Dimethyl Sulfoxide–Trifluoroacetic Anhydride: a New Reagent for Oxidation of Alcohols to Carbonyls[1]

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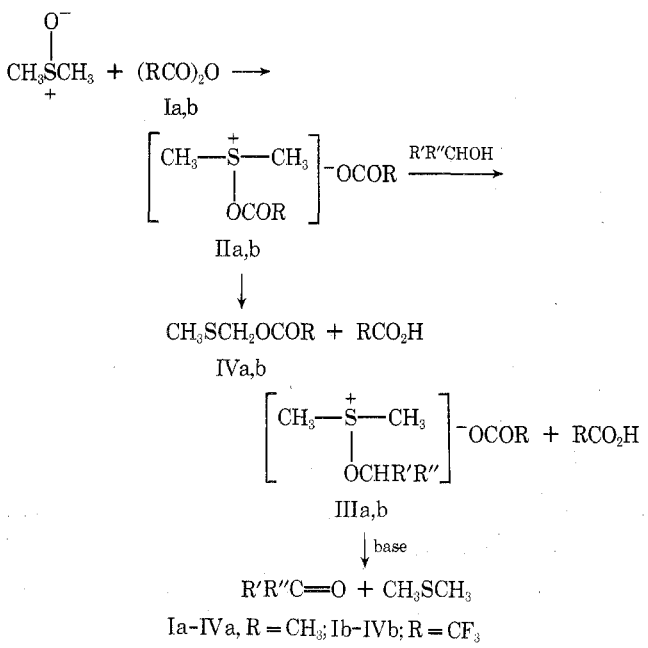
Trifluoroacetoxydimethylsulfonium trifluoroacetate prepared in situ from dimethyl sulfoxide (Me_2SO) and trifluoroacetic anhydride (TFAA) below −50 °C in methylene chloride reacts rapidly with alcohols to give alkoxydimethylsulfonium trifluoroacetates and trifluoroacetic acid. Addition of triethylamine (TEA) to the alkoxysulfonium salts gives carbonyl compounds, alkyl trifluoroacetates, and alkyl methylthiomethyl ethers in varying and controllable amounts depending on the structure of the alcohols and reaction conditions. Yields of carbonyls increase in the order primary < secondary < allylic and benzylic alcohols. Yields of carbonyls from primary and secondary alcohols are highest when TEA is added to the alkoxysulfonium salts at room temperature rather than below −50 °C, or when larger amounts of solvent are employed. Under optimum conditions, yields of carbonyls are in the range of 60% from primary alcohols, 80–85% from secondary alcohols, and 80–100% from benzylic and certain allylic alcohols. Under appropriate conditions, selective oxidation of primary and secondary hydroxyl groups can be effected in the presence of allylic or benzylic hydroxyl groups. Reaction pathways to account for product distribution are proposed.

Acetic anhydride and certain other anhydrides in combination with dimethyl sulfoxide (Me_2SO) can oxidize alcohols to carbonyls under mild conditions.[2] The oxidation has been interpreted as follows (Scheme I). Acetic anhydride reacts slowly with Me_2SO at room temperature to give acetoxydimethylsulfonium acetate (IIa), which on reaction with alcohols is converted to alkoxydimethylsulfonium acetates (IIIa);[2] reaction of the alkoxysulfonium salts (IIIa) with base yields carbonyl compounds and dimethyl sulfide. The intermediate salts (IIa) undergo the Pummerer rearrangement to acetoxymethyl methyl sulfide (IVa) at room temperature.[3] Thus, oxidations conducted at or above room temperature can be inefficient; in addition, other side reactions can occur that lead to extensive formation of methylthiomethyl ethers (V) and esters (VIa,b).

Scheme I



$CH_3SCH_2OCHR'R''$ (V)

$R'R''CHOCOCR$ (VIa, R = CH_3; VIb, R = CF_3)

Although a Me_2SO–trifluoroacetic anhydride (TFAA) reagent should be similarly useful for alcohol oxidations, it has been reported to be ineffective because the presumed intermediate, trifluoroacetoxydimethylsulfonium trifluoroacetate (IIb), is unstable at room temperature and rearranges rapidly to trifluoroacetoxymethyl methyl sulfide (IVb), thereby precluding nucleophilic attack by alcohols to give the necessary alkoxydimethylsulfonium trifluoroacetates (IIIb).[4] (We have confirmed the formation of IVb by NMR.[5]) Furthermore, the reaction of Me_2SO with TFAA can be violent and explosive. Recently, however, we showed that reaction of Me_2SO with TFAA to form IIb can be easily controlled at low temperatures and the intermediate is stable at or below −30 °C.[5] A new method of synthesis of iminosulfuranes was achieved by allowing IIb to react with amines.[5] As an outgrowth of that study, we have investigated the reaction of Me_2SO–TFAA with alcohols, and this paper reports the results.

Results and Discussion

Procedure A. In a typical run, TFAA in methylene chloride is added dropwise with stirring to a cold (<−50 °C) solution of Me_2SO (excess) in dry CH_2Cl_2 over ca. 10 min. During the addition a white precipitate, presumed to be the salt IIb, forms. After 10 min, a solution of benzyl alcohol, for example, in CH_2Cl_2 is added dropwise to the mixture at that temperature over ca. 10 min. After the mixture is stirred for 30 min at or below −50 °C, triethylamine (TEA) is added dropwise below −50 °C. The mixture is then allowed to warm to room temperature and analyzed by gas chromatography. Benzaldehyde (84%) and benzyl trifluoroacetate (11%) are the sole products formed. The aldehyde can also be isolated as its 2,4-dinitrophenylhydrazone (80%).

