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

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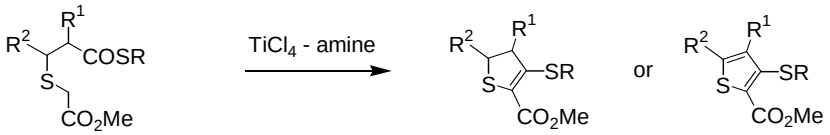
Abstract – Regioselective dehydration-type Ti-Dieckmann condensation of 3-(methoxycarbonylmethylthio)propanethioates successfully afforded methyl thiophene-2-carboxylates and methyl 4,5-dihydrothiophene-2-carboxylates, utilizing $TiCl_4$ – Et_3N and $TiCl_4$ – $(sec\text{-}Bu)_2NH$, respectively.

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]

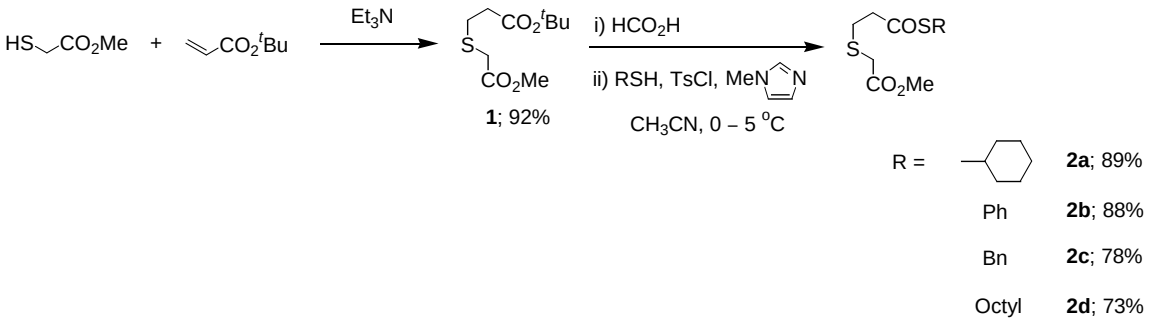
The characteristic mode of this dehydration-type reaction involves a direct incorporation of the thiol moiety into the 1β-methylcarbapenem skeleton, compared with the traditional basic Dieckmann condensation. In general, the thiol function of thioesters is regarded as a more easily displacable moiety,

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

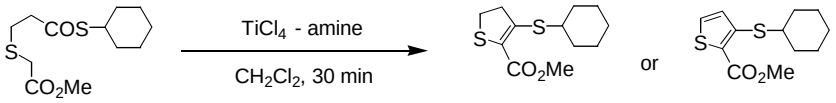
The starting substrate, *S*-alkyl *or S*-phenyl 3-(methoxycarbonylmethylthio)propanethioates **2a-2d**, was readily prepared as follows (Scheme 2). Michael addition of methyl thioglycolate to *t*-butyl acrylate gave *t*-butyl 3-(methoxycarbonylmethylthio)propanoate (**1**) in 92% yield. Acidic hydrolysis 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*).

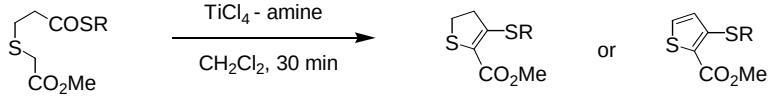
Table 1. Dehydration-type Ti-Dieckmann condensation of half thiol diesters **2a** using four amine reagents.



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**)

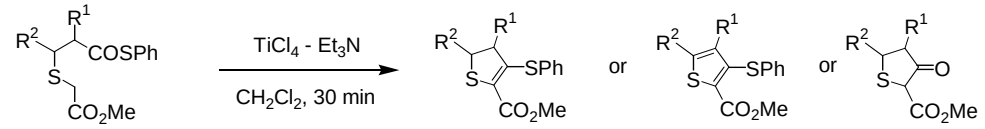
[a] method **A** : $TiCl_4$ (2.2 equiv), (*sec*-Bu$_2$)NH (2.4 equiv), -78 °C.
method **B** : $TiCl_4$ (5.0 equiv), Et_3N (5.2 equiv), -50 – - 45 °C.

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

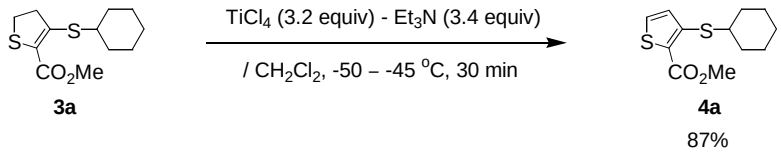
6 **7** **8**

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

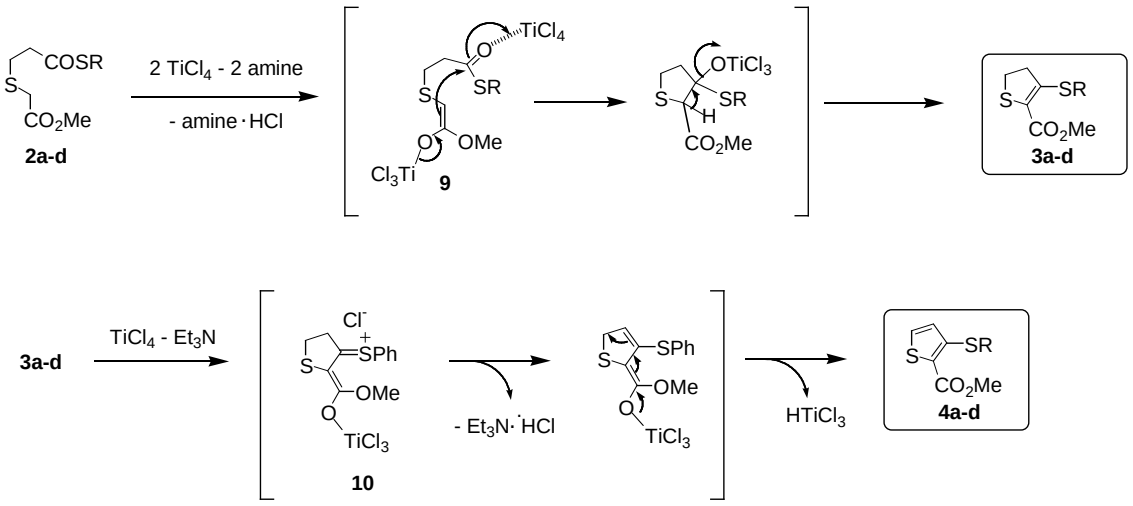
[a)] Bu_3N was used instead of Et_3N.

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}.

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