Oxidation of Methylthiophenes to Thiophenecarboxylic Acids

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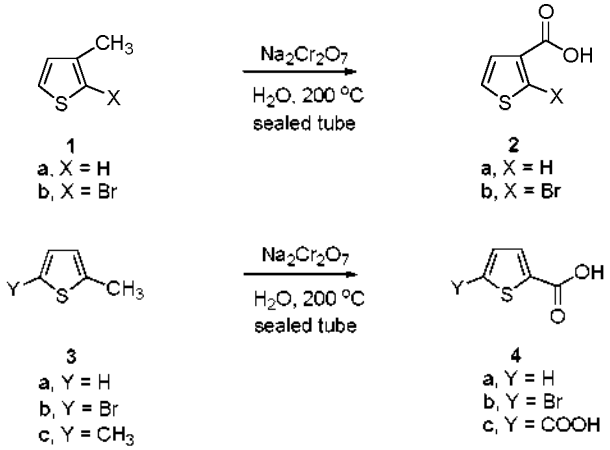
In the course of our continuing study on the positional effect of five-membered monoheteroaromatic compounds,[1] we were in need of 3-thiophenecarboxylic acid (**2a**). Although **2a** is commercially available, the price is about 70 times more expensive than the 2-isomer (**4a**). Therefore, we have 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 to **2a** 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 AcOH[5] 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 $Na_2Cr_2O_7$ 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 $Na_2Cr_2O_7$ 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]



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 CO_2 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 $Pd_2(dba)_3$,[13] $K_4[Fe(CN)_6]$ and $Pd(OAc)_2$ and dppf as catalyst,[14] and $K_4[Fe(CN)_6]$, $Cu(BF_4)_2 \cdot 6H_2O$ 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-bromomethylthiophene 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 ($Na_2Cr_2O_7$).

When a mixture of **1a** and $Na_2Cr_2O_7$ (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 $Na_2Cr_2O_7$ (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.

By applying the best conditions for 0.5 g scale which is heating at 200 °C for 8 h, the oxidation of several methylthiophenes (**1b**, **3a-c**) were carried out. The results are listed in Table 2.

Table 1. Conditions for the Preparation of **2a** and Yields.

Entry	1a, g	$Na_2Cr_2O_7$, g	H_2O, mL	Temp, °C	Time, h	Yield, %[a]
1	0.5	1.80	9.7	200	4	43
2	0.52	1.90	9.3	150	16	28
3	0.5	1.82	9.0	190	6	64
4	0.5	1.80	8.5	200	8	75

[a]After purification.

Table 2. Oxidation of Methylthiophenes.

Compd	Wt (g)	$Na_2Cr_2O_7$ (g)	H_2O (mL)	Product	Yield (%)[a]	Mp (lit.)
1a	0.50	1.80	8.5	**2a**	75	139-140 (137-138[8])
1b	0.44	1.26	9.6	**2b**	63	175 dec (176-178[16])
3a	0.50	1.80	9.9	**4a**	80	125-128 (128.5[17])
3b	0.51	1.01	10.4	**4b**	93	135-137 (137-138[10])
3c	0.50	2.79	9.9	**4c**	80	> 300 (325[11])

[a]After purification.

Table 3. ^{1}H NMR Data of Thiophenecarboxylic Acids in DMSO-d_6, δ.

	2-H	3-H	4-H	5-H
2a	8.25 dd *J* = 1.0, 2.9 Hz		7.42 dd *J* = 1.1, 5.0 Hz	7.60 dd *J* = 3.0, 5.0 Hz
2b			7.31 d, *J* = 5.6 Hz	7.61 d, *J* = 5.6 Hz
4a		7.72 dd *J* = 0.7, 3.7 Hz	7.18 dd *J* = 3.7, 4.9 Hz	7.87 dd *J* = 0.7, 4.9 Hz
4b		7.54 d, *J* = 3.9 Hz	7.32 d, *J* = 3.9 Hz	
4c		7.7 s	7.7 s	

Table 4. ^{13}C NMR (ppm, in DMSO-d_6) and IR (cm^{-1}, in CH_2Cl_2) Data of Thiophenecarboxylic Acids.

	2-C	3-C	4-C	5-C	C = O	νC = O
2a	133.65	134.67	128.09	127.64	163.95	1690
2b	119.14	132.58	129.95	128.23	163.35	1682
4a	135.18	133.79	128.81	133.84	163.49	1669
4b	136.84	134.40	132.45	119.35	162.36	1662
4c	140.36	133.77	133.77	140.36	162.97	1643

It is worth noting that both of the methyl groups in 2,5-dimethylthiophene (**3c**) are oxidized and that the bromo substituent in **1b** and **3b** does not affect the reaction.

The thiophenecarboxylic 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**.[18] 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 $J_{2,5}$ = 2.8 Hz.[19] 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 HMQC and HMBC spectra we were able to find the reported assignments[18] 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 thiophenecarboxylic acids in less than gram scale using $Na_2Cr_2O_7$ 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_2Cl_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 $Na_2Cr_2O_7$ (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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