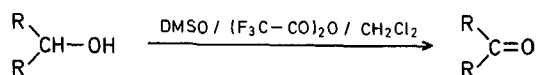


### Further Studies on the Oxidation of Alcohols to Carbonyl Compounds by Dimethyl Sulfoxide/Trifluoroacetic Anhydride<sup>1a</sup>

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In previous papers<sup>2,3</sup>, we showed that dimethyl sulfoxide/trifluoroacetic anhydride in dichloromethane is an efficient reaction system for the oxidation of model saturated primary and secondary aliphatic alcohols, cyclohexanol(s), and cyclododecanol, and allylic and benzylic alcohols, via intermediate dimethylalkoxysulfonium salts, to carbonyl compounds in high yields (60–95%). We have now extended the dimethyl sulfoxide/trifluoroacetic anhydride system focusing on (a) solvent effects; (b) steric factors in the amines used for basification on the yields of carbonyls; (c) oxidation of small ring, allylic, homoallylic, acetylenic and steroidal alcohols; and (d) improvements in the oxidation procedures.



**Solvent Effects.** In our earlier work, dichloromethane was used as the solvent almost exclusively. Two diverse model alcohols (cyclopentanol and *trans*-2-hexen-1-ol) were studied with five other solvents, and the results were compared with those obtained with the same volume of dichloromethane. Dichloromethane and toluene are clearly the best solvents examined; they give essentially identical yields of carbonyl compounds (70–90%) and by-products (10–30%) at  $-65^\circ$ . Ether is not as good, but acceptable yields of carbonyl compounds (60–65%) are obtained. Acetone, acetonitrile, and hexane/dichloromethane (9:1 v/v) give moderately good yields of cyclopentanone (40–60%), but are only fair (30–40%) in the oxidation of the allylic alcohol. With acetonitrile, a temperature range of  $-30$  to  $-40^\circ$  is satisfactory.

**Effect of Steric Factors in Bases on Carbonyl Yields.** Previous studies on the oxidation of sterically hindered alcohols<sup>3</sup> showed that higher yields of carbonyl compounds were obtained with increasing steric hindrance. We surmised that steric factors in the bases might also affect the yields of carbonyl compounds. Supporting data for this hypothesis were obtained using other nitrogen bases and two alkali metal hydroxides in the oxidation of cyclopentanol as a model.

Triethylamine is an efficient tertiary amine customarily employed in the basification step of the oxidation process; with triethylamine the yield of cyclopentanone is 85–89% (control experiment). When a highly hindered, bulkier amine (diisopropylethylamine) is used, however, the yield of carbonyl compound increases to about 94% and by-products are almost totally suppressed, especially methylthiomethyl ethers.

Substantial differences in yields of cyclopentanone are also observed with the secondary amines, di-*n*-propylamine and diisopropylamine (50 and 80%, respectively). With 2,2,6,6-tetramethylpiperidine, a highly hindered secondary amine, the yield of cyclopentanone exceeds 90% again. The basicity of these three amines is virtually the same: the pK<sub>a</sub>'s of their conjugate acids are 11.0, 11.1 and 11.1 respectively<sup>4</sup>.

The increases in yields of carbonyl compounds are nicely correlated with increases in steric hindrance.

2,6-Lutidine and 1,8-bis[*dimethylamino*]naphthalene (Proton Sponge<sup>®</sup>) are much less satisfactory (30–50% yields) than triethylamine. Potassium and sodium hydroxide are totally unsatisfactory (0–2% yields).

To confirm the tentative conclusion that the highly hindered amine, diisopropylethylamine, is generally superior to triethylamine, we compared the yields of carbonyl compounds and by-products from five different classes of alcohols; results are summarized in Table 1. The most striking increases in yields of carbonyl compounds are obtained with primary and small ring alcohols. The yields of aldehydes increase from about 55% to 80% (Table 1); diisopropylethylamine is the base of choice with primary and small ring alcohols.

*Oxidation of Small Ring and Related Alcohols.* No literature describing "activated" dimethyl sulfoxide as the oxidant for these systems could be found. Table 2 summarizes our results with dimethyl sulfoxide/trifluoroacetic anhydride/triethylamine (diisopropylethylamine was used with cyclopropylmethanol). Yields of carbonyl compounds are generally good to excellent (60–100%) utilizing either procedure C or MC; about 10–20% of trifluoroacetates are also formed.

1-Cyclopropylethanol, in contrast, is converted almost entirely to its trifluoroacetate (86%) utilizing procedure MC; only 2% of carbonyl compound is obtained. In procedure MC, basification is conducted only after the reaction mixture (dimethyl sulfoxide/trifluoroacetic anhydride/alcohol) at  $-60^{\circ}$  has been allowed to warm to room temperature. Addition of triethylamine at  $-60^{\circ}$  (MA), however, results in a satisfactory (60–75%) yield of cyclopropyl methyl ketone.

