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A NOVEL SYNTHESIS OF DIARYL ETHERS

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The reactions of 5,5-di-R-4-bromo-2-cyclohexene-1-ones (R=alkyl or aryl) with several silver salts in a variety of solvents is being studied in these laboratories to look at the competition between displacement by anion or solvent at C_4 and migration of an R group from C_5 to C_4 giving the intermediate precursor of a phenol. One of several experiments attempted was the reaction of 4-bromoisophorone (I) (1) with silver perchlorate in anhydrous benzene. This communication reports the isolation and identification of an unexpected product which may signal the importance of this reaction as a broad synthetic method.

The reaction of I with anhydrous silver perchlorate (dried in vacuo over concentrated sulfuric acid and azeotroped in benzene) in anhydrous benzene was continued overnight in a flask protected from light and moisture. An acidic fraction amounting to a 38.1 percent yield was shown to be 3,4,5-trimethylphenol (II). A neutral fraction, m.p. 145-145.5°C, was isolated in 37 percent yield after one recrystallization from acetone. The elementary analysis was 84.65 percent carbon and 8.74 percent hydrogen. If the assumption is made that the remaining element is oxygen, an empirical formula of $C_{18}H_{22}O$ is obtained. The calculated values are: C-84.99 and H-8.72 percent. The infrared spectrum is very similar to that of II, except for the absence of a peak at 3610 cm^{-1} corresponding to the OH stretching, and for the presence of a peak at 1175 cm^{-1}. The NMR spectrum is also practically identical to that of II, except for the absence of a signal at 5.12 δ , owing to the OH group (lost when the solution of II was shaken with D_2O), and changes of no more than 0.05 δ in the chemical shifts of the remaining three peaks. On the basis of this evidence the neutral fraction was assigned the structure bis-3,4,5-trimethylphenyl ether, III. The mass spectral analysis was confirmatory as follows:

a) the parent peak is at m/e = 254.
b) the ratio of the M and M+2 peak is consistent with the molecular formula $C_{18}H_{22}O$.
c) the second most intense band is at m/e = 119, indicating the presence of the trimethylphenyl ion.

d) a low intensity peak is observed at m/e = 135, indicating a trimethylphenoxy fragment (2).

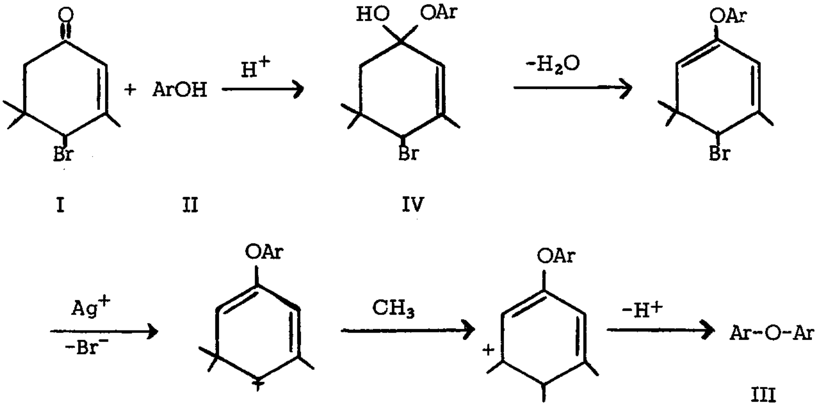
e) the presence of a symmetrical molecule containing three CH_3 groups on one side is indicated by the appearance of peaks at m/e of 239, 224 and 209.

As evidenced by the ultraviolet, infrared and nuclear magnetic resonance spectra of the crude neutral fraction, some α, β-unsaturated ketonic material was present. This material, which may consist of the 4-hydroxy- and/or the 4-perchlorato-derivatives of isophorone, was not identified.

The mechanism of the formation of III could involve the reaction of two moles of pre-formed phenol, or, more likely, involve the reaction of one mole of pre-formed phenol and one mole of bromocyclohexenone. That the former mechanism is not operative was demonstrated by duplicating the conditions of the reaction in the presence of the phenol II, but in the absence of I. Thus, under anhydrous conditions, a solution of II in benzene and a solution of hydrogen bromide in benzene were added over a period of several hours to a solution of silver perchlorate in benzene. In this way the phenol was in contact for several hours with all the possible catalysts, namely, silver ion, perchloric acid and silver bromide. No ether was isolated.

A plausible mechanism is shown in Chart I.

CHART I



Ar = 3,4,5-$(CH_3)_3C_6H_2$

The important intermediate is the hemiketal IV, which in sequence undergoes a) dehydration, b) loss of bromide ion, c) a 1,2-methyl shift, and d) aromatization, to eventually give the diaryl ether, III. Loss of bromide ion and rearrangement of a methyl group could possibly precede dehydration. This mechanism is akin to the one proposed by Fort for the isolation of 3,4,5-trimethylanisole from the reaction of isophorone with cupric bromide in methanol (3), and from the reaction of 6-tosyloxyisophorone with dry hydrogen chloride in methanol (4). The major difference is the fact that in Fort's reactions, methanol rather than a phenol is involved in formation of a hemiketal intermediate.

Diaryl ethers are normally synthesized under the very vigorous conditions of an Ullman-type reaction. The unexpected synthesis of a diaryl ether under such mild conditions encouraged a study of its universality. The structure of the halocyclohexenone is being modified and mixed diaryl ethers are being synthesized by adding other phenols at the start of the reaction. These successful experiments will be reported later in the complete paper.

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