ORGANIC LETTERS

2000
Vol. 2, No. 23
3719−3721

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

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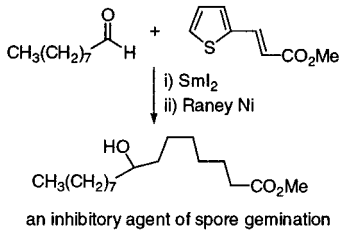
Received September 21, 2000

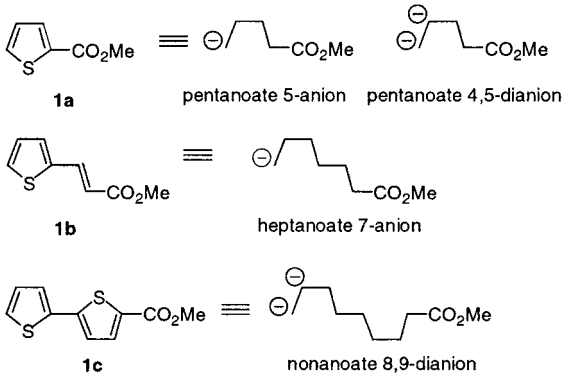
ABSTRACT



an inhibitory agent of spore gemination

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.[1] 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 SmI_2 and HMPA.[2,3] 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,[4] methyl thiophene-2-carboxylate thus served as an attractive mediator for the synthesis of distant functionalized pentanoate esters with

(1) For generation of $Cl_3TiCH_2CH_2CO_2R$ and $ClZnCH_2CH_2CO_2R$ 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 $IZn(CN)Cu(CH_2)_3CO_2R$ 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 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.; Wakatszuki, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11169. (b) Shiue, J.-S.; Lin, C.-C.; Fang, J.-M. *Tetrahedron Lett.* **1993**, *34*, 335.

10.1021/ol006628w CCC: $19.00
Published on Web 10/26/2000

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_2/THF/HMPA solution. As shown in this study (Table 1), hydroxyalkylations with aldehydes and ketones and Michael additions with α,β-unsaturated esters were accomplished in highly regioselective manners. The possible self-coupling reactions[5] of esters and carbonyl compounds were suppressed under such reaction conditions.

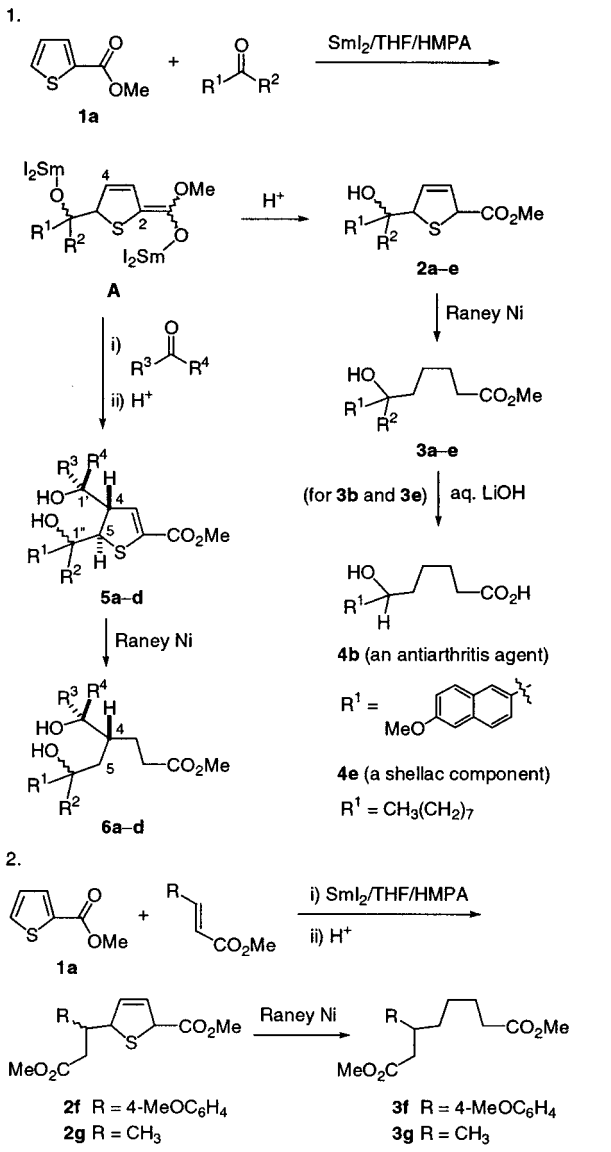
Table 1. SmI_2-Promoted Coupling Reactions[a] and Subsequent Reductive Desulfurizations on Raney Nickel

