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THE ACYLATION OF FURAN AND THIOPHENE WITH ALIPHATIC ANHYDRIDES IN THE PRESENCE OF BORON TRIFLUORIDE-ETHERATE[1]

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In connection with a research program in progress in this laboratory on the use of boron trifluoride in organic syntheses, it was of interest to investigate the acylation of furan and thiophene with anhydrides using the etherate to effect the condensations.

Although our work is not fully completed, it seemed desirable to publish an account of the progress we have made to date, since other workers have used gaseous boron trifluoride or its complexes for certain similar reactions.

Meerwein and Vossen (1) have reported the acylation of benzene and other aromatic compounds with anhydride using gaseous boron trifluoride as the condensing agent. Given and Hammick (2) have aroylated thiophene with benzoic anhydride. By saturating a solution of the anhydride and thiophene with gaseous boron trifluoride, these workers obtained a 40% yield of 2-benzoylthiophene. More recently, Hartough and Kosak (3) have shown that when catalytic amounts of a complex of ortho-phosphoric acid and boron trifluoride $[(H_3PO_4)_3 \cdot BF_3]$ are allowed to react with thiophene and acetic anhydride, a 63% yield of 2-acetylthiophene is obtained. Earlier, these workers found that catalytic amounts of iodine (4), hydriodic acid (5), and anhydrous zinc chloride (5) also cause anhydrides to condense with thiophene and furan in high yields.

In the present investigation we have found that a catalytic amount of boron trifluoride-etherate effects the condensations of thiophene and furan with acetic, propionic, and *n*-butyric anhydrides in high yields. In order to determine the best conditions for carrying out these reactions, a detailed study was made of the acylation of furan with acetic anhydride. These experiments are summarized in Table I. It can be seen that fourteen grams of the complex added rapidly to 1.0 mole of furan and 1.15 moles of acetic anhydride gave the highest yields of 2-acetylfuran. It is of interest to note that when the above quantities of reactants were used and the reaction mixture allowed to stand overnight before being hydrolyzed the yield of the ketone was decreased to 54%. The yields of the 2-acylthiophenes and the 2-acylfurans which have been prepared are given in Table II.

In order to explain how a catalytic amount of boron trifluoride-etherate effects these condensations, we suggest the following possible mechanism for these reactions. The acylation of furan with acetic anhydride is taken as an example.

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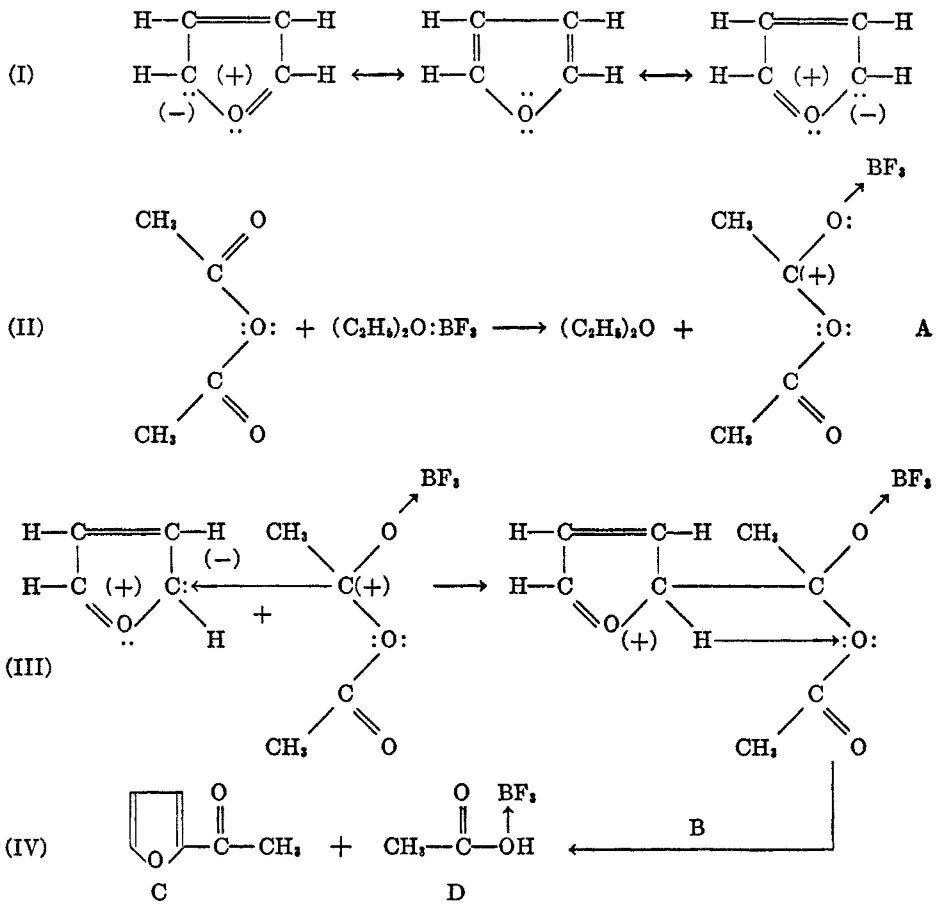
[1] This work is based on a thesis to be submitted by John V. Heid in partial fulfillment of the requirements of the degree of Master of Science at the University of Pittsburgh.



