[CONTRIBUTION NO. 55 FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

CATALYSIS IN ORGANIC CHEMISTRY. I. REACTIONS OF ETHERS WITH ACID CHLORIDES, ACIDS AND ANHYDRIDES[1]

BY H. W. UNDERWOOD, JR., AND R. L. WAKEMAN

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Ethers are usually described as inert compounds; the carbon–oxygen bond is firmly held, and drastic treatments, such as heating with hydriodic acid or anhydrous aluminum chloride, are generally employed to split ethers. Descudé[2] and Wedekind and Haeussermann[2] noted that esters and alkyl chlorides are formed by the reactions of ethyl and methyl *iso*-amyl ethers with acetyl chloride and with benzoyl chloride in the presence of anhydrous zinc or ferric chloride. More information about transformations of this type would be desirable on account of the frequent use of ethers as (presumably inert) solvents or diluents, and also as a contribution to our knowledge of factors which increase the reactivity of ethers. This paper deals with an investigation of the reactions of ethyl ether with a series of representative acid chlorides; experiments with *iso*propyl, *n*-butyl and *iso*-amyl ethers are also described. It was found that diphenyl ether and anisole behave like aromatic hydrocarbons in their reactions with acetyl and benzoyl chlorides, and yield ketones through the introduction of an acetyl or benzoyl group into the ring.

We have shown that a number of acids and anhydrides can be converted into esters by treatment with ethyl ether in the presence of hydrogen bromide.[3]

Discussion of Experiments and Interpretation of Results

All of the temperatures given are uncorrected.

Purification of Ethers.—The ethyl ether employed in our experiments was purified by Norris' procedure.[4] Pure *iso*propyl, *n*-butyl and *iso*-amyl ethers were dried for several days with anhydrous sodium sulfate and distilled before use.

Reactions of Ethers with Acid Chlorides

Preliminary Experiments and General Procedure.—In preliminary experiments the action of anhydrous aluminum, ferric and zinc chlorides in promoting the reactions

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[1] Some of the experimental results described in this paper are taken from a thesis submitted to the Faculty of the Massachusetts Institute of Technology by R. L. Wakeman in partial fulfilment of the requirements for the degree of Master of Science.

[2] Descudé, *Compt. rend.*, **132**, 1129 (1901); *Ann. chim. phys.*, [7] **29**, 497 (1903); Wedekind and Haeussermann, *Ber.*, **34**, 2081 (1901).

[3] Fenton and Gostling [*J. Chem. Soc.*, **73**, 554 (1898)] stated that ethyl esters of dihydroxymaleic, oxalic, acetic, benzoic, boric and stearic acids are obtained by allowing the acids to stand for several days with anhydrous ethyl ether containing dry hydrogen bromide.

[4] Norris, "Experimental Organic Chemistry," McGraw-Hill Book Co., New York City, **1924**, p. 73.

of ethyl ether with acetyl and benzoyl chlorides was investigated. Esters were obtained in each trial; since anhydrous zinc chloride gave the best yields and was most easily handled it was employed in all subsequent work.

The ether was added to a mixture of the acid chloride and finely powdered, anhydrous zinc chloride in a small, dry flask. A reflux water condenser, with a calcium chloride tube in the top, was attached immediately, and the mixture was heated at its boiling point until the reaction appeared to be complete; usually two to three hours of heating was required. The reaction mixture was then cooled in ice and shaken several times with two or three volumes of cold water until practically free from zinc chloride; in some cases a little pure ethyl ether was added to dilute the mixture. The ether layer was next dried with anhydrous sodium sulfate. After most of the ether had been removed by distillation, the residue was fractionated in case the expected reaction product was a liquid, or allowed to stand until crystallization occurred if the ester was a solid. Liquid esters were collected over a range of 5 to 6°; if necessary, solid esters were washed with cold, dilute sodium carbonate solution and crystallized from suitable solvents. A 10 to 15% excess of ether and approximately 0.25 mole of zinc chloride per mole of acid chloride were employed.

Ethyl Ether.—The acid chlorides investigated and the percentage yields of ethyl esters obtained are as follows: acetyl, 40; chloro-acetyl, 35; propionyl, 15; *n*-butyryl, 21; *iso*valeryl, 20; benzoyl, 60; phenylacetyl, 79; oxalyl, 4; diphenic acid chloride, 77. The amounts of the acid chlorides used were 31.4, 15, 20, 20, 16, 56, 9.7, 12.2 and 2.2 g., respectively.

