HETEROCYCLES, Vol. 72, 2007, pp. 697 - 708. © The Japan Institute of Heterocyclic Chemistry
Received, 9th January, 2007, Accepted, 16th February, 2007, Published online, 16th February, 2007. COM-07-S(K)56

# REGIOSELECTIVE SYNTHESIS OF METHYL 3-THIOTHIOPHENE-2-CARBOXYLATE DERIVATIVES UTILIZING A DEHYDRATION-TYPE Ti-DIECKMANN CONDENSATION

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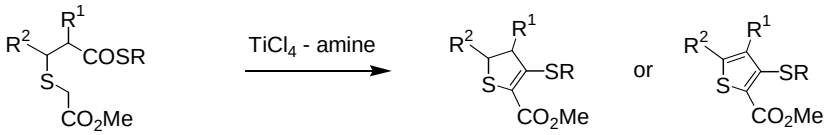
**Abstract** – Regioselective dehydration-type Ti-Dieckmann condensation of 3-(methoxycarbonylmethylthio)propanethioates successfully afforded methyl thiophene-2-carboxylates and methyl 4,5-dihydrothiophene-2-carboxylates, utilizing $TiCl_4$ – $Et_3N$ and $TiCl_4$ – $(sec\text{-}Bu)_2NH$, respectively.

Thiophene is a fundamental 5-membered heterocycle, commonly used for a building block in organic chemistry.[1] Substituted thiophenes have attracted considerable attention due to the recent production of useful synthetic intermediates for opto-electronic devices[2] and biologically active compounds.[3] Thus, there is a high demand for synthetic studies of thiophene derivatives.

Dieckmann condensation (intramolecular Claisen condensation) is recognized as a representative intramolecular C–C bond forming cyclization, widely used for the synthesis of fine chemicals and natural products.[4] The major problem of Dieckmann condensation using unsymmetrical diesters lies in controlling the direction of cyclization. To solve this issue, a few chemoselective methods were disclosed using half thiol esters promoted by basic reagents (NaH, LDA, etc.)[5] and Lewis acid [$AlCl_3$, $Sn(OTf)_2$, $SnCl_4$, $MgX_2$] – $Et_3N$ reagents, the latter of which were developed by Nagao and Sano's group.[6] As part of our ongoing project to develop practical Ti(*or* Zr)-Claisen condensations,[7] we recently reported a dehydration-type Ti-Dieckmann condensation for the practical short synthesis of antibiotic 1β-methylcarbapenems,[8] which attracted much attention in the pharmaceutical industry.[9]

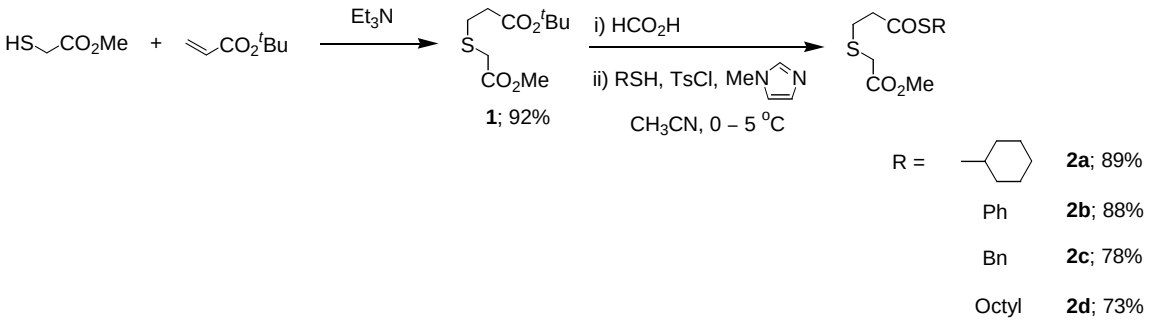
The characteristic mode of this dehydration-type reaction involves a direct incorporation of the thiol moiety into the 1β-methylcarbapenem skeleton, compared with the traditional basic Dieckmann condensation. In general, the thiol function of thioesters is regarded as a more easily displacable moiety,

but this unusual behavior is considered to be due to the greater affinity of $TiCl_4$ toward oxygen than sulfur. This successful result encouraged us to investigate an extension for the synthesis of thiophene derivatives. Here we describe a novel synthesis of methyl 4,5-dihydrothiophene-2-carboxylates and methyl thiophene-2-carboxylates from 3-(methoxycarbonylmethylthio)propanethioates utilizing a dehydration-type Ti-Dieckmann condensation (Scheme 1).




