Oxidation of Methylthiophenes to Thiophenecarboxylic Acids

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In the course of our continuing study on the positional effect of five-membered monoheteroaromatic compounds,1 we were in need of 3-thiophenecarboxylic acid (2a). Although 2a is commercially available, the price is about 70 times more expensive than the 2-isomer (4a). Therefore, we have explored various methods of preparation of 2a from relatively inexpensive sources. To our surprise, there have been a small number of reports on the synthesis of 2a. One of the older methods is the conversion of 3-methylthiophene (1a) to 3-bromomethylthiophene by N-bromosuccinimide (NBS),2 which is converted to 3-thiophenecarboxaldehyde by hexamethylenetetramine,3 and subsequent oxidation of the aldehyde by silver oxide.4 Oxidation of 1a to 2a was reported in a couple of patents using N-hydroxyphthalimide, Mn(OAc)2 and Co(OAc)2 at 150 °C for 5 h in AcOH5 or using Co(OAc)2, Mn(OAc)2, and NaBr in an autoclave at 140 °C for 2 h.6 Enzymatic oxidation of the methyl group in 1a to a carboxylic group was also reported with a yield of 70%.7

On the other hand, oxidation of 1a by Na2Cr2O7 using an rocking autoclave at 250 °C for 16 h resulted in 2a in 82% yield.8 However, the scale of the reaction was quite large (30 g of 1a, 110 g of Na2Cr2O7 and unknown amount of water), and it was not suitable for a few gram scale. A very similar reaction was carried out at a half scale of the reactants, but a lower yield (60%) resulted.9

![Chemical structure](image)

3-Hydroxymethylthiophene was oxidized photochemically in the presence of a catalytic inorganic bromo source such as LiBr or HBr to give 2a in 83% yield.10 However, the method seems to be impractical because the starting alcohol is expensive and difficult to prepare. The preparation of the Grignard reagent from 3-bromothiophene and subsequent treatment with CO2 seems to be an attractive approach to 2a, although there is a possibility of formation of 3,3'-bithiophene.11

An alternative method for the preparation of 2a is the hydrolysis of 3-cyanothiophene.12 There are a few reports for the preparation of 3-cyanothiophene from 3-bromothiophene using Zn powder, Zn(CN)2 and a catalytic amount of Pd2(dba)3,13 K2[Fe(CN)6] and Pd(OAc)2 and dpf as catalyst,14 and K2[Fe(CN)6], Cu(BF4)2·6H2O and N,N'-dimethylethylenediamine in N,N-dimethylacetamide.15 Although the yields of cyanation are high (80 ~ 90%), 3-bromothiophene is about twice as expensive as 3-methylthiophene (1a). Therefore, we developed an efficient method of converting 1a to 2a, and we now report our results.

### Results and Discussion

At first we attempted the Grignard reaction with 3-bromothiophene. Although the reaction with magnesium went smoothly, subsequent treatment with dry ice and acidic work-up gave a poor yield of 2a (< 20%). The major products were 3,3'-bithiophene and thiophene. Alternatively, conversion of 1a to 3-bromothiophene by NBS was also troublesome when the reaction was carried out on a gram scale instead of on a 2.24 mole scale as reported.2 Therefore, we decided to explore suitable conditions for converting 1a to 2a in less than one gram scale using sodium dichromate (Na2Cr2O7).

When a mixture of 1a and Na2Cr2O7 (1 : 1.2 by mole) in water was heated at reflux for 24 h, the starting 1a was quantitatively recovered. On the other hand, a mixture of 0.5 g of 1a (5.1 mmole) and 1.8 g of Na2Cr2O7 (6.4 mmole) in water (8.5 mL) was placed in a stainless steel tube (inner volume 20 mL), sealed, and heated in an oil bath at 200 °C for 8 h. After the acidic work-up, 2a was obtained in 75% yield. Various conditions and yields are listed in Table 1.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>1a, g</th>
<th>Na2Cr2O7, g</th>
<th>H2O, mL</th>
<th>Temp, °C</th>
<th>Time, h</th>
<th>Yield, %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>1.80</td>
<td>9.7</td>
<td>200</td>
<td>4</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>0.52</td>
<td>1.90</td>
<td>9.3</td>
<td>150</td>
<td>16</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>1.82</td>
<td>9.0</td>
<td>190</td>
<td>6</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>1.80</td>
<td>8.5</td>
<td>200</td>
<td>8</td>
<td>75</td>
</tr>
</tbody>
</table>

*aAfter purification.*
It is also interesting to observe the opposite appearance of the 2,5-dimethylthiophene (3c) are oxidized and that the bromo substituent (4c) does not affect the reaction. The thionocarboxylic acids 2 and 4 were identified by $^1$H and $^{13}$C NMR spectroscopy. The results are listed in Tables 3 and 4.

