

**A NEW SIMPLE METHOD FOR THE SYNTHESIS OF THIOPHENE  
DERIVATIVES — GENERATION OF THIOCARBONYL YLIDES  
FROM *S*- $\alpha$ -(DIMETHYLPHENYLSILYL)BENZYL ACYLATES  
AND THEIR CYCLOADDITION WITH ACETYLENIC  
DIPOLAROPHILES —**

Mitsuo Komatsu,<sup>a\*</sup> Jinil Choi,<sup>a</sup> Masatoshi Mihara,<sup>b</sup> Yoji Oderaotoshi,<sup>a</sup> and  
Satoshi Minakata<sup>a</sup>

<sup>a</sup>Department of Applied Chemistry, Graduate School of Engineering, Osaka  
University, Yamadaoka 2-1, Suita, Osaka 565-0871, Japan

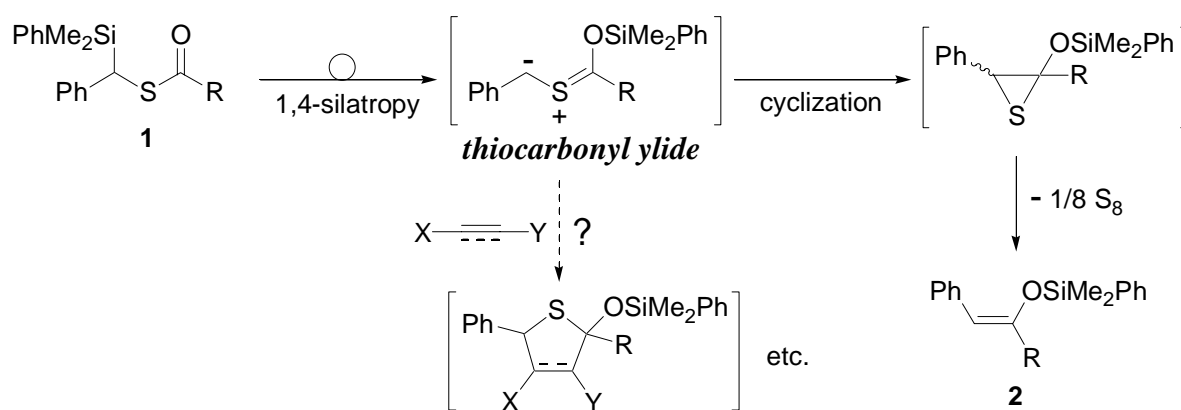
<sup>b</sup>Osaka Municipal, Technical Research Institute, 1-6-50 Morinomiya, Joto-ku,  
Osaka 536-8553, Japan

**Abstract** – The cycloaddition of *S*- $\alpha$ -(dimethylphenylsilyl)benzyl acylates (**1**) with acetylenic dipolarophiles *via* 1,4-silatropy proceeded readily to afford thiophene derivatives. The reaction of thioesters (**1**) with 1-diethylamino-1-propyne (**A**), an electron-rich acetylenic dipolarophile, gave 5-aryl-3-diethylamino-4-methyl-2-phenylthiophenes (**3**) and 4-aryl-2-diethylamino-3-methyl-5-phenylthiophenes (**4**). When dimethyl acetylenedicarboxylate (DMAD), an electron-deficient alkyne, was used, the reaction of thioesters (**1**) afforded thiophene derivatives (**4**) exclusively.

Cycloadditions of various 1,3-dipoles represent a powerful tool for the synthesis of 5-membered heterocyclic compounds.<sup>1</sup> Among these, the cycloaddition of thiocarbonyl ylides, sulfur-centered 1,3-dipoles, with dipolarophiles can be successfully used to prepare thiophene derivatives, and several methods for the generation of thiocarbonyl ylides are available.<sup>2</sup> The thiophene ring structure is widespread in nature and many of these compounds are biologically active.<sup>3</sup> Moreover,

thiophene derivatives are also widely found in functional materials such as dyes and liquid crystals.<sup>3</sup>

