

[CONTRIBUTION NO. 766 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Condensations Effected by Acidic Catalysts. IV. The Acylation of Substituted and Condensed Thiophenes and Furans¹

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In earlier communications^{1,3,4} from this Laboratory, the acylations of furan, thiophene and certain derivatives of these nuclei with aliphatic anhydrides using boron fluoride complexes as condensing agents were discussed. In the present paper, we report the acylation of a number of other thiophene and furan derivatives.

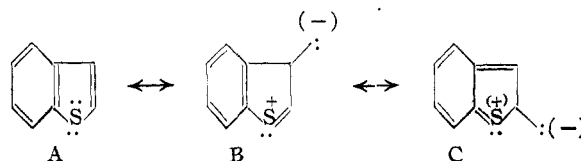
Using the boron fluoride etherate method,^{1,4} it was found that 2,5-dichlorothiophene could not be acetylated with acetic anhydride. Earlier, Steinkopf and Kohler^{5,6} found that this compound could be acetylated in low yield with acetyl chloride using aluminum chloride as the condensing agent. The sluggish acylation of 2,5-dichlorothiophene is not too surprising since the presence of the halogen atoms in the molecule decreases the reactivity of the thiophene in electrophilic substitution reactions. However, when 2,5-dimethylthiophene, in which the three and four positions of the ring are activated toward electrophilic substitution by the inductive and hyperconjugative effects of the methyl groups was acylated with acetic, propionic and *n*-butyric anhydrides, the corresponding 2,5-dimethyl-3-acylthiophenes were obtained in yields of 57, 84 and 93%, respectively.

The acylation of the condensed thiophene system, thianaphthene (benzothiophene) was then studied using the following acidic condensing agents: boron fluoride etherate, orthophosphoric acid, anhydrous ferric chloride, stannic chloride, anhydrous zinc chloride, iodine and aluminum chloride. With the exception of aluminum chloride, all the other condensing agents were used in catalytic amounts.

The acylation of thianaphthene has been studied previously. Thus, Komppa⁷ acetylated this molecule with acetyl chloride in the presence of aluminum chloride and obtained methyl 3-thianaphthenyl ketone as the product. More recently, Hansch and Lindwall⁸ repeated Komppa's work, increased the yield of product considerably and apparently obtained a mixture of isomeric ketones which consisted predominantly of methyl 3-thianaphthenyl ketone. The struc-

ture of the other isomeric ketone was not established. Benzothiophene has also been acetylated with iodine as the condensing agent.⁹ Here, apparently only the 3-acetyl derivative was isolated.

Based on resonance considerations, it appeared that the acetylation of thianaphthene in the presence of an acidic catalyst should give rise to two isomers, methyl 3-thianaphthenyl ketone and methyl 2-thianaphthenyl ketone, with the former compound being produced in larger amounts. The resonance forms which are probably most important in substitution reactions involving the thianaphthene nucleus are represented by the following formulas. It may be seen that in resonance form (B), in which the 3-position of the



thiophene ring is activated, the Kekulé resonance of the benzene ring is not disturbed, while in structure (C), in which the 2-position of the hetero ring is activated, the benzene Kekulé resonance has been destroyed. Hence, although thiophene itself orients substituents to the two or five position of the ring, it is reasonable that in thianaphthene the incoming group should be directed predominantly to the 3-position of the thiophene ring and although a mixture of isomeric products should be expected, the three isomer should be the predominant product formed.

Thus, we have found that when thianaphthene is acetylated in the presence of the seven acidic catalysts mentioned above, a mixture of the 2- and 3-acetyl derivatives is obtained in all cases. The data on these reactions are summarized in Table I. It is interesting to note that the isomeric ketones apparently form an azeotropic mixture since attempts to separate them by distillation at 3 mm., 42 mm. or atmospheric pressure were unsuccessful. Under these conditions the entire ketonic mixture distilled over about a two-degree range. In all cases, the distilled mixtures of the isomers crystallized on standing and the solids thus obtained had a wide melting point range.

In the boron fluoride run, the isomers were separated by fractional crystallization. The infrared absorption spectra of the pure isomers as well as that of the mixture were determined and

(1) For paper III in this series, see Farrar and Levine, *THIS JOURNAL*, **72**, 3695 (1950).

