Graphical Abstract

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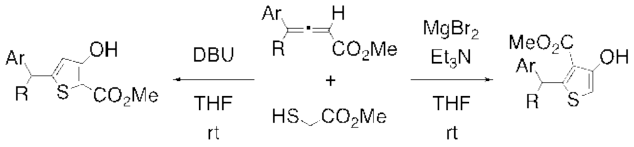

Tetrahedron Letters
journal homepage: www.elsevier.com

Tandem Thia-Michael/Dieckmann Condensation of Allenyl Esters for the Regioselective Synthesis of Trisubstituted Thiophenes

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ARTICLE INFO

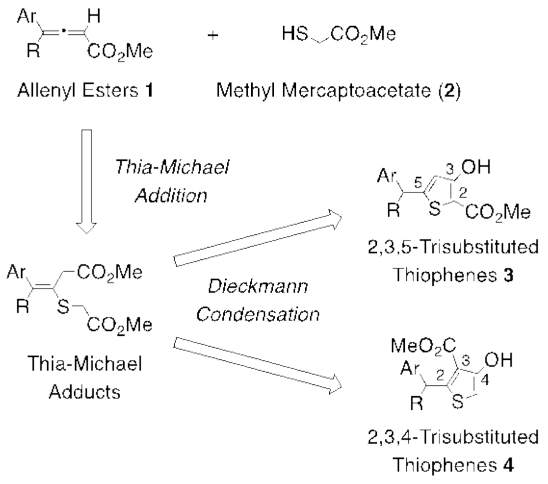
Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Thia-Michael/Dieckmann condensation
Trisubstituted thiophene
Allenyl ester
Methyl mercaptoacetate
Magnesium bromide

ABSTRACT

Tandem thia-Michael/Dieckmann condensation of allenyl esters with methyl mercaptoacetate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene afforded 2,3,5-trisubstituted thiophenes regioselectively. On the other hand, 2,3,4-trisubstituted thiophenes were obtained as the sole product by tandem thia-Michael/Dieckmann condensation employing magnesium bromide and triethylamine.

By virtue of their diverse reactivities, allenyl esters are attractive compounds for the synthesis of various molecules including heterocycles [1-3]. We recently described a facile method of synthesizing disubstituted allenyl esters through the magnesium(II)-mediated Horner-Wadsworth-Emmons (HWE) reaction of methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (Still–Gennari reagent) with disubstituted ketenes [4]. In general, allenyl esters are known to react with thiols to produce thia-Michael adducts [5-8]. Furthermore, we already reported the chemoselective Dieckmann-type cyclization under Lewis acid-triethylamine conditions [9,10]. Therefore, we envisaged that the thia-Michael addition of allenyl ester **1** with a thiol bearing an electrophilic moiety such as an ester group, followed by chemoselective Dieckmann condensation, could be a novel regioselective method of synthesizing 2,3,5- or 2,3,4-trisubstituted thiophenes with ester, hydroxyl, and alkyl groups (Scheme 1). Thiophenes are an important class of heterocyclic compounds for not only biological active compounds [11,12] but also functional materials [13]. Although various methods for the synthesis of trisubstituted thiophenes have been developed [14-17], to our knowledge there are no reports on the construction of functionalized thiophenes by a chemoselective reaction of a common precursor. Herein, we demonstrate tandem thia-Michael/Dieckmann condensation of allenyl esters **1** with methyl mercaptoacetate (**2**) for the regioselective synthesis of trisubstituted thiophenes **3** and **4**.

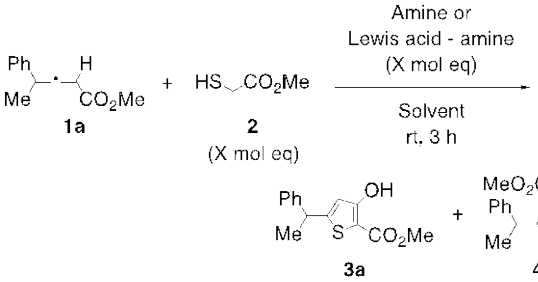


Scheme 1. Tandem thia-Michael/Dieckmann condensation of allenyl esters **1** with methyl mercaptoacetate (**2**) for the regioselective synthesis of trisubstituted thiophenes **3** and **4**.

