Metalation Studies in the Thiophene Series. I. Preparation of 2-Thienylsodium and the 5-Halo-2-thienylsodiums

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It has been found that 2-thienylsodium can be prepared in 84% yields from 2-chlorothiophene and metallic sodium in an inert solvent above 50°. Likewise, yields up to 89% have been obtained from thiophene, sodium amalgam, and an alkyl or aryl halide. The yields were determined from the isolated 2-thiophenecarboxylic acid after carbonation and acidulation.

Schorigin[1] metalated thiophene with diethylmercury and sodium. Gilman and Breuer[2] metalated thiophene in substantially the same fashion with 2,2'-difurylmercury and sodium to obtain a 16% yield of 2-thiophenecarboxylic acid after carbonation.

Investigations in these laboratories indicated that thiophene could not be metalated directly. Further, it was found that thiophene, an alkyl or aryl halide, and sodium gave no 2-thienylsodium. This would indicate that mercury is essential to the metalation.

When 2-chlorothiophene and sodium reacted in an inert solvent above 50°, the normal metathetical reaction occurred to yield 84% of 2-thienylsodium. Table I indicates the solvents and temperatures that were employed and the products that were isolated.

TABLE I

EFFECT OF SOLVENT AND TEMPERATURE ON THE METALATION OF 2-CHLOROTHIOPHENE

Solvent	Temp., °C.	% Yield of 2-thiophenecarboxylic acid
Anisole	40	..
Anisole	50–55	3
Diphenyl ether	40	..
Butyl ether	40–50	..
Butyl ether	50–55	3
Isopropyl ether	67–70	<1
Diethyl ether	−30	..
Diethyl ether	0	16[a]
Diethyl ether	35–39	92[a]
Benzene	80–84	84
Toluene	112	31

[a] The product isolated was 5-chloro-2-thiophenecarboxylic acid.

Solvent volume had a marked effect upon the yield of 2-thiophenecarboxylic acid from 2-chlorothiophene and sodium. The yields decreased from 84 to 20% when the benzene solvent volume was decreased from one liter to 100 ml. per mole of 2-chlorothiophene. A marked increase in reaction rate was noted with lower amount of solvent

(1) Schorigin, Ber., 43, 1938 (1910).
(2) Gilman and Breuer, THIS JOURNAL, 56, 1123 (1934).

and cooling was necessary in order to control the reaction.

Further studies revealed that 5-halo-2-thienylsodium compounds, heretofore unknown, could be prepared by the direct metalation of the 2-halothiophenes with sodium below 50° if ethyl ether was employed as a solvent.

Direct metalation of a heterocyclic ring involving replacement of an acidic hydrogen by an alkali metal has been carried out in small yields by other investigators. Gilman and Breuer[2] metalated furan and 2-methylfuran with a liquid sodium–potassium alloy. Somewhat better yields of the organo-alkali compounds were obtained by indirect metalation, or "transmetalation," through the action of sodium on dialkyl- or diaryl-mercury in the presence of heterocyclic compounds. Wooster and Mitchell[3] and Conant and Wheland[4] arranged the very weak acids (hydrocarbons) in a series of acid strengths, based on their metathetical reaction with organo-alkali compounds.

Gilman and Wright[5] prepared 3-furylsodium by reacting 3-iodofuran with a sodium-potassium alloy. Subsequent carbonation yielded 3-furoic acid.

The 2-halo(chloro-, bromo- and iodo-)-thiophenes are unique in their reaction with sodium in that the same reaction does not occur as with 3-iodofuran. Instead, they metalate in the 5-position with the liberation of hydrogen and the formation of 2-halo-5-thienylsodium (preferable nomenclature is 5-halo-2-thienylsodium). A possible mechanism can be indicated as
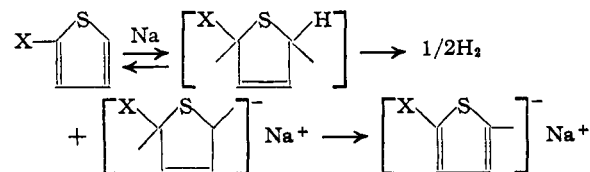
Carbonation and acidulation of the 5-halo-2-thienylsodium yielded the corresponding 5-halo-2-thiophenecarboxylic acid.