Recently, we reported on the formation of enol silyl ethers (**2**) from *S*- $\alpha$ -trimethylsilylbenzyl acylates (**1**) *via* thiocarbonyl ylides (Scheme 1).<sup>4</sup> The thiocarbonyl ylides were easily generated by 1,4-silatropy of the starting acylates, followed by cyclization and elimination of sulfur, leading to enol silyl ethers. The reaction is characterized not only by the development of a new synthesis of enol silyl ethers accompanied by C-C bond formation, but also by the fact that the starting materials can be readily prepared by the condensation of  $\alpha$ -trimethylsilylbenzylthiols and carboxylic acids or carbonyl halides. As a logical offshoot, these results prompted us to trap the thiocarbonyl ylides by intermolecular 1,3-dipolar cycloaddition with dipolarophiles, a reaction that would lead to sulfur-containing heterocyclic compounds. Herein we report on the unprecedented synthesis of thiophene derivatives *via* the cycloaddition of thiocarbonyl ylides generated from the reaction of *S*- $\alpha$ -trimethylsilylbenzyl acylates with acetylenic dipolarophiles.

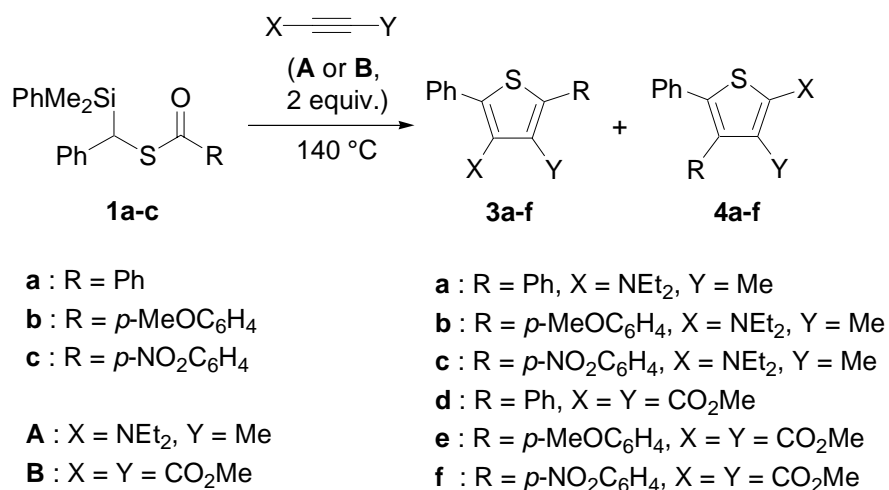


**Scheme 1.** Generation of Thiocarbonyl Ylides and Cycloaddition with Dipolarophiles

In a typical reaction, the treatment of *S*- $\alpha$ -(dimethylphenylsilyl)benzyl thiobenzoate (**1a**, 1.0 mmol) with 2 equiv. of 1-diethylamino-1-propyne (**A**) in benzene (5 mL) at 140 °C for 26 h in a sealed tube gave 3-diethylamino-4-methyl-2,5-diphenylthiophene (**3a**, 40%) and unexpectedly 2-diethylamino-3-methyl-4,5-diphenylthiophene (**4a**, 35%). In the former adduct, the both phenyl rings are vicinal to the sulfur atom, while the phenyl groups are in a vicinal arrangement in the latter adduct. In a similar manner, reactions of

**1a-c** with two acetylenic dipolarophiles were carried out (Table 1). The structures of all of the products were determined by spectroscopic analysis and X-Ray crystal structure analysis.<sup>5</sup>