No esters were obtained from benzenesulfonyl chloride (20 g.) or *p*-toluenesulfonyl chloride (15 g.). In order to determine whether compounds containing labile chlorine atoms would behave like acid chlorides, 50 g. of benzyl chloride and 15 g. each of *o*-nitrochlorobenzene, 2,4-dinitrochlorobenzene and picryl chloride were heated with ethyl ether in the presence of zinc chloride. Each halogen compound was recovered unchanged; benzyl chloride gave some high-boiling tar.

A mixture of 25.4 g. of *o*-phthalyl chloride, 10.3 g. of ethyl ether and 4.2 g. of anhydrous zinc chloride was refluxed for about two hours; white crystals were formed suddenly. After the contents of the flask had been cooled to room temperature, the solid was collected on a filter, washed with water and dried. The crystals, which weighed 15.5 g., were identified as phthalic anhydride. The liquid portion of the reaction mixture was washed twice with an equal volume of water, dried with anhydrous sodium sulfate and fractionated. Two grams of diethyl phthalate was isolated. The results of this experiment indicate that diethyl phthalate may be transformed into phthalic anhydride by zinc chloride; small scale experiments with some known diethyl phthalate proved that this splitting takes place.

Ethyl Ether and 3,5-Dinitrobenzoyl Chloride.—We prepared ethyl 3,5-dinitrobenzoate by treatment of a small quantity of the dinitrobenzoyl chloride with an excess of pure, dry ethyl ether in the presence of anhydrous zinc chloride. An investigation is now being carried out to determine whether this type of reaction can be employed in the identification of aliphatic (and possibly aromatic) ethers; the results will be discussed in a later paper. Mulliken[5] has described the use of 3,5-dinitrobenzoyl chloride for the identification of alcohols.

Higher Aliphatic Ethers.—The reactions of acetyl chloride with *iso*propyl (5 g.), *n*-butyl (20 g.) and *iso*-amyl (15 g.) ethers gave 30, 68 and 48% yields of the corresponding acetates. Benzoyl chloride was converted into *iso*propyl, *n*-butyl and *iso*-amyl benzoates; the yields were 10, 45 and 40%. Twenty-eight and 57% yields of

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[5] Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York City, 1904, Vol. I, pp. 168–172.

n-butyl propionate and *n*-butyl *n*-butyrate were obtained by heating propionyl chloride (16 g.) and *n*-butyryl chloride (23 g.) with *n*-butyl ether.

Isolation of Alkyl Chlorides.—Small amounts of ethyl, *iso*propyl, *n*-butyl and *iso*amyl chlorides were obtained from some of our reaction mixtures. More information about these alkyl chlorides is given in a later paper.[6]

Aromatic Ethers.—The behavior of the following pairs of compounds in the presence of anhydrous zinc chloride was studied: diphenyl ether and acetyl chloride, anisole and acetyl chloride, diphenyl ether and benzoyl chloride, anisole and benzoyl chloride. Each mixture was allowed to stand for half an hour at room temperature, and then heated under reflux in a water-bath for two hours. Hydrogen chloride was evolved and a dark viscous mass was formed in each case. The mixtures were cooled and diluted with several volumes of cold water and some ethyl ether. After being washed with water until practically free from zinc chloride, the ether solutions of the reaction products were dried with anhydrous sodium sulfate; then the solvent was removed by distillation. The products thus isolated were viscous oils which partly solidified upon long standing; in some cases it was necessary to fractionate the oils. The solids were pressed on a porous tile and crystallized from alcohol and water or from pure ethyl ether. The melting points as well as other physical properties and resistance to hydrolysis of our products indicate that they are 4-phenoxyacetophenone, *p*-acetylanisole, 4-phenoxybenzophenone and *p*-benzoylanisole; Kipper, and Gattermann, Ehrhardt and Maisch[7] prepared these compounds from diphenyl ether and anisole by treatment of the ethers with acetyl and benzoyl chlorides in the presence of anhydrous aluminum chloride. From two 17-g. lots of diphenyl ether we obtained 9 g. of 4-phenoxybenzophenone and 7 g. of 4-phenoxyacetophenone; two 10.8-g. lots of anisole gave 6 g. of *p*-benzoylanisole and 0.5 g. of *p*-acetylanisole. There was no evidence of the formation of esters in the reactions. One-gram samples of each (uncrystallized) reaction product were heated under reflux for an hour with 10 cc. of 10% sodium hydroxide solution; by extraction with pure ethyl ether practically all of the initial material was recovered in each case. Evidently the carbon–oxygen bonds in diphenyl ether and anisole are not readily broken by zinc chloride; the ketones which we obtained were previously prepared with better yields by the use of anhydrous aluminum chloride in place of zinc chloride. Consequently, no more aromatic ethers were investigated.