(2) This paper is based on part of the thesis presented by M. W. Farrar to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree.

(3) Levine, Heid and Farrar, *THIS JOURNAL*, **71**, 1207 (1949).

(4) Heid and Levine, *J. Org. Chem.*, **13**, 409 (1948).

(5) Steinkopf and Kohler, *Ann.*, **532**, 265 (1937).

(6) More recently Hartough and Conley (*THIS JOURNAL*, **69**, 3096 (1947)) have repeated this work and increased the yield considerably.

(7) Komppa, *J. prakt. Chem.*, [2] **122**, 322 (1929).

(8) Hansch and Lindwall, *J. Org. Chem.*, **10**, 381 (1945).

(9) Technical Bulletin on Thianaphthene, Jefferson Chemical Co., Inc., New York, N. Y.

TABLE I
ACETYLTION OF THIANAPHTHENE USING 0.5 MOLE OF THIANAPHTHENE AND 0.58 MOLE OF ACYLATING AGENT

Catalyst, g.	Reaction T, 0°		Reaction time, hr.	Mixed ketones		M. p., 0°	Yield, %	2-Acetyl deriv., % ^b	3-Acetyl deriv., % ^b
	Prior to addition of catalyst	After addition of catalyst		B. p., °C.	Min.				
BF ₃ ·Et ₂ O (14)	60	114 ^a	1	126-128	2.5	39-49	67	25	75
AlCl ₃ ^c (38.7)	25	25	16	117-118	0.8	50-60	38	12	88
H ₂ PO ₄ (5.0)	60	100 ^d	2.5	125-126	2	39-49	55	23	77
I ₂ (6.4)	25	110 ^{d,e}	1	120-122	1	43-54	63	23	77
ZnCl ₂ (6.8)	25	100 ^d	1	128-129	2	39-52	45	29	71
SnCl ₄ (12.9)	25	115-120 ^{d,f}	1	132-134	3	37-48	55	33	67
FeCl ₃ (8.0)	25	104 ^d	1	128-130	2.5	42-56	70	28	72

^a Rose to this temperature without application of heat. ^b Determined by quantitative infrared analysis. ^c In this experiment thionaphthene was used as the acylating agent; in all the other runs acetic anhydride was used; to a suspension of 0.29 mole (38.7 g.) of aluminum chloride in 200 ml. of carbon disulfide, a solution of 0.29 mole (23 g.) of acetyl chloride and 0.25 mole (33.5 g.) of thianaphthene in 100 ml. of carbon disulfide was added over a one hour period, the mixture was stirred four hours at room temp. and then allowed to stand for twelve hours at room temp. ^d Heated to this temperature since the addition of catalyst caused no heat rise. ^e After hydrolysis, the organic layer was washed with dilute sodium thiosulfate solution. ^f When the reaction temperature reached 120°, a further temperature rise was checked by cooling the flask in a cold-water-bath.

are found in Fig. 1. The positions of the acetyl groups were established by hypochlorite oxidation^{10,11} to the corresponding known carboxylic acids. In all the other runs, the composition of the isomeric mixtures was merely determined by infrared analysis.

indicates that thiophene is the more aromatic of these two compounds. A possible theoretical explanation lies in the relative electronegativities of oxygen and sulfur. According to Pauling¹⁵ oxygen is the more electronegative of these two elements. Hence, in furan the unshared elec-