**Table 1.** Comparison of Yields of Carbonyl Compounds Using Triethylamine (TEA) and Diisopropylethylamine (DIPEA) for Basification

Alcohol	Base	Procedure <sup>b</sup>	Carbonyl compound	Recovered Alcohol	Yield [%] <sup>a</sup>		
					Methylthiomethyl Ether	Trifluoroacetate	Isolation of 2,4-DNP <sup>d</sup>
Cyclopropylmethanol	TEA	C	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	58
	DIPEA	MC	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	78
Cyclopentanol	TEA	C	85	5	4	8	81
	TEA	MC	89	7	4	3	—
	DIPEA	MC	94	1	<0.5	4	89
2,2-Dimethyl-1-propanol (neopentyl alcohol)	TEA <sup>3</sup>	C	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	81
	DIPEA	MC	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	87
<i>n</i> -Decanol	TEA <sup>2</sup>	C	56	— <sup>c</sup>	8	24	56
	DIPEA	MC	81	5	1	10	81
<i>trans</i> -2-Hexen-1-ol	TEA	MA	69	21	8	5	63
	DIPEA	MA	84	3	1	16	79

<sup>a</sup> Determined by G.L.C. using a 6ft × 0.25 in column packed with 10% FFAP on Chromosorb P, 80–100 mesh, for ketone, alcohol and thioether, and a similar column packed with 10% Apiezon on Chromosorb P for trifluoroacetate. Helium was the carrier gas.

<sup>b</sup> See Experimental Section.

<sup>c</sup> Not determined by G.L.C.

<sup>d</sup> Yield of carbonyl compound calculated from the weight of the isolated 2,4-dinitrophenylhydrazone.

**Table 2.** Oxidation of Small Ring and Related Alcohols to Carbonyl Compounds with Dimethyl Sulfoxide/Trifluoroacetic Anhydride/Triethylamine

Alcohol	Procedure <sup>b</sup>	Carbonyl compound	Yield [%] <sup>a</sup>	
			Trifluoroacetate	Isolation of 2,4-DNP <sup>d</sup>
Cyclopropylmethanol	C	— <sup>c</sup>	— <sup>c</sup>	58
	MC <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	78
1-Cyclopropylethanol	MA	63	19	65
	MC	2	86	— <sup>c</sup>
Cyclobutanol	MC	95	— <sup>c</sup>	81
Cyclopentanol	C	85	8	81
<i>trans</i> -2-Methylcyclopentanol	MC	— <sup>c</sup>	— <sup>c</sup>	83
Cyclohexanol <sup>2</sup>	C	73	17	— <sup>c</sup>
4- <i>t</i> -Butylcyclohexanol <sup>3</sup>	C	88	— <sup>c</sup>	88
2,6-Dimethylcyclohexanol <sup>3</sup>	C	100 <sup>f</sup>	— <sup>c</sup>	76
<i>trans</i> -2-Methylcyclohexanol <sup>3</sup>	C	80	— <sup>c</sup>	71
2-Adamantanol <sup>3</sup>	C	96	— <sup>c</sup>	95
1-Adamantanemethanol <sup>3</sup>	C	— <sup>c</sup>	— <sup>c</sup>	86

<sup>a</sup> Determined by G.L.C.; see footnote a, Table 1. Methylthiomethyl ethers were not determined except in the oxidation of 1-cyclopropylethanol (7%), cyclopentanol (4%), cyclohexanol (5%). Recovered alcohols were not determined except with cyclopropylmethylcarbinol (10–13%).

<sup>b</sup> See Experimental Section.

<sup>c</sup> DIPEA used for basification.

<sup>d</sup> Yield of carbonyl compound calculated from the weight of isolated 2,4-dinitrophenylhydrazone.

<sup>e</sup> Not determined.

<sup>f</sup> An 89% yield of ketone was isolated.

**Oxidation of Allylic Alcohols.** All attempts to oxidize allyl alcohol failed to yield acrolein cleanly (all steps at  $-60^\circ$ ). Allyl alcohol is a special case apparently, as we had shown earlier that 2-cyclohexenol and cinnamyl alcohol give over 80% yields of the corresponding carbonyl compounds<sup>2</sup>. We have extended the oxidation of allylic alcohols to include *trans*-2-hexen-1-ol (65–70% yield of carbonyl) and 1-octen-3-ol (85–98% yields) (all by procedures A or MA).

**Oxidation of Acetylenic Alcohols.** Three model alcohols were studied: 1-butyn-3-ol, 1-heptyn-3-ol, and 1-phenyl-1-pentyn-3-ol. The last one yielded the carbonyl product almost quantitatively (92–95%) by procedure MA but the first two gave dark colored resinous products from which no carbonyl compound, trifluoroacetate esters, nor 2,4-dinitrophenylhydrazones could be isolated. G.L.C. examination showed the presence of small quantities of unconverted alcohol ( $\sim 20\%$ ).

**Miscellaneous Oxidations.** 11-Oxoprogesterone is obtained in essentially quantitative yield from 11 $\alpha$ -hydroxyprogesterone (procedure MC). Cholesterol is also oxidized quantitatively by procedure MC but the product is approximately a 2 : 1 mixture of cholest-5-en-3-one and cholest-4-en-3-one, respectively, based on I.R. spectra. Similarly, 4-penten-2-ol, another homoallylic alcohol, gives a 50% yield of the 2,4-dinitrophenylhydrazone of 3-penten-3-one (procedure MC).