**Table 1.** Cycloaddition of Thioesters (**1**) with Dipolarophiles



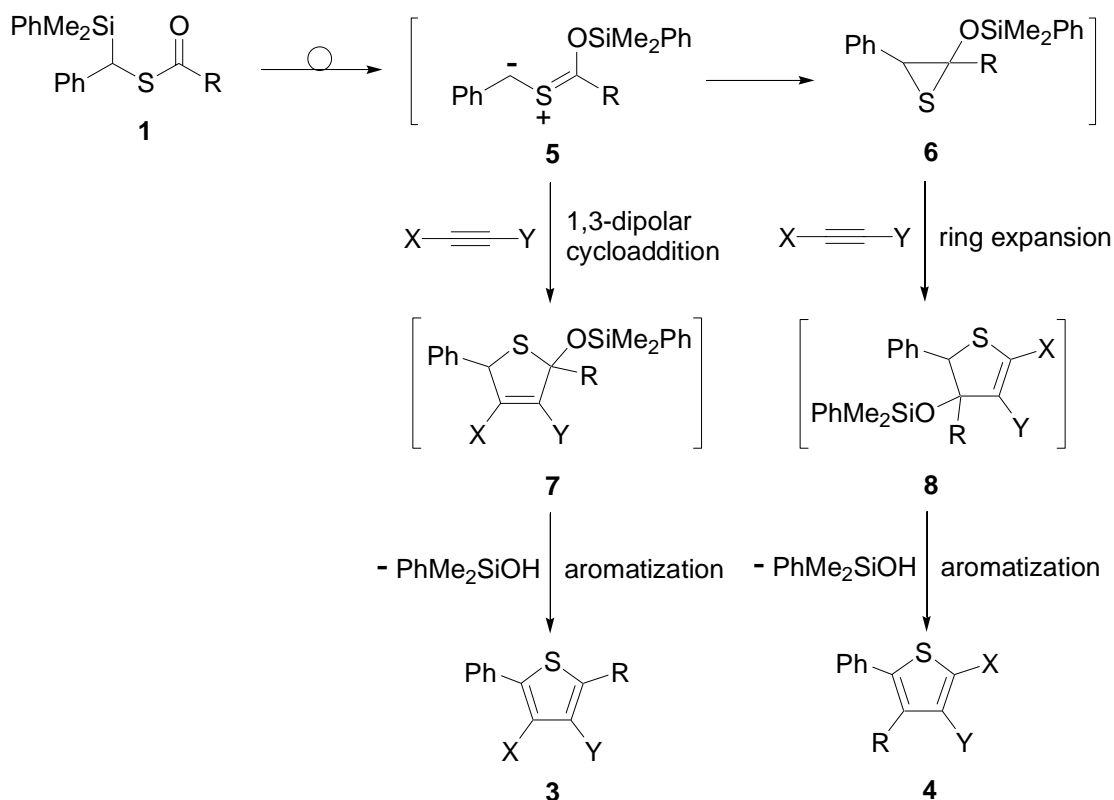
Run	Substrate	Dipolarophile	Solvent	Time (h)	Yield (%) <sup>a</sup>	Ratio <sup>a</sup>
1	<b>1a</b>	<b>A</b>	PhH	26	75	53/47 ( <b>3a</b> / <b>4a</b> )
2	<b>1a</b>	<b>A</b>	THF	25	48	63/37 ( <b>3a</b> / <b>4a</b> )
3	<b>1b</b>	<b>A</b>	PhH	40	51	35/65 ( <b>3b</b> / <b>4b</b> )
4	<b>1c</b>	<b>A</b>	PhH	4	47	57/43 ( <b>3c</b> / <b>4c</b> )
5	<b>1a</b>	<b>B</b>	PhH	50	54	<b>4d</b> only
6	<b>1b</b>	<b>B</b>	PhH	45	18 <sup>b</sup>	<b>4e</b> only
7	<b>1c</b>	<b>B</b>	PhH	50	0 <sup>c</sup>	—

<sup>a</sup> Determined by <sup>1</sup>H NMR spectral analysis. <sup>b</sup> Benzyl *p*-methoxyphenyl ketone was obtained in 32% yield. <sup>c</sup> Enol silyl ether (**2**) (R = *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, 78 %) was obtained.

