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
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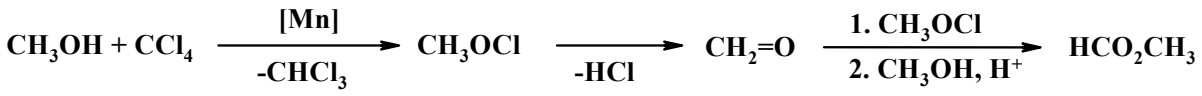
Abstract
2-Thiophenecarboxylic acid and its derivatives were synthesized by the reaction of thiophenes with the CCl_4–CH_3OH–catalyst system in total yields of 44–85%. The probable scheme of the reaction involves successive oxidation of methanol with tetrachloromethane to methyl hypochlorite and formaldehyde. Under the action of the latter, thiophene undergoes oxymethylation, giving rise to 2-oxymethylthiophene, which is oxidized with CH_3OCl to 2-thiophenecarboxylic acid. In the presence of an excess of CH_3OH, 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

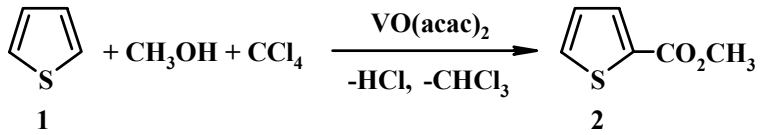
Earlier, we reported[1,2] that the manganese- and vanadium- complexes [$Mn(acac)_3$ and $VO(acac)_2$] catalyze the oxidation of alcohols (ROH) under the action of CCl_4 giving rise to alkyl hypochlorites (ROCl). Subsequent transformations of ROCl depend on the structure of the radical R. Lower primary 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 CH_2Cl_2, CH_3OCH_3, and water were also found in the reaction mixture. In the course of the reaction, CCl_4 is reduced to $CHCl_3$.

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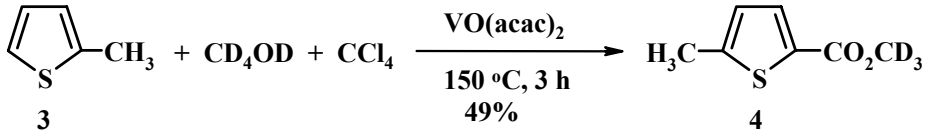
Scheme 1

In the present study, we used the CCl_4–CH_3OH–$VO(acac)_2$ 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.



Scheme 2

Initially we believed that the formation of compound 2 is preceded by methylation of thiophene with CH_3OH 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.

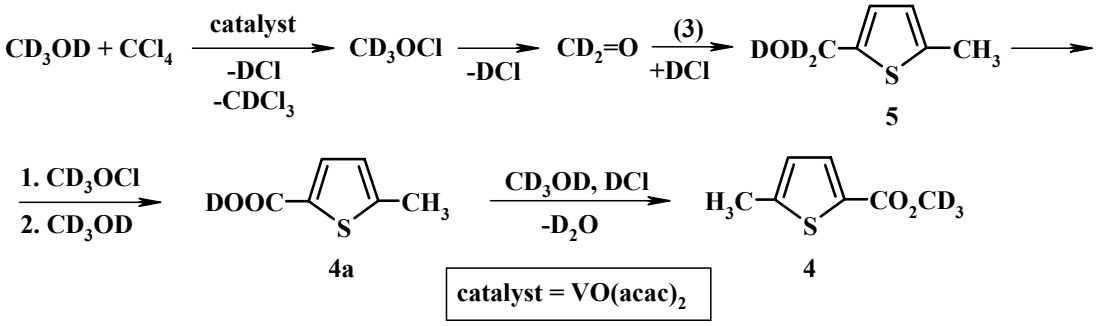


Scheme 3

Taking into account the structure of compound **4**, the following reaction scheme seems to be more reasonable. We suggest that, initially, CD_3OD 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.



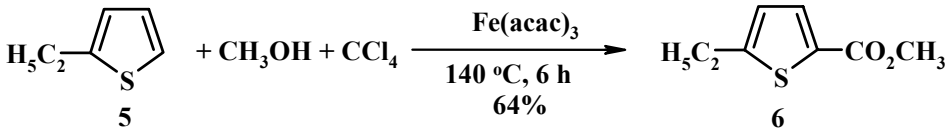
Scheme 4

The optimum concentrations of the catalyst and reagents were found to be [catalyst]:[thiophene]:[CH_3OH]:[CCl_4] = 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 CH_3OH, 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 CH_3OH 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.

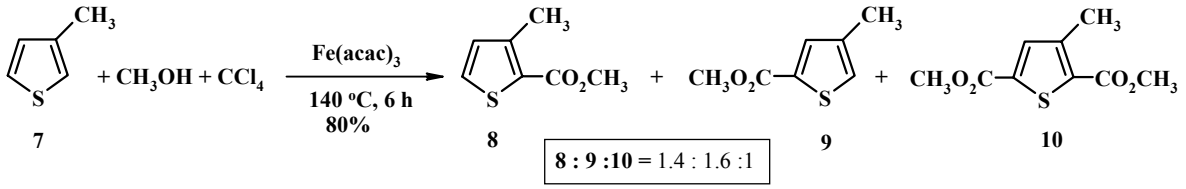
In all experiments with the involvement of $VO(acac)_2$, $Mo(CO)_6$, or $Fe(acac)_3$, the reaction mixture was found to contain methyl hypochlorite at concentrations from 1.0 to 1.2 mg/mL (iodometric titration).

