

phosphoric acid per mole of acid anhydride was added slowly with cooling to maintain the temperature below 90°. The mixture is then warmed to 100–110° (or at the reflux temperature when excess thiophene is used) for two to three hours. The reaction mixture was cooled, 200 ml. of water per mole of acid anhydride added, the mixture thoroughly washed, and finally washed with 10% sodium carbonate solution. The liquid products were rectified through a 12-plate fractionating column. Crystalline products were distilled in suitable apparatus and recrystallized.

With acyl halides the completed reaction mixture was washed with 10% sodium hydroxide solution.

Since the boiling point of furan will not allow the high temperatures used with thiophene the reaction temperature was normally that of the reflux, 40–60°. It was found preferable to cool the completed mixture below 20° before addition of the water.

In general, when an excess of the anhydride was not used, the yields are calculated on the basis that the water in the 85% orthophosphoric acid decomposes a corresponding amount of anhydride.

In preparing footnotes (a) to (k) in Table II the molar ratios of heterocyclic to anhydride used are listed numerically along with any significant departure from the amount of 85% orthophosphoric acid and the temperature or time of reaction.

Preparation of 2-Acetylthiophene Using Anhydrous Hydrogen Fluoride Catalyst.—To 100 g. of anhydrous hydrogen fluoride in a one-liter copper beaker cooled to 15° was added 107 g. (1 mole) of 95% acetic acid. Thiophene, 84 g. (1 mole), was added cautiously and the temperature maintained at 20°. After one hour the hydrogen fluoride was allowed to evaporate off on a steam-bath and the reaction products were processed and rectified as described above. The yield of 2-acetylthiophene was 55 g. (44%).

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carrying out some of the experiments, and Mr. Frank Hochgesang and Mr. John Ehlers for the infrared absorption analyses.

Summary

Strong inorganic oxyacids of fluorine, phosphorus and sulfur having at least one ionizable hydrogen and an ionization constant greater than 1×10^{-2} for the first hydrogen ion were found to be effective catalysts for the acylation of thiophene and furan.

Orthophosphoric acid was found to be the preferable catalyst since it caused little or no deteriorating effects on the heterocyclic nuclei.

Yields of 2-acetylthiophene and 2-acetylfuran as high as 94 and 62%, respectively, are reported. Yields of 2-benzoylthiophene and 2-benzoylfuran as high as 99 and 76%, respectively, are also reported.

3-Methylthiophene with acetic anhydride gave a 92% yield of acetylated product which was a mixture of 80% 2-acetyl-3-methylthiophene and 20% 2-acetyl-4-methylthiophene. 2-Methylthiophene with acetic anhydride gave a 90% yield of 2-acetyl-5-methylthiophene.

Acetylation of 2,5-dichlorothiophene with orthophosphoric acid catalyst gave an 18% yield of 2-acetyl-5-chlorothiophene rather than 3-acetyl-2,5-dichlorothiophene, the normal product obtained with aluminum chloride catalyst.

2,5-Dipropanoylthiophene was obtained from a reaction employing an excess of propanoic anhydride with thiophene.

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Acylation Studies in the Thiophene and Furan Series. V. Thiophene Carboxylic Acids and Semicarbazones Derived from Acetylthiophenes

BY HOWARD D. HARTOUGH AND LORETTA G. CONLEY

The availability of 2-acetylthiophene has led to a study of the possibility of oxidizing this, and substituted acetylthiophenes, to the corresponding thiophenecarboxylic acids by the haloform reaction. In order to characterize properly the acetylthiophenes their semicarbazones were prepared.

Eleven acetylthiophenes, three of which are reported for the first time, have been oxidized with sodium hypochlorite to the corresponding acids. The yields varied from 70 to 95% and appeared to depend upon the ring substituents. For example, 5-(2-pentyl)-2-acetylthiophene gave only a 52% yield of 5-(2-pentyl)-2-thiophenecarboxylic acid while 5-*t*-amyl-2-acetylthiophene gave an 89% yield of 5-*t*-amyl-2-thiophenecarboxylic acid. Products of indefinite structure and low sulfur contents were obtained from 2,5-di-*t*-butyl-3-acetyl

thiophene. Odors of butyric acid were noted and no 2,5-*t*-butyl-3-thiophenecarboxylic acid could be isolated. While this particular acetylthiophene did not give a semicarbazone and appeared to be a hindered ketone, 2,5-dichloro-3-acetylthiophene gave a semicarbazone and an 84% yield of 2,5-dichloro-3-thiophenecarboxylic acid and therefore appeared to be entirely free of steric hindrance.