Factors influencing the yield of 5-chloro-2-thienylsodium are the quantity of ether solvent, the particle size of the sodium, the presence of mercury, and the temperature.

Diethyl ether was the only solvent in which the reaction took place. No reaction was observed in butyl ether, diisopropyl ether, diphenyl ether, anisole, hexane, benzene, and toluene. Judging

(3) Wooster and Mitchell, ibid., 52, 688 (1930).
(4) Conant and Wheland, ibid., 54, 1212 (1932).
(5) Gilman and Wright, ibid., 55, 2893 (1933).

from the work of Scott, Walker and Hansley[6] methyl ether, methyl ethyl ether and the dialkyl ethers of ethylene glycol would also be suitable solvents.

The yields are dependent on the amount of ether solvent used. Yields decreased from 92 to 50% on reducing the amount of solvent from one liter to 100 ml. per mole of 2-chlorothiophene. The reaction rate is increased greatly and cooling is necessary with less solvent.

Reduction of the particle size of the sodium from approximately 16 mesh to a fine dust increased the yields from 20 to 70%. In order to produce more finely divided or more active sodium, a 70% sodium amalgam was employed. In this manner the yields of 5-chloro-2-thiophenecarboxylic acid were increased from 70 to 92%. The mercury was recovered without appreciable loss.

The optimum temperature is the reflux temperature of ethyl ether, 35–39°. Below that temperature the yields decrease for comparable reaction times, and the reaction proceeds slowly below 0°.

The 5-chloro- and 5-bromo-2-thienylsodium are brown amorphous materials while 5-iodo-2-thienylsodium has a blue cast. They are only slightly soluble in ether. They are stable in an inert atmosphere, but when free of solvent and exposed to air they are oxidized rapidly with evolution of light and heat, similarly to Raney nickel.

Lithium did not appear to react in ethyl ether solvent and potassium yielded scission products.

Most of the work was carried out with 2-chlorothiophene. Since only single runs were made with 2-bromothiophene and 2-iodothiophene to study the versatility of the reaction, the yields of 35 and 33%, respectively, need not be considered the highest obtainable.

Experimental

Preparation of Sodium Shot.—The sodium shot was prepared from molten sodium in toluene by vigorous stirring while cooling until there was no chance of coagulation. The excess toluene was decanted through a glasswool plug in the side arm of the flask and the sodium shot was blanketed with the solvent to be used in the next step. Sodium amalgam was prepared in a similar manner.

Transmetalation of Thiophene with Ethyl Chloride and Sodium Amalgam Sand.—A cold mixture of 16 g. (0.25 mole) of ethyl chloride in 200 ml. of anhydrous diethyl ether was added dropwise over a one hour period to a cooled (5–10°), vigorously stirred mixture of 49 g. (0.58 mole) of thiophene, 100 ml. of anhydrous diethyl ether and freshly prepared sodium amalgam sand containing 15 g. (0.65 gram atom) of sodium and 25 g. (0.125 gram atom) of mercury. The reaction was carried out in the usual Grignard type apparatus under a nitrogen atmosphere. After the addition was completed, the ice-bath was removed and the reaction mixture was refluxed for two and one-half hours. After cooling to 25°, it was carbonated with freshly crushed Dry Ice. The temperature rose momentarily, but it was kept below 30°. The unreacted sodium was destroyed with 50 ml. of ethanol after which 150 ml. of distilled water was added cautiously. Acidula-

tion of the aqueous layer with 75 ml. of concentrated hydrochloric acid yielded 19 g. (60%) of crude 2-thiophenecarboxylic acid. White needles were obtained from hot water, m. p. 128–129°. The neutral equivalent was 124 (calculated, 128). A mixed melting point with an authentic sample of 2-thiophenecarboxylic acid[7] gave no depression.

Transmetalation of Thiophene with Bromobenzene and Sodium Amalgam Sand.—A cold mixture of 78 g. (0.5 mole) of bromobenzene in 300 ml. of anhydrous diethyl ether was added dropwise over a one-hour period to a cooled mixture (5–10°) of 200 ml. of anhydrous diethyl ether, 63 g. (0.75 mole) of thiophene and sodium amalgam sand containing 25 g. (1.09 gram atoms) of sodium and 10 g. (0.05 gram atom) of mercury. After the addition was completed, the mixture was stirred an additional half an hour before removing the ice-bath. When the mixture was warmed slightly, the temperature rose rapidly and an ice-bath was required to control the reaction. After subsiding, it was warmed to reflux for two hours after which it was cooled to 5° and carbonated with freshly crushed dry ice. The unreacted sodium was destroyed with 50 ml. of ethanol and 150 ml. of distilled water was added cautiously. The acidulation of the aqueous layer with 70 ml. of concentrated hydrochloric acid yielded 57 g. (89%) of crude 2-thiophenecarboxylic acid.

