BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 39 611—614 (1966)

The Formation of Phenolic Ethers by the Acid-catalyzed Condensation of Phenols and Alcohols[1,2]

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(Received August 2, 1965)

The reaction of phenol with ethyl alcohol in strong acidic media at a somewhat high temperature gave phenyl ethyl ether in a 61% yield. The product isolated from a similar reaction between phenol and *n*-propyl alcohol was practically pure phenyl *n*-propyl ether, and no isopropyl isomer was detected. When ^{18}O-labeled phenol was treated with unlabeled ethyl alcohol, the phenetole isolated was found not to contain any excess ^{18}O. The reaction of phenol with ethyl alcohol in the presence of hydrogen chloride gave no isolable amount of phenetole. The mechanism for these reactions was then discussed.

Previously, we have reported that phenols undergo a facile oxygen-isotopic exchange with solvent water in strong acidic media at a high temperature.[3] It was suggested that, in a strong acidic media, phenol readily accepts a proton at either the ortho- or para-position to form a quasi-stable quinoid-type intermediate, whereby a nucleophilic attack of water at carbon-1 leads to the exchange of the oxygen, as is shown below.[3,4]

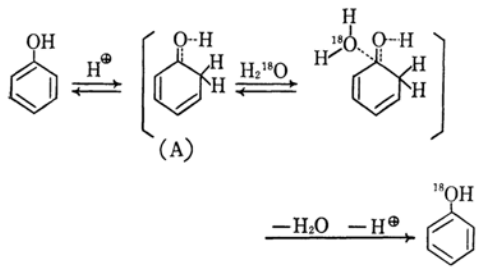

Fig. 1.

As an extension of this remarkable ^{18}O exchange reaction, it was expected that the phenolic hydroxy group would be replaced by more nucleophilic reagents, such as alcohols and mercaptans. Indeed, such reactions have been found to take place, and the details of the acid-catalyzed condensation of phenols with mercaptans have been reported in a previous paper of this series[5]. This paper will describe a more detailed investigation into the nature of the acid-catalyzed condensation of phenols and alcohols.

Results and Discussion

The acid-catalyzed formation of aryl ethers from aromatic phenols and alcohols[6] is not an entirely new reaction. Wiberg and Saegebarth[7] have reported recently that β-naphthyl methyl ether was obtained in a 70% yield when β-naphthol was heated at 100°C with methanol for 40 hr. in the presence of anhydrous *p*-toluenesulfonic acid in a sealed tube. It was suggested, on the basis of the ^{18}O tracer experiments using ^{18}O-labeled methanol, that this reaction proceeds in the following manner, similar to what was suggested by us for the oxygen-exchange reaction of phenols:

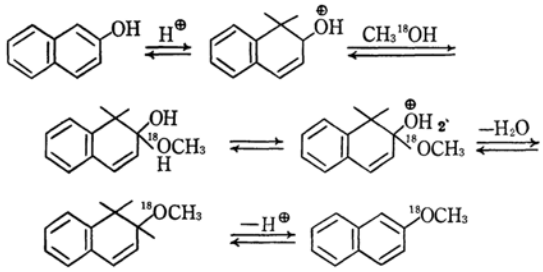

Fig. 2.

Resorcinol, which is known to have a carbonyl character, was also found to undergo a condensation reaction with methanol. However, phenol, catechol and hydroquinone were found not to undergo any condensation under the same reaction conditions.

Under the somewhat more drastic conditions under

1) Paper VII: Reactions of Phenols and Phenolic Esters.
2) For preliminary account of this paper, see S. Oae and R. Kiritani, This Bulletin, **36**, 346 (1963); **37**, 770 (1964); **38**, 765, 1381, 1543 (1965).
3) S. Oae, T. Fukumoto and R. Kiritani, ibid., **36**, 346 (1963).
4) S. Oae and R. Kiritani, ibid., **37**, 770 (1964).
5) S. Oae and R. Kiritani, ibid., **38**, 1381 (1965).
6) L. Gattermann, *Ann.*, **244**, 72 (1888).
7) K. B. Wiberg and K. A. Saegebarth, *J. Org. Chem.*, **25**, 832 (1960).

which the ^{18}O exchange takes place, phenol undergoes a condensation with alcohol, as is shown in Table I.