First, we investigated the reaction of allenyl ester **1a** with methyl mercaptoacetate (**2**) in the presence of tertiary amine bases (Table 1). Using 1 equiv of triethylamine, no thia-Michael addition occurred (Entry 1). However, tandem thia-Michael/Dieckmann condensation of **1a** with **2** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) proceeded to afford 2,3,5-trisubstituted thiophene **3a** and 2,3,4-trisubstituted thiophene **4a** as an inseparable mixture with a **3a**/**4a** ratio of 97:3

∗ Corresponding author. Tel.: +81-88-633-7273; fax: +81-88-633-9503; e-mail: ssano@tokushima-u.ac.jp in 99% yield (Entry 2). The molar ratios of **3a** and **4a** were determined by integrating the appropriate proton absorptions obtained by ^{1}H NMR (400 MHz, $CDCl_3$) analysis. The yields of trisubstituted thiophenes **3a** and **4a** were decreased in CH_2Cl_2 or 1,4-dioxane (Entries 3 and 4). On the other hand, 2,3,4-trisubstituted thiophene **4a** was obtained in 77% yield as the sole product in the presence of 1.2 equiv of lithium chloride and triethylamine (Entry 5). Use of DBU instead of triethylamine in the presence of lithium chloride resulted in the formation of a mixture of **3a** and **4a** (**3a**/**4a** = 31 : 69) (Entry 6). Finally, the most satisfactory results were obtained using 1.2 equiv of magnesium bromide–triethylamine (85% yield) or magnesium bromide–DBU (80% yield) in the regioselective synthesis of 2,3,4-trisubstituted thiophene **4a** (Entries 7 and 8).

Table 1. Tandem thia-Michael/Dieckmann condensation of allenyl ester **1a** with methyl mercaptoacetate (**2**).



Entry	Amine or Lewis acid - amine	X (mol eq)	Solvent	Yield of **3a** + **4a** (%)^a	**3a**/**4a**
1	Et_3N	1	THF	0	–
2	DBU	1	THF	99	97:3 ^{b}
3	DBU	1	CH_2Cl_2	81	93:7 ^{b}
4	DBU	1	1,4-dioxane	70	97:3 ^{c}
5	$LiCl/Et_3N$	1.2	THF	77	0:100 ^{c}
6	LiCl/DBU	1.2	THF	91	31:69 ^{c}
7	$MgBr_2/Et_3N$	1.2	THF	85	0:100 ^{c}
8	$MgBr_2$/DBU	1.2	THF	80	0:100 ^{c}

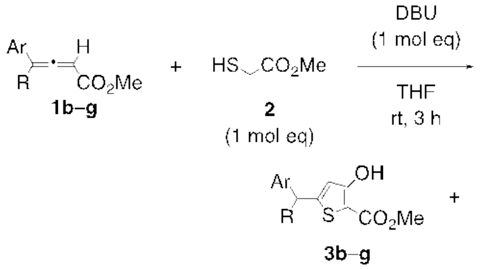
^{a}Isolated yield.

^{b}Determined by ^{1}H NMR (400 MHz, $CDCl_3$) analysis.

^{c}Determined by ^{1}H NMR (500 MHz, $CDCl_3$) analysis.

Next, the tandem thia-Michael/Dieckmann condensation of allenyl esters **1b–g** in the presence of DBU was performed as shown in Table 2. The reaction of allenyl esters **1b–e** with the para-substituted phenyl group afforded 2,3,5-trisubstituted thiophenes **3b–e** with high yields and high regioselectivity (Entries 1-4). In addition, 2,3,5-trisubstituted thiophenes **3f**,**g** bearing ethyl or phenyl substituent (R) were regioselectively obtained from the reaction of allenyl esters **1f**,**g** in good to high yields (Entries 5 and 6) [18,19].

Table 2. Tandem thia-Michael/Dieckmann condensation of allenyl esters **1b–g** with methyl mercaptoacetate (**2**) in the presence of DBU.



Entry	Allenyl esters **1**	Ar	R	Yield of **3** + **4** (%)^a	**3**/**4**
1	**1b**	$4\text{-}MeOC_6H_4$	Me	93 (**3b** + **4b**)	95:5 ^{c}
2	**1c**	$4\text{-}MeC_6H_4$	Me	91 (**3c** + **4c**)	98:2 ^{b}
3	**1d**	$4\text{-}ClC_6H_4$	Me	92 (**3d** + **4d**)	98:2 ^{b}
4	**1e**	$4\text{-}NO_2C_6H_4$	Me	95 (**3e** + **4e**)	97:3 ^{c}
5	**1f**	Ph	Et	92 (**3f** + **4f**)	98:2 ^{b}
6	**1g**	Ph	Ph	79 (**3g** + **4g**)	100:0 ^{c}

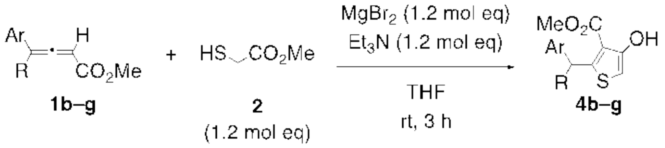
^{a}Isolated yield.

^{b}Determined by ^{1}H NMR (400 MHz, $CDCl_3$) analysis.

