New method for the synthesis of 2-thiophenecarboxylic acids in the presence of V-, Fe-, or Mo- containing catalysts


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Dedicated to Professor Oleg N Chupakhin on the occasion of his 70th birthday
(received 12 July 04; accepted 23 Nov 04; published on the web 3 Dec 04)

Abstract
2-Thiophenecarboxylic acid and its derivatives were synthesized by the reaction of thiophenes with the CCl₄–CH₃OH–catalyst system in total yields of 44–85%. The probable scheme of the reaction involves successive oxidation of methanol with tetrachloromethane to methyl hypochlorite and formaldehyde. Under the action of the latter, thiophene undergoes oxymethylation, giving rise to 2-oxymethylthiophene, which is oxidized with CH₃OCl to 2-thiophenecarboxylic acid. In the presence of an excess of CH₃OH, the latter is subjected to esterification. It was found that Fe(acac)₃, VO(acac)₂, and Mo(CO)₆ are the catalysts of choice for this reaction.

Keywords: Catalysis, iron, vanadium and molybdenum compounds, methyl hypochlorite, thiophene, 2-thiophenecarboxylic acid, oxidation

Results and Discussion

Earlier, we reported¹² that the manganese- and vanadium- complexes [Mn(acac)₃ and VO(acac)₂] catalyze the oxidation of alcohols (ROH) under the action of CCl₄ giving rise to alkyl hypochlorites (ROCl). Subsequent transformations of ROCl depend on the structure of the radical R. Lower primary alcohols are most readily oxidized. For example, oxidation of methanol with tetrachloromethane in the presence of Mn(acac)₃ affords predominantly methyl formate along with small amounts of formaldehyde. Hydrochloric acid and trace amounts of CH₂Cl₂, CH₃OCH₃, and water were also found in the reaction mixture. In the course of the reaction, CCl₄ is reduced to CHCl₃.
CH$_3$OH + CCl$_4$ $\xrightarrow{[\text{Mn}] - \text{CHCl}_3}$ CH$_3$OCl $\xrightarrow{-\text{HCl}}$ CH$_2$=O $\xrightarrow{1. \text{CH}_3\text{OCl}}$ $\xrightarrow{2. \text{CH}_3\text{OH, H}^+}$ HCO$_2$CH$_3$

Scheme 1

In the present study, we used the CCl$_4$–CH$_3$OH–VO(acac)$_2$ system for oxidation of thiophene and its derivatives. Unexpectedly, the reaction of thiophene 1 with this system gave, along with CHCl$_3$ and HCl, methyl 2-thiophenecarboxylate 2 as the major product.

1. CH$_3$OCl
2. CH$_3$OH, H$^+$

Scheme 2

Initially we believed that the formation of compound 2 is preceded by methylation of thiophene with CH$_3$OH to give 2-methylthiophene 3, which is then oxidized to compound 2. However, the reaction starting from 2-methylthiophene 3 and the CCl$_4$–CD$_3$–VO(acac)$_2$ system afforded 2-methyl-5-trideuteriomethylthiophenecarboxylate, 4, *i.e.*, the reaction product contained deuterium exclusively in the methoxy group, which argues against the above assumption.

Scheme 3

Taking into account the structure of compound 4, the following reaction scheme seems to be more reasonable. We suggest that, initially, CD$_3$OD is rapidly oxidized with CCl$_4$ to D$_2$-formaldehyde. Under the action of the latter, compound 3 undergoes oxymethylation to form 2-methyl-5-oxymethylthiophene 5, which is oxidized with methyl hypochlorite to the acid 4a. Finally, acid 4a is esterified with the excess of methanol, giving rise to compound 4.

