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

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Abstract — The cycloaddition of S-α-(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.1 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.2 The thiophene ring structure is widespread in nature and many of these compounds are biologically active.3 Moreover,
thiophene derivatives are also widely found in functional materials such as dyes and liquid crystals.\(^3\)

Recently, we reported on the formation of enol silyl ethers (2) from S-α-trimethylsilylbenzyl acylates (1) via thiocarbonyl ylides (Scheme 1).\(^4\) 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 α-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-α-trimethylsilylbenzyl acylates with acetylenic dipolarophiles.

Scheme 1. Generation of Thiocarbonyl Ylides and Cycloaddition with Dipolarophiles

In a typical reaction, the treatment of S-α-(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.5

Table 1. Cycloaddition of Thioesters (1) with Dipolarophiles

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

a Determined by 1H NMR spectral analysis. b Benzyl p-methoxyphenyl ketone was obtained in 32% yield. c Enol silyl ether (2) (R = p-NO2C6H4, 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.7 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 cycloadditon with dipolarophiles. 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 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-α-silylbenzyl thioesters and acetylenic dipolarophiles. The method is the first example of the 1,4-silatropic 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


5. Structures of 1a-c,4 2,4 and 4a6 were determined by comparison of their 1H and 13C NMR spectra with known, published data. The structures of 3a-f and 4b-f were determined by spectroscopic analysis (1H, 13C NMR, IR, HRMS, NOE experiments etc., and/or X-Ray crystal structure analysis). Selected spectroscopic data are as follows.

3a : 1H-NMR (270 MHz, CDCl3) δ 1.02 (t, 6H, J = 7.2 Hz, NCH2CH3), 2.24 (s, 3H, thiophene-CH3), 3.02 (q, 4H, J = 7.2 Hz, NCH2CH3), 7.3 – 7.6 (m, 10H, Ph); 13C NMR (68 MHz, CDCl3) δ 14.3, 14.4 (NCH2CH3 and thiophene-CH3), 47.2 (CH2CH3), 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 C21H23NS, 321.1551, Found
321.1552.

4a: $^1$H-NMR (270 MHz, CDCl$_3$) $\delta$ 1.11 (t, 6H, $J = 7.1$ Hz, NCH$_2$CH$_3$), 1.96 (s, 3H, thiophene-CH$_3$), 3.01 (q, 4H, $J = 7.1$ Hz, NCH$_2$CH$_3$), 7.1 – 7.3 (m, 10H, Ph); $^{13}$C NMR (68 MHz, CDCl$_3$) $\delta$ 13.1, 13.6 (NCH$_2$CH$_3$ and thiophene-CH$_3$), 51.4 (NCH$_2$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 C$_{21}$H$_{23}$NS, 321.1551, Found 321.1548.

3b: $^1$H NMR (CDCl$_3$) $\delta$ 1.01 (t, 6H, $J = 7.0$ Hz, NCH$_2$CH$_3$), 2.20 (s, 3H, thiophene-CH$_3$), 3.01 (q, 4H, $J = 7.0$, NC$_2$H$_5$CH$_3$), 3.85 (s, 3H, OC$_3$H$_3$), 6.95 (br d, 2H, $J = 8.9$ Hz, 3-H and 5-H of C$_6$H$_4$OCH$_3$), 7.29 – 7.37 (m, 3H, Ph), 7.61 (br d, 2H, $J = 7.0$ Hz, 2-H and 6-H of C$_6$H$_4$OCH$_3$); $^{13}$C NMR (CDCl$_3$) $\delta$ 14.4 (NCH$_2$CH$_3$ and thiophene-CH$_3$), 47.3 (NC$_2$H$_5$CH$_3$), 55.3 (OC$_3$H$_3$), 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 (M$^+$, 100), 336 (100), 306 (66); HRMS Calcd for C$_{22}$H$_{25}$NOS 351.1657, Found 351.1649.

