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Catalytic Synthesis of Aromatic–Aliphatic and Heterocyclic–Aliphatic Ketones. I. Simple Ketones Derived from Benzene, Pyridine and Furan

BY JAMES L. A. WEBB AND JEANNE D. WEBB

The well known catalytic decomposition of carboxylic acids and esters may result in the formation of ketones in high yields.[1] Although this reaction is not satisfactory with aromatic acids alone, mixtures of sufficiently volatile aromatic acids with aliphatic acids give aromatic–aliphatic ketones in good yields.[2] In the heterocyclic series nicotinic acid gave 3,3′-dipyridyl ketone[3] in 2.7% yield when distilled over thorium dioxide at 300°. An unsuccessful attempt to prepare 3-acetyl-4-methylpyridine[4] by reaction of 4-methylpyridine-3-carboxylic acid with acetic acid over the same catalyst was attributed in part to the low volatility of the heterocyclic acid.

At elevated temperatures in the presence of thorium dioxide the reaction of aliphatic acids to form ketones, carbon dioxide and water is rapid[5]; under these same conditions the reaction with aliphatic esters with water to form acids and alcohols is reversible.[2] Ester interchange in an acid–ester mixture would seem probable under these conditions. Thus it seemed possible that these reactions might be utilized to bring together a volatile and a non-volatile acid on the catalyst surface and make possible the synthesis of aromatic–aliphatic as well as certain difficultly prepared heterocyclic–aliphatic ketones. Although direct acylation by the Friedel–Crafts-type reaction is successful in the case of benzene and its derivatives, and on acylation furan forms furyl-2 ketones in good yields,[6] pyridine does not undergo direct acylation.

The present paper is concerned with a new method of preparation of ketones from certain heterocyclic and aromatic acids by the passage of their volatile esters, mixed with an excess of a volatile aliphatic acid, over a catalyst at elevated temperatures (see Table I). Esters of benzoic, picolinic, nicotinic, isonicotinic and furoic acids were passed with acetic and butyric acids over thorium dioxide in the range 290–550°. The reported catalytic activity and ease of preparation of thorium dioxide on pumice prompted its use in this study.

Side reactions of decarboxylation of the free acid and dehydration of the alcohol formed proceed simultaneously to a greater or lesser extent depending upon the temperature. One run (not included in Table I) was made using ethyl 3,4-dichlorobenzoate and acetic acid in the ratio of one mole of ester to four moles of acid at 518-520° and at the rate of 0.29 g./min., using tube-1 and catalyst-1. None of the desired ketone, 3,4-dichloroacetophenone, was obtained, but a considerable quantity of the free aromatic acid was formed by de-esterification and/or ester interchange and failing to decarboxylate or undergo ketone formation with the excess aliphatic acid, passed through the furnace unchanged. In runs using the esters of nicotinic acid at the higher temperatures, an appreciable amount of pyridine was formed. In comparable runs of ethyl and methyl benzoate styrene was formed in small quantities.

The desired ketones in varying yields were obtained except in the case of esters of picolinic and isonicotinic acids where the apparent course of the reaction was de-esterification and/or ester interchange followed by decarboxylation to yield pyridine. Both of these acids are known to decarboxylate readily. Since the pyridine nucleus does not undergo direct acylation, of particular significance is the successful preparation here of 3-acetylpyridine and 3-butyrylpyridine in yields of 36 and 38%, respectively.

Numerous other runs at different temperatures and rates not shown in Table I were made. The temperature ranges for maximum yields of ketone were: acetophenone, 504–537°; 3-acetylpyridine and 3-butyrylpyridine, 520–544°; 2-acetylfuran and 2-butyrylfuran, 460–473°. An increase or decrease in temperature or a decrease in the acid–ester molar ratio below four generally resulted in lowered yields of the desired ketone. The rate for maximum yields of all ketones, using the apparatus described, was in the range 0.25–0.35 g./min. of the ester–acid mixture.

The available data show no consistent difference in yields obtained by the use of the methyl and ethyl esters.

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Experimental

Apparatus and Catalyst.—Tube-1 and catalyst-1 were those described by Herbst and Manske.[2] Tube-2 was essentially that described by Kistler, Swann and Appel[1]: length of main tube, 61 cm.; length of inner tube, 58 cm.;

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[1] Kistler, Swann and Appel, *Ind. Eng. Chem.*, **26**, 389, 1014 (1934).

[2] Sabatier and Mailhe, *Compt. rend.*, **152**, 360, 669 (1911); Herbst and Manske, "Organic Syntheses," Coll. Vol. II, 389 (1941).

[3] Linsker and Evans, THIS JOURNAL, **68**, 907 (1946).

[4] Webb and Corwin, *ibid.*, **66**, 1456 (1944).

[5] Senderens, *Ann. Chim.*, [8] **4**, 476 (1905); Mailhe, *Chem. Ztg.*, **33**, 242 (1909), and later papers.

[6] Reichstein, *Helv. Chim. Acta*, **13**, 365 (1930); Gilman and Calloway, THIS JOURNAL, **55**, 4197 (1933); Heid and Levine, Paper 37, Division of Organic Chemistry, AMERICAN CHEMICAL SOCIETY, St. Louis, Mo., September 7, 1948.