The reaction of thioester (**1a**) with ynamine (**A**) in THF gave thiophene derivatives (**3a**) and (**4a**) in lower yield than when benzene as the solvent (Runs 1 and 2). This tendency has often been observed in our silatropic generation of 1,3-dipoles where nonpolar solvents such as benzene and toluene are more effective than polar solvents such as THF, acetonitrile, and chloroform.<sup>7</sup> In the present case, coordination of THF to the silyl atom of thioesters (**1**) may interfere interaction between the silyl atom and the carbonyl oxygen atom to retard the 1,4-silatropic reaction. In the case of thioester (**1b**) or (**1c**), bearing an electron donating group or an electron deficient group on the benzoyl group, the yields of products were lower than those of the cycloadducts from thioester (**1a**), while the electron deficient group accelerated the reaction probably

because of stabilization of the electron-rich  $\alpha$ -carbon of the ylide intermediate (Runs 3 and 4). Contrary to the reaction with an electron rich alkyne, thioester (**1a**) reacted with dimethyl acetylenedicarboxylate (DMAD, **B**) to afford thiophene derivative (**4d**) in 54% yield and no cycloadduct (**3d**) was detected (Run 5). In the case of thioester (**1b**), cycloadduct (**4e**) was obtained in low yield, but the reaction of thioester (**1c**) afforded the enol silyl ether (**2**) rather than thiophene derivatives (Runs 6 and 7).

The formation of two types of thiophene derivatives (**3**) and (**4**) can be explained by the proposed reaction paths shown in Scheme 2 based on our previous investigations of the generation of 1,3-dipoles, azomethine ylides and azomethine imines, *via* 1,4-silatropy and their cycloaddition with dipolarophiles.<sup>8</sup> Thiocarbonyl ylides (**5**) are initially generated from thioesters (**1**) by a 1,4-shift of the silyl group (1,4-silatropy) onto the oxygen of the thioesters. Thiiranes (**6**) should be formed by cyclization of the dipoles (**5**), while the cycloaddition of the dipoles (**5**) with alkynes affords cycloadducts (**7**), followed by aromatization by elimination of dimethylphenylsilanol leading to give the thiophene derivatives (**3**). The ring opening of thiiranes (**6**) by heterolytic cleavage of the C-S bond<sup>9</sup> and cyclization of the ring opening compounds with



**Scheme 2.** Proposed Mechanism for the Formation of Thiophene Derivatives (**3**) and (**4**)

acetylenic dipolarophiles would proceed to give intermediates (**8**). In a similar manner, products (**4**) are formed by the aromatization of intermediates (**8**). Yields and selectivity of the cycloaddition products (**3**) and (**4**) seem to be governed by combination of stability and reactivity of thiocarbonyl ylides, which is under investigation.

In summary, we report on a novel synthesis of thiophene derivatives starting from *S*- $\alpha$ -silylbenzyl thioesters and acetylenic dipolarophiles. The method is the first example of the 1,4-silotropic generation of thiocarbonyl ylides and their cycloaddition with alkynes leading to substituted thiophenes. The reaction of thioesters (**1**) with olefins did not proceed under the reaction conditions employed here. Further investigations of these types of reactions are currently underway.