The product distribution is not appreciably changed by (a) using nearly equimolar quantities of Me_2SO (12.1 mmol), TFAA (11.6 mmol), and benzyl alcohol (11.1 mol) (PhCHO, 81%; $PhCH_2OCOCF_3$, 11%); (b) blanketing the reaction with argon instead of dry air (86, 10%); (c) using toluene instead of CH_2Cl_2 (87, 8%); or (d) having a small amount of added trifluoroacetic acid (TFA, 3.0 mmol) present before adding the alcohol (85, 8%). Relatively large amounts of TFA in the system cause a decrease in yields of carbonyls; this effect was studied only with cyclohexanol and 2-octanol (Table I, runs 4 and 6). One equivalent of TFA, a reaction product, is not deleterious. If benzyl alcohol is added to Me_2SO before the TFAA, yields of aldehyde and ester are 78 and 20%, respectively. This indicates that, surprisingly, the reaction of TFAA with Me_2SO is faster than with the alcohol, a reaction that proceeds violently at

Table I. Procedure A:[a] Oxidation of Alcohols to Carbonyls with Me_2SO–TFAA at −50 °C

Run no.	Alcohols	Registry no.	Products, %[b] Carbonyls	Alkyl trifluoroacetates (VIb)	Methylthiomethyl ethers (V)
1	*n*-Decanol	112-30-1	37[c]	35	21
2	Phenethyl alcohol	60-12-8	32	34	≤9
3	Cyclohexanol	108-93-0	65[d]	22	12
4	Cyclohexanol[e]		47	39	13
5	2-Octanol	123-96-6	67	21	10
6	2-Octanol[f]		49	18	19
7	Cyclododecanol	1724-39-6	72[g]	15	N.E.[h]
8	Cyclododecanol[i]		79[j]	8	N.E.[h]
9	2-Cyclohexenol	822-67-3	82[k]	8	N.E.[h]
10	Cinnamyl alcohol	104-54-1	83[l]	14	N.E.[h]
11	Benzyl alcohol	100-51-6	84[m]	11	~0
12	*sec*-Phenethyl alcohol	98-85-1	97[n]	1	N.E.[h]
13	Benzhydrol	91-01-0	98+	0	N.E.[h]

[a] Alcohol (10 mmol), Me_2SO (20 mmol), TFAA (15 mmol), TEA (4 ml), and CH_2Cl_2 (20–25 ml); all steps at or below −50 °C (see Experimental Section). No detailed effort was made to optimize yields of carbonyls. [b] Yields estimated by GLC unless otherwise stated. The starting alcohols are entirely consumed or present in trace amounts after the reaction is complete. [c] As the 2,4-dinitrophenylhydrazone (2,4-D), mp 100–101 °C (lit.[7] mp 104 °C). [d] As the 2,4-D, mp 156–158 °C (lit.[8] mp 162 °C). [e] TFA (25 mmol) was added before TFAA. [f] TFA (27 mmol) was added before TFAA. [g] 71% as the 2,4-D, mp 147–149.5 °C (lit.[9] mp 152–153 °C). [h] Not examined. [i] A larger amount of CH_2Cl_2 (ca. 50 ml) was employed. [j] 79% as the 2,4-D, mp 147–149.5 °C. [k] 75% as the 2,4-D, mp 157–162 °C (lit.[10] mp 163 °C). [l] 81% as the 2,4-D, mp 245–250 °C (lit.[11] mp 248 °C). [m] 80% as the 2,4-D, mp 240–241 °C (lit.[12] mp 238–239 °C). [n] 94% as the 2,4-D, mp 245–247 °C (lit.[8] mp 249 °C).

Table II. Procedure B:[a] Oxidation of Alcohols to Carbonyls with Me_2SO–TFAA at Higher Temperatures

Run no.	Alcohols	Temp, °C	Products, %[b] Carbonyls	Alkyl trifluoroacetates (VIb)	Methylthiomethyl ethers (V)
14	*n*-Decanol	−20 to −26	28[c]	54	10
15	*n*-Decanol	5–10	0	98	N.E.[d]
16	Benzyl alcohol	−20 to −23	56	44	N.E.[d]
17	Benzyl alcohol	5–10	0	97	N.E.[d]
17a	*sec*-Phenethyl alcohol	5–10	0	>97	N.E.[d]

[a] Alcohol (10 mmol), Me_2SO (20 mmol), TFAA (15 mmol), TEA (4 ml), and CH_2Cl_2 (20–25 ml). Procedure A, Table I, except that reaction temperatures throughout are as listed until addition of TEA is complete. The mixtures were stirred for 10–15 min, instead of 30 min as in procedure A, after addition of the alcohols but before addition of TEA. [b] Yields estimated by GLC unless otherwise stated. [c] As the 2,4-D, mp 97–99.5 °C (lit.[7] mp 104 °C). [d] Not examined.

room temperature to form the ester.[6] Table I summarizes the results obtained with procedure A in the oxidation of benzyl and other alcohols to carbonyls.

Besides the anticipated carbonyls (32–98%) and trifluoroacetate esters (VIb, 0–35%), methylthiomethyl ethers (V, 0–21%) are obtained from primary and secondary alcohols.

In general, yields of carbonyls from alcohols increase in the order primary alcohols < secondary alcohols < allylic and benzylic alcohols while those of trifluoroacetates (VIb) and methylthiomethyl ethers (V) increase in the reverse order.