Using thiophene as an example, it was demonstrated that the reaction is catalyzed not only by VO(acac)$_2$ but also by iron- and molybdenum compounds. Of the iron and molybdenum compounds examined in the present study (FeCl$_3$, FeBr$_2$, Fe(OAc)$_2$, Fe(acac)$_3$, MoO$_3$, MoCl$_5$, Mo(CO)$_6$, Fe(acac)$_3$, and Mo(CO)$_6$), proved to be most efficient in this reaction.

It should be noted that the reaction requires drastic conditions and occurs at 130, 140, and 175 °C in the presence of Mo(CO)$_6$, Fe(acac)$_3$, and VO(acac)$_2$, respectively.
The optimum concentrations of the catalyst and reagents were found to be [catalyst]:[thiophene]:[CH₃OH]:[CCl₄] = 1:100:200:100–200. Because of high temperature, the reaction was carried out in a sealed tube or a stainless-steel micro-autoclave. It is essential that the reaction should be carried out in the presence of a large excess of methanol because this is readily oxidized to methyl formate. With the aim of decreasing the consumption of CH₃OH, we added this reagent, portionwise, simultaneously with fresh portions of the catalyst. Although this procedure did not allow us to reduce greatly the amount of CH₃OH consumed, it led to a substantial increase in the yield of the target product. For example, when Fe(acac)₃ was added in portions (25% each) simultaneously with methanol, the reaction produced compound 2 in 25, 36, and 44% yield after 2, 4, and 6 hours, respectively.

The yield of compound 2 depends substantially on the concentration of the catalyst. Under typical conditions (175°C, 5 h), the reaction in the presence of VO(acac)₂ at concentrations of 0.1, 0.2, and 1.0 mol. % with respect to thiophene afforded product 2 in 25, 31, and 45% yield, respectively.

In all experiments with the involvement of VO(acac)₂, Mo(CO)₆, or Fe(acac)₃, the reaction mixture was found to contain methyl hypochlorite at concentrations from 1.0 to 1.2 mg/mL (iodometric titration).

The analogous reaction of 2-ethylthiophene, 5, with the CCl₄–CH₃OH–Fe(acac)₃ system proceeds rather smoothly and leads to the insertion of the ester group at position 5, while the ethyl substituent remained intact.

Scheme 5
Under analogous conditions, 3-methylthiophene 7 is transformed into a mixture of three products 8–10, among which dimethyl 3-methyl-2,5-thiophenedicarboxylate 10 is of most interest as a promising monomer for the preparation of electroconductive polymers.

\[ \text{Scheme 6} \]

The reaction of thiophene derivatives bearing polar substituents at position 2 with the CH\textsubscript{3}OH–CCl\textsubscript{4}–VO(acac)\textsubscript{2} system also occurs regioselectively and results in the insertion of the CO\textsubscript{2}CH\textsubscript{3} group at position 5. For example, under typical conditions 2-acetylthiophene 11 is transformed into methyl 2-acetyl-5-thiophenecarboxylate 12 in 85% yield.

\[ \text{Scheme 7} \]

A more interesting situation arises in the reaction of 1-(2-thienyl)ethanol 13 with the CH\textsubscript{3}OH–CCl\textsubscript{4}–VO(acac)\textsubscript{2} system. Initially, compound 13 is rapidly and quantitatively oxidized to 2-acetylthiophene 11. Subsequent heating of the latter affords compound 12. The reaction occurs according to the known scheme but produces compound 12 in lower yield than obtained in the reaction starting from 2-acetylthiophene 11.

\[ \text{Scheme 8} \]

The reactions of 2-chlorothiophene (14) and 2-bromothiophene 15 take place readily. It should be noted that the reaction of 2-chlorothiophene 14 with the CCl\textsubscript{4}–CH\textsubscript{3}OH–Fe(acac)\textsubscript{3} system proceeds without complication to give only one product, viz., methyl 5-chlorothiophene-2-carboxylate 16, whereas the reaction of 2-bromothiophene 15 produces the expected methyl 5-bromothiophene-2-carboxylate 17 along with the 5-chloro derivative 16. The formation of the
latter can be accounted for by the side reaction, which occurs with the involvement of CCl₄ or CH₃OCl and results in the replacement of the bromine atom with chlorine.