The semicarbazones form easily in nearly quantitative yields but are somewhat unsuitable for identification purposes in that nearly all melt above 200° and most of them are extremely insoluble in most common solvents and are difficult to recrystallize. Despite recrystallization difficulties samples of high purity are obtained without recrystallization by digesting first with water and then with alcohol to remove impurities.

TABLE I
ACETYLTHIOPHENES AND THEIR SEMICARBAZONES

Compound	Yield, %	B. p., °C. (mm.)	M. p., °C.	n_D^{20}	Semicarbazones		
					M. p.	Nitrogen, % Calcd.	Found
2-Acetylthiophene	94 ^b	77 (4) ^a	10-11 ^a	1.5666 ^a	188-189 ^d	22.94	23.09
2-Acetyl-5-methylthiophene	91 ^b	82.5 (2) ^f	27-28 ^f	1.5622	215-217 dec. ^g	21.32	21.50
2-Acetyl-4-methylthiophene	18 ^b	86 (3) ^b		1.5600	219-220	21.32	21.24
2-Acetyl-3-methylthiophene	74 ^b	72-73 (2) ^c		1.5618	207-208 ^h	21.32	21.26
2-Acetyl-5-bromothiophene	75	107.5-110 (5)	94-95 ⁱ		232-233	16.03	16.00
2-Acetyl-5-chlorothiophene	70 ^b	73 (2.5)	46.5-47 ^j		232.5-233.5	19.35	19.21
2-Acetyl-5- <i>t</i> -amylthiophene ⁿ	84	111 (2)		1.5356	214-215	16.60	16.62
2-Acetyl-5-(2-pentyl)-thiophene ^{l,m}	71 ^c	121-125 (6)		1.5313	184-186	16.60	16.70
2-Acetyl-5- <i>t</i> -butylthiophene ⁿ	81	114 (4)		1.5343	209-210	17.61	17.44
3-Acetyl-2,5-di- <i>t</i> -butylthiophene ^{m,n}	41	105 (3)	54-55		Does not form		
3-Acetyl-2,5-dichlorothiophene	77	87 (3)	38-38.5 ^k		212-213 dec.	16.67	16.63

^a Johnson, *THIS JOURNAL*, **69**, 150 (1947), lists physical constants. ^b Original preparations listed in ref. 1. ^c Hartough, Kosak and Sardella, *THIS JOURNAL*, **69**, 1014 (1947), "obtained 70% yield." ^d Steinkopf and Jaffe, *Ann.*, **413**, 339 (1917), list m. p. of 190-191°. ^e Demuth, *Ber.*, **18**, 3024 (1885), lists b. p. of 224° at 760 mm. ^f Steinkopf and Schubert, *Ann.*, **424**, 15 (1920), list b. p. of 231-232° and m. p. of 27-28°. ^g *Ibid.*, **16** (1920), lists m. p. of 225°. ^h Steinkopf and Nitschke, *Arch. Ber. pharm. Ges.*, **278**, 360 (1940), list m. p. of 207-207.5°. ⁱ Gattermann and Römer, *Ber.*, **19**, 689 (1886), list m. p. of 94°. ^j *Ibid.*, **693** (1886), lists m. p. of 52°. ^k Steinkopf and Kohler, *Ann.*, **532**, 265 (1937), list m. p. of 39°. ^l *Anal.* Calcd. for C₁₁H₁₆OS: S, 16.32. Found: S, 16.31. ^m *Anal.* Calcd. for C₁₁H₂₂OS: S, 13.44. Found: S, 13.48. ⁿ Samples of alkylated thiophenes obtained from P. D. Caesar of this Laboratory. Data will be published later.