Procedure B. In procedure A, reaction temperatures are not permitted to exceed −50 °C until after addition of TEA. Procedure B explores the effect of higher reaction temperatures on products obtained.

As Table II shows, a considerable decrease in yields of *n*-decanal and benzaldehyde is observed when the reactions are carried out at −20 to −26 °C (compare run 14, Table II, with run 1, Table I, and run 16 with run 11); yields of trifluoroacetates are markedly increased. When the reactions are conducted at even higher temperatures (5–10 °C), no aldehydes are formed; trifluoroacetates are obtained quantitatively.

The alteration in products occurs because the required intermediate salts (IIb) undergo facile Pummerer rearrangement to IVb at the higher temperatures before conversion to alkoxysulfonium salts (IIIb), the necessary precursors to carbonyls. As we show below under procedure C, many of the salts (IIIb) are stable at the temperatures used here and if they had formed they would have been converted to carbonyls on reaction with TEA. The main source of trifluoroacetate esters is the TEA-assisted alcoholysis of IVb by the alcohols added after salts IIb have been converted to IVb by Pummerer rearrangement (see Experimental Section). Esters do not form in significant quantities at these higher reaction temperatures until TEA is added.

Procedure C. This procedure was studied to assess the thermal stability of alkoxysulfonium salts in the reaction system and to gain insight into the origin of the trifluoroacetates. Procedure C parallels procedure A exactly until addition of alcohol is complete (preparation of salts IIIb at low temperature). The mixture is then allowed to warm to room temperature (ca. 30–40 min) during which period it becomes homogeneous. After an additional 30 min at room temperature, TEA is added dropwise and the reaction mixture is analyzed by GLC. Results are summarized in Table III.

With typical primary and secondary alcohols (runs 18 and 19, Table III), yields of carbonyls increase significantly compared with those from procedure A (Table I). The increase in yield of carbonyls from primary alcohols is larger than that from secondary alcohols; currently we have no explanation for this. In sharp contrast, allylic and benzylic alcohols (except benzyl alcohol) (runs 23–27) yield no carbonyls and only trifluoroacetates in excellent yields (93–98%). The decrease in yield of benzaldehyde from 84% (run 11, Table I) to 40% (run 25, Table III), although substan-

Table III. Procedure C:[a] Oxidation of Alcohols to Carbonyls with Me_2SO–TFAA. Room Temperature Addition of TEA

Run no.	Alcohols	Products, %[b] Carbonyls	Alkyl trifluoroacetates (VIb)	Methylthiomethyl ethers (V)
18	1-Decanol	56[c]	24	8
19	Phenethyl alcohol	50[d]	27	≤11
20	Cyclohexanol	73[e]	17	5
21	2-Octanol	78	14	5
22	Cyclododecanol[f]	86[g]	8	N.E.[h]
23	2-Cyclohexenol	0	93	N.E.[h]
24	Cinnamyl alcohol	0	98	N.E.[h]
25	Benzyl alcohol	42	58	N.E.[h]
26	*sec*-Phenethyl alcohol	0	96	N.E.[h]
27	Benzhydrol	0	96	N.E.[h]

[a] Alcohol (10 mmol), Me_2SO (20 mmol), TFAA (15 mmol), and CH_2Cl_2 (20–25 ml) at −50 °C following procedure A, then addition of TEA (4 ml) after 30 min at room temperature. [b] Yields estimated by GLC unless otherwise stated. [c] As the 2,4-D, mp 100–102 °C (lit.[7] mp 104 °C). [d] Over 45% yield as the 2,4-D, mp 109–113 °C (lit.[11] mp 110 °C). [e] As the 2,4-D, mp 156–158 °C (lit.[8] mp 162 °C). [f] 50 ml of CH_2Cl_2 was used. [g] 85% as the 2,4-D, mp 146.5–149.5 °C (lit.[9] mp 152–153 °C). [h] Not examined.

tial, is not so drastic (run 25) and the yield of trifluoroacetate increases to almost 60% from 11%.

Solutions of alkoxysulfonium salts (IIIb) prepared from the Me_2SO–TFAA intermediate (IIb) and cyclohexanol or cyclododecanol are stable for at least 2 days at room temperature if moisture is excluded. Addition of TEA at that time yields cyclohexanone (73%) and cyclododecanone (86%), respectively, and the corresponding trifluoroacetates (17 and 8%) (see runs 20 and 22, Table III, for comparison). In contrast, the salt from benzyl alcohol and IIb gives considerably less benzaldehyde (42%) and considerably more trifluoroacetate (58%) even when TEA is added only 30 min after the reaction solution has been maintained at room temperature (run 25; compare with run 11, Table I). If 7 h is allowed to elapse at room temperature before TEA is added the yield of benzaldehyde drops to 5% and that of trifluoroacetate increases to 89%; after 14 h no aldehyde is obtained and the yield of ester is 99%.

Even more striking, *sec*-phenethyl alcohol (run 26) yields no ketone and exclusively trifluoroacetate if only 30 min elapses at room temperature before TEA is added to the salt IIIb (compare results with run 12, Table I, in which all steps are conducted at or below −50 °C). If TEA is added just as the solution of IIIb reaches room temperature the yield of ketone is 10% and that of ester 90%. In contrast, addition of TEA at 0–5 °C (about 20 min is required for the reaction to warm up from −50 to 5 °C) still provides a substantial yield of acetophenone (87% at 0–5 °C vs. 97% at −50 °C) and little *sec*-phenethyl trifluoroacetate (10%).