^{c}Determined by ^{1}H NMR (500 MHz, $CDCl_3$) analysis

Table 3 summarizes the result of tandem thia-Michael/Dieckmann condensation of **1b–g** with **2** employing magnesium bromide and triethylamine [20-22]. The reactions proceeded completely regioselectively, and 2,3,4-trisubstituted thiophenes **4b–g** were obtained in high yields in all cases [23,24].

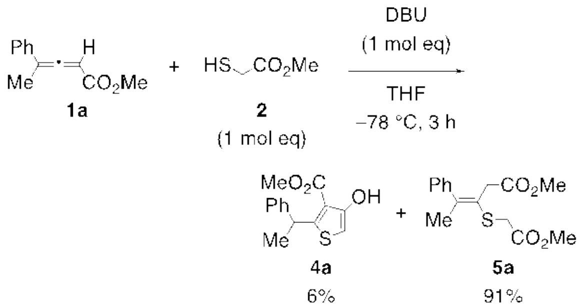
Table 3. Tandem thia-Michael/Dieckmann condensation of allenyl esters **1b–g** with methyl mercaptoacetate (**2**) in the presence of $MgBr_2/Et_3N$.



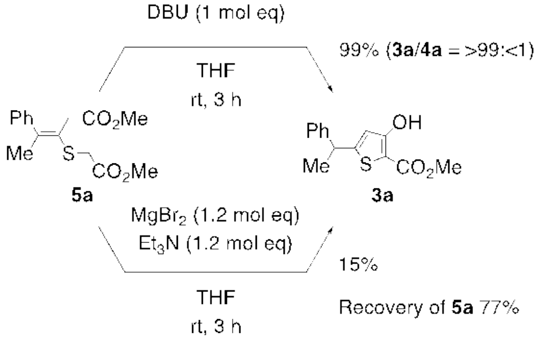
Entry	Allenyl esters **1**	Ar	R	Yield of **4** (%)^a
1	**1b**	$4\text{-}MeOC_6H_4$	Me	80 (**4b**)
2	**1c**	$4\text{-}MeC_6H_4$	Me	92 (**4c**)
3	**1d**	$4\text{-}ClC_6H_4$	Me	80 (**4d**)
4	**1e**	$4\text{-}NO_2C_6H_4$	Me	89 (**4e**)
5	**1f**	Ph	Et	86 (**4f**)
6	**1g**	Ph	Ph	77 (**4g**)

^{a}Isolated yield.

We investigated the reaction of **1a** and **2** in the presence of DBU at –78 °C (Scheme 2). Compared to the result at room temperature (Table 1, Entry 2), the formation of 2,3,5-trisubstituted thiophene **3a** was not observed at –78 °C. Instead, thia-Michael adduct **5a** (91%) was obtained together with a small amount of 2,3,4-trisubstituted thiophene **4a** (6%). Thia-Michael adduct **5a** was almost quantitatively cyclized to 2,3,5-trisubstituted thiophene **3a** in the presence of DBU. In addition, a small amount of **3a** (15%) was obtained with the recovery of **5a** (77%) employing magnesium bromide and triethylamine (Scheme 3). The geometry of **5a** was determined on the basis of the ^{1}H-^{1}H nuclear Overhauser effects (NOEs).

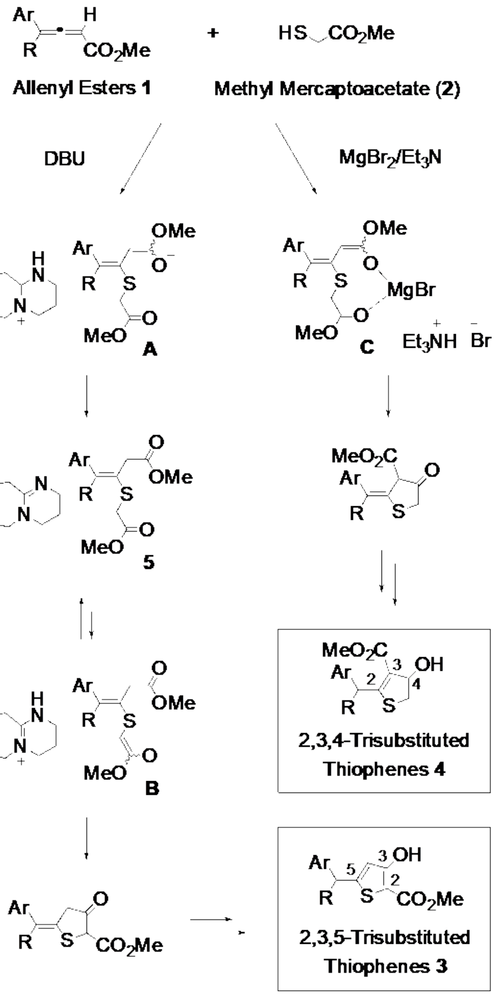


Scheme 2. Reaction of allenyl ester **1a** in the presence of DBU at –78 °C.