TABLE II
THIOPHENECARBOXYLIC ACIDS

Compound, acid	Yield, %	Melting point, °C.		S Analyses, %	
		Observed	Lit.	Calcd.	Found
2-Thiophenecarboxylic	95	129-130	129 ^e	25.00	25.02
5-Methyl-2-thiophenecarboxylic	79	137-138	138-139 ^d	22.53	22.72
4-Methyl-2-thiophenecarboxylic	85	120-121	118-119 ^e	22.53	22.34
3-Methyl-2-thiophenecarboxylic	85	147-148	148 ^{f,g}	22.53	22.69
5-Bromo-2-thiophenecarboxylic	70	141-141.5	141-142 ^{h,i}	15.45	15.79
5-Chloro-2-thiophenecarboxylic	92	153-153.5	146-147 ^j	19.70	19.57
5- <i>t</i> -Amyl-2-thiophenecarboxylic	89	85-86		16.16	16.40
5- <i>t</i> -Butyl-2-thiophenecarboxylic	94	128-128.5		17.39	17.32
5-(2-Pentyl)-2-thiophenecarboxylic	52	Oil ^a		16.16	16.40
2,5-Di- <i>t</i> -butyl-3-thiophenecarboxylic	None isolated.	Products of indefinite structure obtained.			
2,5-Dichloro-3-thiophenecarboxylic	84	147-148		16.24 ^b	16.21 ^b

^a B. p. 152-155 at 11 mm.; n_D^{20} 1.5405. ^b Calcd. for C₈H₆Cl₂OS: Cl, 36.04. Found: Cl, 36.09. ^c Steinkopf, "Die Chemie des Thiophenes," Verlag von Theodor Steinkopff, Dresden, 1941, pp. 85. ^d Rinke, *Rec. trav. chim.*, **51** [4], 1141 (1932). ^e *Ibid.*, **54** [4], 940 (1935). ^f *Ibid.*, **52** [4], 1052 (1933). ^g Steinkopf and Jacob, *Ann.*, **515**, 277 (1935). ^h Gattermann and Römer, *Ber.*, **19**, 69 (1886). ⁱ Steinkopf, Jacob and Penz, *Ann.*, **512**, 160 (1934). ^j *Ibid.*, p. 161.

Since it has previously been shown that 2,5-dichlorothiophene in the presence of acetic anhydride and orthophosphoric acid underwent a carbon to chlorine bond cleavage to give 5-chloro-2-acetylthiophene,¹ it was anticipated that 2,5-di-*t*-butylthiophene would yield some 5-*t*-butyl-2-acetylthiophene, but this was not the case. Instead, upon distillation of the crude product, a 41% yield of 2,5-di-*t*-butyl-3-acetylthiophene was obtained along with a 55% yield of a residue having the same sulfur analysis as the distillate.

Experimental

Preparation of the Acetylthiophenes.—With the exception of 2,5-dichloro-3-acetylthiophene the acetylthiophenes listed in Table I were prepared using 85% orthophosphoric acid and acetic anhydride with the corresponding thiophene.¹

The general procedure utilized one mole of the thio-

phene, one mole of acetic anhydride and 10 g. of 85% orthophosphoric acid. The reactions were carried out at the reflux temperature of the mixture or at 140° maximum temperature.

The 2,5-dichloro-3-acetylthiophene was prepared according to the method of Steinkopf and Kohler,² with the exception that a hundred-fold increase in reactants was used, by treating 2,5-dichlorothiophene, acetyl chloride, and aluminum chloride suspended in petroleum ether. A 77% yield of 2,5-dichloro-3-acetylthiophene was obtained (Steinkopf and Kohler² reported a 16% yield).

The 2,5-di-*t*-butyl-3-acetylthiophene was prepared by both methods and identical yields of the monomer were obtained along with a like amount of the residue which appeared to be a polymer of 2,5-di-*t*-butyl-3-acetylthiophene and contained 16.3% sulfur.

Preparation of Semicarbazones of Acetylthiophenes.—The procedure followed was that of Shriner and Fuson.³ The semicarbazone of 2,5-di-*t*-butyl-3-acetylthiophene does not form.

The compounds crystallized easily and were recrystal-

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

(3) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, New York, N. Y., 1945, p. 142.

(1) Hartough and Kosak, *THIS JOURNAL*, **69**, 3093 (1947).

lized from boiling alcohol, or a mixture of benzene and alcohol. The semicarbazone of 5-bromo-2-acetylthiophene was the most difficult to recrystallize.

