

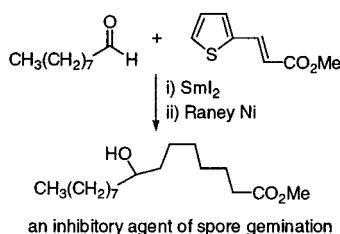
# Distant Functionalization via Incorporation of Thiophene Moieties in Electrophilic Reactions Promoted by Samarium Diiodide

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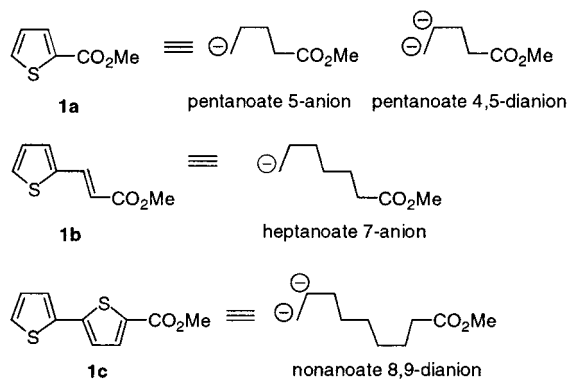
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## ABSTRACT



Methyl thiophene-2-carboxylate, methyl 3-(thien-2-yl)acrylate, and methyl 5,2'-bithiophene-2-carboxylate were utilized as the synthetic equivalents of pentanoate 5-anion, pentanoate 4,5-dianion, heptanoate 7-anion, and nonanoate 8,9-dianion. By the promotion of samarium diiodide, these thiophene-incorporating compounds reacted with aldehydes, ketones, and conjugated esters regioselectively at the thienyl rings. Long-chain esters with remote hydroxyl and carboxyl groups, including an antiarthritis agent, a shellac component, and an inhibitory agent of spore germination, were prepared after reductive desulfurization on Raney nickel.

Functionalization at the remote positions with respect to an activating group remains a challenging task in organic synthesis.<sup>1</sup> We describe herein a new strategy by using **1a–c** to generate the synthetic equivalents of the terminal anions and dianions of long-chain aliphatic esters.



We reported previously that methyl thiophene-2-carboxylate (**1a**) reacts with carbonyl compounds by the promotion

of  $\text{SmI}_2$  and HMPA.<sup>2,3</sup> The reaction may involve a dienolate intermediate **A**, which could undergo protonation at C-2 to give 2,5-dihydrothiophenes (e.g., **2a–g**) or react further with a second carbonyl compound to give 4,5-dihydrothiophenes (e.g., **5a–d**). Since dihydrothiophenes could undergo reductive desulfurization by using Raney nickel,<sup>4</sup> methyl thiophene-2-carboxylate thus served as an attractive mediator for the synthesis of distant functionalized pentanoate esters with

(1) For generation of  $\text{Cl}_3\text{TiCH}_2\text{CH}_2\text{CO}_2\text{R}$  and  $\text{ClZnCH}_2\text{CH}_2\text{CO}_2\text{R}$  as nucleophilic reagents, see: (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1983**, *105*, 651. (b) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368. The organo-copper reagent  $\text{IZn}(\text{CN})\text{Cu}(\text{CH}_2)_3\text{CO}_2\text{R}$  has been used as an equivalent of butanoate 4-anion, see: (c) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2392. (d) Yeh, M. C.; Knochel, P.; Santa, L. *Tetrahedron Lett.* **1988**, *29*, 3887. (e) Lipshutz, B. H.; Wood, M. R.; Tirado, R. *J. Am. Chem. Soc.* **1995**, *117*, 6126.

(2) Yang, S.-M.; Fang, J.-M. *Tetrahedron Lett.* **1997**, *38*, 1589.