4b: $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 1.10 (t, 6H, $J = 7.0$ Hz, NCH$_2$CH$_3$), 1.95 (s, 3H, thiophene-CH$_3$), 3.00 (q, 4H, $J = 7.0$, NCH$_2$CH$_3$), 3.82 (s, 3H, OCH$_3$), 6.85 (br d, 2H, $J = 8.6$ Hz, 3-H and 5-H of C$_6$H$_4$OCH$_3$), 7.14 – 7.17 (m, 5H, Ph), 7.10 (br d, 2H, $J = 8.6$ Hz, 2-H and 6-H of C$_6$H$_4$OCH$_3$); $^{13}$C NMR (270 MHz, CDCl$_3$) $\delta$ 13.2, 13.7 (NCH$_2$CH$_3$ and thiophene-CH$_3$), 51.4 (NCH$_2$CH$_3$), 55.2 (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 (M$^+$, 100), 336 (53), 322 (44); HRMS Calcd for C$_{22}$H$_{25}$NOS 351.1657, Found 351.1678.

3c: $^1$H NMR (CDCl$_3$) $\delta$ 1.02 (t, 6H, $J = 7.0$ Hz, NCH$_2$CH$_3$), 2.28 (s, 3H, thiophene-CH$_3$), 3.01 (q, 4H, $J = 7.0$, NCH$_2$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 C$_6$H$_4$NO$_2$), 7.61 (br d, 2H, $J = 7.0$ Hz, 3-H and 5-H of C$_6$H$_4$NO$_2$); $^{13}$C NMR (CDCl$_3$) $\delta$ 14.3, 14.9 (NCH$_2$CH$_3$ and thiophene-CH$_3$), 47.3, (NCH$_2$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 (M$^+$, 100), 351 (99), 321 (34), 275 (15); HRMS Calcd for C$_{21}$H$_{22}$N$_2$O$_2$S 366.1401, Found 366.1405.

4c: $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 1.10 (t, 6H, $J = 7.1$ Hz, NCH$_2$CH$_3$), 1.95 (s, 3H, thiophene-CH$_3$), 3.02 (q, 4H, $J = 7.0$ Hz, NCH$_2$CH$_3$), 7.08 – 7.18 (m, 5H, Ph), 7.35 (br d, 2H, $J = 8.9$ Hz, 2-H and 6-H of C$_6$H$_4$NO$_2$), 8.61 (br d, 2H, $J = 8.9$ Hz, 3-H and 5-H of C$_6$H$_4$NO$_2$); $^{13}$C NMR (270 MHz, CDCl$_3$) $\delta$ 13.2,
13.6 (NCH₂CH₃ and thiophene-CH₃), 51.4 (NCH₂CH₃), 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⁺, 100), 351 (53), 337 (24); HRMS Calcd for C₂₁H₂₂N₂O₂S 366.1401, Found 366.1411.

4d: ¹H-NMR (270 MHz, CDCl₃) δ 3.75 (s, 3H, COOCH₃), 3.90 (s, 3H, COOCH₃), 7.2 – 7.3 (m, 10H, Ar); ¹³C NMR (68 MHz, CDCl₃) δ 52.6, 52.7 (COOCH₃), 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 (COOCH₃); Anal. Calcd for C₂₀H₁₆O₄S: C, 68.16; H 4.63; S, 8.93.

4e: ¹H NMR (270 MHz, CDCl₃) δ 3.77 (s, 3H, COOCH₃), 3.79 (s, 3H, OCH₃), 3.90 (s, 3H, COOCH₃), 6.81 (br d, 2H, J = 8.7 Hz, 3-H and 5-H of C₆H₄OCH₃), 7.12 (br d, 2H, J = 8.7 Hz, 2-H and 6-H of C₆H₄OCH₃), 7.18 – 7.27 (m, 5H, Ph); ¹³C NMR (270 MHz, CDCl₃) δ 52.5, 52.7 (COOCH₃), 55.1 (OCH₃), 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 (COOCH₃); EI-MS m/z: 382 (M⁺, 100), 351 (20); HRMS Calcd for C₂₁H₁₈O₅S 382.0875, Found 382.0882.