Table I. The reactions of phenols with alcohols

Reactants		Reaction condition			Yield %
Phenol	Alcohol	Mole ratio	Time hr.	Temp. °C	
Phenol	EtOH	1 : 5	48	180	58.4
Phenol	EtOH[a]	1 : 5	48	180	61.0
Phenol	EtOH[b]	1 : 5	48	180	none
Phenol	EtOH[c]	1 : 5	48	180	none
Phenol	EtOH[c]	1 : 5	48	110	none
Phenol	*n*-PrOH	1 : 5	48	180	55.1
β-Naphthol	EtOH	1 : 1	48	180	52.3
p-Cresol	EtOH	1 : 5	48	180	33.3
p-Nitrophenol	EtOH	1 : 5	48	180	trace

a) no H_2O; *p*-toluenesulfonic acid catalyst
b) no H_2O; no catalyst
c) no H_2O; hydrogen chloride catalyst

Although the reaction is considered to proceed through the following pathway, similar to that proposed by Wiberg for the formation of β-naphthyl methyl ether:

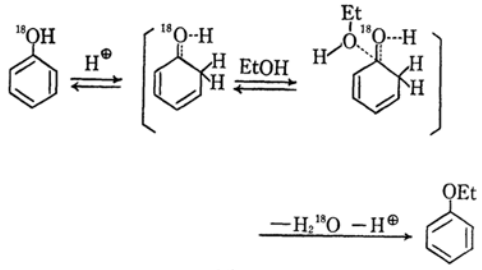

Fig. 3.

other possibilities have also to be scrutinized, because, after all, the conditions used here are so drastic that the formation of alkyl chloride or of the alkyl carbonium ion intermediate is quite conceivable during this reaction.

However, the mechanism involving the incipient formation of the alkyl carbonium ion or of alkyl chloride was excluded on the basis of the following observations:

a) When ^{18}O-labeled phenol (1.3 atom.% ^{18}O) was treated with unlabeled ethyl alcohol in an ^{18}O-enriched water (1.3 atom.% ^{18}O) solution of 12 N hydrochloric acid, the phenetole obtained was found to possess a natural abundance of oxygen (0.20 atom.% ^{18}O).

b) The product isolated in a 55.1% yield from the similar reaction between phenol and *n*-propyl alcohol was practically pure phenyl *n*-propyl ether; no isopropyl isomer was detected in the product within the range of experimental error. The carbonium ion formed from *n*-propyl alcohol must be the isopropyl cation. Hence, the reaction involving the alkyl carbonium ion should definitely give phenyl isopropyl ether as the product.

c) The reaction was found to proceed quite well with a small amount of anhydrous toluenesulfonic acid as the acid catalyst under anhydrous conditions. However, when water was excluded in the hydrochloric acid-catalyzed reaction between phenol and ethanol, no isolable amount of phenetole was obtained. The evolution of gas, presumably ethyl chloride, was noticed when the sealed tubes were opened. Probably, under anhydrous conditions, hydrochloric acid was consumed in the formation of ethyl chloride in the following equilibrium:

$$EtOH + HCl \rightleftharpoons EtCl + H_2O$$

On the other hand, the equilibrium of the reaction between ethanol and toluenesulfonic acid is undoubtedly shifted toward the left-hand side.

$$EtOH + TsOH \rightleftharpoons EtOTs + H_2O$$

It is also difficult to accept the direct aromatic nucleophilic substitution, shown below, in view of the results of previous work on the oxygen exchange reaction[8] as well as in view of the sulfide-

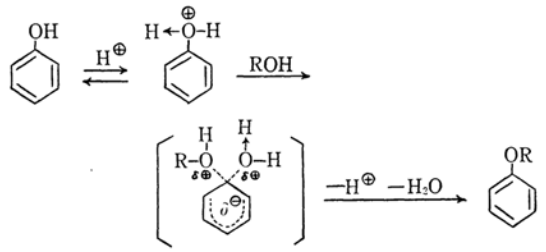

Fig. 4.

forming reaction.[5] According to this reaction scheme, the substitution of an electron-withdrawing group at the *o*- or *p*-position will accelerate the reaction; however, the nitro group at the para position was found to retard the reaction substantially.