We conclude that (a) alkoxysulfonium salts (IIIb) from primary and secondary alcohols are relatively stable at room temperature in the reaction media with little decomposition or rearrangement for at least 2 days, (b) the corresponding salts from allylic and benzylic alcohols are considerably more reactive and, with the exception of IIIb from benzyl alcohol, are converted at room temperature exclusively to trifluoroacetates (benzyl alcohol is converted only partially to the ester under the conditions of Table III), and (c) IIIb from *sec*-phenethyl alcohol is converted to ester at a significant rate above 0 °C.

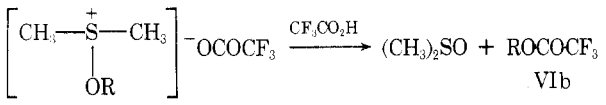
By-Product Formation. The formation of trifluoroacetates in virtually every run in yields as high as 98%, depending on the reaction conditions and the alcohol used, cannot be explained simply as the reaction between TFAA and alcohols. Even at −50 °C, TFAA reacts almost instantaneously and quantitatively with Me_2SO which is always present in some excess to yield a precipitate of IIb, thereby effectively eliminating the anhydride from the reaction medium *before* alcohols are added. Several other pathways may be invoked to account for ester formation; to obtain information bearing on that point we first ascertained whether esters are formed before or after the addition of TEA using selected model systems.

The cyclohexyloxydimethylsulfonium salt (IIIb) was prepared in solution from cyclohexanol (10 mmol) and IIb at −50 °C and the stirred mixture was allowed to warm to room temperature (procedure C, Table III). The homogeneous solution was divided into three parts. TEA was added to one part yielding cyclohexanone (72%), the trifluoroacetate (17%), and methylthiomethyl cyclohexyl ether (6%), results in excellent agreement with our earlier result (run 20). The second part was diluted with ether (to increase its volume and ease of handling) and the solution was shaken with excess aqueous sodium carbonate solution. The organic phase was analyzed by GLC: cyclohexanol (94%), methylthiomethyl cyclohexyl ether (V, 7%), cyclohexyl trifluoroacetate (VIb, 0%), cyclohexanone (0%). An authentic sample of the ester prepared from TFAA and cyclohexanol is stable to hydrolysis by aqueous sodium carbonate at room temperature; thus VIb cannot be the source of cyclohexanol. To the third part, authentic ester was added and the solution was treated with aqueous sodium carbonate as above. Analysis by GLC gave trifluoroacetate (100% recovery) as well as cyclohexanol (93%) and methylthiomethyl cyclohexyl ether. We conclude that cyclohexyl trifluoroacetate (as well as cyclohexanone) is formed only *after* TEA is added.

In contrast, *sec*-phenethyloxydimethylsulfonium salt (IIIb), worked up at room temperature in the same three-part manner as its cyclohexyloxy analogue, yielded *sec*-phenethyl trifluoroacetate (95–97%) exclusively on treatment with TEA or with aqueous sodium carbonate solution. No alcohol could be detected. The third part was evaporated to dryness under vacuum; the ir spectrum of the residue showed the presence of trifluoroacetate. We conclude that *sec*-phenethyl trifluoroacetate is completely formed at room temperature from IIIb *before* addition of TEA. The yield of ester can be held to less than 1%, however, by adding TEA at −50 °C (run 12, Table I).

Interestingly, when 1-decanol, benzyl alcohol, or *sec*-phenethyl alcohol is added to Me_2SO–TFAA that has been allowed to reach room temperature, and therefore contains no IIb but is a mixture of IVb and TFA, followed by TEA, an almost quantitative yield of trifluoroacetate esters is obtained (Table II). With 1-decanol or benzyl alcohol we did not ascertain whether the esters form before or after addition of TEA. With *sec*-phenethyl alcohol, however, the ester is formed only *after* addition of TEA (contrast with preceding paragraph). This was confirmed by working up a portion of the reaction mixture with aqueous sodium carbonate (no TEA used) and demonstrating that the organic components isolated consisted exclusively of ester (10%) and free alcohol (90%).

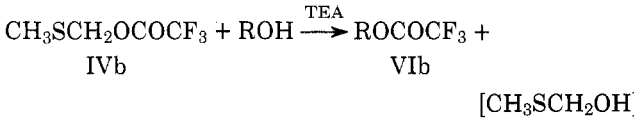
These apparently anomalous results are readily interpreted: when reaction temperatures are maintained at or below −50 °C up to the point where alcohol is to be added (procedures A and C) little or no Pummerer rearrangement to IVb has yet occurred and alkoxysulfonium salts (IIIb) form cleanly in all cases. The salts (IIIb) from benzylic and allylic alcohols, however, can more easily undergo solvolytic attack by trifluoroacetic acid (TFA) (1 mol of TFA is al-



IIIb, R = allylic or benzylic group

ways present per mole of salt) *at room temperature* than salts from primary and secondary alcohols, with displacement of Me_2SO. Thus even before TEA is added VIb form in excellent yields at the higher temperatures in the allylic and benzylic salt cases in which cations form more readily (by solvolysis).

In contrast, when reaction temperatures are at or above −30 °C and especially above 0 °C during the mixing of Me_2SO with TFAA (procedure B), the Pummerer rearrangement product (IVb) forms largely or exclusively.[5] Addition of an alcohol at that point cannot yield an alkoxysulfonium salt (IIIb) since intermediate IIb has been converted to IVb. The formation of esters VIb now occurs only *after* addition of TEA in a base-catalyzed alcoholysis reaction from IVb and alcohols, a process we have demonstrated experimentally with *sec*-phenethyl alcohol and 1-decanol and confirmed by model experiments with authentic IVb.