Scheme 1

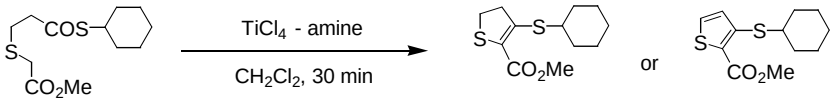
The starting substrate, *S*-alkyl *or S*-phenyl 3-(methoxycarbonylmethylthio)propanethioates **2a-2d**, was readily prepared as follows (Scheme 2). Michael addition of methyl thioglycolate to *t*-butyl acrylate gave *t*-butyl 3-(methoxycarbonylmethylthio)propanoate (**1**) in 92% yield. Acidic hydrolysis of *t*-butyl ester **1** with $HCO_2H$, followed by direct thioesterification of the acid with four thiols using TsCl – *N*-methylimidazole reagent,[10] gave the corresponding half thiol esters **2a-2d** in good yield.




Scheme 2

The initial attempt of the Ti-dehydration-type Dieckmann condensation was guided by the reaction using **2a** (Table 1). The desired reaction proceeded smoothly to give 4,5-dihydrothiophene **3a** in 20–52% yield using 2.2 equiv of $TiCl_4$ and 2.4 equiv of amines under standard conditions[6-8] for the Ti-Claisen condensation (entries 1-3). Among the amines screened, (*sec*-Bu)$_2$NH produced the best result for the synthesis of **3a** (entry 4). In clear contrast, the use of 5.0 equiv of $TiCl_4$ and 5.2 equiv of $Et_3N$ resulted in the selective formation of thiophene **4a** (entries 5-8). Note that the amine structure [$Et_3N$ and (*sec*-Bu)$_2$NH] affected the production selectivity between **3a** and **4a** (See the mechanistic consideration, *vide infra*).

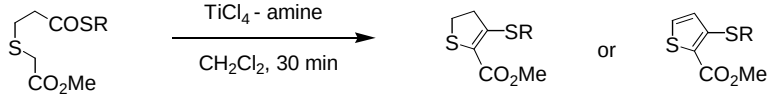
**Table 1.** Dehydration-type Ti-Dieckmann condensation of half thiol diesters **2a** using four amine reagents.




**2a** **3a** **4a**

| entry | equiv of $TiCl_4$ | amine / equiv | temp. / °C | yield / % | |
|---|---|---|---|---|---|
| | | | | **3a** | **4a** |
| 1 | 2.2 | *i*-$Pr_2NEt$ / 2.4 | -78 | 20 | trace |
| 2 | | $Bu_3N$ / 2.4 | | 52 | trace |
| 3 | | $Et_3N$ / 2.4 | | 46 | trace |
| 4 | | (*sec*-Bu)$_2$NH / 2.4 | | **58** | 0 |
| 5 | 5.0 | *i*-$Pr_2NEt$ / 5.2 | -50 – -45 | 17 | 57 |
| 6 | | $Bu_3N$ / 5.2 | | 0 | 80 |
| 7 | | $Et_3N$ / 5.2 | | 0 | **83** |
| 8 | | (*sec*-Bu)$_2$NH / 5.2 | | 21 | 54 |

**Table 2.** Dehydration-type Ti-Dieckmann condensation of half thiol diesters **2a-d** by two methods.




**2a-d** **3** **4**

| entry | R | method [a] | yield / % | |
|---|---|---|---|---|
| | | | **3** | **4** |
| 1 |  | **A** | **58** (**3a**) | 0 |
| 2 | **2a** | **B** | 0 | **83** (**4a**) |
| 3 |  | **A** | **56** (**3b**) | trace |
| 4 | **2b** | **B** | 0 | **85** (**4b**) |
| 5 |  | **A** | **67** (**3c**) | 0 |
| 6 | **2c** | **B** | 0 | **87** (**4c**) |
| 7 |  | **A** | **73** (**3d**) | 0 |
| 8 | **2d** | **B** | 0 | **82** (**4d**) |

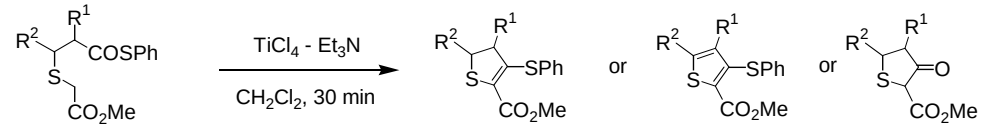
[a] method **A** : $TiCl_4$ (2.2 equiv), (*sec*-Bu$_2$)NH (2.4 equiv), -78 °C.
method **B** : $TiCl_4$ (5.0 equiv), $Et_3N$ (5.2 equiv), -50 – - 45 °C.

