Nitriles with Alcohols.—One mole of acetonitrile was mixed with three moles of *n*-propyl alcohol and one mole of boron fluoride in a 500-cc. Erlenmeyer flask. After refluxing for one hour the contents was treated with a solution of sodium carbonate and the compounds, excess *n*-propyl alcohol, *n*-propyl acetate, and *n*-propyl ether were separated, respectively, in the usual manner. A yield of *n*-propyl acetate of 28% and of *n*-propyl ether of 27% was obtained.

An analogous experiment with *n*-butyl alcohol gave 40% yield of *n*-butyl acetate and a 38% yield of *n*-butyl ether.

With benzonitrile, *n*-propyl alcohol and boron fluoride a 30% yield of *n*-propyl benzoate and a 26% yield of *n*-propyl ether resulted.

Ethyl Orthoformate with Boron Fluoride.—One-third mole of ethyl orthoformate was saturated with boron fluoride (0.56 mole). The unreacted ethyl orthoformate separated in an upper layer and was removed. Upon careful distillation of the lower layer 0.28 mole of ether–boron fluoride and 0.28 mole of ethyl formate–boron fluoride was recovered. These compounds were identified by agreement of physical properties as described by Gasselin[8] and Bowlus and Nieuwland,[9] respectively.

Esters with Aniline.—Aniline, an ester and boron fluoride were refluxed for a period of time, then cooled and the boron fluoride hydrolyzed off with sodium carbonate solution. Upon steam distillation of the mixture a poor yield of the anilide was recovered. Ethyl acetate gave 1.8% acetanilide; isopropyl acetate gave 5.9% of acetanilide; *n*-butyl propionate gave 10% of propionanilide and ethyl benzoate yielded 9.6% of benzanilide.

Butyl Alcohols with Phenol.—Thirty grams of boron fluoride was passed into 188 g. of phenol contained in a Florence flask. To this mixture 150 g. of *t*-butyl alcohol was added and then refluxed for one hour. Two layers appeared after about thirty minutes. After purification in the usual manner[5] several small fractions were isolated that contained substituted phenyl ethers, the main fraction being *p*-*t*-butylphenol 165 g., b. p. 233–36°, m. p. 98°.

By repeating the above experiment with *i*-butyl alcohol, 205 g. of *p*-*t*-butylphenol, b. p. 233–36°, m. p. 98°, was isolated.

Summary

A method for the preparation of fluorescein and phenolphthalein using boron fluoride as the condensing agent has been outlined.

The reactions of alcohols with nitriles and phenols in the presence of boron fluoride have been studied.

Esters reacted with aniline in the presence of boron fluoride to give poor yields of anilides.

NOTRE DAME, INDIANA RECEIVED NOVEMBER 8, 1937

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[8] Gasselin, *Bull. soc. chim.*, [3] **7**, 17 (209) (1892).

[9] Bowlus and Nieuwland, THIS JOURNAL, **53**, 3835 (1931).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Organic Reactions with Boron Fluoride.[1] XVIII. The Reaction of Ethers with Benzene

BY MICHAEL J. O'CONNOR AND FRANK J. SOWA

In previous articles[2,3] it has been shown that alcohols and esters react with benzene in the presence of boron fluoride to give alkylbenzenes through the olefin stage rather than by double decomposition.

The purpose of this work was to investigate the cleavage of various ethers in the presence of boron fluoride and to determine the mechanism these reactions undergo. The reaction of ethers, as in the case of alcohols and esters, with benzene to give alkylbenzenes might proceed by double decomposition (equation I), or by the intermediate olefin formation (equations II and III):

$$CH_3(CH_2)_3CH_2\text{–}\boxed{\text{–}O\text{—}CH_2(CH_2)_3CH_3 + H}C_6H_5 \longrightarrow CH_3(CH_2)_3CH_2C_6H_5 + CH_3(CH_2)_3CH_2OH \quad (I)$$

$$CH_3(CH_2)_3CH_2\text{—}O\text{—}CH_2(CH_2)_3CH_3 \longrightarrow CH_3(CH_2)_2CH{=}CH_2 + CH_3(CH_2)_3CH_2OH \quad (II)$$

$$CH_3(CH_2)_2CH{=}CH_2 + C_6H_6 \longrightarrow CH_3CH_2CH_2(CH_3)C_6H_5 \quad (III)$$