Apparatus, diagnostic techniques, and purification and storage of dimethyl sulfoxide, triethylamine, and trifluoroacetic anhydride have been described<sup>2, 3, 4</sup>. Diisopropylamine and diisopropylethylamine were stored overnight over pellets of sodium hydroxide and were distilled after decantation; heart cuts were retained and stored over Linde 4A molecular sieves. The best commercial grade of 2,6-lutidine was dried over Linde 4A sieves before use. Other nitrogen bases were used as received from Aldrich or Eastman. Alcohols were the best grades available and they were used as received. All had purities in excess of 97%.

#### Oxidation and Identification Procedures:

Procedures A and C have been described<sup>2</sup>; they differ only in the basification temperature (A,  $-60^\circ$ ; C, room temperature). Procedures MA and MC are modified versions of A and C that give superior yields in the oxidation of small ring and primary alcohols; molar ratios of trifluoroacetic anhydride/dimethyl sulfoxide/alcohol are essentially stoichiometric (1 : 1.2 : 0.8–0.95, respectively); the solvent of choice is dichloromethane. When the oxidation was complete, reaction mixtures were washed with water, and the aqueous phase was reextracted with dichloromethane or other solvent.

Composition of the combined organic layers was usually determined by G.L.C. (Table 1)<sup>2, 5</sup>, with authentic compounds used to calibrate peak areas, and for determination of retention times. Yields of carbonyl compounds determined by G.L.C. (Table 1) were checked by preparation of 2,4-dinitrophenylhydrazones or by isolation<sup>2, 3, 5</sup>. The melting points of the dinitrophenylhydrazones checked with literature values. In favorable cases (yields  $> 95\%$ ), evaporation of solvent yielded residual carbonyl compounds whose N.M.R., I.R. and/or U.V. spectra, m.p., and T.L.C. (ether/silica gel)  $R_f$  values were virtually indistinguishable from those of pure authentic specimens. Column chromatography on silica gel (eluent: ether/petroleum ether) was used in a few cases for isolation.

#### Miscellaneous Oxidations:

1-Phenyl-1-pentyn-3-ol (1.6 g, 10 mmol) is best oxidized by procedure MA. The crude oxidation mixture is diluted with ether (100 ml), washed several times with water (20 ml), the organic phase is dried (magnesium sulfate), and the solvent evaporated. The crude reaction product is dissolved in a minimum quantity of petroleum ether and chromatographed on silica gel (30 g). Elution is conducted successively with petroleum ether (150 ml),

20% ether/petroleum ether (100 ml), and 30% ether/petroleum ether, collected in 50-ml fractions (monitored by G.L.C.). Evaporation of the fourth eluate yielded 1-phenyl-1-pentyn-3-one; yield: 1.48 g (92%); 98% purity by G.L.C.; m.p. 2,4-DNP: 166–167 $^\circ$ . (Procedure MC gave only 80% yields of ketone.)

<sup>1</sup>H-N.M.R. (CDCl<sub>3</sub>/TMS):  $\delta = 1.20$  (t, 3H); 2.65 (q, 2H); 7.24–7.64 ppm (m, 5H).

I.R. (KBr):  $\nu_{\max} = 3060, 2980, 2202$  (m), 1680 (s), 1495, 1356, 1163, 1116, 1048, 960, 757, 690  $\text{cm}^{-1}$ .

1-Octen-3-ol is similarly oxidized by procedure MA and worked up as described for the acetylenic alcohol. The crude oxidation mixture contains 98% 1-octen-3-one and 2% of starting material. Column chromatography as described gives the 1-octen-3-one; yield: 85%.

I.R. (KBr):  $\nu_{\max} = 2950$  (s), 2930, 2860, 1703, 1687 (s), 1619, 1407, 1405, 1190, 1078, 968, 960, 725  $\text{cm}^{-1}$ .

11 $\alpha$ -Hydroxyprogesterone is oxidized to 11-oxoprogesterone in essentially quantitative yield by procedures MA or MC (the latter is preferred). Additional dichloromethane is required to dissolve the alcohol. The crude ketone has m.p. 170–172 $^\circ$  (Lit.<sup>7</sup> 171–172 $^\circ$ ) and is contaminated with a trace of starting material (T.L.C.). Recrystallization from petroleum ether/acetone (1 : 1 v/v) yields the pure product; m.p. 174.5–175.5 $^\circ$ .

Cholesterol is oxidized by procedure MC; it yields a 2 : 1 mixture of cholest-5-en-3-one and cholest-4-en-3-one, respectively, in quantitative yield. The cholesterol (10 mmol) is predissolved in the minimum quantity of dichloromethane/dimethyl sulfoxide (20 : 5 ml). The composition is estimated from the intensity of the carbonyl absorptions in the I.R. (1722 and 1680  $\text{cm}^{-1}$ , respectively, for the nonconjugated and conjugated ketones).

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