Although the chemical shift values have been reported, assignments of the values for the corresponding nuclei have not been made except for 2a and 4a. Based on the interpretation of the coupling constants and the $^1$H-$^{13}$C HETCOR spectra we were able to make accurate assignments for 2 and 4. It is known that the typical coupling constants for the protons in the thiophene ring are: $J_{2,3}(= J_{4,5}) = 4.8$ Hz, $J_{2,4}(= J_{3,5}) = 1.0$ Hz, $J_{3,4} = 3.5$ Hz, and $J_{2,5} = 2.4$ Hz. The observed values listed in Table 3 are quite consistent with the typical values. Therefore, the proton signals are readily assigned. On the other hand, the proton-decoupled $^{13}$C spectra show close values as shown in Table 4. With the aid of the HMOC and HMBC spectra we were able to find the reported assignments for 4a are not accurate. The literature reported 5-C (133.5 ppm) is further up-field than for the 3-C (134.2 ppm). However, we have found an opposite assignment for the 5-C (133.84 ppm) and the 3-C (133.79 ppm).

It is also interesting to observe the opposite appearance of the proton and carbon signals in 2b. Thus, the signal of the 4-H (δ 7.31) appears to be more up-field than that of the 5-H (δ 7.61), but the signal corresponding to the 4-C (129.95 ppm) appears to be more down-field than that of the 5-C (128.23 ppm). On the other hand, the H and C signals of 4b, which is a positional isomer of 2b, appear in the same order.

The carbonyl stretching frequencies of the 3-isomers (2) appear at higher wavenumber (1682 ~ 1690 cm$^{-1}$) region than those of the 2-isomers (4, 1643 ~ 1669 cm$^{-1}$). However, the carbonyl stretching frequencies and the chemical shift of the carbonyl carbon nuclei do not show any correlation.

In conclusion, we have developed an efficient method for oxidation of methylthiophenes to thionocarboxylic acids in less than gram scale using Na$_2$Cr$_2$O$_7$ and a stainless steel sealed tube.

**Experimental Section**

Melting points were determined on a Fischer MEL-TEMP apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX-400 FT NMR spectrometer in the Central Lab of Kangwon National University at 400 MHz for $^1$H and 100 MHz for $^{13}$C and were referenced to tetramethylsilane. The concentration of the solution was 0.10 M in DMSO-$d_6$. Infrared spectra were recorded on a JASCO FT/IR-460 Plus spectrophotometer in CH$_2$Cl$_2$ solution. Methylthiophenes (1 and 3) are all commercially available products and used as delivered.

**Oxidation of Methylthiophenes, An Illustrative Procedure:**
A mixture of 3-methylthiophene (1a, 0.50 g, 5.1 mmol) and Na$_2$Cr$_2$O$_7$ (1.80 g, 6.04 mmol) in distilled water (8.5 mL) was placed in a stainless steel tube (inner volume 20 mL) and sealed. The reactor was placed in an oil bath at 200 °C and stirred for 8 h. After cooling, the mixture was filtered to give a pale brown filtrate. The filtrate was acidified to pH 1 by adding 1 M-HCl.
solution to form a precipitate. The precipitate was collected by filtration and dried to give 0.2 g of 2a (30%). The filtrate was extracted with ether (2 × 20 mL). After drying and evaporation of the solvent 0.4 g of 2a (40%) was collected. The residue of the initial filtration was stirred with ether (30 mL) to extract additional amount of 2a (0.06 g, 10%). All the products were combined and recrystallized from water to give a pure compound of 2a (0.49 g, 75%).

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References