An Improved Synthesis of Thiophene-2,3-dicarboxylic Acid by Sequential Carboxylation

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Thiophene-2,3-dicarboxylic acid (**1**) and its derivatives are useful precursors to a variety of polycyclic aromatic compounds[1-4] and probably the five-membered heteroaryne, 2,3-didehydrothiophene[5]. Our continuing interest in the chemistry of this latter species prompted an examination of the known preparations of the diacid **1** with the goal of developing a more efficient and less expensive synthesis.

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The oldest[6] and most cited method[1,2,6-9] for the preparation of the diacid **1** involves oxidation of the Friedel-Crafts acetylation product of 3-methylthiophene (**2**). The most efficient version of this process (34% overall yield) is the Baker modification[1] of the Linstead procedure[7]. Another method beginning with the same starting material (**2**) involves directed metalation[10] and carboxylation in the 2-position after the methyl group has been converted to a good coordinating ligand. For a methoxymethyl group, subsequent oxidation gives the desired diacid **1** in an overall yield (from **2**) of 46%[3].

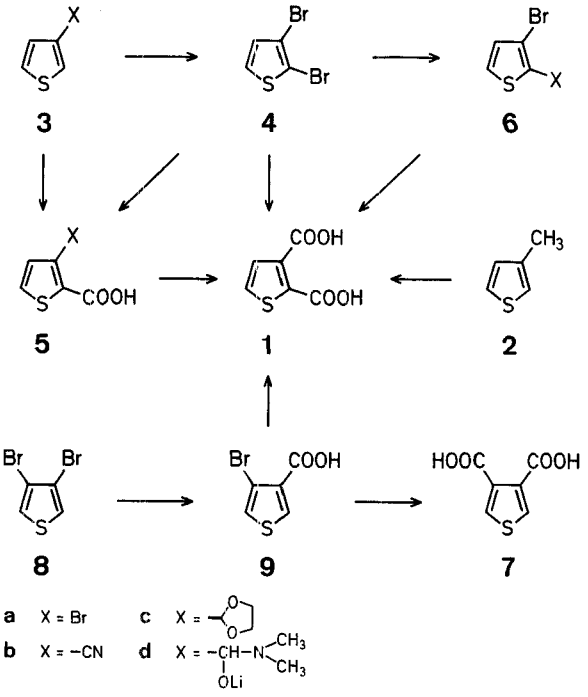
Except for a recently described five-step cyclization[11] and a low-yield abnormal Grignard reaction of 2-thienylmethylmagnesium chloride[12], all other reported preparations of thiophene-2,3-dicarboxylic acid (**1**) proceed via halothiophenes which are more or less directly available from the least expensive thiophene compound, thiophene itself. One of these syntheses involves a novel seven-step procedure via 2,5-dichlorothiophene[13] (obtainable in two steps from thiophene)[14] but all others utilize 3-bromothiophene (**3a**) which can be made from thiophene in two steps either by debromination of 2,3,5-tribromothiophene[15] or by rearrangement of 2-bromothiophene[16]. The first of these methods produces **3a** in higher overall yield (72 vs. 56%) while the latter is usually less expensive because less bromine is required.

The C-atoms which will become the carboxyl groups of diacid **1** may be introduced either simultaneously or sequentially and either directly from 3-bromothiophene (**3a**) or via 2,3-dibromothiophene (**4**) which is available from **3a** in 97% yield[17]. Unfortunately, the most direct approach, the reaction of **3a** with excess butyllithium followed by carboxylation of the resulting dilithiothiophene, gives the desired diacid **1** in only 7% yield[18]. Although generation of dilithio intermediates by halogen-metal interchange of dihalo compounds is usually[19] a useful synthetic procedure, when it is applied to 2,3-dibromothiophene (**4**) subsequent carboxylation gives only 37% of the desired diacid **1** and that is contaminated with 38% of the bromoacid **5a**[3]. Independent studies in our laboratory of both of the above methods failed to improve or even achieve the reported yields of **1**. The best preparation of **1** by the simultaneous introduction strategy (30% overall yield from thiophene) appears to be via 2,3-dicyanothiophene[4].

The sequential introduction of carboxyl groups into the 2- and 3-positions of thiophene via organolithium species thus far has been achieved only indirectly. Gronowitz successfully prepared the thiophene-2-carboxylic acids (**5**) by metalation and carboxylation of several 3-substituted thiophenes (**3**) including nitrile **3b**[20], acetal **3c**[21], and, in a one-pot reaction from 3-bromothiophene (**3a**), the dimethylformamide addition product **3d**[22]. Each of these monoacids **5** have been converted to diacid **1** but in overall yields from thiophene of less than 30%. Stepwise halogen-metal exchange of 2,3-dibromothiophene (**4**) via the 3-bromoacetal **6c**[23] or the dimethylformamide addition product **6d**[22] also can lead to diacid **1** with similar efficiency.

