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Metalation Studies in the Thiophene Series. II. Transmetalation of the Alkylthiophenes

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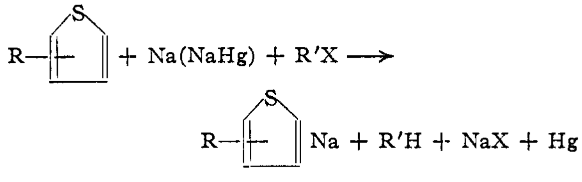
The authors previously reported the metalation of the thiophene and 2-halothiophenes to yield 2-thienylsodium and 5-halo-2-thienylsodium. Subsequent carbonation and acidulation yielded the 2-thiophenecarboxylic acid and 5-halo-2-thiophenecarboxylic acids,[1] respectively.

An extension of these studies to the alkylthiophenes, namely, 2-methyl-, 3-methyl-, 2-*t*-butyl-, 2-*t*-amyl-, 2-(1,1,3,3-tetramethylbutyl)- and 2-(1-phenylethyl)thiophene, has produced a convenient method for preparing alkyl-substituted 2-thiophenecarboxylic acids.

5-Methyl-2-thiophenecarboxylic acid was prepared in low yield by Gilman and Breuer[2] from 2-methylthiophene, dibenzylmercury and sodium. Hartough and Conley[3] have prepared the substituted acids by the sodium hypochlorite oxidation of the acetylalkylthiophenes.

It was found that the alkylthiophenes do not metalate directly with sodium. Metalation, however, was accomplished via the transmetalation reaction by interaction of an alkylthiophene, metallic sodium, and an alkyl or aryl halide in a neutral solvent.



Substitution of a 70–90% sodium amalgam for metallic sodium gave increased yields in some cases.

Table I records the substituted alkyl-2-thiophenecarboxylic acids that were prepared by the described general procedure.

TABLE I

ALKYL-2-THIOPHENECARBOXYLIC ACIDS FROM THE CORRESPONDING ALKYLTHIOPHENES

Alkyl-2-thiophene-carboxylic acid	Yield, %	Recrystallized from	Melting point, °C.	Neutral equivalent Calcd.	Obs.
5-Methyl-	70	Water	138–138.5[a]	142	143
4-Methyl-[c]	42	Water	119–121[b]	142	141.6
5-*t*-Butyl-	85	Water	124–125	184	186
5-*t*-Amyl-	46	Pet. ether	86.5–87.5	198	198
5-(1,1,3,3-Tetramethylbutyl)-	66	Pet. ether	122–123	240	241
5-(1-Phenylethyl)-	60	Water	99.5–101.5	232	235

[a] Ref. 3, m. p. 137–138°. [b] Ref. 3, m. p. 120–121°. [c] 3-Methylthiophene metalated exclusively in the 5-position. No trace of the normal substitution product, 3-methyl-2-thiophenecarboxylic acid, could be detected.

Experimental

General Procedure.—A cold mixture of 16 g. (0.25 mole) of ethyl chloride, in 200 ml. of anhydrous ether, was cooled dropwise over a one hour period to a stirred, externally cooled mixture of 12 g. (0.5 gram atom) of freshly prepared sodium sand, 49 g. (0.5 mole) of 2-methylthiophene and 100 ml. of anhydrous ether. The reaction was carried out under nitrogen. After the addition of the ethyl chloride was completed, the reaction mixture was stirred for an additional two hours at room temperature. Carbonation of the organo-metallic compound was accomplished with pieces of Dry Ice. The temperature was kept below 30° with ice. Two hundred milliliters of distilled water was added cautiously to destroy the small amount of unreacted sodium. The aqueous layer was separated and acidified with 70 ml. of hydrochloric acid. The crystalline product was filtered and recrystallized.

Bromobenzene and *n*-butyl bromide were also substituted for ethyl chloride with good results.

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Summary

The alkylthiophenes, namely, 2-methyl-, 3-methyl-, 2-*t*-butyl-, 2-*t*-amyl-, 2-(1,1,3,3-tetramethylbutyl)-, and 2-(1-phenylethyl)-thiophene were metalated with metallic sodium or sodium amalgam to yield the corresponding 2-thiophenecarboxylic acid upon carbonation and acidulation.

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[1] Schick and Hartough, THIS JOURNAL, **70**, 286 (1948).

[2] Gilman and Breuer, *ibid.*, **56**, 1123 (1934).

[3] Hartough and Conley, *ibid.*, **69**, 3096 (1947).