydrazine (110–120 ml).[3] Precipitation of the hydrazone (2,4-DNP) was usually immediate but an additional 30 min was allowed to elapse before filtration. Melting points of crude derivatives agreed well with literature values.

Effect of amine bases on carbonyl yields (*Table* 4). Oxidation of *n*-decanol 3 or 2-octanol 4 with "activated" DMSO was conducted according to the procedures described by the original workers, using amines differing in steric hindrance.

Improved preparation of alkyl methylthiomethyl ethers. To a stirred solution of DMSO (21 mmol) in CH_2Cl_2 (15 ml) cooled to −55 to −60°C, a solution of TFAA (18 mmol) in CH_2Cl_2 (5 ml) was added in *ca.* 5 min. The heterogeneous reaction mixture was stirred for an additional 10 min followed by dropwise addition of a solution of an alcohol (15 mmol) in CH_2Cl_2 (10–15 ml). After 10 min, $BF_3{\cdot}Et_2O$ (5 ml, 41 mmol) was added dropwise and the reaction mixture was stirred for 30 min at or below −55°C. TEA (13 ml, 95 mmol) was added dropwise (10–15 min) and the reaction mixture was then allowed to warm to room temp. Petroleum ether (250 ml) was added and the organic phase was washed successively with water, dil. HCl, water, dil. Na_2CO_3, and water. The organic layer was evaporated to about one-fifth its volume and analyzed for methylthiomethyl ether yield by GLC (10% FFAP on Chromosorb W). Thiothers were isolated by complete evaporation of solvent under vacuum from the dried (Na_2SO_4) solution followed by fractional distillation under vacuum. Methylthiomethyl ethers thus obtained had purities in excess of 96% as estimated by GLC. Table 5 summarizes the results.

Spectral data for methylthiomethyl ethers. NMR and IR spectral assignments for *n*-decyl, 2-octyl and cyclohexyl methylthiomethyl ethers were reported in our previous paper.[3]

Phenethyl methylthiomethyl ether.[16] NMR ($CDCl_3$) δ 2.00 (s, 3 H), 2.89 (t, 2 H), 3.74 (t, 2 H), 4.59 (s, 2 H), and 7.0–7.5 (m, 5 H). IR (liquid film) 680, 700, 730, 750, 1080–1100 (s), 1305, 1390, 1437, 1459, 1500, 1609 and 2840–3220 cm^{-1}.

Trans-2-*Hexenyl methylthiomethyl ether.* NMR ($CDCl_3$) δ 0.89 (t, 3 H), 1.2–2.4 (m, 4 H), 2.14 (s, 3 H), 4.03 (d, 2 H), 4.52 (s, 2 H) and 5.3–6.0 (m, 2 H). IR (liquid film) 683, 732, 973, 1067 (s), 1100, 1303, 1384, 1440, 1475, 1672 and 2840–3020 cm^{-1}.

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Table 5. Alkyl methylthiomethyl ethers, $ROCH_2SCH_3$

R	BP, °C (mmHg)	Yield, % GLC	Yield, % Isolated
n-Decyl	90–91 (0.25)	65[a]	40
2-Octyl	99–101 (7.5)	70	50
Cyclohexyl	100 (10)	60	50
Phenethyl	103 (2)	60	50
trans-2-Hexenyl	83 (6)	60	40

[a]Other products identified: n-decanal, 10%; n-decanol, 6%. When $BF_3{\cdot}Et_2O$ was omitted, the yield of thioether dropped to about 14%; yield of n-decanal, 50%.

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