IVb VIb

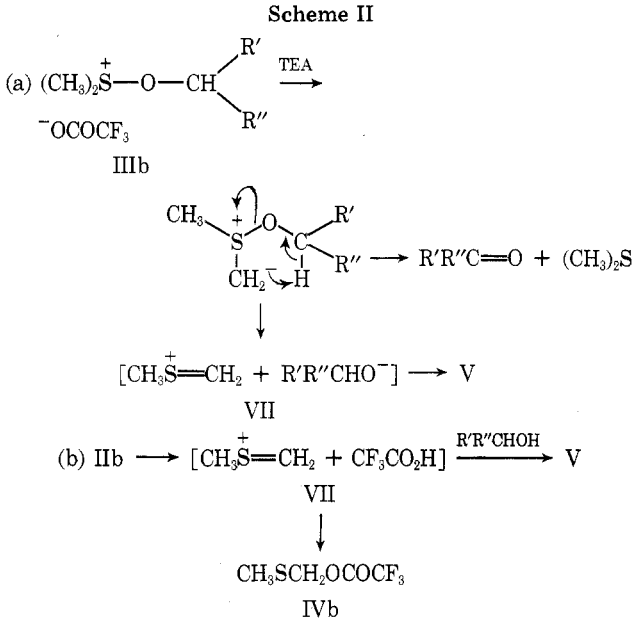
$[CH_3SCH_2OH]$

We have isolated IVb (65% yield) and have shown that it forms less than 1% of ester in methylene chloride solution on reaction with *sec*-phenethyl alcohol for 2 h at 5–10 °C with TEA *absent* (99% recovery of unreacted alcohol). In contrast, if TEA is *present* a 96% yield of ester is obtained within 10 min (4% recovery of unreacted alcohol). Similar results are obtained with 1-decanol; in the *absence* of TEA at least 96% of the alcohol remains unreacted whereas when TEA is *present* the alcohol is completely converted to the trifluoroacetate in less than 1 min.

Since TFA is also present in the reaction media before TEA is added, the possibility must be considered that VIb form, at least in part, by the direct esterification of alcohols in those cases where they are not able to be converted to alkoxysulfonium salts (IIIb) because the Pummerer rearrangement has already intervened (conditions of Table II) and has depleted the system of the required intermediate (IIb). Solutions of *sec*-phenethyl alcohol (10 mmol) and excess TFA (16 mmol) in methylene chloride at room temperature require 18 h to achieve 85% esterification, a reaction time far in excess of that employed in the oxidation reactions. If excess TEA is also present with TFA, direct esterification is completely inhibited. These results confirm that esterification observed in runs 14–17a, Table II, requires the presence of both IVb and TEA.

The formation of by-product methylthiomethyl ethers (V) from primary and secondary alcohols in Me_2SO–anhydride oxidation reactions of alcohols is well known.[2,4,13-15] We have shown that these by-products are present before or after addition of TEA to IIIb. Their formation can be readily explained (Scheme II): (a) treatment of alkoxydimethylsulfonium salts (IIIb) with TEA, the reaction leading to the desired carbonyls, can also yield V by a competitive Pummerer-type rearrangement and (b) the initial intermediate IIb before addition of TEA may also undergo a Pummerer rearrangement in which the reactive cationic intermediate, $CH_3S^+{=}CH_2$ (VII), is trapped partly by alcohol and partly by TFA thus explaining the formation of IVb along with V. Pathway b seems very unlikely as alcohol is rapidly converted to IIIb which does not reconvert to IIb and alcohol.

Scheme II



Solvent Effects. The use of larger volumes of solvent was investigated to try to eliminate or reduce the quantities of undesirable by-products and direct the reaction to carbonyl formation exclusively. Yields of cyclohexanone (83%), cyclododecanone (79%), and 1-decanal (63%) are usually significantly increased when a four- to fivefold increase in volume of methylene chloride is employed (procedures A and C). In contrast, yields of benzaldehyde (84%, procedure A, run 11) and 2-cyclohexenone (82%, procedure A, run 9) remain unchanged.

Also, yields of carbonyls are reported to increase at the expense of methylthiomethyl ethers as solvent polarity decreases.[15-17] We therefore prepared the *n*-decyloxydimethylsulfonium salt (IIIb) at low temperatures following procedure C (CH_2Cl_2, 20 ml). Addition of dry hexane (80 ml) followed by addition of TEA resulted in no change in yield of 1-decanal (64 vs. 63%) over that with a larger volume of neat methylene chloride but the yield in both cases was slightly higher than in more concentrated solutions (56%).

Primary and secondary alcohols are best converted to carbonyls (60–85%) with the Me_2SO–TFAA reagent by procedure C using larger quantities of solvent; allylic and benzylic alcohols are converted to carbonyls (80–100%) only by procedure A and the volume of solvent has no observable effect on yields.

Selective Oxidation. By procedure C primary and secondary alcohols can be oxidized to carbonyls in good yields but allylic and benzylic alcohols are converted to trifluoroacetates. It should, therefore, be possible to oxidize primary and/or secondary hydroxyl groups in molecules that also contain allylic or benzylic hydroxyl groups. These latter types are usually more easily oxidized by conventional methods. Furthermore, double bonds are inert toward the Me_2SO–TFAA reagent, a situation that does not prevail with conventional oxidants.