(3) Transfer of one electron from  $\text{SmI}_2$  to methyl thiophene-2-carboxylate initiated the reaction sequence. The generated samarium-bound ketyl anion radical did not trap hydrogen atom or undergo acyloin coupling, presumably because of the hindrance of the ligated HMPA molecules; see: (a) Hou, Z.; Yoshimura, T.; Wakatsuki, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11169. (b) Shiue, J.-S.; Lin, C.-C.; Fang, J.-M. *Tetrahedron Lett.* **1993**, *34*, 335.

remote hydroxyl and carboxyl groups (e.g., **3a–g** and **6a–d**).

The coupling reactions were simply carried out by mixing thiophenecarboxylate **1a** with appropriate electrophiles in a freshly prepared SmI<sub>2</sub>/THF/HMPA solution. As shown in this study (Table 1), hydroxyalkylations with aldehydes and

**Table 1.** SmI<sub>2</sub>-Promoted Coupling Reactions<sup>a</sup> and Subsequent Reductive Desulfurizations on Raney Nickel

no.	substr	electrophiles	coupling products (% yield)	desulfirzn products (% yield) <sup>c</sup>
1	<b>1a</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO/H <sup>+</sup>	<b>2a</b> (85%) <sup>b</sup>	<b>3a</b> (66%) <sup>c</sup>
2	<b>1a</b>	6-methoxy-2-naphthaldehyde/H <sup>+</sup>	<b>2b</b> (74%) <sup>b</sup>	<b>3b</b> (91%) <sup>c</sup>
3	<b>1a</b>	4-ClC <sub>6</sub> H <sub>4</sub> COMe/H <sup>+</sup>	<b>2c</b> (74%) <sup>b</sup>	<b>3c</b> (64%) <sup>c</sup>
4	<b>1a</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> CHO/H <sup>+</sup>	<b>2d</b> (81%) <sup>b</sup>	<b>3d</b> (91%) <sup>c</sup>
5	<b>1a</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> CHO/H <sup>+</sup>	<b>2e</b> (73%) <sup>b</sup>	<b>3e</b> (90%) <sup>c</sup>
6	<b>1a</b>	4-MeOC <sub>6</sub> H <sub>4</sub> CH=CHCO <sub>2</sub> Me/H <sup>+</sup>	<b>2f</b> (55%) <sup>b</sup>	<b>3f</b> (87%) <sup>c</sup>
7	<b>1a</b>	MeCH=CHCO <sub>2</sub> Me/H <sup>+</sup>	<b>2g</b> (60%) <sup>b</sup>	<b>3g</b> (81%) <sup>c</sup>
8	<b>1a</b>	cyclohexanone/cyclohexanone	<b>5a</b> (91%) <sup>d</sup>	<b>6a</b> (80%)
9	<b>1a</b>	cyclopentanone/cyclopentanone	<b>5b</b> (57%) <sup>d</sup>	<b>6b</b> (81%)
10	<b>1a</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO/4-ClC <sub>6</sub> H <sub>4</sub> COMe	<b>5c</b> (63%) <sup>b</sup>	<b>6c</b> (73%) <sup>e</sup>
11	<b>1a</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> COMe/4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> COMe	<b>5d</b> (62%) <sup>b</sup>	<b>6d</b> (75%) <sup>f</sup>
12	<b>1b</b>	4-MeOC <sub>6</sub> H <sub>4</sub> CHO/H <sup>+</sup>	<b>7a</b> (78%) <sup>b</sup>	<b>8a</b> (86%) <sup>c</sup>
13	<b>1b</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> CHO/H <sup>+</sup>	<b>7b</b> (68%) <sup>b</sup>	<b>8b</b> (89%) <sup>c</sup>
14	<b>1b</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> COMe/H <sup>+</sup>	<b>7c</b> (69%) <sup>b</sup>	<b>8c</b> (62%) <sup>c</sup>
15	<b>1b</b>	4-MeOC <sub>6</sub> H <sub>4</sub> CH=CHCO <sub>2</sub> Me/H <sup>+</sup>	<b>7d</b> (70%) <sup>b</sup>	<b>8d</b> (83%) <sup>c</sup>
16	<b>1c</b>	cyclohexanone/cyclohexanone	<b>10</b> (43%) <sup>b</sup>	<b>11</b> (85%) <sup>c</sup>