\[
\begin{align*}
\text{SCl} & \quad \text{Br} \\
\text{14} & \quad \text{15}
\end{align*}
\]

\[\text{CH}_3\text{OH} + \text{CCl}_4 - \text{Fe(acac)}_3 \quad 140 \degree \text{C}, 6 \text{ h} \]

\[\begin{align*}
\text{65\%} & \quad \text{SCl} - \text{CO}_2\text{CH}_3 \\
\text{16} & \quad \text{57\%} \quad (\text{16}) + \text{Br} - \text{SCl} - \text{CO}_2\text{CH}_3 \\
\text{17} & \quad \text{16 : 17 = 1 : 3}
\end{align*}\]

Scheme 9

To summarize, we have developed a rather general procedure for the preparation of 2-thiophenecarboxylic acid and its derivatives, based on the reaction of thiophenes with the CCl₄–CH₃OH system in the presence of vanadium-, molybdenum-, or iron-containing catalysts.

Experimental Section

General Procedures. IR spectra were recorded on a UR-20 instrument in KBr pellets or a thin film. \(^1\)H- and \(^13\)C- NMR spectra were measured on a JEOL FX-Q instrument operating at 90 and 22.5 MHz, respectively, in CDCl₃; the chemical shifts are given in ppm relative to (CH₃)₄Si. Mass spectra were obtained on a Finnigan MAT-112S GLC mass spectrometer (E.I., 7.0 eV, direct inlet of the sample). Chromatographic analysis was carried out on a Chrom-5 instrument [flame ionization detector, 1200 x 33 mm column, SE-30 silicone (5\%) on Chromaton N-AW-HMDS as the stationary phase; the temperature was raised from 50 to 250\degree\text{C} at 8\degree\text{C} min\(^{-1}\), with helium as carrier gas (47 ml min\(^{-1}\)), or on a 3000x3mm PEG-6000 column, with the same support as stationary phase, operating at 50–170\degree\text{C}, with helium carrier gas. The concentration of hypochlorite was determined by iodometric titration.\(^3\) The structures of most of the compounds synthesized were confirmed by the identity of the their physical properties to those of authentic samples, and by the fact that these properties are in complete agreement with the reference data.\(^4\)–\(^9\)

Materials. Commercial alcohols used as the starting reagents were distilled before use. Carbon tetrachloride was purified according to a known procedure.\(^10\) The commercially available vanadium (VO(acac)₂), molybdenum (Mo(CO)₆), and iron (Fe(acac)₃) compounds used as the
catalysts were purified according to standard procedures, recrystallized, and dried in vacuo (20 h, 80°C).

**General procedures for reaction of thiophenes with the CCl₄–CH₃OH catalyst system**

The starting thiophene (10 mmol), Fe(acac)₃ or [(VO(acac)₂)] (0.1 mol), CCl₄ (20–30 mmol), and methanol (20–30 mmol) were placed under argon in a stainless steel micro-autoclave (V = 17 mL) or a glass tube (V = 20 mL) (the results of independent experiments gave virtually the same results). The autoclave was hermetically closed (the tube was sealed) and heated at 140–170 °C for 3–6 hours with continuous stirring. After completion of the reaction, the autoclave (tube) was cooled to room temperature and opened. The reaction mixture was filtered through a layer of silica gel (hexane:diethyl ether, 1:1 as eluent). The solvent was removed and the residue distilled in vacuo.