## REFERENCES AND NOTES

1. R. Huisgen, “*1,3-Dipolar Cycloaddition Chemistry*,” Volume 1, ed. by A. Padwa, John Wiley and Sons, Inc., 1984, pp. 1-176.
2. J. Nakayama, “*Comprehensive Heterocyclic Chemistry II*,” ed. by A. R. Katritzky, C. W. Rees, E. F. V. Scriven, and A. Padwa, Pergamon Press, Vol. 2, 1996, pp. 607-677.
3. R. K. Russell and J. B. Press, “*Comprehensive Heterocyclic Chemistry II*,” ed. by A. R. Katritzky, C. W. Rees, E. F. V. Scriven, and A. Padwa, Pergamon Press, Vol. 2, 1996, pp. 679-729.
4. M. Komatsu, J. Choi, E. Imai, Y. Oderaotoshi, and S. Minakata, *Tetrahedron Lett.*, 2001, **42**, 9221.
5. Structures of **1a-c**,<sup>4</sup> **2**,<sup>4</sup> and **4a**<sup>6</sup> were determined by comparison of their <sup>1</sup>H and <sup>13</sup>C NMR spectra with known, published data. The structures of **3a-f** and **4b-f** were determined by spectroscopic analysis (<sup>1</sup>H, <sup>13</sup>C NMR, IR, HRMS, NOE experiments etc., and/or X-Ray crystal structure analysis). Selected spectroscopic data are as follows.  
**3a** : <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$  1.02 (t, 6H, *J* = 7.2 Hz, NCH<sub>2</sub>CH<sub>3</sub>), 2,24 (s, 3H, thiophene-CH<sub>3</sub>), 3.02 (q, 4H, *J* = 7.2 Hz, NCH<sub>2</sub>CH<sub>3</sub>), 7.3 – 7.6 (m, 10H, Ph); <sup>13</sup>C NMR (68 MHz, CDCl<sub>3</sub>)  $\delta$  14.3, 14.4 (NCH<sub>2</sub>CH<sub>3</sub> and thiophene-CH<sub>3</sub>), 47.2 (CH<sub>2</sub>CH<sub>3</sub>), 126.95, 127.01, 128.0, 128.4, 128.8, 129.0, 132.3, 134.2, 135.0, 135.1, 135.4, 145.4 (Ph and thiophene); HRMS Calcd for C<sub>21</sub>H<sub>23</sub>NS, 321.1551, Found

321.1552.

**4a** :  $^1\text{H-NMR}$  (270 MHz,  $\text{CDCl}_3$ )  $\delta$  1.11 (t, 6H,  $J = 7.1$  Hz,  $\text{NCH}_2\text{CH}_3$ ), 1.96 (s, 3H, thiophene- $\text{CH}_3$ ), 3.01(q, 4H,  $J = 7.1$  Hz,  $\text{NCH}_2\text{CH}_3$ ), 7.1 – 7.3 (m, 10H, Ph);  $^{13}\text{C}$  NMR (68 MHz,  $\text{CDCl}_3$ )  $\delta$  13.1, 13.6 ( $\text{NCH}_2\text{CH}_3$  and thiophene- $\text{CH}_3$ ), 51.4 ( $\text{NCH}_2\text{CH}_3$ ), 126.3, 126.7, 128.0, 128.2, 128.8, 130.3, 131.5, 132.5, 135.3, 137.4, 137.6, 150.2 (Ph and thiophene); HRMS Calcd for  $\text{C}_{21}\text{H}_{23}\text{NS}$ , 321.1551, Found 321.1548.

**3b** :  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.01 (t, 6H,  $J = 7.0$  Hz,  $\text{NCH}_2\text{CH}_3$ ), 2.20 (s, 3H, thiophene- $\text{CH}_3$ ), 3.01 (q, 4H,  $J = 7.0$ ,  $\text{NCH}_2\text{CH}_3$ ), 3.85 (s, 3H,  $\text{OCH}_3$ ), 6.95 (br d, 2H,  $J = 8.9$  Hz, 3-H and 5-H of  $\text{C}_6\text{H}_4\text{OCH}_3$ ), 7.29 – 7.37 (m, 3H, Ph), 7.40 (br d, 2H,  $J = 8.9$  Hz, Ph), 7.61 (br d, 2H,  $J = 7.0$  Hz, 2-H and 6-H of  $\text{C}_6\text{H}_4\text{OCH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.4 ( $\text{NCH}_2\text{CH}_3$  and thiophene- $\text{CH}_3$ ), 47.3 ( $\text{NCH}_2\text{CH}_3$ ), 55.3 ( $\text{OCH}_3$ ), 113.8, 126.8, 127.9, 128.9, 129.9, 131.7, 133.4, 134.8, 135.1, 145.2, 158.6 (Ar and thiophene); EI-MS  $m/z$  : 351 ( $\text{M}^+$ , 100), 336 (100), 306 (66); HRMS Calcd for  $\text{C}_{22}\text{H}_{25}\text{NOS}$  351.1657, Found 351.1649.