Reactions of Ethyl Ether with Acids and with Anhydrides

Preliminary Experiments and General Procedure.—The acids and most of the anhydrides employed in our experiments were pure Eastman products; succinic and diphenic anhydrides were synthesized. It was found that treatment of glacial acetic acid with a slight excess of pure, dry ethyl ether in the presence of anhydrous zinc chloride did not give a good yield of ethyl acetate.

Hydrogen bromide was prepared by dropping bromine on moist red phosphorus; moisture and bromine were removed by passing the gas through a drying train containing red phosphorus, calcium chloride and phosphorus pentoxide. The dry hydrogen bromide was passed into pure, anhydrous ethyl ether in a flask attached to a reflux water condenser, with a calcium chloride tube in the top, for about seven hours; the mixture was cooled from time to time but not continuously. This procedure did not completely saturate the ether, but it gave a fairly concentrated solution. It was found that treatment with hydrogen bromide for a longer time and continuous cooling were necessary for the complete saturation of the ether.

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[6] Underwood and Toone, THIS JOURNAL, **52**, 391 (1930).

[7] Kipper, *Ber.*, **38**, 2490 (1905); Gattermann, *ibid.*, **22**, 1129 (1889); Gattermann, Ehrhardt and Maisch, *ibid.*, **23**, 1199 (1890).

About 75 cc. of the ether–hydrogen bromide mixture was added to each of the acids and anhydrides in an Erlenmeyer flask. The latter was closed by a tight-fitting stopper held in place by wire and covered with collodion. The reaction mixtures were allowed to stand for ten to twelve days. Each flask was then attached to a reflux water condenser provided with a calcium chloride tube, and the contents were boiled for three hours. After being cooled to room temperature, each reaction mixture was shaken two or three times with an equal volume of cold 10% sodium hydroxide solution until very slightly alkaline; then it was washed with an equal volume of cold water and dried with anhydrous sodium sulfate. Finally the excess ether was removed by distillation and the residue was fractionated if the expected ester was a liquid, or allowed to stand until crystallization occurred if the ester was a solid; if necessary, solid esters were washed with cold, dilute sodium carbonate solution and crystallized from suitable solvents.

Yields of Esters.—The acids investigated and the percentage yields of ethyl esters obtained are as follows: acetic, 8; chloro-acetic, 30; propionic, 34; *n*-butyric, 41; *iso*valeric, 42; oxalic, 8; malonic, 6; succinic, 16; benzoic, 28; phenylacetic, 56; hydrocinnamic, 80; *p*-toluic, 23; mandelic, 24; anisic, 5; *p*-chlorobenzoic, 10; *o*-nitrobenzoic, 5; *m*-nitrobenzoic, 42; *p*-nitrobenzoic, 10; 3,5-dinitrobenzoic, 27; *p*-aminobenzoic, 1; *o*-phthalic, 9; diphenic, 16. Three grams of hydrocinnamic acid, 4 g. of *p*-toluic acid and 10 g. each of the other acids were used. No esters were obtained from stearic, picric, *p*-toluenesulfonic and 2,4,6-trinitrobenzoic acids; Victor Meyer's esterification rule would lead one to expect that the trinitrobenzoic acid would not esterify.

The anhydrides investigated and the percentage yields of ethyl esters obtained are as follows: acetic, 13; propionic, 23; *n*-butyric, 38; *iso*valeric, 41; succinic, 13; benzoic, 49; *o*-phthalic, 13; diphenic, 25. Ten grams of each anhydride was used.