Metalation of 2-Chlorothiophene with Sodium.—A mixture of 118 g. (1 mole) of 2-chlorothiophene was added directly to 1000 ml. of benzene and sodium amalgam sand containing 50 g. (2.17 gram atoms) of sodium and 29 g. (0.145 gram atom) of mercury. The mixture was warmed at 80–82° for four hours. The reaction was cooled to 5–10° and carbonated with freshly crushed Dry Ice. The excess sodium was destroyed with 20 ml. of ethanol after which 400 ml. of distilled water was added cautiously. The aqueous solution was filtered and acidulated with 225 ml. of concentrated hydrochloric acid, yielding 108 g. (84%) of crude 2-thiophenecarboxylic acid.

The same procedure was followed when solvents other than benzene were used.

Preparation of 5-Chloro-2-thienylsodium and 5-Chloro-2-thiophenecarboxylic Acid. a. 2-Chlorothiophene and Sodium.—A solution of 118 g. (1.0 mole) of 2-chlorothiophene in 700 ml. of anhydrous diethyl ether was added dropwise with stirring (in an atmosphere of nitrogen) over a period of four hours to a suspension of 35 g. (1.5 gram atoms) of freshly prepared sodium shot in 300 ml. of refluxing anhydrous diethyl ether in the usual Grignard reaction apparatus. The surfaces of the sodium shot darkened immediately and in a short time the ether solution acquired a gray cast. After the addition was complete, the reaction mixture was refluxed for an additional two hours. It was then cooled in an ice-bath to 25° and carbonated by adding freshly crushed Dry Ice. The temperature rose momentarily, but was never permitted to rise above 30°. The temperature fell rapidly when the carbonation was complete. One hundred milliliters of ethanol was added dropwise to destroy the unreacted sodium after which 350 ml. of distilled water was added cautiously. The aqueous solution was separated and acidulated with 230 ml. of concentrated hydrochloric acid. The precipitated 5-chloro-2-thiophenecarboxylic acid weighed 115 g. (70%). White needles were obtained from hot water—m. p. 153–153.5°.[8,9] The observed neutral equivalent was 163 (calcd. 162.5). A mixed melting point with an authentic sample of 5-chloro-2-thiophenecarboxylic acid[7] gave no depression.

b. 2-Chlorothiophene and Sodium Amalgam Sand.—A solution of 118 g. (1.0 mole) of 2-chlorothiophene in 700

(6) Scott, Walker and Hansley, THIS JOURNAL, **58**, 2442 (1936).

(7) Prepared by the method of Hartough and Conley, THIS JOURNAL, **69**, 3096 (1947).

(8) Gattermann and Romer, Ber., **19**, 690 (1886), lists the melting points of 5-chloro-, 5-bromo- and 5-iodo-2-thiophenecarboxylic acid as 140, 139.5 and 131°, respectively.

(9) Steinkopf, Jacob and Penz, Ann., **512**, 161 (1934), gave m. p. of 146–147° for 5-chloro-2-thiophenecarboxylic acid and 141–142° for 5-bromo-2-thiophenecarboxylic acid.

ml. of anhydrous diethyl ether was added dropwise with stirring (in an atmosphere of nitrogen) over a period of two hours to a suspension of sodium amalgam sand containing 35 g. (1.5 gram atoms) of sodium and 25 g. (0.125 gram atom) of mercury dispersed in 300 ml. of refluxing anhydrous diethyl ether. The same procedure was followed as described in "a." Acidulation of the aqueous layer with 174 ml. of concentrated hydrochloric acid yielded 150 g. (92%) of 5-chloro-2-thiophenecarboxylic acid.