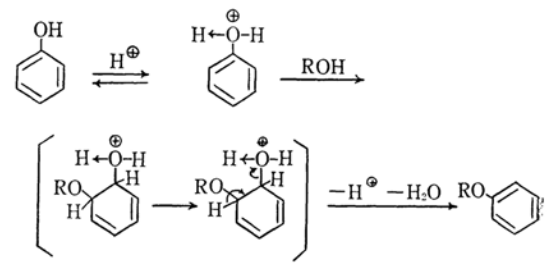

Fig. 5.

8) S. Oae and R. Kiritani, This Bulletin, to be submitted.

The other possible pathway (shown below), involving the nucleophilic attack of alcohol at the ortho or para-position of phenol and the subsequent elimination of water, can also be excluded.

There was no formation of any detectable amount of the rearranged ether from the reaction with *p*-cresol and β-naphthol.

Therefore, the only plausible pathway that can explain all these observations is the one involving the nucleophilic attack of alcohol on the incipient carbonium ion (A) formed during the reaction.

Recently, Gold and Satchell[9] have also postulated a similar ortho- or para-protonated σ-complex formation in a strong acid solution of phenolic compounds, while Kresge et al.[10] have obtained rather conclusive evidence for the protonated σ-complex through proton NMR spectroscopic measurements and through a study of the ultraviolet spectra in the case of phloroglucinol.

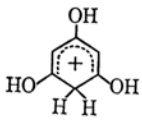

Fig. 6.

On the other hand, the formation of the σ-complex intermediate has never been successfully observed in the case of monohydroxylic phenol. However, in view of the very facile hydrogen isotopic exchange in strong acid solutions of phenol, the steady concentration of the incipient carbonium ion (A) or of the σ-complex will probably increase substantially, or the nucleophilic attack of alcohol on the carbonium ion (A) will take place more readily, or more probably the combination of the two reactions will become more facile, when the reaction temperature is elevated.

In order to shed further light on the nature of this and related reactions, condensation reactions with other nucleophilic reagents are now underway in these laboratories.

Experimental

β-Naphthyl Ethyl Ether.—β-Naphthol (1 g.) was added to 5 ml. of 10 N hydrochloric acid containing ^{18}O-enriched water (0.74 atom.% ^{18}O). The mixture was then heated in a sealed tube at 180°C for 24 hr. The recovered β-naphthol was subjected to ^{18}O analysis (0.53 atom.% ^{18}O). A mixture of 4.8 g. (0.033 mol.) of the labeled β-naphthol and 1 ml. of 12 N hydrochloric acid in 1.6 g. (0.033 mol.) of ethyl alcohol was sealed in a tube and heated at 180°C for 48 hr. Then the sealed tube was broken and, after the excess alcohol had been removed in vacuo, the whole content was extracted with ether. The ether layer was sufficiently washed with aqueous sodium carbonate and water to remove unreacted β-naphthol, and then dried over calcium chloride. When the ether extract was distilled under reduced pressure, 3 g. of a fragrant white precipitate was obtained (yield 52.3%). The product, β-naphthyl ethyl ether, was identified by means of its infrared spectrum and subjected to ^{18}O analysis (0.20 atom.% ^{18}O). M. p. 37—38°C; b. p. 124°C/5 mmHg; n_D^{20} 1.5932. Found: C, 83.78; H, 7.11%.

Phenetole.—A mixture of 2 g. (0.021 mol.) of phenol and 1 ml. of 12 N hydrochloric acid in 5 g. (0.109 mol.) of ethyl alcohol was sealed in a tube and kept at 180°C for 48 hr. After it had cooled the sealed tube was treated as has been described above. The distillate gave 1.5 g. of phenetole (yield 58.4%). The infrared spectrum was identical with that of an authentic sample. In a separate experiment, a mixture of 2 g. (0.021 mol.) of phenol and 0.2 g. (0.0012 mol.) of *p*-toluenesulfonic acid in 5 g. (0.109 mol.) of absolute ethyl alcohol was sealed in a tube and heated at 180°C for 48 hr. The sealed tube was then treated as has been described above. The ether layer was washed with aqueous sodium carbonate to remove unreacted phenol and *p*-toluenesulfonic acid, and then distilled under reduced pressure; thereby 1.6 g. of phenetole was obtained (yield 61%). B. p. 171—173°C; n_D^{20} 1.5129. Found: C, 78.68; H, 8.20%.

