

### 1072. A General Synthesis of Ethers.

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Hydrogenation of ketones in presence of platinum oxide in alcoholic acid leads to ethers with good yields.

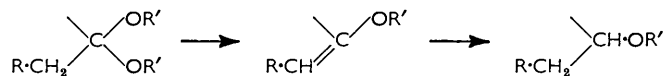
THE reaction  $\text{COR}^1\text{R}^2 + \text{R}^3\text{OH} \longrightarrow \text{R}^1\text{R}^2\text{CH}\cdot\text{OR}^3$  seems generally to occur on hydrogenation in alcoholic acid in presence of platinum. A variety of ketones and also an aldehyde have been tested (see Table I) and have given reasonable to excellent yields. As side products, the alkane and alcohol related to the carbonyl compound are also formed, in yields varying greatly according to the conditions. Possible intermediates are the hemiketal,  $\text{R}^1\text{R}^2\text{C}(\text{OH})\cdot\text{OR}^3$ , the ketal,  $\text{R}^1\text{R}^2\text{C}(\text{OR}^3)_2$ , and the enol ether  $\text{R}^2\cdot\text{CH}:\text{CR}^1\cdot\text{OR}^3$ , the first seeming to be the most likely.

TABLE I.

Ketone	Yields of ethers obtained in presence of alcohols.*				
	MeOH	EtOH	Pr <sup>n</sup> OH	Pr <sup>i</sup> OH	Cyclohexanol
COMe <sub>2</sub> .....				57	
COMeEt .....	95.5	60.5			
COEt <sub>2</sub> .....	70, 70, 69	52.5			
COMePr <sup>i</sup> .....	93	75	92, 89.5	58	
COPr <sup>n</sup> <sub>2</sub> .....	80	53	67.5		
COPr <sup>i</sup> <sub>2</sub> .....	59, 70				
COBu <sup>n</sup> <sub>2</sub> .....	54	52			
COBu <sup>i</sup> <sub>2</sub> .....	77				
Cyclopentanone .....	84	84, 90, 79	92	80	
Cyclohexanone .....	95	66.5, 60.5	85	52	39
2-Methylcyclohexanone ...	74, 67, 80				
Camphor .....	46				
Cycloheptanone .....	98				
Pr <sup>i</sup> -CHO .....	48				

\* Reactions were carried out in conditions which were optimum for cyclohexanone and methanol (cyclohexanone : methanol = 1 : 15; 2.5M-HCl). Some of the yields could certainly be improved.

In 1929 Sigmund and Uchann<sup>1</sup> reported that ketals are converted into ethers when heated at 180° with hydrogen and a nickel-kieselguhr catalyst; the alcohol is first eliminated, giving the enol ether, which is then hydrogenated to the saturated ether:



Howard and Brown<sup>2</sup> found that the hydrogenation of ketals in the presence of acid, with rhodium or palladium as catalyst, also yields ether and alcohols.

<sup>1</sup> Sigmund and Uchann, *Monatsh.*, 1927, **48**, 267; 1929, **51**, 234.

<sup>2</sup> Howard and Brown, *J. Org. Chem.*, 1961, **26**, 1026.

In strong acid, ketal formation occurs to a significant extent with cyclohexanone and methanol,<sup>3</sup> but there is also considerable evidence that acidification of ketals results in the formation of hemiketals and/or enol ethers. It is not surprising, then, that in acid solution, hydrogenation of a ketal gives the same results as that of the carbonyl compound. Enol ethers such as 1-methoxycyclopentene also give a mixture of alkane and saturated ether, but in a ratio different from that found for direct hydrogenation of cyclopentanone in acid methanol. This could be an indication that the hemiacetal is the most important intermediate.

Higher alcohols, which form ketals only in very low yields in equilibrium conditions, and ketones whose methyl ketals are formed with difficulty (*e.g.*, di-isopropyl ketone), nevertheless give satisfactory yields of the ethers.