Equation (I) represents two of the resonance hybrid forms of the furan molecule. In equation (II) the boron trifluoride-etherate reacts with the acetic anhydride to form an acetic anhydride-boron trifluoride complex (A). In equation (III) this active complex then condenses with furan to give the complex (B) which may then lose the elements of acetic acid and boron trifluoride to form the ketone (C) and the boron trifluoride-acetic acid complex (D). This complex may then react with more of the anhydride in the same way as the boron trifluoride-etherate does in step (II) and thus the reaction could proceed using catalytic amounts of boron trifluoride-etherate as the condensing agent.

Some support for this mechanism is given by the fact that $(H_3PO_4)_3 \cdot BF_3$ in catalytic amounts gives a good yield of 2-acetylthiophene when thiophene is condensed with acetic anhydride (2). A mechanism, similar to the one proposed above, could account for the successful use of catalytic amounts of anhydrous zinc chloride in these condensations by Hartough and Kosak (4).

In order to find more experimental evidence for the proposed mechanism, work is under way in this laboratory using the boron trifluoride-acetic acid complex as the condensing agent. The results of this work will be reported at a later date.

The furan used in this investigation was contributed by E. J. du Pont de Nemours and Co., Inc.

EXPERIMENTAL

The 2-acylfurans. (a) *2-Acetylfuran.* The apparatus used in these experiments consisted of a 500-ml. three-necked round-bottomed flask equipped with a mercury-sealed stirrer, a reflux condenser (protected by Drierite), and a cork carrying a thermometer so that the temperature of the reaction mixture could be recorded. One mole (68 g.) of furan and 1.15 moles (123 g.) of 95% acetic anhydride were placed in the flask. The reaction mixture was cooled to 0° in an ice-bath. To the rapidly stirred reaction mixture, 14 g. of redistilled boron trifluoride-etherate[2] was added rapidly (all at once). The temperature of the reaction mixture rose to 110°, then quickly dropped to 0°. The ice-bath was removed and the contents of the flask allowed to come to room temperature. Stirring was continued for one-half hour longer, and about 200 ml. of water was added to hydrolyze the reaction mixture. The phases were separated and the aqueous phase was extracted several times with chloroform. The organic phases were separated again and the chloroform solution of the 2-acetylfuran was dried over Drierite. The chloroform was distilled at atmospheric pressure and the residue fractionated *in vacuo* through a Spitz-Vigreux flask. In this way 85 g.

TABLE I

YIELDS OF 2-ACETYLFURAN FROM ONE MOLE OF FURAN UNDER VARIOUS EXPERIMENTAL CONDITIONS

MOLES OF ACETIC ANHYDRIDE	GRAMS OF $BF_3 \cdot (C_2H_5)_2O$	RATE OF ADDITION OF CATALYST	YIELD, %
1	3.5	rapid[a]	44
1	3.5	rapid[a]	51
1.15	3.5	rapid[a]	56
1.15	6.9	slow[b]	54
1.15	11.5	slow[b]	54
1.15	14	rapid[a]	77

[a] Added all at once.