An investigation of the mechanism of the reactions of ethyl ether with acids and anhydrides in the presence of dry hydrogen bromide[6] has shown that the amount of the latter present influences the yields of esters. If two moles of hydrogen bromide per mole of ethyl ether is used, all of the ether is converted into ethyl bromide. In the experiments described above the same ether–hydrogen bromide mixture was used for each compound in a series and the results are comparable. Check runs with acetyl chloride, benzoyl chloride and acetic anhydride and different lots of ether–hydrogen bromide mixtures gave yields of esters which were nearly the same as those previously obtained.

Summary

In the presence of anhydrous zinc chloride, pure ethyl ether reacts with the chlorides of acetic, chloro-acetic, propionic, *n*-butyric, *iso*valeric, benzoic, phenylacetic, diphenic, *o*-phthalic, oxalic and 3,5-dinitrobenzoic acids to form ethyl esters. *o*-Phthalyl chloride gives phthalic anhydride as well as diethyl phthalate. Under the conditions tried, benzenesulfonyl and *p*-toluenesulfonyl chlorides do not form esters, and the chlorine atoms in benzyl chloride, *o*-nitrochlorobenzene, 2,4-dinitrochlorobenzene and picryl chloride are not replaced by ethoxy groups. *Iso*propyl, *n*-butyl and *iso*-amyl acetates and benzoates are obtained by the treatment of acetyl and benzoyl chlorides with *iso*propyl, *n*-butyl and *iso*-amyl ethers. Diphenyl ether and anisole behave like aromatic hydrocarbons when heated with acetyl and benzoyl chlorides in the presence of anhydrous zinc

chloride; ketones are formed by the introduction of an acetyl or benzoyl group into the aromatic nucleus.

Acetic, chloro-acetic, propionic, *n*-butyric, *iso*valeric, oxalic, malonic, succinic, benzoic, phenylacetic, hydrocinnamic, *p*-toluic, mandelic, anisic, *p*-chlorobenzoic, *o*-, *m*- and *p*-nitrobenzoic, 3,5-dinitrobenzoic, *p*-aminobenzoic, *o*-phthalic and diphenic acids and the anhydrides of acetic, propionic, *n*-butyric, *iso*valeric, succinic, benzoic, *o*-phthalic and diphenic acids are converted into ethyl esters by treatment with anhydrous ethyl ether containing dry hydrogen bromide. Stearic, picric, *p*-toluenesulfonic and 2,4,6-trinitrobenzoic acids do not react with ethyl ether in the presence of hydrogen bromide.

CAMBRIDGE, MASSACHUSETTS

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CATALYSIS IN ORGANIC CHEMISTRY. II. MECHANISM OF THE REACTIONS OF ETHERS WITH ACID CHLORIDES, ACIDS AND ANHYDRIDES

BY H. W. UNDERWOOD, JR., AND G. C. TOONE

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In a previous paper[1] it was pointed out that a number of acid chlorides, acids and anhydrides are converted into esters by treatment with aliphatic ethers in the presence of anhydrous zinc chloride or hydrogen bromide. Zinc chloride might increase the reactivity of aliphatic ethers by loosening the alkyl groups so that a metathesis of the type $RCOCl + R'OR' = RCOOR' + R'Cl$ would occur. The possibility that aliphatic ethers may be split into two or more compounds capable of independent existence also deserves consideration. Experiments described in this paper show that ethyl, *iso*propyl, *n*-butyl and *iso*-amyl ethers yield small amounts of the corresponding alcohols and unsaturated hydrocarbons when heated with anhydrous zinc chloride. When an alcohol thus formed is esterified by an acid chloride, splitting of the ether continues, and the hydrogen chloride produced may convert some of the alcohol into an alkyl chloride. Equations for the transformations of acetyl chloride and ethyl ether might be written as follows

$$CH_3CH_2OCH_2CH_3 = CH_3CH_2OH + CH_2{=}CH_2$$
$$CH_3CH_2OH + CH_3COCl = CH_3COOCH_2CH_3 + HCl$$
$$CH_3CH_2OH + HCl = CH_3CH_2Cl + H_2O$$

The reaction of ethyl ether with acetyl chloride takes place in the presence of a very small amount of anhydrous zinc chloride, and the latter can be used several times; apparently zinc chloride acts as a true catalyst.

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[1] Underwood and Wakeman, THIS JOURNAL, **52**, 387 (1930).