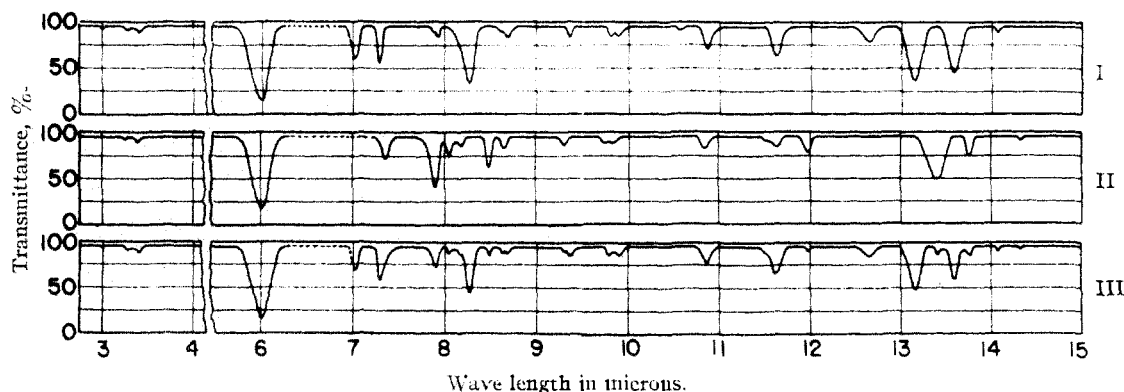


Fig. 1.—I, methyl 3-thianaphthenyl ketone, 0.0216 g. in 0.2449 g. CS₂; II, methyl 2-thianaphthenyl ketone, 0.0158 g. in 0.2483 g. CS₂; III, mixture obtained using BF₃·Et₂O, 0.0206 g. in 0.2486 g. CS₂.

Next, benzofuran, the oxygen analog of thianaphthene, was prepared by the decarboxylation of coumarilic acid^{12,13} and acetylated using catalytic amounts of boron fluoride etherate or stannic chloride¹⁴ as the condensing agents. In both runs, only one compound, methyl 2-benzofuryl ketone, was isolated.

It is apparent that the differences in orientation between the two ring systems, benzofuran and thianaphthene, must be associated with the nature of the hetero atom. In considering the relative aromaticities of the simple heterocyclics, thiophene and furan, experimental evidence

trons around the hetero atom are held more tightly than those around the sulfur atom in thiophene. Such an electronic situation makes it possible for important contributions to be made to the actual state of the molecule by resonance structures in which a pair of unshared electrons is not on the sulfur atom but elsewhere in the ring.

This same effect of the hetero atom is also manifested in thianaphthene and benzofuran although perhaps in a somewhat different manner. Experimental evidence indicates that thianaphthene is the more aromatic of these two systems. Typical of an aromatic system, thianaphthene reacts with bromine by a substitution process¹⁶ to give 3-bromothianaphthene, while benzofuran reacts with bromine by an addition process¹³

(10) Newman and Holmes, "Organic Syntheses," 2nd Coll. Vol., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 428.

(11) Farrar and Levine, *THIS JOURNAL*, **71**, 1496 (1949).

(12) Fuson, Kneisley and Kaiser, "Org. Synth.," Vol. 24, p. 33.

(13) Smith, Ph.D. Thesis, Iowa State College (1936); Smith, *Iowa State Coll. J. Sci.*, **12**, 155 (1937).

(14) Smith¹³ carried out this acetylation using two equivalents of stannic chloride per mole of benzofuran.

(15) Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940.

(16) Komppu and Weekman, *J. prakt. Chem.*, [2], **138**, 109 (1933).

to give 2,3-benzofuran dibromide. This latter reaction is typical of an olefinic system. Thus, it should be expected that thianaphthene should be acylated predominantly at the 3-position of the thiophene ring and that benzofuran, which may be regarded as a furan molecule which contains substituents in the two and three positions of the ring, should direct the entering group in an electrophilic substitution reaction to the unoccupied α -position.

Finally, since it has been possible to acetylate thianaphthene in the presence of catalytic amounts of stannic chloride and anhydrous ferric chloride and since these reagents have been reported¹⁷ to be unsuccessful in the acetylation of thiophene, these condensations were reinvestigated. Using these catalysts, 2-acetylthiophene has been prepared in yields of 83 and 87.5%, respectively. It has further been found that the boron fluoride-acetic anhydride complex is an effective condensing agent for the acetylation of thiophene, but that catalytic amounts of the aluminum chloride-ethyl ether or nitromethane complex are ineffective in this reaction. The results of this phase of the study are summarized in Table II.