1-Methoxycyclopentene, referred to above, was prepared in quantitative yield by passage of cyclopentanone dimethyl ketal through a preparative-scale gas chromatograph. The influence of the acidity of the medium on the hydrogenation of this ether and of 1-chlorocyclopentene is shown in Table 2.

TABLE 2.

HCl (M)	Yield (%) of alkane	Yield (%) of ether	HCl (M)	Yield (%) of alkane	Yield (%) of ether
<i>1-Methoxycyclopentene</i>			<i>1-Chlorocyclopentene</i>		
0	20	80	0	58	42
0.025	40	60	2.5	91	9
0.25	50	50			
2.5	30	70			

We are further investigating the mechanism of this new ether synthesis as well as its preparative possibilities. The synthesis is comparable with the alkylation of amines by hydrogenation with carbonyl compounds<sup>4</sup> and with the *N*-alkylation of amides reported by Johnson and Crosby.<sup>5</sup>

## EXPERIMENTAL

Purity of the ketones was controlled by gas chromatography. Methanol was of "spectrograde" quality and was not especially dried. The ethanol was dried over calcium oxide, and the other alcohols were distilled from calcium. Dry hydrochloric acid was absorbed in the required solvent until the molarity was 2.5. Adams catalyst was obtained from Baker Platinum Division, Engelhard Industries, Ltd., London.

*Hydrogenations.*—Ketones were hydrogenated at atmospheric pressure at room temperature. The 15 molar excess of alcohol acted as solvent. The weight of platinum oxide used was 5% of that of the ketone. The reactions were carried out with an amount sufficient to allow gas-chromatographic analysis. Cyclopentanone, cyclohexanone, and cycloheptanone were also hydrogenated on a preparative scale. In these cases, the catalyst was filtered off and sodium hydrogen carbonate was added, to neutralization. Water was added and the mixture was

TABLE 3.

Preparative-scale hydrogenations in 2*N*-methanolic hydrogen chloride (70 ml.).

Ketone, g.	Yield (%)	B. p.	Purity (%)
Cyclopentanone, 8.4	42	104—106°	98
Cyclohexanone, 9.8	63	133—135	95
Cycloheptanone, 11.2	82, 83	160—165.5, 162—163	99, 95

extracted with pentane. After drying (Drierite), the pentane was recovered and the ether produced was fractionated. The purity was checked by gas chromatography. The amounts used and the yields are shown in Table 3. The differences between the yields there mentioned and those obtained by gas-liquid chromatography (Table 1) are due to the volatility of the

<sup>3</sup> Kubler and Sweeney, *J. Org. Chem.*, 1960, **25**, 1437.

<sup>4</sup> Emerson, *Org. Reactions*, 1948, **4**, 174.

<sup>5</sup> Johnson and Crosby, *J. Org. Chem.*, 1962, **27**, 2205.

ethers and the difficulties of small-scale separation. Gas-chromatographic analysis of the preparative-scale reaction mixtures gave the same results as those shown in Table 1.

*Chromatography.*—Analysis of the reaction mixtures was carried out with an Aerograph dual-column temperature-programming gas chromatograph, model A-350-B, from Wilkens Instrument & Research, Inc., Berkely, Calif. The columns (3 m.) were filled with Chromosorb W coated with 15% of Silicone oil 550 or Apiezon L. Analysis was programmed or isothermal according to the needs of each case.

Since we found that the relative surfaces of the plots for ether, alcohol, and alkane were equal to the amounts in several standard mixtures with an error of at most 5%, and that in the conditions of our reaction the yield of the alkane is commonly only 2–5%, analysis was made by measuring the relative surfaces of the alcohol and ether peaks only.

*1-Methoxycyclopentene.*—Cyclopentanone dimethyl ketal was obtained from cyclopentanone and tetramethoxysilane. It was automatically injected in 0.5-ml. portions into a chromatograph (A-700 Autoprep, Wilkens Instrument & Research, Inc., Berkely, Calif.). The column was filled with Chromosorb P containing 30% of SE. 30 silicone oil and heated at 160°. Only one peak appeared on the chromatograms and this proved to be the pure enol ether.

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