Preparation of 5-Bromo-2-thienylsodium and 5-Bromo-2-thiophenecarboxylic Acid from Sodium and 2-Bromothiophene.—Following the procedure described in "a" above, 41 g. (0.25 mole) of 2-bromothiophene was reacted with 13.5 g. (0.59 gram atom) of sodium and the mixture worked up as before: eighteen grams (35%), of a red oil separated which crystallized on cooling. White needles of 5-bromo-2-thiophenecarboxylic acid were obtained by sublimation, m. p. 140.5–141.5°.[8,9] The observed neutral equivalent was 202 (calcd. 207). A mixed melting point with an authentic sample (m. p. 141–141.5°) of 5-bromo-2-thiophenecarboxylic acid[7] gave no depression.

Preparation of 5-Iodo-2-thienylsodium and the Corresponding 5-Iodo-2-thiophenecarboxylic Acid from Sodium and 2-Iodothiophene.—Following the procedure described in "a" above, 55 g. (0.25 mole) of 2-iodothiophene was treated with 9 g. (0.38 gram atom) of sodium and worked up as before. Twenty-one grams (33%) of a red oil separated from solution which crystallized on cooling. White needles of 5-iodo-2-thiophenecarboxylic acid were obtained by sublimation, m. p. 132.5–133.5°.[5,10]

(10) Rinkes, Rec. trav. chim., 53 [4], 640 (1934), lists m. p. of 133–134° for 5-iodo-2-thiophenecarboxylic acid.

The observed neutral equivalent was 250 (calcd. 253).

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Summary

2-Thienylsodium has been prepared in yields of 60–89% from an alkyl or aryl halide, sodium amalgam, and thiophene, and in yields of 84% from 2-chlorothiophene and sodium amalgam.

2-Chloro-, 2-bromo- and 2-iodothiophenes have been metalated with sodium without replacement of the halo- atom, and the 5-halo-2-thienyl sodium compounds so formed were carbonated to give 2-chloro-, 5-bromo- and 5-iodo-2-thiophenecarboxylic acids in yields of 70, 35 and 33%, respectively. With 70% sodium amalgam, instead of sodium, the yield of 5-chloro-2-thiophenecarboxylic acid was 92%. Diethyl ether was the only solvent which gave satisfactory results. A decrease in solvent volume resulted in lower yields, but increases in the rate of reaction were noted. The reaction proceeded satisfactorily at 30–40°, but above 50° normal replacement of the halogen atom by sodium occurred.

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Aromatization Studies. VI. Aminobiphenyls and Naphthylamines

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The preparation of alkyl anilines from alkylcyclohexenones, by aromatization of the corresponding azines, was described in a previous paper.[2] This method provides a way of obtaining amines with alkyl substituents whose character or position are such that the compound would be difficult or impossible to obtain by ordinary aromatic substitution routes. Further investigation of this method has now shown that it can be applied also to the preparation of aminobiphenyls and naphthylamines; it appears therefore to be generally applicable in the aromatic series.

The aminobiphenyls obtained were 3-amino-5-methyl-4'-methoxy-biphenyl, 3-amino-5-methyl-2',3'-dimethoxybiphenyl and 3-amino-5-methyl-3',4'-dimethoxybiphenyl. The azines were prepared from the corresponding arylcyclohexenones,[3] and the aromatization was carried out in triethylbenzene with a 5% palladium–carbon catalyst. The amines were isolated in the form of their acetyl derivatives. The yields were uniformly in the vicinity of 50%, as in the case of alkylanilines,[2] but we have as yet no information on the fate of

(1) Rohm and Haas Research Assistant.
(2) Horning and Horning, THIS JOURNAL, 69, 1907 (1947).
(3) Horning and Field, ibid., 68, 384 (1946).

the rest of the material or on the mechanism of the reaction.

The tetralones which were converted to the corresponding aminonaphthalenes were tetralone-1, 7-methyltetralone-1 and 7-ethyltetralone-1. 7-Substituted tetralones may be obtained readily by the usual succinoylation method from benzene derivatives, and this route offers a means of obtaining many 7-substituted 1-naphthylamines. The yields here were lower (about 20%), although this appeared to be due more to difficulties in isolation of pure acetyl derivatives than to the aromatization itself.

The aromatization of these azines in a boiling solvent at a moderate temperature (214°) with a reflux period of only thirty minutes indicates the high degree of effectiveness of Hartung's palladium–carbon catalyst[4] in aromatization reactions.

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Experimental

All melting points are corrected. Analyses are by Miss Sarah H. Miles.

(4) "Organic Syntheses," 26, 77 (1946).