Preparation of the Thiophenecarboxylic Acids.—The procedure followed was a modification of that given for the preparation of 2-naphthoic acid from 2-acetylnaphthalene in *Organic Syntheses*.⁴

The sodium hypochlorite solution was freshly prepared for each experiment, heated on a steam-bath to 55°, and the corresponding acetylthiophene introduced slowly over a period of thirty to sixty minutes. In the case of 2-acetylthiophene and the three isomeric methylacetylthiophenes, cooling was necessary to maintain the reaction mixture below 75°. With the other acetylthiophenes it was necessary to apply heat until the reaction was complete.

Attempts to use a more concentrated sodium hypochlorite solution in general were unsuccessful since the reactions were sluggish and the products were obtained in lower yields and in a lower state of purity.

The acids were purified by recrystallization from water or from benzene. It was found advantageous to recrystallize the higher alkyl thiophenecarboxylic acids from petroleum ether to effect final purification.

(4) "Organic Syntheses," Coll. Vol. II, 428 (1943).

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Summary

Eleven acetylthiophenes, three of which are described for the first time, are listed with some of their physical properties.

The semicarbazones of each of the acetylthiophenes have been prepared and characterized.

Each of the acetylthiophenes was subject to oxidation with sodium hypochlorite solution and converted to the corresponding thiophenecarboxylic acid with the single exception of 2,5-*t*-butyl-3-acetylthiophene. This compound appeared to be a hindered ketone and oxidation seemed to take place at the sulfur atom rather than at the ketone group. Four new acids have been prepared and characterized for the first time.

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Acylation Studies in the Thiophene and Furan Series. VI. Direct Acylation with Carboxylic Acids and Phosphorus Pentoxide

BY HOWARD D. HARTOUGH AND ALVIN I. KOSAK¹

The authors reported previously that iodine thiophene with acid anhydrides and acyl halides. and hydriodic acids,² zinc chloride,³ naturally It has now been found that acylation of thio-

TABLE I

	ACYLATION OF THIOPHENE AND FURAN						
	Yield, %	°C.	B. p.	Mm.	M. p., °C.	<i>n</i> _D ²⁰	Formula
2-Acetylthiophene ^a	44	87		7	10-11	1.5666	
2-(2-Ethylbutanoyl)-thiophene	65	91-93		2		1.5390 ^b	C ₁₀ H ₁₄ OS
2-(2-Ethylhexanoyl)-thiophene	65	116-117		4		1.5176	C ₁₂ H ₁₈ OS
2-Decanoylthiophene	42	179-180		8		1.5083	C ₁₄ H ₂₂ OS
2,5-Didecanoylthiophene ^a	23	230-250		8	109-109.5 ^c		C ₂₄ H ₄₀ OS
2-(Δ9,10-Octadecenyl)-thiophene	55	250-255		2			C ₂₂ H ₃₆ OS
Dimer of 2-(Δ9,10-octadecenyl)-thiophene ^{f,g}	42						C ₄₄ H ₇₂ O ₂ S ₂
2-Benzoylthiophene	66	160-163		6	56.5-57 ^{d,h}		
2-Thenoylthiophene	52	189-190		10	88-89 ^{d,i}		
2-Acetylfuran	7	47-48		3	30-32 ^{d,j}		
2-Decanoylfuran	18	150-154		4			
2-Benzoylfuran ^k	40	142-145		2	43.5-44 ^d		

occurring clays of the montmorillonite type and synthetic silica-metal oxide gels,⁴ and strong oxyacids of fluorine, phosphorus and sulfur⁵ were efficient catalysts for the acylation of furan and

thiophene and furan with organic acids may be effected in one operation by means of phosphorus pentoxide.⁶ This method is particularly adaptable to the preparation of the higher aliphatic and aromatic ketones since the halides and anhydrides

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(2) Hartough and Kosak, *THIS JOURNAL*, **68**, 2639 (1946).

(3) Hartough and Kosak, *ibid.*, **69**, 1012 (1947).

(4) Hartough, Kosak and Sardella, *ibid.*, **69**, 1014 (1947).

(5) Hartough and Kosak, *ibid.*, **69**, 3093 (1947).

(6) Steinkopf, *Ann.*, **413**, 346 (1917), and Steinkopf and Schubert, *Ann.*, **424**, 1 (1921), reported that catalytic amounts of phosphorus pentoxide caused acylation of thiophene with acid anhydrides and acyl halides. The yields were of the order of 50%.