**Methyl 2-thiophenecarboxylate (2).** Yield 45%, b.p. 120–121 °C/10 Torr (lit.⁴ b.p. 40–44 °C/0.5 Torr); ¹³C-NMR δ 133.42 (2-C); 133.70 (3-C); 127.11 (4-C); 131.86 (5-C); 161.64 (C=O); 51.22 (Me); MS m/z (intensity) 142 [M]+ (35); 38(12), 39(45), 45(7), 57(9), 81(5), 82(7), 83(12), 110(39), 11(100), 112(10), 113(7), 141(24). Anal. Calcd. for C₆H₆O₂S: C, 57.11; H, 4.79; S, 25.41. Found: C, 57.05; H, 4.72; S, 25.45%.

**Methyl 5-methyl-2-thiophenecarboxylate (4).** Yield 49%, b.p. 95–96 °C/10 Torr (lit.⁵ b.p. 77–79 °C/5 Torr); ¹³C-NMR δ 131.36 (2-C); 139.90 (3-C); 125.94 (4-C); 147.43 (5-C); 161.95 (C=O); 51.18 (OMe); 14.87 (Me); MS m/z 156[M]+ (40); 39(5), 45(12), 57(24), 69(5), 97(10), 125(100), 126(12), 127(5), 155(5). Anal. Calcd. for C₇H₈O₂S: C, 53.82; H, 5.16; S, 20.52. Found: C, 53.79; H, 5.11; S, 20.57%.

**Methyl 5-ethyl-2-thiophenecarboxylate (6).** Yield 64%, b.p. 119–120 °C/10 Torr (lit.⁶ b.p. 120 °C/12 Torr); ¹³C-NMR δ 133.84 (2-C); 131.14 (3-C); 126.13 (4-C); 147.20 (5-C); 161.90 (C=O); 51.13 (OMe); 29.95 (CH₂); 15.64 (Me); MS m/z: 170[M]+ (60); 39(17), 41(7), 45(17), 51(7), 53(6), 57(5), 58(4), 59(5), 65(10), 66(5), 67(9), 69(10), 70(8), 71(6), 77(10), 78(7), 95(5), 96(10), 97(6), 111(17), 124(10), 127(12), 139(71), 154(7), 155(100), 156(8), 169(7). Anal. Calcd. for C₈H₁₀O₂S: C, 56.44; H, 5.92; S, 18.35. Found: C, 56.35; H, 5.89; S, 18.85%.

**Methyl 3-methyl-2-thiophenecarboxylate (8).** Yield 34.4%, b.p. 87–88 °C/2 Torr; ¹³C-NMR δ 126.67 (2-C); 145.86 (3-C); 131.33 (4-C); 129.78 (5-C); 162.80 (C=O); 51.23 (OMe), 15.46 (Me); MS m/z: 156[M]+ (51); 39(5), 45(24), 53(22), 69(7), 70(8), 85(7), 96(10), 97(15), 124(20), 125(100), 126(10), 127(7), 141(12). Anal. Calcd. for C₇H₈O₂S: C, 53.82; H, 5.16; S, 20.52. Found: C, 53.71; H, 5.13; S, 20.45%.

**Methyl 4-methyl-2-thiophenecarboxylate (9).** Yield 40.6%, b.p. 84–85 °C/2 Torr; ¹³C-NMR δ 133.82 (2-C); 135.32 (3-C); 138.09 (4-C); 128.21 (5-C); 162.28 (C=O); 52.02 (OMe), 15.08(Me); MS m/z: 156[M]+ (46); 39(5), 45(24), 51(5), 53(24), 69(7), 70(6), 85(7), 96(7), 97(14), 124(20), 125(100), 126(10), 127(5), 141(12). Anal. Calcd. for C₇H₈O₂S: C, 53.82; H, 5.16; S, 20.52. Found: C, 53.77; H, 5.08; S, 20.55%.