It was noted that if the reaction followed the course given in equation (I), then *n*-amyl ether should give *n*-amylbenzene. Instead, *s*-amylbenzene resulted. Likewise, isoamyl ether gave *t*-amylbenzene. The results of these experiments definitely indicate that the mechanism of the reaction of ethers with benzene proceeds according to equations (II) and (III), that is, by the intermediate olefin formation, with subsequent condensation into the benzene nucleus, rather than by double decomposition as shown in equation (I). Thus, the products of alkylation of benzene with ethers indicate that an unsaturated compound was first formed, and this compound then condensed with benzene.

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[1] For previous paper see McKenna and Sowa, THIS JOURNAL, **60**, 124 (1938).

[2] McKenna and Sowa, *ibid.*, **59**, 470 (1937).

[3] McKenna and Sowa, *ibid.*, **60**, 124 (1938).

It is believed that the alcohol which results upon the cleavage of the ether further reacts with benzene to give alkylbenzenes; first by dehydration to an unsaturated compound, and then with subsequent condensation of the olefin with benzene according to equations (IV) and (V)

$$CH_3(CH_2)_3CH_2OH \longrightarrow CH_3(CH_2)_2CH{=}CH_2 + H_2O \quad (IV)$$

$$CH_3(CH_2)_2CH{=}CH_2 + C_6H_6 \longrightarrow CH_3CH_2CH_2CH(CH_3)C_6H_5 \quad (V)$$

These reactions, (IV) and (V), are assumed to take place because more than 50% of the ether reacted, as in the case of diisopropyl ether illustrated by the graph in Fig. 1. This may be accounted for only by the hypothesis of olefin formation from the alcohol and condensation with benzene.

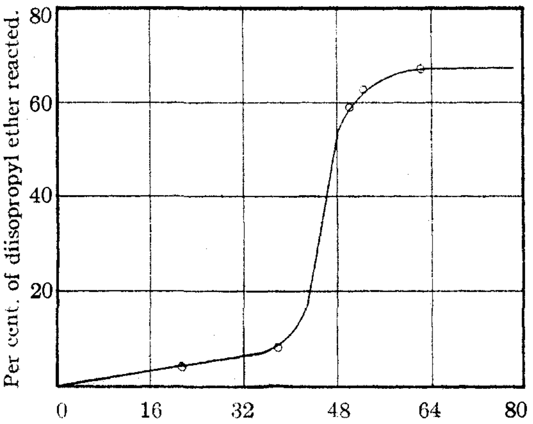
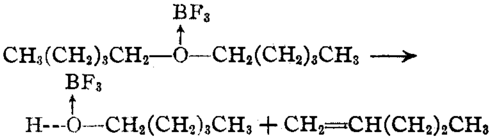


Fig. 1.—Concentration of boron fluoride in grams per mole of ether.

Diisopropyl ether and isopropyl phenyl ether gave isopropylbenzene derivatives; dibenzyl and benzyl ethyl ethers both gave diphenylmethane and di- and tribenzylbenzenes; isoamyl ether gave *t*-amylbenzene derivatives while *n*-amyl yielded the *s*-amyl derivatives; ethyl ether gave mono-, di-, and triethylbenzenes.

The relative ease of reaction varied considerably with the different ethers. The ethers, diisopropyl and dibenzyl, reacted vigorously upon saturation with boron fluoride, while isopropyl phenyl and benzyl ethyl ethers reacted with explosive violence. Ethyl, isoamyl, and *n*-amyl ethers would not react under ordinary conditions but required higher pressures and temperatures.