In preliminary studies, an equimolar mixture of cyclododecanol and *sec*-phenethyl alcohol was oxidized following procedure C. After addition of TEA, GLC analysis showed no acetophenone formation and exclusive conversion of the benzylic alcohol to its trifluoroacetate (97%). Addition of 2,4-dinitrophenylhydrazone reagent to the reaction mixture gave yellow crystals of the 2,4-dinitrophenylhydrazone of cyclododecanone (84%), mp 148–149.5 °C (lit.[9] 152–153 °C). A similar oxidation of an equimolar mixture of 1-decanol and 2-cyclohexenol yielded no cyclohexenone; only 2-

cyclohexenyl trifluoroacetate (97%) and 1-decanal (61%, as its 2,4-dinitrophenylhydrazone, mp 99–101 °C) were formed. The areas of selective oxidation and the oxidation of sterically hindered alcohols are being actively pursued.

Experimental Section[18,19]

General Procedures. Procedure A. Methylene chloride (10 ml) and Me_2SO (20 mmol) were placed in a 50-ml three-neck flask equipped with a magnetic stirrer, thermometer, addition funnel, and drying tube. The contents of the flask were cooled below −50 °C with a dry ice–acetone bath and TFAA (15 mmol) in CH_2Cl_2 (ca. 5 ml) was added dropwise to the stirred cold solution in ca. 10 min (exothermic). During the addition, a white precipitate of the salt IIb formed. After 10 min at −50 °C, a solution of an alcohol (10 mmol) in CH_2Cl_2 (5–10 ml) was added dropwise in ca. 10 min to the mixture maintained at −50 °C. The reaction of the alcohol with IIb was exothermic. The mixture was stirred at −50 °C for 30 min, followed by addition of TEA (4 ml) dropwise in ca. 10 min. The contents of the flask were maintained at or below −50 °C until addition of TEA was complete. The cooling bath was removed and the reaction mixture was allowed to warm up to room temperature (ca. 40 min) and then subjected to GLC analysis. When a larger quantity of CH_2Cl_2 was required to dissolve the alcohol (ca. 15 ml for benzhydrol and cyclododecanol), the total volume of CH_2Cl_2 was adjusted to ca. 25 ml by reducing the volume of CH_2Cl_2 used in the Me_2SO–TFAA reaction. Table I summarizes the results.

Procedure B. This procedure was identical with procedure A except that the temperature of the reaction mixture was kept at −20 to −26 °C (with a dry ice–acetone bath) or 5–10 °C (with an ice–water bath) until addition of TEA was complete. Also, TEA was added to the mixture after it was stirred for only 10–15 min, instead of 30 min as in procedure A after addition of the alcohol. Table II summarizes the results.

Procedure C. This procedure was identical with procedure A through the addition of alcohol. Stirring was continued for an additional 5 min at or below −50 °C, the dry ice–acetone bath was removed, and the stirred mixture was allowed to warm up to room temperature (ca. 40 min). The reaction mixture became homogeneous on warming. The solution was stirred for an additional 30 min at room temperature followed by dropwise addition of TEA (4 ml) in ca. 10 min at room temperature. Table III summarizes the results.

Product Separation, Identification, and Yields. Carbonyls. Carbonyls were quantitatively determined by GLC and/or isolation as their 2,4-dinitrophenylhydrazones. (Authentic carbonyls were used for standardizing GLC analysis.) A 2,4-dinitrophenylhydrazine (2,4-D) solution was prepared by dissolving 2,4-D (0.1 mol) in a mixture of sulfuric acid (100 ml) and water (150 ml) followed by dilution with ethanol (ca. 750 ml) to a total volume of 1 l. A 10–20% excess of the 2,4-D solution was added at room temperature to the reaction mixtures after TEA addition. When reactions were conducted with larger quantities of CH_2Cl_2 than 20–25 ml, the reaction mixtures were concentrated to ca. 30 ml before addition of the 2,4-D solution. Precipitation of the hydrazones was usually immediate but an additional 30 min was allowed to elapse before they were filtered. Yields of carbonyls by the hydrazone method agreed well with those obtained by GLC but were often a few percent lower.

Trifluoroacetates. Detection and determination of yields were done by GLC. Authentic esters were prepared simply by mixing the alcohols with a slight excess of TFAA in CH_2Cl_2 at room temperature. After the exothermic reaction ceased, the mixtures were left at room temperature until the alcohols were completely converted to esters. The solvent, excess TFAA, and TFA were evaporated under vacuum; the residues consisted of pure esters. The trifluoroacetates had typical carbonyl absorption bands around 1790 cm^{-1}. Carbonyls could be cleanly separated by GLC from the corresponding trifluoroacetates, with the exception of 2-octanone and 2-octyl trifluoroacetate, which had virtually the same retention times on both GLC columns used.[18]

Oxidation of 2-Octanol and Product Determination (Runs 5, 6, 21). Attempts to isolate 2-octanone as its 2,4-D were unsatisfactory. Since 2-octanone and 2-octyl trifluoroacetate could not be separated on the available GLC columns, determination of yields was accomplished by a combination of GLC and ir. An aliquot of the oxidation reaction mixture was dissolved in ether and the ether solution was washed successively with dilute sulfuric acid, aqueous potassium carbonate, and water and dried over anhydrous sodium sulfate. Solvent evaporation yielded a residue which was purified by preparative GLC (SE-30 column, 135 °C).[18] The ir spectrum of the fraction collected showed that it consisted only of ketone and trifluoroacetate; composition was estimated by comparing the absorbance at 1725 cm^{-1} (ketone) with that at 1789 cm^{-1} (trifluoroacetate), using authentic samples for reference. Total yield of ketone plus ester was obtained by GLC.