TABLE II
ACYLATION OF THIOPHENE

2-Acetylthiophene, %	Catalyst	Mole % catalyst per mole of thiophene	Reaction time in hours
82 ^a	BF ₃ ·Et ₂ O	10	0.5
75 ^a	BF ₃ ·HOAc	10	.5
69	BF ₃ ·Ac ₂ O	10	.5
83, (69.4)	SnCl ₄	1, (10)	.5 (0.5)
87.5, (82.3)	FeCl ₃	1, (10)	.5, (0.5)
5.7, (9.5), ^b (4.1) ^b	AlCl ₃	10, (10), (10)	.5, (2), (15)
Trace	AlCl ₃ ·Et ₂ O	10	2
Trace	AlCl ₃ ·CH ₃ NO ₂	10	2

^a Included for comparison, see refs. 3 and 4. ^b Acetyl chloride used as acylating agent, in all other runs acetic anhydride was used.

Experimental¹⁸

Preparation of 2,5-Dimethylthiophene.—The following procedure is a modification of that described by Paal.¹⁹ To 0.50 mole (111 g.) of phosphorus pentasulfide contained in a one-liter three-neck round-bottom flask, fitted with a large bore reflux condenser and a dropping funnel with the third neck closed by means of a cork, is added 20 g. of acetylacetone. The mixture is heated with a small luminous flame until the reaction has started as evidenced by the darkening of the liquid in contact with the phosphorus pentasulfide and the formation of a fog of vapor in the reaction flask. The burner is removed and the remainder of two moles of acetylacetone (total 228 g.) is added dropwise over a one-hour period. The heat of reaction causes the mixture to reflux and occasional cooling in a cold water bath is necessary in order to prevent the reaction from becoming violent. After the diketone has been added and the refluxing has subsided (about one-half hour), the mixture is heated cautiously and refluxed one hour longer. When the mixture has cooled to room temperature, the liquid is poured from the flask into ice water, the residue in the flask rinsed with ether and the washings

added to the rest of the reaction product. The mixture is extracted several times with ether and the combined extracts washed with sodium carbonate solution until free of acid, dried over Drierite and distilled. After removing the solvent, there is obtained 145 g. of light yellow liquid, b. p. 125–135° which on redistillation gives 129 g. (58%) of water-white 2,5-dimethylthiophene, b. p. 133–135°.

General Acylation Procedure.—One-half mole of the heterocyclic compound and 0.58 mole of the appropriate anhydride (in the acetylation of benzofuran, 0.25 mole of the compound and 0.29 mole of the anhydride were used) were placed in a three-neck round-bottom flask equipped with a mercury-sealed stirrer, a reflux condenser (carrying a Drierite-filled drying tube) and a thermometer dipping into the reaction mixture. To the rapidly stirred mixture at the appropriate temperature, the catalyst was added all at once. The temperature rose or the reaction mixture was heated (see below) and then stirring was continued for the time interval indicated (see below). Then, about 200 ml. of water was added, the contents of the flask extracted with several portions of ether, the combined extracts washed with 10% sodium carbonate solution until free of acid and dried over Drierite. After removing the solvent, the residue was fractionated in vacuum.

The Boron Fluoride-Etherate (I) Catalyzed Acylations of 2,5-Dimethylthiophene (II).—Seven grams of I was added to a mixture of II and the appropriate anhydride and the mixture heated and stirred at 100–110° for one-half hour, and then worked as described above. Thus, there were obtained 43.6 g. (57%) of methyl 2,5-dimethyl-3-thienyl ketone, b. p. 109–110° at 14 mm., semicarbazone, m. p. 214–215°²⁰; 70.5 g. (84%) of ethyl 2,5-dimethyl-3-thienyl ketone, b. p. 78–79° at 1 mm., semicarbazone, m. p. 181–182°²⁰ and 84.4 g. (93%) of *n*-propyl 2,5-dimethyl-3-thienyl ketone; b. p. 95–97° at 2 mm., semicarbazone. m. p. 183–184°.²⁰

Acetylation of Thianaphthene (III) with Acetic Anhydride (IV)