<sup>a</sup> The coupling reactions were generally conducted in SmI<sub>2</sub>/THF/HMPA solution at 0 °C, except for the Michael reactions (entries 6, 7, and 15), which were conducted at -78 °C. For 1 mmol of substrate, 3.6 mmol of SmI<sub>2</sub> and 16 mmol of HMPA were used. <sup>b</sup> The coupling product was obtained as a mixture of diastereomers. <sup>c</sup> Reductive desulfurization of the isomeric mixture of coupling product gave a single product. <sup>d</sup> Compounds **5a** and **5b** with the 4,5-*trans* configuration were obtained. <sup>e</sup> The reductive desulfurization of (4*S*\*,5*R*\*,1'*S*\*,1''*S*\*)-**5c** gave (4*R*\*,6*R*\*,1'*S*\*)-**6c**. <sup>f</sup> The reductive desulfurization of (4*S*\*,5*R*\*,1'*S*\*,1''*R*\*)-**5d** gave (4*R*\*,6*S*\*,1'*S*\*)-**6d**.

ketones and Michael additions with  $\alpha,\beta$ -unsaturated esters were accomplished in highly regioselective manners. The possible self-coupling reactions<sup>5</sup> of esters and carbonyl compounds were suppressed under such reaction conditions.

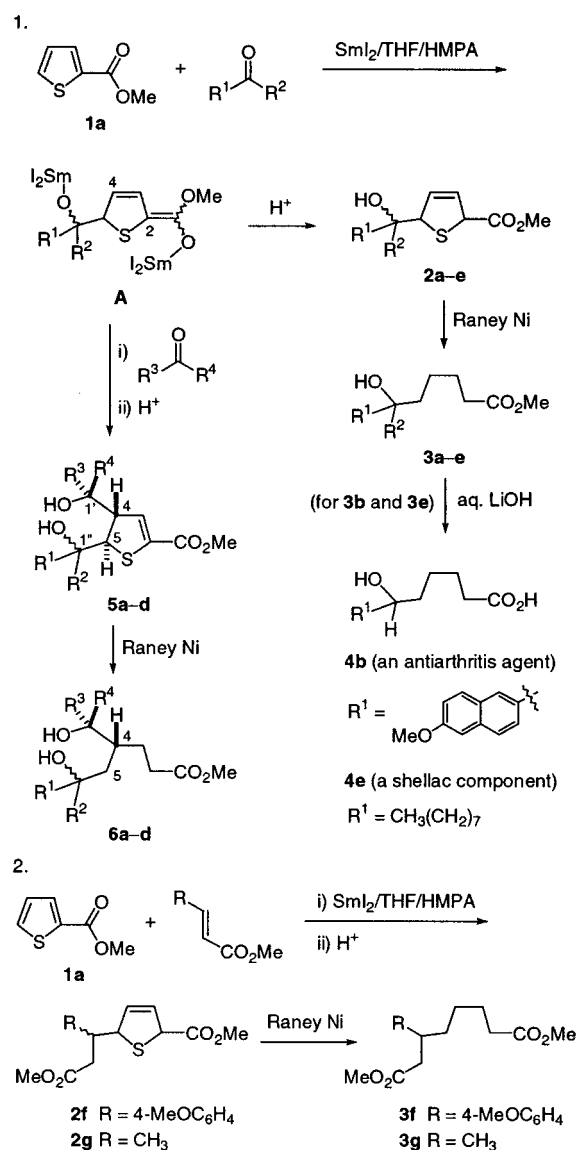
Although individual coupling product (**2a–g**) existed as a mixture of diastereomers, a single long-chain ester was obtained after removal of the sulfur atom (Scheme 1). For example, an antiarthritis agent **4b**, 6-hydroxy-6-(6-methoxynaphth-2-yl)hexanoic acid,<sup>6</sup> was prepared in an overall 67% yield by a three-step sequence: (i) coupling of **1a** with 6-methoxy-2-naphthaldehyde by the promotion of SmI<sub>2</sub>, (ii)