TABLE I[j]

CATALYTIC PREPARATION OF SIMPLE KETONES DERIVED FROM BENZENE, PYRIDINE AND FURAN

Ester[a]	Acid	Temp., °C.	Rate, g./min.	Product	B. p. °C.	B. p. Mm.	Yield, %
Ethyl benzoate[b]	Acetic	524–537	0.35	Acetophenone[d,e]	87–90	22–23	56
Methyl benzoate[c]	Acetic	504–516	.33	Acetophenone[d,e]	87–90	22–23	48
Ethyl nicotinate[c]	Acetic	520–528	.29	3-Acetylpyridine[d,f]	105–108	22–23	36
Methyl nicotinate[c]	Acetic	520–525	.28	3-Acetylpyridine[d,f]	105–108	22–23	28
Ethyl nicotinate[b]	Butyric	530–544	.24	3-Butyrylpyridine[g]	124–129	22–23	33
Methyl nicotinate[b]	Butyric	538–544	.25	3-Butyrylpyridine[g]	124–129	22–23	38
Ethyl furoate[b,k]	Acetic	464–466	.23	2-Acetylfuran[d,h]	71–75	21–22	25
Methyl furoate[b]	Acetic	460–464	.23	2-Acetylfuran[d,h]	71–75	21–22	31
Ethyl furoate[b]	Butyric	466–473	.27	2-Butyrylfuran[i]	93–96	21–22	12
Methyl furoate[b]	Butyric	462–470	.25	2-Butyrylfuran[i]	93–96	21–22	11

[a] Ratio of one mole of ester to four moles of acid used. [b] Tube-2 and catalyst-2 used. [c] Tube-1 and catalyst-1 used. [d] Purity by refractive index determination. [e] 2,4-Dinitrophenylhydrazone m. p. 250°. [f] Picrate m. p. 133.8–134.8°. [g] n^{20}D 1.5212; phenylhydrazone m. p. 129–130°; mercuric chloride salt m. p. 114.5–115.5°. [h] Semicarbazone m. p. 148.4–149.4°. [i] n^{20}D 1.4930; semicarbazone m. p. 190.7–191.7°. [j] Microfilm of the complete table of runs made is obtainable from the American Documentation Institute, 1719 N Street, N.W., Washington 6, D.C., on remitting 50¢ for microfilm or 50¢ for photoprints of Document 2648. [k] Furoic acid kindly supplied by the Quaker Oats Company.

o. d. outside jacket, 3.5 cm.; annular space, 0.75 cm. Catalyst-2 was prepared from pumice, screened to pass 10 but not 18 mesh, digested with hot cond. nitric acid and washed exhaustively with distilled water. Sufficient pumice to fill tube-2 was soaked in a water solution of 72.0 g. of C. P. thorium nitrate tetrahydrate (Eimer and Amend) and decomposed to thorium dioxide by heating with a direct flame in an open evaporating dish with stirring. The same electrically heated cylindrical furnace was used with both tubes. Immediately preceding the furnace and catalyst tube was a preheater consisting of a glass tube tilted slightly from horizontal toward the furnace and heated by a small, broad (4 cm.) flame.

General Procedure.—At the beginning of each run 5-10 cc. of the aliphatic acid was dropped at a constant rate into the pre-heater leading directly into the catalyst tube. This was followed immediately by a freshly prepared solution of the aromatic or heterocyclic ester in the C. P. aliphatic carboxylic acid. When the addition of the ester-acid solution was complete another 5-10 cc. of the aliphatic carboxylic acid was run through the furnace. The products were led through an air-cooled glass tube 60 cm. long and 7 cm. in diameter into two spiral water-cooled condensers in series, one 42 cm. and the other 30 cm. long, then through four salt-ice-traps.

Since a slight amount of carbonization frequently accompanied the reaction, regeneration was accomplished by pulling air slowly over the catalyst while at 450-550° for at least three hours. The furoates caused considerably more carbonization than the other compounds run.

The distillate collected from the furnace was treated with an excess of 10% sodium hydroxide solution to remove unreacted acid and was allowed to stand at least twelve hours to remove most of the unreacted ester. The basic mixture was extracted with ether, dried over "Drierite" and fractionated at atmospheric pressure or under a water pump vacuum through a 10-in. Widmer column.

Analysis of Products.—In all cases the ketone product of the reaction was identified by the preparation of suitable known derivatives (see Table I). In several instances the starting aromatic or heterocyclic ester (not removed by base) and the ketone resulting from the reaction of the ester with acetic acid boil too close together for complete separation by fractionation with the Widmer column. In such cases where the final fraction contained both the desired ketone and a small amount of the ester, the composition of the mixture was determined from its refractive index using an Abbe refractometer. The refractive index as a function of concentration of each of the following pairs of compounds was determined experimentally and found to be substantially linear in each case: ethyl benzoate-acetophenone; methyl benzoate-acetophenone; ethyl nicotinate-3-acetylpyridine; methyl nicotinate-3-acetylpyridine; ethyl furoate-2-acetylfuran; methyl furoate-2-acetylfuran. Yields are reported to the nearest whole per cent. All melting points and boiling points are corrected.

Summary

A new method is described for the preparation of certain aliphatic acyl derivatives of benzene, pyridine and furan. Esters of solid benzene, pyridine and furan carboxylic acids were passed with aliphatic acids over thorium dioxide at elevated temperatures to yield the mixed aromatic–aliphatic and heterocyclic–aliphatic ketones.

Of particular significance is the successful preparation by this method of 3-acetylpyridine and 3-butyrylpyridine.

This catalytic method of preparation should be applicable to the higher homologs of the corresponding aliphatic acyl derivatives of benzene, pyridine and furan.

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