Methylthiomethyl Ethers. An aliquot of the reaction mixture was diluted with ether, washed successively with dilute sulfuric acid, aqueous sodium or potassium carbonates, and water, and dried over anhydrous sodium sulfate. The residue was chromatographed on a silica gel column. Elution with petroleum ether first yielded a mixture of carbonyl and trifluoroacetate. Further elution with the same solvent or with petroleum ether–benzene (9:1 v/v) yielded pure methylthiomethyl ethers as colorless liquids. Their purities were checked by GLC.

***n*-Decyl Methylthiomethyl Ether.** NMR δ 4.75 (s, 2 H), 3.63 (t, 2 H), 2.17 (s, 3 H), and 0.8–1.9 (m, 19 H); ir 675, 721, 1090 (s), 1195, 1257, 1298, 1373, 1435, 1466, 2845, and 2920 cm^{-1}.

Phenethyl Methylthiomethyl Ether. The ether separated by column chromatography was contaminated by a small quantity of unknown impurity.

NMR δ 7.0–7.4 (m), 4.49 (s), 3.68 (t), 2.82 (t), and 1.93 (s). (Integration is not shown because resonances of the impurity were superimposed on some of the resonances listed.) Ir 702, 1099 (s), 1152, 1209, 1390, 1443, 1461, 1504, 1554, 1611, 1697 (impurity), 2880, 2930, and 3040 cm^{-1}.

Cyclohexyl Methylthiomethyl Ether. NMR δ 4.53 (s, 2 H), 3.3–3.8 (m, 1 H), 2.07 (s, 3 H), and 1.0–2.0 (m, 10 H); ir 677, 727, 889, 935, 1072 (s), 1260, 1301, 1379, 1450, 2860, and 2940 cm^{-1}.

2-Octyl Methylthiomethyl Ether. NMR δ 4.53 (s, 2 H), 3.4–4.0 (m, 1 H), 2.17 (s, 3 H), 0.7–1.6 (m, 13 H), and 1.09 (d, 2 H); ir 684, 733, 1063 (s), 1126, 1306, 1384, 1474, 2870, and 2940 cm^{-1}. Yields of ethers were estimated by GLC using the isolated ethers as reference samples. Retention times of the ethers were much longer than those of the corresponding ketones or trifluoroacetates. No evidence could be obtained for the formation of benzyl methylthiomethyl ether (run 11); no GLC peaks were obtained other than those of benzaldehyde and benzyl trifluoroacetate.

Preparation of Pummerer Rearrangement Product (IVb). To a cooled, stirred solution (ca. −30 °C) of Me_2SO (4.0 ml, 56 mmol) in CH_2Cl_2 (10 ml), TFAA (7.3 ml, 51 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature at which point GLC analysis indicated that IVb was virtually the exclusive product. The reaction mixture was dissolved in *n*-pentane (100 ml) and washed with aqueous $NaHCO_3$ to remove TFA. The organic layer was separated, dried (Na_2SO_4), and fractionally distilled to yield IVb (5.8 g, 65%) as a colorless liquid: bp 59° (86 Torr); NMR δ 2.29 (s, 2 H), 5.37 (s, 3 H); ir 696, 725, 777, 896, 1142, 1180, 1230, 1305, 1375, 1435, 1790, and 2930–3000 cm^{-1}.

Reaction of Pummerer Rearrangement Product (IVb) with *sec*-Phenethyl Alcohol. A. TEA Absent. To a solution of IVb (1.3 g, 7.5 mmol) in CH_2Cl_2 (5 ml) a solution of *sec*-phenethyl alcohol (0.60 g, 4.9 mmol) in CH_2Cl_2 (5 ml) was added at 5–10 °C over 1 min. The mixture was maintained at 10 °C for 2 h with exclusion of moisture. Product analysis by GLC showed that the mixture consisted almost exclusively of unreacted alcohol (99%) contaminated with trifluoroacetate (ca. 1%).

B. TEA Present. This was conducted as in A but TEA (2.5 ml) was added to the mixture at 5–10 °C over 2 min. The reaction mixture was then stirred at 10 °C with periodic analysis by GLC. Within 10 min after addition of TEA, *sec*-phenethyl trifluoroacetate had formed in 96% yield. Some unreacted alcohol (4%) was still present in the reaction mixture even after 2 h.

Virtually identical results were obtained with 1-decanol. In the absence of TEA, the product ratio after 1 h was trifluoroacetate (4%) and unreacted alcohol (96%). In the presence of TEA, only trifluoroacetate was obtained after 1 min; the alcohol was completely consumed.

Reaction of *sec*-Phenethyl Alcohol with TFA. To a solution of the alcohol (10 mmol) in CH_2Cl_2 (25 ml), TFA (16 mmol) in CH_2Cl_2 (5 ml) was added in one portion at room temperature. The reaction solution was analyzed periodically by GLC. *sec*-Phenethyl trifluoroacetate was obtained in 12, 24, 39, 60, and 85% yield after 10, 30, 60, 150, and 1080 min, respectively. A duplicate of this reaction which also contained TEA (4 ml) showed only trace formation of ester; recovery of starting alcohol was almost quantitative.

Selective Oxidations. A. Equimolar Mixture of Cyclododecanol and *sec*-Phenethyl Alcohol (Procedure C). The reaction was carried out according to procedure C except that the following

quantities of solvent and reactants were used: cyclododecanol (10 mmol), *sec*-phenethyl alcohol (10 mmol), Me_2SO (24 mmol), TFAA (22 mmol), TEA (8 ml), and CH_2Cl_2 (ca. 100 ml). GLC of the reaction mixture showed that the products consisted of *sec*-phenethyl trifluoroacetate (97%), acetophenone (0%), cyclododecyl trifluoroacetate (5%), and cyclododecanone (84%). The reaction mixture was concentrated to ca. 40 ml under vacuum at room temperature, and excess 0.1 M 2,4-D-solution (120 ml) was added. A yellow precipitate of cyclododecanone 2,4-D, mp 148–149.5 °C (lit.[9] 152–153 °C), was obtained (85%).