(4) Reviews of desulfurization on Raney nickel: (a) Caubere, P.; Coutrot, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds., Pergamon: Oxford, 1991; Vol. 8, pp 835–870. (b) Pettit, G. R.; van Tamelen, E. E. *Org. React.* **1962**, *12*, 356. (c) Gol'dfarb, Y. L.; Fabrichnyi, B. P.; Shalavina, I. F. *Tetrahedron* **1962**, *18*, 21. (d) Meyers, A. I. *Heterocycles in Organic Synthesis*; Wiley: New York, 1974.

(5) On treatment with SmI<sub>2</sub>, carbonyl compounds and conjugated esters could undergo reductive self-coupling reactions; see: (a) Namy, J. L.; Soupe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765. (b) Inanaga, J.; Handa, Y.; Tabuchi, T.; Otsubo, K. *Tetrahedron Lett.* **1991**, *32*, 6557. (c) Fujita, Y.; Fukuzumi, S.; Otera, J. *Tetrahedron Lett.* **1997**, *38*, 2121. (d) Cabrerera, A.; Le Lagadec, R.; Sharma, P.; Arias, J. L.; Toscano, R. A.; Velasco, L.; Gavino, R.; Alvarez, C.; Salmon, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3609.

(6) Murray, W. V.; Wachter, M. P.; Kasper, A. M.; Argentieri, D. C.; Capetola, R. J.; Ritchie, D. M. *Eur. J. Med. Chem. Chim. Ther.* **1991**, *26*, 159.

**Scheme 1**



reductive desulfurization using Raney Ni in MeOH, and (iii) saponification using LiOH in aqueous THF. A shellac component **4e**, 6-hydroxytetradecanoic acid,<sup>7</sup> was prepared in 66% yield from **1a** and nonanal by a similar procedure.

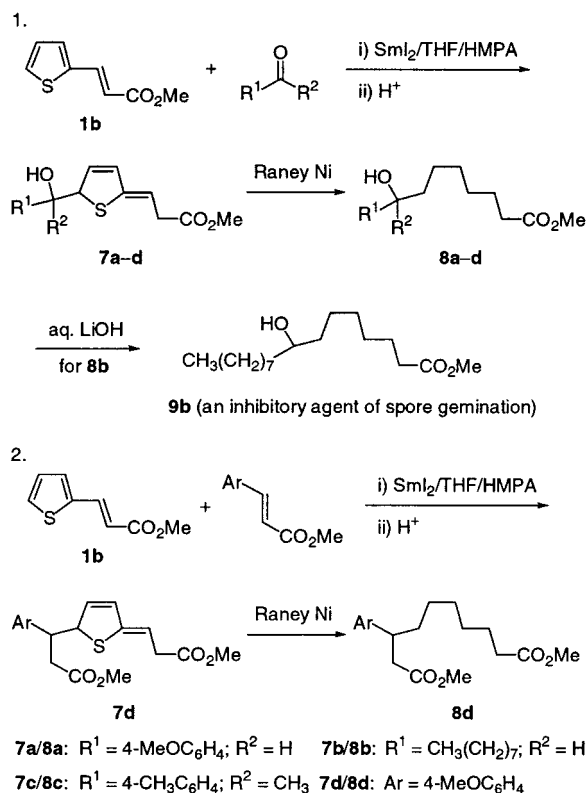
Saponification of **3a** and **3d** afforded the corresponding 6-hydroxyacids, which were subjected to lactonization by treatment with 1,1'-carbonyldiimidazole/DBU or *p*-TsOH to give 7-tolyl and 7-pentylloxepan-2-ones in 86% and 91% yields.