Based on these results, reactions using three other substrates **2b-2d** were examined by the two methods (A and B), and the results are listed in Table 2. Note that there was an apparent switching mode

between methods A and B: in every case examined, both **3** and **4** were exclusively produced in good yield.

Next, we examined the reaction using the half thiol diester **5a** and **5b** possessing a Me group as either $R^1$ or $R^2$. Table 3 lists the results. When **5a** was treated with $TiCl_4$ (2.0 equiv) and $Et_3N$ (2.2 equiv) at -78 °C, a conventional Ti-Dieckmann condensation occurred instead of the dehydration-type reaction to selectively give β-keto ester **8a** (entry 1). In contrast, using method B of Table 2, the dehydration-type Ti-Dieckmann reaction proceeded predominantly to give the desired thiophenes **7** (entry 2). The use of $Bu_3N$ resulted in poor selectivity (entry 3). The reaction using **5b** proceeded in better total yield to give mainly **7b**, though with poor selectivity (entry 4).

**Table 3.** Dehydration-type Ti-Dieckmann cyclization of half thiol diesters **5a** and **5b**




**5a**: $R^1$ = Me, $R^2$ = H
**5b**: $R^1$ = H, $R^2$ = Me

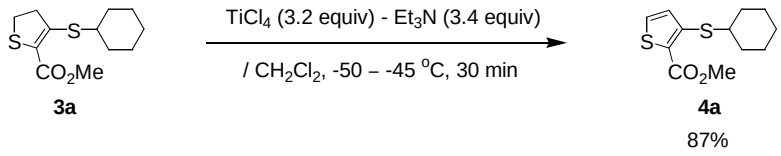
**6** **7** **8**

| entry | substrate | $TiCl_4$ / equiv | $Et_3N$ / equiv | temp. / °C | yield / % | | |
|---|---|---|---|---|---|---|---|
| | | | | | **6** | **7** | **8** |
| 1 | **5a** | 2.2 | 2.4 | -78 | trace | trace | **65** (**8a**) |
| 2 | | 5.0 | 5.2 | -50 – -45 | trace | **44** (**7a**) | - |
| 3[a)] | | | | | trace | 34 | 29 |
| 4 | **5b** | | | | trace | **65** (**7b**) | 23 |
| 5[a)] | | | | | trace | 57 | 23 |

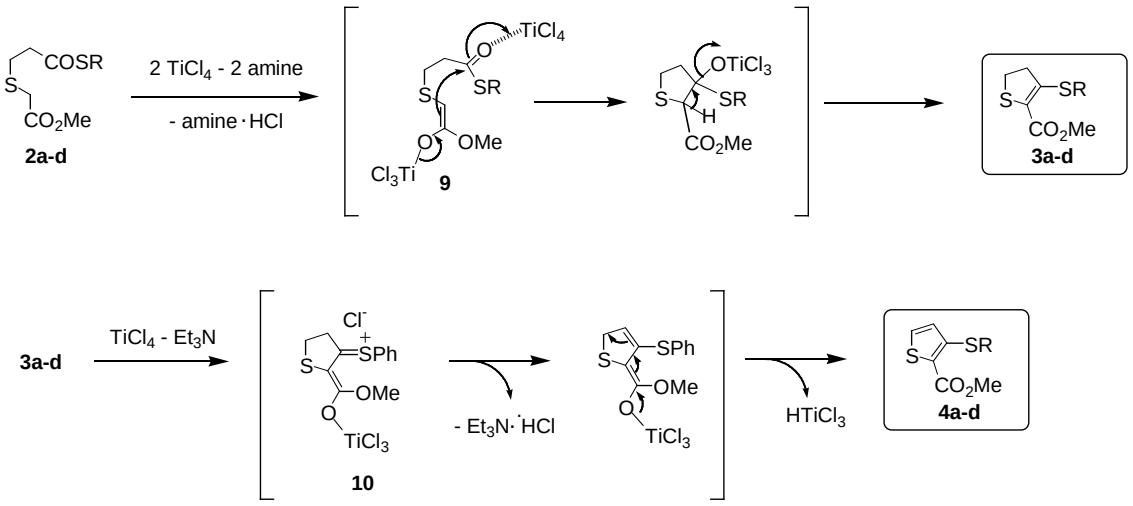
[a)] $Bu_3N$ was used instead of $Et_3N$.