(a) **I as the Catalyst.**—The rapidly stirred solution of III and IV was heated to 60° and 14 g. of I was added all at once. The reaction temperature rose to 114° after which stirring was continued for an hour and the run worked up in the usual manner. Distillation gave 9.3 g. (14%) of unreacted thianaphthene, b. p. 57–60° at 2.5 mm., and 59.9 g. (67%) of ketonic material, b. p. 126–128° at 2.5 mm., which crystallized on standing, m. p. 39–49°. Ten grams of this material was recrystallized twice from 65% ethanol to give methyl 3-thianaphthenyl ketone (V), m. p. 64–65°. The mother liquors were concentrated and by repeating the recrystallization process two more fractions of (V) were obtained. Further concentration of the mother liquors and recrystallization of the solid obtained from 65% ethanol gave a solid material, m. p. 45–50°, whose composition could not be changed by further recrystallization from this solvent. This solid was next recrystallized from petroleum ether, b. p. 60–70°, to give methyl 2-thianaphthenyl ketone (VI), m. p. 87–88°. Concentration of the mother liquor gave another portion of (VI). Continued concentration of the mother liquors and recrystallization of the solid obtained from 60–70° petroleum ether gave a material, m. p. 45–50°, whose composition could not be further altered by repeated recrystallization from this solvent. Then, 65% ethanol was used again to give another fraction of V. By alternating the use of the two solvents, from the original 10.0 g. of ketonic material there was obtained 7.4 g. (74%) of V, 1.7 g. (17%) of VI and 0.1 g. of material, m. p. 48–55°, which was not further separated into its constituent isomers.

The semicarbazone of V melted at 249–250°. Oxidation of 0.5 g. of this ketone with sodium hypochlorite solution¹⁰ gave 0.3 g. (60%) of thianaphthene-3-carboxylic acid, m. p. 179–180°.

The semicarbazone of VI melted at 249–250°. *Anal.* Calcd. for C₁₁H₁₁N₃OS: N, 18.02. Found: N, 18.12.

(17) Hartough and Kosak, *THIS JOURNAL*, **69**, 1012 (1947).

(18) All melting points are corrected.

(19) Paal, *Ber.*, **18**, 2251 (1885).

(20) Buu-Hoi and Nguyen-Hoan, *Rec. trav. chim.*, **67**, 309 (1948).

(21) Mayer, *Ann.*, **488**, 259 (1931).

Hypochlorite oxidation¹⁰ of VI to thianaphthene-2-carboxylic acid, m. p. 240–241.5^{21,22} was effected in 75% yield. The infrared absorption spectra of the pure ketones V and VI as well as the spectrum of the mixture are found in Fig. 1. Quantitative analysis of the mixture by infrared analysis showed it to consist of 75% V and 25% VI.

Acylation of Thiophene with Acetic Anhydride. (a) **Stannic Chloride as the Catalyst.**—The addition of 1.3 g. of stannic chloride to the solution of thiophene and acetic anhydride at room temperature caused the temperature to rise slowly to 81°. Stirring was continued for one-half hour after which the reaction was worked up in the regular way to give 52.2 g. (83%) of methyl 2-thienyl ketone, b. p. 86–87° at 10 mm., semicarbazone, m. p. 188–189°. ⁶

(b) **Anhydrous Ferric Chloride as the Catalyst.**—Ferric chloride (0.8 g.) was added to the thiophene-anhydride solution at room temperature. This caused a rapid rise in temperature to 113°, after which the reaction was completed by stirring for one-half hour to give 55.2 g. (88%) of methyl 2-thienyl ketone, b. p. 76–77° at 5 mm.

Acetylation of Benzofuran with Acetic Anhydride. (a) **Boron Fluoride Etherate as the Catalyst.**—To 0.25 mole (29.5 g.) of benzofuran, prepared by the decarboxylation of coumarilic acid,^{13,14} and 0.29 mole of acetic anhydride at room temperature was added 3.5 g. of boron fluoride etherate. The mixture was heated to 50° and then the heat was removed. The reaction temperature rose spontaneously to 76° and the reaction was completed by stirring for one-half hour and worked up in the regular way. There were obtained 10.0 g. of unreacted benzofuran, b. p. 50–60° at 8 mm., and 14.8 g. (37%) of methyl 2-benzofuryl ketone, b. p. 118–119° at 5 mm., m. p. 69–71°. After one recrystallization from petroleum ether, b. p. 60–70°, this product melted at 71–72°¹⁵; semicarbazone, m. p. 206–207° (from ethanol). *Anal.* Calcd. for C₁₁H₁₁N₃O₃: N, 19.34. Found: N, 19.63. Hypochlorite oxidation¹⁰ of the ketone gave benzofuran-2-carboxylic (coumarilic) acid, m. p. 195–196°¹² alone and when mixed with an authentic sample.