We also demonstrated the efficient use of methyl thiophene-2-carboxylate as an equivalent of pentanoate 4,5-dianion (entries 8–11). The double electrophilic reaction of **1a**, followed by reductive desulfurization, provided a route for the generation of functionalized 1,4-diols such as **6a–d**.

The methodology using SmI<sub>2</sub>-promoted electrophilic reactions was easily extended to its higher vinylogous compounds

(7) Wadia, M. S.; Khurana, R. G.; Mhaskar, V. V.; Dev. S. *Tetrahedron* **1969**, *25*, 3841.

### Scheme 2

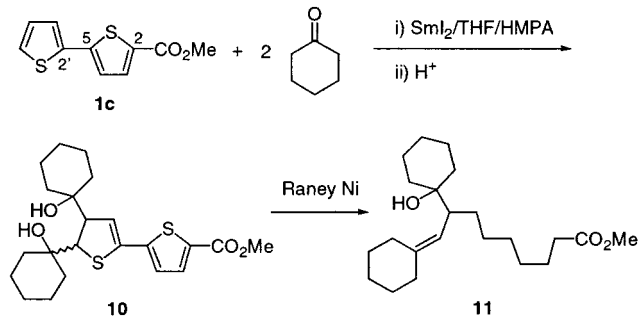


such as 3-(thien-2-yl)acrylate **1b** (Scheme 2). The protocol featured an excellent regioselectivity wherein the incoming electrophile reacted exclusively at the C-5 position of the thiophene ring, giving **7a-d** after protonation. Thus 3-(thien-2-yl)acrylate played as an equivalent of heptanoate-7-anion to furnish long-chain esters **8a-d**. Our current method for the synthesis of methyl 8-hydroxyhexadecanoate<sup>8</sup> (**8b**), an inhibitory agent of spore germination, appeared to have the advantage of simple operation, few steps, and high overall yield (61%), by comparison with the previous preparation<sup>8</sup> with 8–12 steps in merely 10–12% yields.

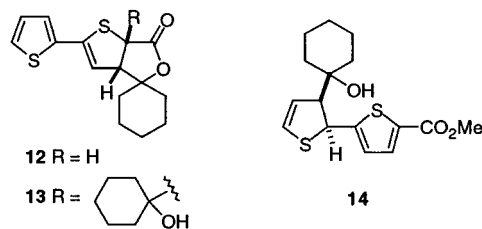
(8) (a) Tulloch, A. P. *Can. J. Chem.* **1965**, *43*, 415. (b) Yamane, H.; Sato, Y.; Takahashi, N.; Takeno, K.; Furuya, M. *Agric. Biol. Chem.* **1980**, *44*, 1697. (c) Masaoka, Y.; Sakakibara, M.; Mori, K. *Agric. Biol. Chem.* **1982**, *46*, 2319. (d) Sugai, T.; Mori, K. *Agric. Biol. Chem.* **1984**, *48*, 2155.

Bithiophenecarboxylate **1c** could also be utilized as an equivalent of nonanoate-8,9-dianion (Scheme 3). Thus,

### Scheme 3



treatment of **1c** with cyclohexanone (2.5 equiv) in  $SmI_2/THF/HMPA$ , at 0 °C for 30 min and 25 °C for 3 h, afforded the C-8,9 double hydroxyalkylation products **10** (43%) accompanied by 25% recovery of **1c**. This reaction was somewhat complicated by side products **12** (10%), **13** (6%), and **14** (14%) derived from additions at C-3 or C-3' of **1c**.



Stirring of **10** with Raney Ni in refluxing EtOH for 16 h furnished the long-chain ester **11** (85%). The <sup>1</sup>H NMR spectrum of **11** exhibited a vinyl proton at  $\delta$  4.83 as a doublet ( $J = 10.5$  Hz).

**Acknowledgment.** We thank the National Science Council for financial support.

**Supporting Information Available:** Experimental procedures, physical and spectral data for new compounds, and ORTEP drawings of compounds **5a**, **5c**, **6d**, and **10**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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