Notice that dihydrothiophene **3a** was easily converted (oxidized) to thermodynamically favorable thiophene **4a** in 87% yield (Scheme 3). Based on all these results, we propose the following plausible mechanism (Scheme 4). Similar to the reported dehydration-type Ti-Dieckmann condensation using 2.2 equiv of $TiCl_4$ and 2.4 equiv of an amine,[8] site selective enolate formation from **2a-d** to **9** proceeds due to stabilization by an α-sulfinyl substituent. The enolate **9** attacks the counter thioester moiety, followed by the elimination of $Ti(=O)Cl_2$ and HCl affords dihydrothiophenes **3a-d** (net process is dehydration of **2**). Excess $TiCl_4$ (additional ca. 3 equiv) – $Et_3N$ (additional ca. 3 equiv) promotes the oxidation of **3a-d** to give thiophenes **4a-d**. Periasamy's group extensively studied this type of oxidation reaction utilizing a redox-system of the $TiCl_4$ – amine reagent.[11] Consistent with their investigations, $TiCl_4$ – $Et_3N$ reagent

reacts with dihydrothiophenes **3** to give sulfinyl Ti-enolate intermediate **10**, which is in turn transformed (aromatized) to thiophenes **4a-d** with eliminating $Et_3N \cdot HCl$ and $HTiCl_3$.




Scheme 3 Oxidation of **3a** promoted by $TiCl_4$-$Et_3N$ reagent.




Scheme 4 Proposed mechanisms for dehydration-type Ti-Dieckmann condensation and thiophene formation.

In conclusion, we developed a regioselective synthesis of methyl thiophene-2-carboxylates and 4,5-dihydrothiophene-2-carboxylates utilizing a dehydration-type Ti-Dieckmann condensation. The reaction mode depends on the choice of amine; $Et_3N$ facilitated the synthesis for thiophene-2-carboxylates, while $(sec\text{-}Bu)_2NH$ facilitated the synthesis 4,5-dihydrothiophene-2-carboxylates. This cyclization reaction is characteristic for direct incorporation of the thiol moiety into the thiophene derivatives, compared with the traditional basic Dieckmann condensation.

## EXPERIMENTAL

**General:** Melting points were determined on a hot stage microscope apparatus (Yanagimoto) and were uncorrected. NMR spectra were recorded on a JEOL DELTA 300 spectometer, operating at 300 MHz for $^1H$ NMR and 75 MHz for $^{13}C$ NMR. Chemical shifts (δ ppm) in $CDCl_3$ were reported downfield

from TMS (= 0) for $^1$H NMR. For $^{13}$C NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.00 ppm) as an internal reference. IR Spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. Mass spectra were measured on a JEOL JMS-T100LC spectrometer.

***t*-Butyl 3-(methoxycarbonylmethylthio)propanoate (1):** *t*-Butyl acrylate (3.85 g, 30.0 mmol) in $CH_3CN$ (5 mL) was added to a stirred solution of methyl thioglycolate (3.18 g, 30.0 mmol) and $Et_3N$ (6.07 g, 60.0 mmol) in MeCN (40 mL) at 0 – 5 °C under an Ar atmosphere, and the mixture was stirred at rt for 1 h. Water was added to the mixture, which was extracted twice with $Et_2O$. The combined organic phase was washed with water, brine, dried ($Na_2SO_4$) and concentrated. The obtained crude product was purified by $SiO_2$-column chromatography (hexane : $Et_2O$ = 5 : 1) to give the desired product **1** (6.50 g, 92%).

Pale yellow oil; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.46 (9H, s), 2.55 (2H, t, *J* = 7.2 Hz), 2.87 (2H, t, *J* = 7.2 Hz), 3.26 (2H, s), 3.75 (3H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 27.8, 28.0, 33.4, 35.4, 52.4, 80.9, 170.77, 170.84; IR (neat) 2980, 1730, 1437, 1393, 1368, 1279, 1256, 1155, 1011, 756 cm$^{-1}$.

***S*-Cyclohexyl 3-(methoxycarbonylmethylthio)propanethioate (2a):** A solution of *tert*-butyl 3-(methoxycarbonylmethylthio)propanoate (**1**; 6.38 g, 27.0 mmol) in formic acid (20 mL) was stirred at the rt for 7 h. The mixture was concentrated under reduced pressure and gave crude oil of 3-(methoxycarbonylmethylthio)propanoic acid. TsCl (2.75 g, 14.4 mmol) was added to a stirred solution of the obtained crude oil (2.14 g, 12.0 mmol) and *N*-methylimidazole (2.46 g, 30.0 mmol) in $CH_3CN$ (24 mL) at 0 – 5 °C under an Ar atmosphere, followed by being stirred at the same temp. for 30 min. A solution of cyclohexanethiol (1.39 g, 12.0 mmol) in $CH_3CN$ (1.0 mL) was added to the mixture, which was stirred at the same temp. for 2 h. Water was added to the mixture, which was extracted twice with $Et_2O$. The combined organic phase was washed with water, brine, dried ($Na_2SO_4$) and concentrated. The obtained crude product was purified by $SiO_2$-column chromatography (hexane : AcOEt = 5 : 1) to give **2a** (2.93 g, 89%)