Boron fluoride coördinates with the oxygen of the ether molecule. This weakens the carbon to oxygen linkage, which results in the formation of an olefin (equation VI)



$$CH_3(CH_2)_3CH_2{-}\overset{\overset{BF_3}{\uparrow}}{O}{-}CH_2(CH_2)_3CH_3 \longrightarrow H{-}{-}{-}\overset{\overset{BF_3}{\uparrow}}{O}{-}CH_2(CH_2)_3CH_3 + CH_2{=}CH(CH_2)_2CH_3 \quad (VI)$$

The disubstituted benzenes were the para derivatives with very small quantities of the ortho compounds.

Experimental Part

The procedures for the ethers that react spontaneously and those that required more drastic treatment were quite uniform, so only two descriptions will be given.

One mole of either isopropyl, isopropyl phenyl, dibenzyl, or benzyl ethyl ether and two moles of benzene were weighed into a 500-cc. Erlenmeyer flask which was fitted with an inlet tube that extended to within 2 cm. of the bottom, and a short outlet tube. Boron fluoride was then added in quantities that varied from one-half to one mole depending upon the particular ether used. Upon the addition of boron fluoride some of these ethers gave a spontaneous reaction and two layers formed, while other reaction mixtures formed layers after standing overnight or after refluxing for thirty minutes or so.

After the reaction mixture cooled the two layers were separated. The lower layer proved to be water, hydroxyfluoboric acid (b. p. 160°) and hydrofluoric acid. The upper layer was washed several times with saturated sodium carbonate solution, then several times with water, dried over calcium chloride, and carefully fractionated.

For ethyl, isoamyl, and *n*-amyl ethers the same procedure was followed until after the addition of boron fluoride. These mixtures were placed in a small, tightly sealed autoclave, which was equipped with a pressure gage and immersed in an oil-bath. The bath was heated to a temperature of about 160° and the pressure rose to 100 pounds per square inch (7 atm.). At this point the pressure rapidly rose to 260 pounds (17 atm.) or a little higher. It was further heated for three hours at 200 pounds (13 atm.) pressure and at a temperature of about 150°.

The products were identified from their boiling points, densities, and indices of refraction. The position of the alkyl groups in the dialkyl products was proved by oxidation with hot nitric acid to phthalic acid and subsequent methylation to the dimethyl ester.[4]

The results of these runs are given in Table I, and the physical properties of the alkylbenzenes are given in Table II.

TABLE I

ALKYLBENZENES FROM ETHERS AND BENZENE

Ether used	Nature of alkyl group in benzene	Yield of alkylbenzenes, g. Mono	Di	Poly
Ethyl	Ethyl	25.0	12.5	14.6
i-Propyl	*i*-Propyl	25.6	15.2	19.2
i-Propyl phenyl	*i*-Propyl	26.5	7.2	..
Dibenzyl	Benzyl	28.0	32.0	64.0
Benzyl ethyl	Benzyl	31.0	20.0	20.0
i-Amyl	*t*-Amyl	12.4	..	32.0
n-Amyl	*s*-Amyl	29.6	..	40.4

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(4) Slanina, Sowa and Nieuwland, THIS JOURNAL, **57**, 1547 (1935).

TABLE II

PHYSICAL PROPERTIES OF ALKYLBENZENES

Alkylbenzene	B. p., °C.	n^{25}D	Sp. gr. 25°
i-Propylbenzene	151	1.4885	0.8581
Diisopropylbenzene	204.5	1.4892	.8550
t-Amylbenzene	189	1.4860	.8550
t-Diamylbenzene	260	1.4841	.8491
s-Amylbenzene	193	1.4884	.8576
s-Diamylbenzene	265	1.4845	.8496
Benzylbenzene	261	1.5782	1.0000
Dibenzylbenzene	M. p. 84		
Ethylbenzene	135	1.4928	0.8603
Diethylbenzene	183	1.4949	0.8673

Derivatives of Alkylbenzenes.—The acetamido derivative of the various monoalkylbenzenes was prepared according to the procedure outlined by Ipatieff and Schmerling.[5] The compounds formed had melting points that agreed closely with those reported in the literature and are as follows: diacetaminoethylbenzene (m. p. 224°), monoacetaminoisopropylbenzene (m. p. 103°), diacetaminoisopropylbenzene (m. p. 114°), and monoacetamino-*t*-amylbenzene (m. p. 139°).