An obvious strategic improvement of the above procedures would be the introduction of both carboxyl groups directly as such. This would require that the second carboxylation take place via an *o*-lithiothiophenecarboxylic acid. Although related intermediates with protected carboxyl groups are well known[10,24] the recent studies by Parham[25] of an earlier observation by Gilman[26] on *o*-lithiobenzoic acids suggests that even unprotected acids may be used. Accordingly, the halogen-metal exchange and carboxylation of 3-bromothiophene-2-carboxylic acid (**5a**) was examined.

Selective halogen-metal interchange and carboxylation of 2,3-dibromothiophene (**4**) with one equivalent of butyllithium at −78 °C produced 3-bromothiophene-2-carboxylic acid (**5a**) in 85% yield compared to only a 72% yield by metalation and carboxylation of 3-bromothiophene (**3a**) with phenyllithium[27]. Although further reaction of bromoacid **5a** with butyllithium and carbon dioxide under Parham's conditions[25] at −100 °C led only to recovered starting material, at −78 °C the diacid **1** was obtained in 71% yield. The overall yield from thiophene by the sequential carboxylation method is therefore 42%. Only directed metalation[3] gives higher yields but at considerably greater expense[28]. Metalation and carboxylation of thiophene-3-carboxylic acid under a variety of conditions[31] gave significantly inferior yields of diacid **1**.



Application of the sequential carboxylation to 2,3-dibromo-1-benzothiophene produces 1-benzothiophene-2,3-dicarboxylic acid in 68% overall yield compared to 50% via the dilithio intermediate[32], or 30% by a lengthy cyclization procedure[7,33].

Preparation of thiophene-3,4-dicarboxylic acid (**7**) by sequential carboxylation appeared promising since the more reactive but less accessible 3,4-diiodothiophene can be dilithiated and carboxylated in 74% yield[8]. With 3,4-dibromothiophene (**8**), however, a similar reaction is incomplete, giving substantial amounts of bromoacid **9**[3], or, if more severe conditions are used, products arising by rearrangement to the more stable 2-lithiothiophenes[34,35]. A similar rearrangement was observed when bromoacid **9** was treated with butyllithium in that either **1** or **7** or a mixture thereof was obtained depending on the reaction time. A much simpler and better synthesis of **7** is described in the literature[36].

3-Bromothiophene-2-carboxylic Acid (5a):

A mixture of 1.9 molar butyllithium (0.38 mol, 200 ml) in hexane and anhydrous ether (100 ml) is placed in a 1000 ml, two-necked flask equipped with a 250 ml addition funnel, magnetic stirrer, and a dry nitrogen sweep. The mixture is cooled to −78 °C and a solution of 2,3-dibromothiophene[17] (**4**; 80 g, 0.33 mol) in anhydrous ether (100 ml) is added slowly with stirring. Stirring is continued for 10 min and then an excess of freshly powdered Dry Ice is added. After an additional 60 min, the mixture is hydrolyzed with water (10 ml) and extracted with 10% aqueous sodium hydroxide (3 × 75 ml). The aqueous extract is acidified with 6 normal hydrochloric acid, the precipitated product is collected by filtration, and recrystallized from water/ethanol (4/1); yield: 58 g (85%); snow-white crystals, m.p. 194–195 °C (Ref. [27], m.p. 195–197 °C).

Thiophene-2,3-dicarboxylic Acid (1):
A solution of 3-bromothiophene-2-carboxylic acid (**5a**; 1.0 g, 4.8 mmol) in anhydrous ether (30 ml) is placed in a 50 ml, three-necked flask equipped with a nitrogen sweep, stirrer, serum cap, addition funnel, and thermometer. The solution is cooled to −78 °C and a precooled (−78 °C) mixture of 1.6 molar butyllithium (9 ml, 14.4 mmol) in hexane and anhydrous ether (5 ml) is rapidly added. After 10 min, gaseous carbon dioxide is introduced by means of a needle through the serum cap for 10 min, the cooling bath removed, and the mixture allowed to warm to room temperature while maintaining the carbon dioxide sweep. The mixture is hydrolyzed with water and extracted with 1 normal aqueous sodium hydroxide (3 × 10 ml). The combined extracts are acidified with 6 normal hydrochloric acid and placed in a refrigerator overnight. The precipitate is collected by filtration, the filtrate extracted with ether, and the ether evaporated. The product is combined with the residue from the extraction and recrystallized from a minimal amount of water; yield: 59 mg (72%); m.p. 270–272 °C (Ref. [21], m.p. 271–272 °C).

1-Benzothiophene-2,3-dicarboxylic Acid:
The procedure is analogous to that described for the preparation of **1** except that tetrahydrofuran is used in place of ether. The starting material is 3-bromo-1-benzothiophene-2-carboxylic acid which is available from 2,3-dibromo-1-benzothiophene in 79% yield[37]. The filtrate from the final crystallization is worked up to give a second crop of product; total yield: 86%; m.p. 250–252 °C (Ref. [38], m.p. 249.5–251.5 °C).

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