Pale yellow oil; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.18-1.50 (5H, m), 1.52-1.76 (3H, m), 1.84-1.98 (2H, m), 2.78-2.87 (2H, m), 2.88-2.97 (2H, m), 3.25 (2H, s), 3.47-3.61 (1H, m), 3.75 (3H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 25.4, 25.8, 27.8, 32.9, 33.5, 42.5, 43.4, 52.4, 170.6, 197.1; IR (neat) 2930, 2853, 1739, 1686, 1439, 1283, 1155, 1051, 968 cm$^{-1}$; HRMS (ESI) calcd for $C_{12}H_{20}O_3S_2$ ($M+Na^+$) 299.0752, found 299.0756.

***S*-Phenyl 3-(methoxycarbonylmethylthio)propanethioate (2b):** Yellow oil; $^1$H NMR (300 MHz, $CDCl_3$) δ 2.95-3.00 (4H, m), 3.27 (2H, s), 3.74 (3H, s), 7.39-7.43 (5H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ

27.7, 33.6, 43.0, 52.4, 127.2, 129.2, 129.5, 134.4, 170.6, 195.5; IR (neat) 2951, 1736, 1705, 1439, 1281, 1157, 1130, 1044, 961, 748 $cm^{-1}$; HRMS (ESI) calcd for $C_{12}H_{14}O_3S_2$ ($M+Na^+$) 293.0282, found 293.0276.

***S*-Benzyl 3-(methoxycarbonylmethylthio)propanethioate (2c):** Pale yellow oil; $^1H$ NMR (300 MHz, $CDCl_3$) δ 2.83-3.00 (4H, m), 3.24 (2H, s), 3.73 (3H, s), 4.14 (2H, s), 7.20-7.33 (5H, m); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 27.8, 33.3, 33.5, 43.1, 52.4, 127.3, 128.6, 128.8, 137.2, 170.6, 196.6; IR (neat) 2951, 1736, 1688, 1435, 1281, 1155, 1132, 1049, 968, 704 $cm^{-1}$; HRMS (ESI) calcd for $C_{13}H_{16}O_3S_2$ ($M+Na^+$) 307.0439, found 307.0442.

***S*-Octyl 3-(methoxycarbonylmethylthio)propanethioate (2d):** Colorless oil; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, $J$ = 6.9 Hz), 1.18-1.41 (10H, m), 1.50-1.65 (2H, m), 2.81-2.99 (6H, m), 3.25 (2H, s), 3.75 (3H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 14.0, 22.6, 27.9, 28.8, 29.0, 29.1, 29.4, 31.7, 33.5, 43.4, 52.4, 170.6, 197.4; IR (neat) 2928, 2855, 1742, 1690, 1460, 1437, 1279, 1155, 1130, 1049 $cm^{-1}$; HRMS (ESI) calcd for $C_{14}H_{26}O_3S_2$ ($M+Na^+$) 329.1221, found 329.1228.

**Methyl 3-(cyclohexylthio)-4,5-dihydrothiophene-2-carboxylate (3a):** $TiCl_4$ (87 μL, 0.79 mmol) and *sec*-$Bu_2NH$ (112 mg, 0.86 mmol) were successively added to a stirred solution of **2a** (100 mg, 0.36 mmol) in $CH_2Cl_2$ (1.0 mL) at -78 °C under an Ar atmosphere, and the mixture was stirred at the same temp. for 30 min. Water was added to the mixture, which was extracted twice with $Et_2O$. The combined organic phase was washed with water, brine, dried ($Na_2SO_4$) and concentrated. The obtained crude product was purified by $SiO_2$-column chromatography (hexane : AcOEt = 10 : 1) to give the desired product **3a** (54 mg, 58%).

Yellow oil; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.13-1.53 (5H, m), 1.55-1.87 (3H, m), 1.90-2.08 (2H, m), 3.04-3.16 (4H, m), 3.77 (3H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 25.26, 25.91, 29.85, 34.21, 40.61, 44.84, 51.86, 119.64, 145.36, 162.95; IR (neat) 2932, 2853, 1699, 1534, 1433, 1314, 1248, 1107, 1055, 766 $cm^{-1}$; HRMS (ESI) calcd for $C_{12}H_{18}O_2S_2$ ($M+Na^+$) 281.0646, found 281.0654.