When the other sealed tube, which contained the same reactants, was kept at 110°C for 48 hr., no detectable amount of the product was obtained, while all of the reactants were recovered.

A solution of phenol 2 g. (0.021 mol.) in 5 g. (0.109 mol.) of ethyl alcohol in the absence of an acid catalyst was sealed in a tube. An alcohol solution of 1.3 N acid was then prepared by absorbing hydrogen chloride dried over sulfuric acid into absolute ethyl alcohol. A solution of phenol 2 g. (0.021 mol.) in 6 g. of the acidic ethyl alcohol was sealed in another tube. Both sealed tubes were heated at 180°C for 48 hr. and treated as described above; however, no phenetole was obtained.

^{18}O labeled phenol was prepared by the acid-catalyzed oxygen exchange reaction.[6] Using the ^{18}O enriched phenol (1.3 atom.% ^{18}O) thus prepared and unlabeled ethyl alcohol, the condensation reactions were carried out in the presence of an unlabeled or ^{18}O enriched (1.3 atom.% ^{18}O) water solution of hydrochloric acid in sealed tubes at 180°C for 48 hr. The products obtained in both reactions were unlabeled phenetole.

***n*-Propyl Phenyl Ether.**—A mixture of 2 g. (0.021 mol.) of phenol and 1 ml. of 12 N hydrochloric acid in 6 g. (0.1 mol.) of *n*-propyl alcohol was sealed in a tube. After the solution had been heated at 180°C for 48 hr., the sealed tube was broken and treated as has been described above. *n*-Propyl phenyl ether (0.75 g.) was obtained (yield 55.1%). The infrared spectrum was found to be identical within the range of experimental error with that of the authentic sample. B. p. 188—189°C, n_D^{20} 1.5056. Found: C, 79.41; H, 8.89%. Meanwhile, the authentic sample of *n*-propyl phenyl ether was prepared by reacting sodium phenolate with *n*-propyl bromide in a 95.6% yield.

***p*-Tolyl Ethyl Ether.**—A mixture of 2.2 g. (0.02 mol.) of *p*-cresol and 1 ml. of 12 N hydrochloric acid in 5 g. (0.109 mol.) of ethyl alcohol was sealed in a tube.

9) V. Gold and D. P. N. Satchell, *J. Chem. Soc.*, **1955**, 3619.
10) A. J. Kresge, G. W. Barry, K. R. Charles and Y. Chiarry, *J. Am. Chem. Soc.*, **80**, 4343 (1962).

After the mixture had been heated at 180°C for 52 hr. the sealed tube was broken and treated as has been described above. *p*-Tolyl ethyl ether (0.9 g.) was obtained (yield 33.3%). The infrared spectrum was identical with that of an authentic sample. B. p. 188—189°C, n_D^{20} 1.5038. Found: C, 79.39; H, 8.86%. Meanwhile, an authentic sample of *p*-tolyl ethyl ether was prepared in a 100% yield by reacting sodium *p*-methyl phenolate with ethyl bromide.

***p*-Nitrophenyl Ethyl Ether.**—A mixture of 1.4 g. (0.01 mol.) of *p*-nitrophenol and 1 ml. of 12 N hydrochloric acid in 2.3 g. (0.05 mol.) of ethyl alcohol was sealed in a tube. After the tube had been heated at 180°C for 48 hr., it was broken and treated as above. Only a small amount of yellow crystals of *p*-nitrophenyl ehtyl ether was obtained; this was recrystalized from ethanol. M. p. 60°C. Found: C, 57.48; H, 5.41%. Most of the reactants were decomposed. Meanwhile, an authentic sample of *p*-nitrophenyl ethyl ether was prepared in a 24% yield by reacting sodium *p*-nitro phenolate with ethyl bromide. M. p. 59—60°C.

Analysis for Oxygen-18.—The experimental procedure and method of calculation were similar to those described in the previous paper.[11]

11) S. Oae, T. Kitao and Y. Kitaoka., *J. Am. Chem. Soc.*, **84**, 3359 (1962).