no.	substr	electrophiles	coupling products (% yield)	desulfrzn products (% yield)[c]
1	**1a**	4-$CH_3C_6H_4CHO$/H^+	**2a** (85%)[b]	**3a** (66%)[c]
2	**1a**	6-methoxy-2-naphthaldehyde/H^+	**2b** (74%)[b]	**3b** (91%)[c]
3	**1a**	4-ClC_6H_4COMe/H^+	**2c** (74%)[b]	**3c** (64%)[c]
4	**1a**	$CH_3(CH_2)_4CHO$/H^+	**2d** (81%)[b]	**3d** (91%)[c]
5	**1a**	$CH_3(CH_2)_7CHO$/H^+	**2e** (73%)[b]	**3e** (90%)[c]
6	**1a**	4-$MeOC_6H_4CH{=}CHCO_2Me$/H^+	**2f** (55%)[b]	**3f** (87%)[c]
7	**1a**	$MeCH{=}CHCO_2Me$/H^+	**2g** (60%)[b]	**3g** (81%)[c]
8	**1a**	cyclohexanone/cyclohexanone	**5a** (91%)[d]	**6a** (80%)
9	**1a**	cyclopentanone/cyclopentanone	**5b** (57%)[d]	**6b** (81%)
10	**1a**	4-$CH_3C_6H_4CHO$/4-ClC_6H_4COMe	**5c** (63%)[b]	**6c** (73%)[e]
11	**1a**	4-$CH_3C_6H_4COMe$/4-$CH_3C_6H_4COMe$	**5d** (62%)[b]	**6d** (75%)[f]
12	**1b**	4-$MeOC_6H_4CHO$/H^+	**7a** (78%)[b]	**8a** (86%)[c]
13	**1b**	$CH_3(CH_2)_7CHO$/H^+	**7b** (68%)[b]	**8b** (89%)[c]
14	**1b**	4-$CH_3C_6H_4COMe$/H^+	**7c** (69%)[b]	**8c** (62%)[c]
15	**1b**	4-$MeOC_6H_4CH{=}CHCO_2Me$/H^+	**7d** (70%)[b]	**8d** (83%)[c]
16	**1c**	cyclohexanone/cyclohexanone	**10** (43%)[b]	**11** (85%)[c]

[a] The coupling reactions were generally conducted in SmI_2/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_2 and 16 mmol of HMPA were used. [b] The coupling product was obtained as a mixture of diastereomers. [c] Reductive desulfurization of the isomeric mixture of coupling product gave a single product. [d] Compounds **5a** and **5b** with the 4,5-*trans* configuration were obtained. [e] The reductive desulfurization of (4*S**,5*R**,1′*S**,1″*S**)-**5c** gave (4*R**,6*R**,1′*S**)-**6c**. [f] The reductive desulfurization of (4*S**,5*R**,1′*S**,1″*R**)-**5d** gave (4*R**,6*S**,1′*S**)-**6d**.

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,[6] 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_2, (ii) reductive desulfurization using Raney Ni in MeOH, and (iii) saponification using LiOH in aqueous THF. A shellac component **4e**, 6-hydroxytetradecanoic acid,[7] was prepared in 66% yield from **1a** and nonanal by a similar procedure.