Scheme 3. Cyclization of thia-Michael adduct **5a**.

Although the reaction mechanism underlying the tandem thia-Michael/Dieckmann condensation is not fully understood, a plausible pathway is shown in Scheme 4. In the presence of DBU, the thia-Michael addition of **2** to allenyl esters **1** affords the kinetic enolate **A**, which would be rapidly protonated to give thia-Michael adducts **5**. Then, the quick equilibrium between **5** and its thermodynamic enolate **B** could have been caused by DBU at room temperature. As a result, the cyclization of enolate **B** followed by tautomerization furnished 2,3,5-trisubstituted thiophenes **3** as the major product. However, enolate **B** could not be formed by the proton abstraction of **5** at –78 °C. Therefore, thia-Michael adduct **5a** was obtained as the major product as shown in Scheme 2. DBU conditions could allow the slight generation of 2,3,4-trisubstituted thiophenes **4** attributed to the cyclization pathway of enolate **A**. On the other hand, in the presence of magnesium bromide and triethylamine, relatively stable magnesium enolate **C** could be generated in association with the thia-Michael addition. Afterwards, the cyclization of enolate **C** could proceed to provide 2,3,4-trisubstituted thiophenes **4** as the sole product.



Scheme 4. Plausible reaction pathways for the regioselective formation of 2,3,5-trisubstituted thiophenes **3** and 2,3,4-trisubstituted thiophenes **4**.

In conclusion, we have developed a novel tandem thia-Michael/Dieckmann condensation of allenyl esters **1** with methyl mercaptoacetate (**2**) for the regioselective synthesis of 2,3,5-trisubstituted thiophenes **3** and 2,3,4-trisubstituted thiophenes **4**. The present method may be expanded to provide wide application for convenient syntheses of highly functionalized heterocycles.

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18. Typical procedure for the thia-Michael/Dieckmann condensation in the presence of DBU: To a solution of allenyl ester **1a** (53.8 mg, 0.286 mmol) and methyl mercaptoacetate (**2**) (26.0 μL, 0.286 mmol) in anhydrous THF (2 mL) was added DBU (42.7 μL, 0.286 mmol) at room temperature under argon. After stirring for 3 h, the reaction mixture was treated with 1N HCl aq (3 mL) and then extracted with $CHCl_3$ (20 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel PSQ 60B: *n*-hexane–AcOEt (8 : 1)] to afford a mixture of **3a** and **4a** (74.0 mg, 99%, **3a**/**4a** = 97 : 3) as a colorless oil. The analytical sample of **3a** was obtained by further purification by PTLC.
19. The spectroscopic data of **3a** are as follows: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.67 (d, *J* = 7.2 Hz, 3H), 3.83 (s, 3H), 4.21 (q, *J* = 7.1 Hz, 1H), 6.50 (d, *J* = 0.8 Hz, 1H), 7.21–7.26 (m, 3H), 7.29–7.35 (m, 2H), 9.54 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 41.5, 51.7, 101.9, 116.5, 127.1, 127.2, 128.7, 144.1, 157.7, 164.3, 166.7; IR (neat) 2955, 1657, 1560, 1442, 1352, 1174, 1104 cm^{-1}; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{14}O_3SNa$: 285.0561; found: 285.0537.
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23. Typical procedure for the thia-Michael/Dieckmann condensation in the presence of $MgBr_2/Et_3N$: To a solution of magnesium bromide (51.6 mg, 0.280 mmol), allenyl ester **1a** (44.0 mg, 0.234 mmol), and methyl mercaptoacetate (**2**) (25.5 μL, 0.280 mmol) in anhydrous THF (2 mL) was added triethylamine (39.2 μL, 0.280 mmol) at room temperature under argon. After stirring for 3 h, the reaction mixture was treated with 1N HCl aq (3 mL) and then extracted with $CHCl_3$ (20 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel PSQ 60B: *n*-hexane–AcOEt (9 : 1)] to afford **4a** (52.3 mg, 85%) as a colorless oil.
24. The spectroscopic data of **4a** are as follows: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (d, *J* = 7.2 Hz, 3H), 3.85 (s, 3H), 5.04 (q, *J* = 7.2 Hz, 1H), 6.23 (s, 1H), 7.19–7.23 (m, 3H), 7.27–7.31 (m, 2H), 9.18 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.1, 40.6, 51.7, 96.5, 114.9, 126.6, 127.2, 128.4, 145.0, 156.1, 158.6, 166.5; IR (neat) 2958, 1672, 1448, 1423, 1357, 1085 cm^{-1}; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{14}O_3SNa$: 285.0561; found: 285.0536. Anal. Calcd for $C_{14}H_{14}O_3S$: C, 64.10; H, 5.38. Found: C, 63.87; H, 5.44%.

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.