**4b** :  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ )  $\delta$  1.10 (t, 6H,  $J = 7.0$  Hz,  $\text{NCH}_2\text{CH}_3$ ), 1.95 (s, 3H, thiophene- $\text{CH}_3$ ), 3.00 (q, 4H,  $J = 7.0$  Hz,  $\text{NCH}_2\text{CH}_3$ ), 3.82 (s, 3H,  $\text{OCH}_3$ ), 6.85 (br d, 2H,  $J = 8.6$  Hz, 3-H and 5-H of  $\text{C}_6\text{H}_4\text{OCH}_3$ ), 7.14 – 7.17 (m, 5H, Ph), 7.10 (br d, 2H,  $J = 8.6$  Hz, 2-H and 6-H of  $\text{C}_6\text{H}_4\text{OCH}_3$ );  $^{13}\text{C}$  NMR (270 MHz,  $\text{CDCl}_3$ )  $\delta$  13.2, 13.7 ( $\text{NCH}_2\text{CH}_3$  and thiophene- $\text{CH}_3$ ), 51.4 ( $\text{NCH}_2\text{CH}_3$ ), 55.2 ( $\text{OCH}_3$ ), 113.6, 126.1, 127.9, 128.7, 129.8, 131.2, 131.5, 132.2, 135.3, 136.9, 150.0, 158.2 (Ar and thiophene); EI-MS  $m/z$  : 351 ( $\text{M}^+$ , 100), 336 (53), 322 (44); HRMS Calcd for  $\text{C}_{22}\text{H}_{25}\text{NOS}$  351.1657, Found 351.1678.

**3c** :  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.02 (t, 6H,  $J = 7.0$  Hz,  $\text{NCH}_2\text{CH}_3$ ), 2.28 (s, 3H, thiophene- $\text{CH}_3$ ), 3.01 (q, 4H,  $J = 7.0$ ,  $\text{NCH}_2\text{CH}_3$ ), 7.32 – 7.41 (m, 3H, Ph), 7.57 - 7.61 (m, 2H, Ph), 7.63 (br d, 2H,  $J = 8.6$  Hz, 2-H and 6-H of  $\text{C}_6\text{H}_4\text{NO}_2$ ), 7.61 (br d, 2H,  $J = 7.0$  Hz, 3-H and 5-H of  $\text{C}_6\text{H}_4\text{NO}_2$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.3, 14.9 ( $\text{NCH}_2\text{CH}_3$  and thiophene- $\text{CH}_3$ ), 47.3, ( $\text{NCH}_2\text{CH}_3$ ), 123.8, 127.6, 128.1, 128.8, 129.0, 132.5, 134.3, 134.7, 136.7, 142.1, 146.0, 146.1 (Ar and thiophene); EI-MS  $m/z$  : 366 ( $\text{M}^+$ , 100), 351 (99), 321 (34), 275 (15); HRMS Calcd for  $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$  366.1401, Found 366.1405.

**4c** :  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ )  $\delta$  1.10 (t, 6H,  $J = 7.1$  Hz,  $\text{NCH}_2\text{CH}_3$ ), 1.95 (s, 3H, thiophene- $\text{CH}_3$ ), 3.02 (q, 4H,  $J = 7.0$  Hz,  $\text{NCH}_2\text{CH}_3$ ), 7.08 – 7.18 (m, 5H, Ph), 7.35 (br d, 2H,  $J = 8.9$  Hz, 2-H and 6-H of  $\text{C}_6\text{H}_4\text{NO}_2$ ), 8.61 (br d, 2H,  $J = 8.9$  Hz, 3-H and 5-H of  $\text{C}_6\text{H}_4\text{NO}_2$ );  $^{13}\text{C}$  NMR (270 MHz,  $\text{CDCl}_3$ )  $\delta$  13.2,

13.6 (NCH<sub>2</sub>CH<sub>3</sub> and thiophene-CH<sub>3</sub>), 51.4 (NCH<sub>2</sub>CH<sub>3</sub>), 123.4, 126.9, 128.3, 129.0, 130.4, 131.1, 134.2, 134.3, 134.8, 144.7, 146.4, 151.3 (Ar and thiophene); EI-MS *m/z* : 366 (M<sup>+</sup>, 100), 351 (53), 337 (24); HRMS Calcd for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>S 366.1401, Found 366.1411.