The analogous reaction of 2-ethylthiophene, **5**, with the CCl_4–CH_3OH–$Fe(acac)_3$ system proceeds rather smoothly and leads to the insertion of the ester group at position 5, while the ethyl substituent remained intact.



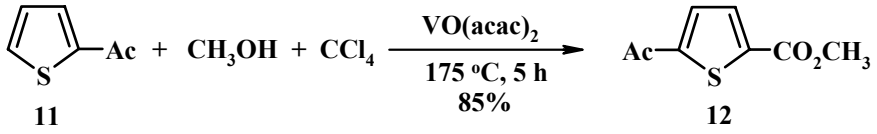
Scheme 5

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.



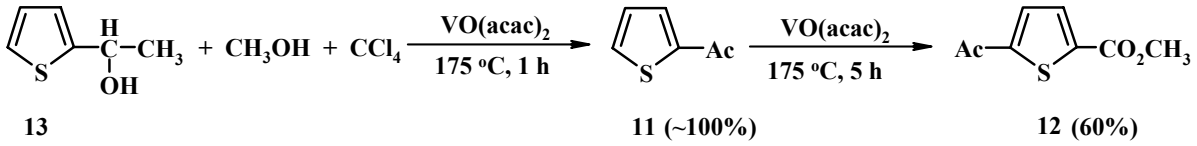
Scheme 6

The reaction of thiophene derivatives bearing polar substituents at position 2 with the $CH_3OH–CCl_4–VO(acac)_2$ system also occurs regioselectively and results in the insertion of the CO_2CH_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.



Scheme 7

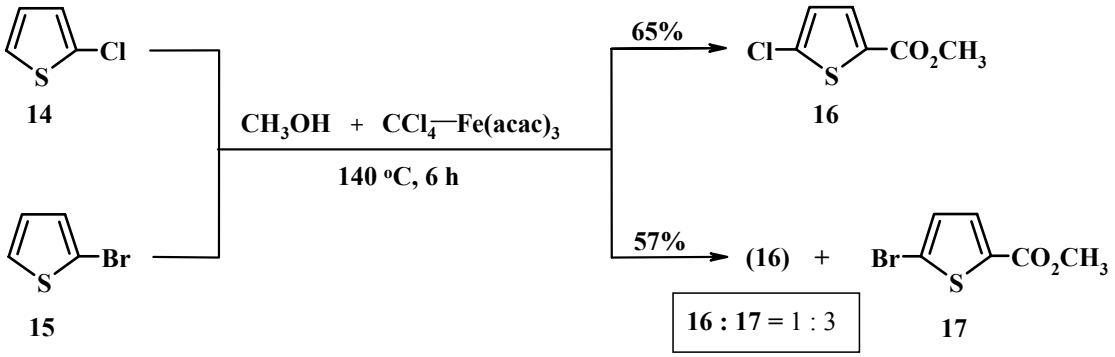
A more interesting situation arises in the reaction of 1-(2-thienyl)ethanol **13** with the $CH_3OH–CCl_4–VO(acac)_2$ system. Initially, compound **13** is rapidly and quantitatively oxidized to 2-acetylthiophene **11**. Subsequent heating of the latter affords compound **12**. The reaction occurs according to the known scheme but produces compound **12** in lower yield than obtained in the reaction starting from 2-acetylthiophene **11**.



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 $CCl_4–CH_3OH–Fe(acac)_3$ 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 CCl_4 or CH_3OCl and results in the replacement of the bromine atom with chlorine.



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 CCl_4–CH_3OH 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 $CDCl_3$; the chemical shifts are given in ppm relative to $(CH_3)_4Si$. 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°C at 8°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°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,[11] recrystallized, and dried *in vacuo* (20 h, 80°C).

General procedures for reaction of thiophenes with the CCl_4–CH_3OH 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); ^{13}C-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 $C_6H_6O_2S$: 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); ^{13}C-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 $C_7H_8O_2S$: 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); ^{13}C-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 (CH_2); 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 $C_8H_{10}O_2S$: 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; ^{13}C-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), 122(7), 141(12). Anal. Calcd. for $C_7H_8O_2S$: 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; ^{13}C-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 $C_7H_8O_2S$: 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); ^{13}C-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 $C_9H_{10}O_4S$, 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 ^{o}C/10 Torr (lit.[8] b.p. 208–209 ^{o}C/748 Torr), η_D^{20} 1.5650; ^{13}C-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(7), 58(6), 83(17), 110(5), 111(100), 112(7), 113(6). Anal. Calcd. for C_6H_6OS: 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 ^{o}C/1 Torr; ^{13}C-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 $C_7H_8O_2S$: 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 ^{o}C/5 Torr (lit.[9] b.p. 95–97 ^{o}C/7 Torr); ^{13}C-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 $C_6H_5ClO_2S$: 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 ^{o}C; ^{13}C-NMR δ 134.64 (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 $C_6H_5BrO_2S$: 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

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