**Methyl 3-(phenylthio)-4,5-dihydrothiophene-2-carboxylate (3b):**[11] Following the procedure for the preparation of **3a**, the condensation of **2b** (100 mg, 0.37 mmol) using $TiCl_4$ (89 μL, 0.81 mmol) and *sec*-$Bu_2NH$ (115 mg, 0.89 mmol) gave **3b** (52 mg, 56%).

Yellow oil; $^1H$ NMR (300 MHz, $CDCl_3$) δ 2.71 (2H, t, $J$ = 8.6 Hz), 3.09 (2H, t, $J$ = 8.6 Hz), 3.82 (3H, s), 7.30-7.69 (5H, m); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 29.62, 42.12, 52.10, 119.72, 129.11, 129.30, 131.84, 134.86, 145.26, 163.06; IR (neat) 2949, 1701, 1545, 1437, 1312, 1256, 1109, 1055, 752, 693 $cm^{-1}$; HRMS (ESI) calcd for $C_{12}H_{12}O_2S_2$ ($M+Na^+$) 275.0176, found 275.0170.

**Methyl 3-(benzylthio)-4,5-dihydrothiophene-2-carboxylate (3c):** Following the procedure for the preparation of **3a**, the condensation of **2c** (100 mg, 0.35 mmol) using $TiCl_4$ (85 μL, 0.77 mmol) and *sec*-$Bu_2NH$ (109 mg, 0.84 mmol) gave **3c** (62 mg, 67%).

Yellow crystals; mp 54 – 57 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 3.13-3.18 (4H, m), 3.76 (3H, s), 4.10 (2H, s), 7.22-7.38 (5H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 29.68, 37.10, 40.79, 51.95, 127.44, 128.67, 136.49, 145.38, 162.99; IR (KBr) 2948, 1686, 1437, 1318, 1258, 1192, 1111, 1055, 704 cm$^{-1}$; HRMS (ESI) calcd for $C_{13}H_{14}O_2S_2$ ($M+Na^+$) 289.0333, found 289.0326.

**Methyl 3-(octylthio)-4,5-dihydrothiophene-2-carboxylate (3d):** Following the procedure for the preparation of **3a**, the condensation of **2d** (101 mg, 0.33 mmol) using $TiCl_4$ (80 μL, 0.73 mmol) and *sec*-$Bu_2NH$ (102 mg, 0.79 mmol) gave **3d** (69 mg, 73%).

Yellow oil; $^1$H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.9 Hz), 1.17-1.47 (10H, m), 1.63 (2H, quint, *J* = 7.6 Hz), 2.86 (2H, t, *J* = 7.6 Hz), 3.12-3.28 (4H, m), 3.78 (3H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.00, 22.54, 28.74, 29.04, 29.66, 29.75, 31.68, 32.54, 40.59, 51.89, 118.95, 146.30, 163.06; IR (neat) 2926, 2853, 1701, 1537, 1433, 1252, 1111, 1055 cm$^{-1}$; HRMS (ESI) calcd for $C_{14}H_{24}O_2S_2$ ($M+Na^+$) 311.1115, found 311.1127.

**Methyl 3-(cyclohexylthio)thiophene-2-carboxylate (4a):** $TiCl_4$ (198 μL, 1.80 mmol) and $Et_3N$ (347 mg, 1.87 mmol) were successively added to a stirred solution of **2a** (100 mg, 0.36 mmol) in $CH_2Cl_2$ (1.0 mL) at -50 – -45 °C under an Ar atmosphere, and the mixture was stirred at the same temp. for 30 min. Water was added to the mixture, which was extracted twice with $Et_2O$. The combined organic phase was washed with water, brine, dried ($Na_2SO_4$) and concentrated. The obtained crude product was purified by $SiO_2$-column chromatography (hexane : AcOEt = 20 : 1) to give the desired product **4a** (74 mg, 83%).

Yellow oil; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.19-1.91 (8H, m), 1.99-2.16 (2H, m), 3.31 (1H, tt, *J* = 3.4, 10.3 Hz), 3.87 (3H, s), 7.02 (1H, d, *J* = 5.5 Hz), 7.49 (1H, d, *J* = 5.5 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 25.58, 25.95, 33.25, 44.86, 51.86, 122.05, 126.66, 131.00, 143.75, 162.45; IR (neat) 2932, 2853, 1701, 1493, 1252, 1188, 1078, 895, 770 cm$^{-1}$; HRMS (ESI) calcd for $C_{12}H_{16}O_2S_2$ ($M+Na^+$) 279.0489, found 279.0491.