**4d** : <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>) δ 3.75 (s, 3H, COOCH<sub>3</sub>), 3.90 (s, 3H, COOCH<sub>3</sub>), 7.2 – 7.3 (m, 10H, Ar); <sup>13</sup>C NMR (68 MHz, CDCl<sub>3</sub>) δ 52.6, 52.7 (COOCH<sub>3</sub>), 128.0, 128.5, 128.6, 129.2, 129.7, 132.5, 133.8, 137.4, 141.1, 146.4 (Ph and thiophene), 161.4, 166.0 (COOCH<sub>3</sub>); Anal. Calcd for C<sub>20</sub>H<sub>16</sub>O<sub>4</sub>S: C, 68.16; H 4.57; S, 9.09. Found: C, 67.80; H, 4.63; S, 8.93.

**4e** : <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) δ 3.77 (s, 3H, COOCH<sub>3</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 3.90 (s, 3H, COOCH<sub>3</sub>), 6.81 (br d, 2H, *J* = 8.7 Hz, 3-H and 5-H of C<sub>6</sub>H<sub>4</sub>OCH<sub>3</sub>), 7.12 (br d, 2H, *J* = 8.7 Hz, 2-H and 6-H of C<sub>6</sub>H<sub>4</sub>OCH<sub>3</sub>), 7.18 – 7.27 (m, 5H, Ph); <sup>13</sup>C NMR (270 MHz, CDCl<sub>3</sub>) δ 52.5, 52.7 (COOCH<sub>3</sub>), 55.1 (OCH<sub>3</sub>), 113.9, 125.9, 127.7, 128.5, 128.6, 129.1, 130.8, 132.7, 137.0, 141.2, 145.8, 159.2, (Ar and thiophene), 161.1, 161.8 (COOCH<sub>3</sub>); EI-MS *m/z* : 382 (M<sup>+</sup>, 100), 351 (20); HRMS Calcd for C<sub>21</sub>H<sub>18</sub>O<sub>5</sub>S 382.0875, Found 382.0882.

6. J. Nakayama, R. Yomoda, and M. Hoshino, *Heterocycles*, 1987, **26**, 2215.; T. Simizu, H. Murakami, and N. Kamigata, *J. Org. Chem.*, 1999, **64**, 8489.
7. M. Ohno, M. Komatsu, H. Miyata, and Y. Ohshiro, *Tetrahedron Lett.*, 1991, **32**, 5813; M. Komatsu, M. Ohno, S. Tsuno, and Y. Ohshiro, *Chem. Lett.*, **1990**, 575.
8. K.-I. Washizuka, K. Nagai, S. Minakata, I. Ryu, and M. Komatsu, *Tetrahedron Lett.*, 2000, **41**, 691; K.-I. Washizuka, S. Minakata, I. Ryu, and M. Komatsu, *Tetrahedron*, 1999, **55**, 12969; K.-I. Washizuka, K. Nagai, S. Minakata, I. Ryu, and M. Komatsu, *Tetrahedron Lett.*, 1999, **40**, 8849; M. Iyoda, F. S. A. Kato, M. Yoshida, Y. Kuwatani, M. Komatsu, and S. Nagase, *Chem. Lett.*, **1997**, 63; M. Ohno, M. Komatsu, H. Miyata, and Y. Ohshiro, *Tetrahedron Lett.*, 1991, **32**, 5813.
9. For an example of the ring expansion reaction of thiiranes with alkenes or alkynes, see.; G. L'abbé, J.-P. Dekerk, C. Martens, and S. Toppet, *J. Org. Chem.*, 1980, **45**, 4366.