(b) **Stannic Chloride as the Catalyst.**—To the solution of benzofuran and acetic anhydride was added 3.25 g. of

stannic chloride all at once. The temperature of the mixture rose to 65–70° at which point the flask was cooled in a cold-water-bath. Stirring was continued for one-half hour and then worked up as described above to give 6.0 g. of unreacted benzofuran, b. p. 52–60° at 8 mm., and 16.4 g. (40%) of methyl 2-benzofuryl ketone, b. p. 118–119° at 5 mm., m. p. 67–70°. After one recrystallization from petroleum ether, b. p. 60–70°, this product melted at 71–72°. ¹⁵

Acknowledgment.—The authors gratefully acknowledge the financial support of the Atomic Energy Commission during the course of this investigation and the assistance of Dr. Robert Friedel of the U. S. Bureau of Mines, Bruceton, Pennsylvania, in interpreting the infrared data.

Summary

2,5-Dimethylthiophene has been successfully acylated with three aliphatic anhydrides in high yields by the boron fluoride etherate method but 2,5-dichlorothiophene could not be acylated by this method.

Thianaphthene has been acetylated using seven Lewis acids as condensing agents. In every case, a mixture of methyl 3-thianaphthenyl and methyl 2-thianaphthenyl ketones was obtained. However, when benzofuran was acetylated only one compound, methyl 2-benzofuryl ketone, was obtained. An explanation of these apparently anomalous results is offered.

Thiophene has been acetylated using catalytic amounts of anhydrous ferric chloride or stannic chloride to effect the condensations but trace amounts of the aluminum chloride-diethyl ether or nitromethane complexes can apparently not be used in this reaction.

(22) Weissberger and Kruber, *Ber.*, **53**, 1551 (1920).

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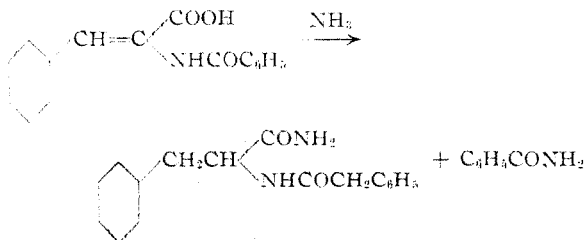
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[CONTRIBUTION FROM THE GALAT CHEMICAL CORPORATION]

The Reaction of Phenylpyruvic Acid and Related Compounds with Ammonia

BY ALEXANDER GALAT

In 1897 Erlenmeyer reported the formation of the amide of N-phenylacetylphenylalanine as the product of the reaction between α -(N-benzamido)-cinnamic acid and ammonia¹



Since phenylpyruvic acid, the hydrolysis product of α -(N-benzamido)-cinnamic acid, reacted

(1) Erlenmeyer, *Ber.*, **30**, 2976 (1897); **31**, 2238 (1898); *Ann.*, **307**, 71, 146 (1899).

with ammonia in the same manner, Erlenmeyer concluded that the formation of phenylpyruvic acid was the first step in this reaction. Several years later Kropp and Decker found that 3,4-dimethoxy- and 3,4-methylenedioxyphenylacetic acids reacted with ammonia in the same way to give the corresponding amides of N-phenylacetylphenylalanines.²

This unusual reaction appeared promising to us as a new route to some of the less accessible amino-acids, phenylacetic acids and isoquinolines and the present communication deals with our work in this direction.

It was found that 4-alkoxy-, 3,4-alkoxy- and 3,4-methylenedioxybenzamidocinnamic acids readily react with ammonia under pressure to give the expected amides of N-phenylacetylphenylala-

(2) Kropp and Decker, *Ber.*, **42**, 1184 (1900).