Summary

Benzene has been alkylated by various ethers in the presence of boron fluoride.

Normal ethers give secondary, while isoethers give tertiary alkylbenzenes.

The disubstituted products in the presence of boron fluoride were the para derivatives.

A mechanism has been proposed for the reaction of ethers with benzene.

NOTRE DAME, INDIANA RECEIVED JUNE 9, 1937

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(5) Ipatieff and Schmerling, *ibid.*, **59**, 1056 (1937).

[CONTRIBUTION FROM THE DEPARTMENT OF MEDICAL RESEARCH OF THE UNIVERSITY OF TORONTO]

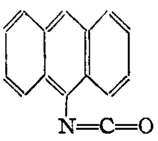
Anthranyl and 1,2,5,6-Dibenzanthranyl Isocyanates. I

BY HUGH J. CREECH AND W. R. FRANKS

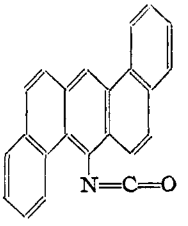
The primary purpose behind the synthesis of anthranyl and 1,2,5,6-dibenzanthranyl isocyanates was the formation of artificial protein antigens[1] for an investigation of the possibility of immunization against the action of carcinogenic agents (i) applied experimentally and (ii) normally active in the organism.[2] Also, it has been found recently that some of the addition compounds of 1,2,5,6-dibenzanthranyl isocyanate possess carcinogenic activity. The water-soluble sodium salt of 1,2,5,6-dibenzanthranylcarbamidoacetic acid[1b] produces tumors rapidly in mice.

Anthranyl isocyanate (I) and 1,2,5,6-dibenzanthranyl isocyanate (II) were prepared by the action of phosgene on the 9-amino derivatives of anthracene and 1,2,5,6-dibenzanthracene according to the method used by Vittenet[3] for the preparation of naphthyl isocyanates.

(I)



(II)



The well recognized instability of *meso*-substituted anthracenes together with the great reactivity of the isocyanate grouping seriously complicate the essentially simple syntheses of the isocyanates. The extent of the occurrence of the side reactions to which the isocyanates are subject has been summarized by Porter,[4] Franklin[5] and Shriner, Horne and Cox.[6]

The success of the syntheses depends to an unusual degree upon the purity of the reactants and solvents and the reduction to a minimum of the main side reactions in which quinones and disubstituted ureas result from an insufficient supply of phosgene, excessive heating, or exposure to dampness and oxygen. Solubility relationships and the instability of the isocyanates make extremely difficult the removal of side products. The amines and isocyanates must be stored in the dark under nitrogen. Consideration of these facts has allowed an increase of yield from 5 to 70% of the anthranyl isocyanate from anthranylamine.

The 1,2,5,6-dibenzanthranyl isocyanate is fairly stable. The work of Cook[7] supports this observation. The addition products of the isocyanates with alcohols are also quite stable.

The isocyanates react rapidly with amines to

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(1) Creech and Franks, (a) *Can. Chem. Met.*, **21**, 50 (1937); (b) *Am. J. Cancer*, **30**, 555 (1937).

(2) Franks and Creech, unpublished.

(3) Vittenet, *Bull. soc. chim.*, [3] **21**, 586 and 957 (1899).

(4) Porter, "Molecular Rearrangements," Chemical Catalog Co., New York, 1928, pp. 13–30.

(5) Franklin, "The Nitrogen System of Compounds," Reinhold Publishing Corp., New York, 1936, pp. 108–127.

(6) Shriner, Horne and Cox, *Org. Syntheses*, **14**, 72 (1934).

(7) Cook, *J. Chem. Soc.*, 3273 (1931).