**Dimethyl 2,5-thiophenedicarboxylate (10).** Yield 25%, m.p. 82–83 °C (lit.⁷ m.p. 84 °C); ¹³C-NMR δ 136.560 (2-C); 145.75 (3-C); 135.83 (4-C); 138.39 (5-C); 162.09, 162.58 (C=O); 52.37,
51.95 (OMe), 15.81 (Me); MS m/z: 241[M]⁺ (40); 39(5), 41(3), 45(10), 51(5), 53(5), 59(11), 65(5), 67(60), 69(7), 70(7), 83(5), 95(7), 96(9), 125(5), 155(7), 181(5), 182(14), 183(100), 184(12), 185(6), 199(14), 211(5). Anal. Calcd. for C₉H₁₀O₄S, C, 50.45; H, 4.70; S, 14.96. Found: C, 50.35; H, 4.68; S, 15.03%.

2-Acetylthiophene (11). Yield 100%, b.p. 85–86 °C/10 Torr (lit. b.p. 208–209 °C/748 Torr), ηD²⁰ 1.5650; ¹³C-NMR δ: 143.56 (2-C); 131.99 (3-C); 127.43 (4-C); 132.96 (5-C); 189.47 (C=O); 25.66 (Me); MS m/z: 126[M]⁺ (45); 39(33), 43(17), 45(9), 57(5), 58(6), 69(5), 70(7), 83(5), 95(7), 96(9), 125(100), 126(12), 127(5), 155(5). Anal. Calcd. for C₆H₆OS: C, 57.11; H, 4.79; S, 25.41. Found: C, 57.08; H, 4.71; S, 25.43%.

Methyl 2-acetyl-5-thiophenecarboxylate (12). Yield 85%, b.p. 127–128 °C/1 Torr; ¹³C-NMR δ: 139.36 (2-C); 133.40 (3-C); 131.58 (4-C); 148.43 (5-C); 161.95 (C=O); 52.18 (OMe); 190.50 (C=O); 26.87 (Me); MS m/z: 156[M]⁺ (40); 39(5), 45(12), 57(24), 69(5), 97(10), 125(100), 126(12), 127(5), 155(5). Anal. Calcd. for C₇H₈O₂S: C, 53.82; H, 5.16; S, 20.52. Found: C, 53.79; H, 5.11; S, 20.57%.

Methyl 5-chlorothiophene-2-carboxylate (16). Yield 65%, b.p. 87–88 °C/5 Torr (lit. b.p. 95–97 °C/7 Torr); ¹³C-NMR δ: 132.01 (2-C); 133.13 (3-C); 127.17 (4-C); 137.64 (5-C); 161.46 (C=O); 52.21 (Me); MS m/z: 176[M]⁺ (43); 37(5), 38(7), 45(5), 53(5), 57(7), 59(4), 69(4), 73(24), 75(7), 81(7), 82(9), 117(12), 118(5), 119(7), 144(5), 145(100), 146(12), 147(41), 175(5). Anal. Calcd. for C₇H₅ClO₂S: C, 40.80; H, 2.85; Cl, 20.07; S, 18.15. Found: C, 40.73; H, 2.81; Cl, 19.98; S, 18.09%.

Methyl 5-bromothiophene-2-carboxylate (17). Yield 57%, m.p. 87–88 °C; ¹³C-NMR δ: 143.64 (2-C); 133.61 (3-C); 130.94 (4-C); 120.17 (5-C); 161.46 (C=O); 52.21 (Me); MS m/z: 221[M]⁺ (12); 37(10), 38(17), 45(10), 53(4.2), 57(10), 59(5), 69(5), 76(14), 77(33), 117(10), 119(9), 141(4), 161(10), 163(10), 188(9), 188(8), 189(98), 190(19), 191(100), 192(10), 193(7), 219(10), 220(45). Anal. Calcd. for C₇H₅BrO₂S: C, 32.59; H, 2.28; Br, 36.14; S, 14.47. Found: C, 32.41; H, 2.25; Br, 36.17; S, 14.35%.

**Acknowledgements**

We thank the Department of Education and Science of the Russian Federation for financial support (Grant NSh2189.2003.3).

**References**