Scheme 1



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-pentyloxepan-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_2-promoted electrophilic reactions was easily extended to its higher vinylogous compounds

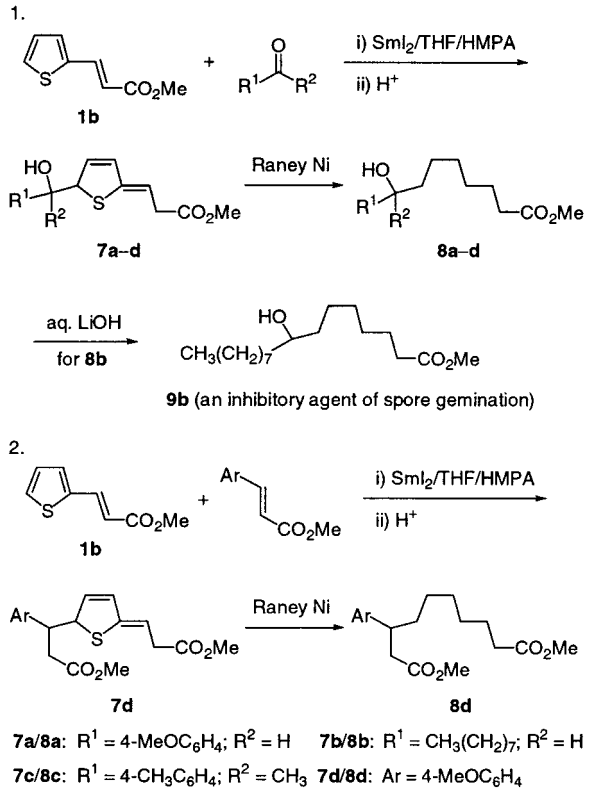
(4) Reviews of desulfurization on Raney nickel: (a) Caubere, P.; Coutrot, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds., Pergamon: Oxford, 1991; Vol. 8, pp 835−870. (b) Pettit, G. R.; van Tamelen, E. E. *Org. React.* **1962**, *12*, 356. (c) Gol'dfarb, Y. L.; Fabrichnyi, B. 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_2, carbonyl compounds and conjugated esters could undergo reductive self-coupling reactions; see: (a) Namy, J. L.; Souppe, 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) Caberera, 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.

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

Scheme 2

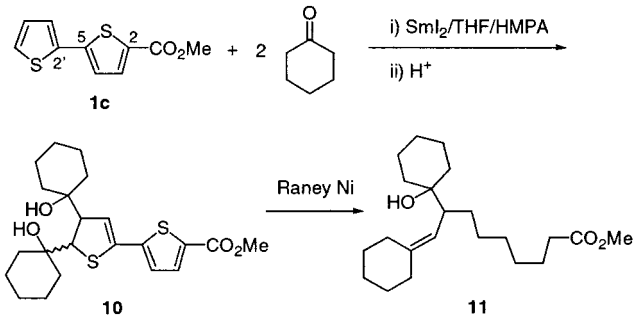


such as 3-(thien-2-yl)acrylate **1b** (Scheme 2). The protocol featured an excellent regioselectivity wherein the incoming electrophile reacted exclusively at the C-5 position of the thiophene ring, giving **7a**−**d** after protonation. Thus 3-(thien-2-yl)acrylate played as an equivalent of heptanoate-7-anion to furnish long-chain esters **8a**−**d**. Our current method for the synthesis of methyl 8-hydroxyhexadecanoate[8] (**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[8] with 8−12 steps in merely 10−12% yields.

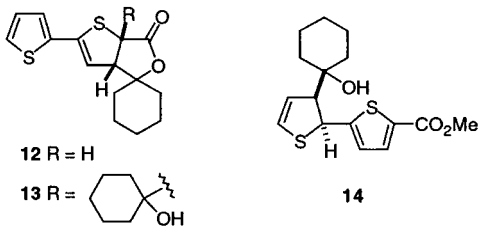
(8) (a) Tulloch, A. P. *Can. J. Chem.* **1965**, *43*, 415. (b) Yamane, H.; Sato, Y.; Takahashi, N.; Takeno, K.; Furuya, M. *Agric. Biol. Chem.* **1980**, *44*, 1697. (c) Masaoka, Y.; Sakakibara, M.; Mori, K. *Agric. Biol. Chem.* **1982**, *46*, 2319. (d) Sugai, T.; Mori, K. *Agric. Biol. Chem.* **1984**, *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 ^{1}H NMR spectrum of **11** exhibited a vinyl proton at δ 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.

OL006628W