B. Equimolar Mixture of 1-Decanol and 2-Cyclohexenol (Procedure C). The reaction was carried out according to procedure C as in A above except that the following quantities of solvent and reactants were used: 1-decanol (10 mmol), 2-cyclohexenol (10 mmol), Me_2SO (24 mmol), TFAA (21 mmol), TEA (8 ml), and CH_2Cl_2 (ca. 105 ml). GLC analysis of the reaction mixture showed that the products consisted of 2-cyclohexenyl trifluoroacetate (97%), 2-cyclohexenone (0%), *n*-decyl trifluoroacetate (26%), and 1-decanal (61%). The reaction mixture was concentrated to ca. 30 ml, and excess 0.1 M 2,4-D (120 ml) was added to the concentrate. Yellow crystals of 1-decanal 2,4-D, mp 99–101 °C (lit.[7] 104 °C), were obtained (61%).

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Registry No.—Ib, 407-25-0; IIb, 57738-66-6; IVb, 57738-67-7; V (R′ = H; R″ = C_9H_{19}), 57738-68-8; V (R′ = H; R″ = Ph-CH_2), 57738-69-9; V (R′, R″ = $-(CH_2)_5-$), 19182-88-8; V (R′ = CH_3; R″ = C_6H_{13}), 57738-70-2; Me_2SO, 67-68-5; TEA, 121-44-8.

References and Notes

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(18) Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were obtained as liquid films using a Pye Unicam SP 1000 infrared spectrophotometer. NMR spectra were obtained with a Varian A-60A spectrometer, using CCl_4 as solvent and Me_4Si as internal standard. Gas chromatographic analyses were performed on a Wilkens Aerograph Model A-700 using a 12 ft × 0.25 in. column packed with 20% dilauryl phthalate on Chromosorb P or a 10 ft × 0.25 in. column packed with 20% SE-30 on Chromosorb W with He as carrier gas. Me_2SO was distilled from calcium hydride under atmospheric pressure, and the heart cut was stored over Linde molecular sieve, Type 3A, in a brown bottle sealed with a serum cap. TFAA, containing ca. 0.1% of TFA as an impurity, was used as purchased. Triethylamine (TEA) was stored over NaOH pellets overnight, then distilled and stored over Linde molecular sieve, Type 3A, in a sealed bottle. Methylene chloride was distilled from phosphorus pentoxide and kept over Linde molecular sieve, Type 3A, in a sealed bottle. Cyclohexenol, 3-butyn-2-ol, and allyl alcohol were distilled under nitrogen before use. Other alcohols were used as received; their purity was >96%.
(19) **Note Added in Proof.** Benzoin yields benzil (88%, procedure A), ethyl lactate yields ethyl pyruvate (70%, A; 78%, C), and 2-chlorocyclohexane yields 2-chlorocyclohexanone (67%, A; 63%, C).

Friedel–Crafts Thioacylation with Ethoxycarbonyl Isothiocyanate. A One-Step Synthesis of Aromatic Thioamides

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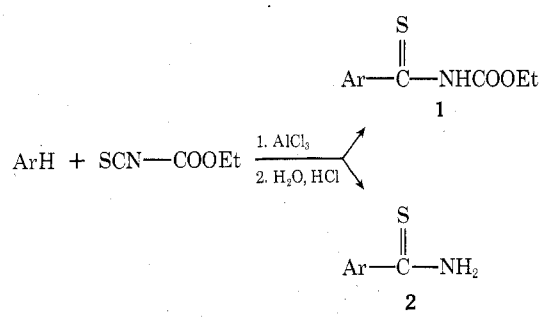
The aluminum chloride catalyzed reaction of ethoxycarbonyl isothiocyanate with aromatic compounds yields *N*-ethoxycarbonylthioamides when equimolar amounts of the two reagents are allowed to react in dichloromethane at 0–3 °C. The same reaction, however, leads directly to the corresponding thioamides when run in an excess of the aromatic compound as solvent, at room or higher temperature.

In the course of an investigation of cyclization reactions of *N*-ethoxycarbonylthioamides, the need arose for a method of preparation of such derivatives of aromatic thioamides. A Friedel–Crafts thioacylation using ethoxycarbonyl isothiocyanate appeared to be the most straightforward approach to these compounds, in view of the known, aluminum chloride catalyzed reactions of isocyanates[1] and isothiocyanates[2] with aromatic compounds.

As anticipated, it has been found that ethoxycarbonyl isothiocyanate reacts readily with various aromatic compounds in the presence of anhydrous aluminum chloride. However, depending upon the conditions, the reaction yields either the expected *N*-ethoxycarbonylthioamide (1), or the thioamide itself (2). The latter result is closely analogous to the formation of benzamide when benzene reacts with chlorosulfonyl isocyanate in the presence of $AlCl_3$.[3] Typically, the reaction of equimolar quantities of reagents,



dissolved in CH_2Cl_2, run in the presence of 1.5 or 2.0 molar equiv of $AlCl_3$, at 0–3 °C, yields the original adduct 1. On the other hand, when a large excess of the aromatic reagent is used as solvent and the reaction is run with 2.0 or more mol of $AlCl_3$ at ambient or higher temperature, addition of