**Methyl 3-(phenylthio)thiophene-2-carboxylate (4b):**[12] Following the procedure for the preparation of **4a**, the condensation of **2b** (100 mg, 0.37 mmol) with $TiCl_4$ (203 μL, 1.85 mmol) and $Et_3N$ (195 mg, 1.92 mmol) gave **4b** (79 mg, 85%).

Brown crystals; mp 84 – 85 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 3.91 (3H, s), 6.34 (1H, d, *J* = 5.2 Hz), 7.29

(1H, d, *J* = 5.2 Hz), 7.38-7.44 (3H, m), 7.56-7.63 (2H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 51.99, 121.17, 127.96, 129.20, 129.53, 130.50, 132.34, 134.86, 145.24, 162.49; IR (KBr) 1690, 1491, 1439, 1404, 1260, 1103, 1078, 775, 750, 687 cm$^{-1}$. HRMS (ESI) calcd for $C_{12}H_{10}O_2S_2$ (M+Na$^+$) 273.0020, found 273.0016.

**Methyl 3-(benzylthio)thiophene-2-carboxylate (4c):** Following the procedure for the preparation of **4a**, the condensation of **2c** (100 mg, 0.35 mmol) with $TiCl_4$ (192 μL, 1.75 mmol) and $Et_3N$ (184 mg, 1.82 mmol) gave **4c** (81 mg, 87%).

Brown crystals; mp 80 – 82 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 3.86 (3H, s), 4.23 (2H, s), 6.98 (1H, d, *J* = 5.2 Hz), 7.20-7.45 (5H, m), 7.43 (1H, d, *J* = 5.2 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 37.59, 51.89, 121.88, 126.39, 127.40, 128.59, 128.76, 131.13, 136.12, 144.12, 162.43; IR (KBr) 1686, 1487, 1437, 1399, 1254, 1179, 1080, 774, 711, 694 cm$^{-1}$. HRMS (ESI) calcd for $C_{13}H_{12}O_2S_2$ (M+Na$^+$) 287.0176, found 287.0179.

**Methyl 3-(octylthio)thiophene-2-carboxylate (4d):** Following the procedure for the preparation of **4a**, the condensation of **2d** (101 mg, 0.33 mmol) with $TiCl_4$ (181 μL, 1.65 mmol) and $Et_3N$ (174 mg, 1.72 mmol) gave **4d** (78 mg, 82%).

Yellow oil; $^1$H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.5 Hz), 1.16-1.56 (10H, m), 1.73 (2H, quint, *J* = 7.6 Hz), 3.00 (2H, t, *J* = 7.6 Hz), 3.87 (3H, s), 6.99 (1H, d, *J* = 5.2 Hz), 7.49 (1H, d, *J* = 5.2 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.03, 22.58, 28.91, 29.10, 31.72, 32.87, 51.84, 121.40, 125.95, 131.06, 144.90, 162.53; IR (neat) 2924, 2853, 1690, 1491, 1439, 1402, 1258, 1080, 898, 772 cm$^{-1}$. HRMS (ESI) calcd for $C_{14}H_{22}O_2S_2$ (M+Na$^+$) 309.0959, found 309.0963.

***S*-Phenyl 3-(methoxycarbonylmethylthio)-3-methyl propanethioate (5a):** Pale yellow oil; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.35 (3H, d, *J* = 6.8 Hz), 2.69-2.84 (1H, m), 2.97-3.11 (2H, m), 3.27 (2H, s), 3.76 (3H, s), 7.35-7.46 (5H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 17.5, 33.9, 35.8, 47.8, 52.5, 127.2, 129.2, 129.4, 134.4, 170.7, 200.0; IR (neat) 2924, 1736, 1703, 1441, 1283, 957, 748 cm$^{-1}$; HRMS (ESI) calcd for $C_{13}H_{12}O_3S_2$ (M+Na$^+$) 307.0439, found 307.0431.