[b] Added over a period of one hour.

TABLE II

YIELDS OF 2-ACYLFURANS AND 2-ACYLTHIOPHENES

PRODUCT	B.P.		YIELD, %
	°C	mm.	
2-Acetylfuran	45–48	5	77
2-Propionylfuran	61–63	6	81
2-*n*-Butyrylfuran	76–78	7	93
2-Acetylthiophene	80–81	7	73
2-Propionylthiophene	88–89	6	79
2-*n*-Butyrylthiophene	96	4	89

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[2] The boron trifluoride-etherate used in this investigation was purchased from General Chemical Company, New York, N. Y.

(77%) of 2-acetylfuran, b.p. 45–48° at 5 mm., was obtained. Its semicarbazone melted at 149–150° corr. (6).

(b) *2-Propionylfuran.* The procedure followed was the same as that for 2-acetylfuran with the following changes. Propionic anhydride (150 g., 1.15 moles) was used. Upon addition of the catalyst, the temperature rose to 65° and dropped to 0° more slowly. In this experiment, 100 g. (81%) of 2-propionylfuran, b.p. 61–63° at 6 mm., was obtained. Its semicarbazone melted at 186–187° corr. (6).

(c) *2-n-Butyrylfuran.* The above procedure was used with the following changes. *n*-Butyric anhydride (182 g., 1.15 moles) was used. Upon addition of the catalyst, the temperature of the reaction mixture rose to 40° and dropped to 15° slowly. In this experiment 128 g. (93%) of 2-*n*-butyrylfuran, b.p. 76–78° at 7 mm., was obtained. Its semicarbazone melted at 190–191° corr. (6).

The 2-acylthiophenes. (a) *2-Acetylthiophene.* The procedure used was similar to that used with the furan compounds with the following changes. Thiophene (84 g., 1.0 mole) was used and the reaction mixture was not cooled in an ice-bath before the catalyst was added. Rapid addition of the catalyst caused the temperature of the reaction mixture to rise to 30°. The reaction mixture was rapidly heated to 110° and then the temperature was allowed to drop to room temperature. In this experiment there was obtained 92.5 g. (73%) of 2-acetylthiophene, b.p. 80–81° at 7 mm. Its semicarbazone melted at 190–191° (7).

(b) *2-Propionylthiophene.* The procedure was the same as that with 2-acetylthiophene with the following changes. Propionic anhydride (1.15 moles, 140 g.) was used. Upon the addition of the catalyst the temperature of the reaction mixture rose to 70°, then slowly dropped to 45°. The reaction mixture was heated to 110° and then allowed to come to room temperature. The ketone was isolated in the regular fashion. In this experiment there was obtained 110 g. (79%) of 2-propionylthiophene, b.p. 88–89° at 6 mm. Its semicarbazone melted at 172.5–173.5° corr. Steinkopf and Schubart (8) reported the melting point as 167°. We prepared a sample of 2- propionylthiophene by their method and found that the melting point of its semicarbazone was 172.5–173.5° corr. A mixed melting point of this semicarbazone with ours showed no depression.

(c) *2-n-Butyrylthiophene.* The procedure followed was the same as that given above with the following changes.) *n*-Butyric anhydride (182 g., 1.15 mole) was used. Upon the addition of the catalyst the temperature rose to 70° and then dropped to 60°. The reaction mixture was then heated to 110° and allowed to cool to room temperature. In this experiment, there was obtained 137 g. (89%) of 2-*n*-butyrylthiophene, b.p. 96° at 4 mm. Its semicarbazone melted at 177° corr. (8).

SUMMARY

Furan and thiophene have been acylated with acetic, propionic, and *n*-butyric anhydrides in high yields using catalytic amounts of boron trifluoride-etherate as the condensing agent.

A possible mechanism for the reaction has been presented.

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