***S*-Phenyl 3-(methoxycarbonylmethylthio)-2-methyl propanethioate (5b):** Yellow oil; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.38 (3H, d, *J* = 6.9 Hz), 2.80 (1H, dd, *J* = 8.3 Hz, *Jgem* = 15.5 Hz), 3.02 (1H, dd, *J* = 5.9 Hz, *Jgem* = 15.5 Hz), 3.28-3.34 (2H, m), 3.35-3.51 (1H, m), 3.74 (3H, s), 7.36-7.44 (5H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 20.7, 32.6, 37.3, 50.2, 52.4, 127.3, 129.2, 129.5, 134.3, 170.8, 195.0; IR (neat) 2953, 1738, 1705, 1439, 1281, 1196, 1134, 992, 748 cm$^{-1}$; HRMS (ESI) calcd for $C_{13}H_{12}O_3S_2$ (M+Na$^+$) 307.0439, found 307.0428.

**Methyl 4-methyl-3-(phenylthio)thiophene-2-carboxylate (7a):** Following the procedure for the preparation of **4a**, the condensation of **5a** (284 mg, 1.0 mmol) with $TiCl_4$ (548 μL, 5.0 mmol) and $Et_3N$ (526 mg, 5.2 mmol) gave the desired product **7a** (116 mg, 44%)

Colorless crystals; mp 100 – 102 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 2.08 (3H, d, *J* = 1.0 Hz), 3.85 (3H, s), 7.07-7.15 (4H, m), 7.18-7.25 (2H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 15.6, 52.1, 125.7, 126.8, 127.6, 128.9, 134.2, 135.2, 136.8, 142.9, 161.7; IR (KBr) 1709, 1437, 1408, 1238, 1107, 1082, 1013, 822, 747, 693 cm$^{-1}$; HRMS (ESI) calcd for $C_{13}H_{12}O_2S_2$ ($M+Na^+$) 287.0176, found 287.0180.

**Methyl 5-methyl-3-(phenylthio)thiophene-2-carboxylate (7b):** Following the procedure for the preparation of **4a**, the condensation of the desired product **5b** (284 mg, 1.0 mmol) with $TiCl_4$ (548 μL, 5.0 mmol) and $Et_3N$ (526 mg, 5.2 mmol) gave **7b** (172 mg, 65%)

Yellow oil; $^1$H NMR (300 MHz, $CDCl_3$) δ 2.33 (3H, d, *J* = 1.0 Hz), 3.88 (3H, s), 6.03 (1H, d, *J* = 1.0 Hz), 7.37-7.48 (3H, m), 7.55-7.63 (2H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 15.7, 51.8, 118.7, 126.4, 129.1, 129.5, 132.5, 134.9, 145.2, 145.7, 162.5; IR (neat) 1698, 1522, 1454, 1331, 1263, 1192, 1088, 872, 752, 693 cm$^{-1}$; HRMS (ESI) calcd for $C_{13}H_{12}O_2S_2$ ($M+Na^+$) 287.0176, found 287.0177.

**Methyl tetrahydro-4-methyl-3-oxothiophene-2-carboxylate (8a):**[13] Following the procedure for the preparation of **4a**, the condensation of **5a** (284 mg, 1.0 mmol) with $TiCl_4$ (241 μL, 2.2 mmol) and $Et_3N$ (243 mg, 2.4 mmol) gave **8a** (113 mg, 65%)

Diasteromixture; Pale yellow oil; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H x 2/5, d, *J* = 6.9 Hz), 1.26 (3H x 3/5, d, *J* = 6.9 Hz), 2.56-2.72 (1H x 2/5, m), 2.68 (1H x 2/5, dd, *J* = 7.9 Hz, *Jgem* = 10.7 Hz), 2.80-2.93 (1H x 3/5, m), 3.06 (1H x 3/5, dd, *J* = 10.7 Hz, *Jgem* = 11.4 Hz), 3.19 (1H x 3/5, dd, *J* = 7.9 Hz, *Jgem* = 11.4 Hz), 3.34 (1H x 2/5, dd, *J* = 7.9 Hz, *Jgem* = 10.7 Hz), 3.76 (3H x 3/5, s), 3.77 (3H x 2/5, s), 4.09 (1H x 2/5, s), 4.13 (1H x 3/5, s); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.5, 14.7, 31.9, 33.7, 43.5, 45.3, 51.9, 52.9, 53.1, 168.9, 169.5, 207.6, 209.0; IR (neat) 1748, 1437, 1294, 1262, 1206, 1157, 988 cm$^{-1}$.

## ACKNOWLEDGEMENTS

Dedicated to Prof. Yoshito Kishi on the occasion of his 70$^{th}$ birthday.

This research was partially supported by Grant-in-Aids for Scientific Research on Basic Areas (B) “18350056”, Priority Areas (A) “17035087” and “18037068”, and Exploratory Research “17655045” from the Ministry of Education , Culture, Sports, Science, and Technology (MEXT).

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