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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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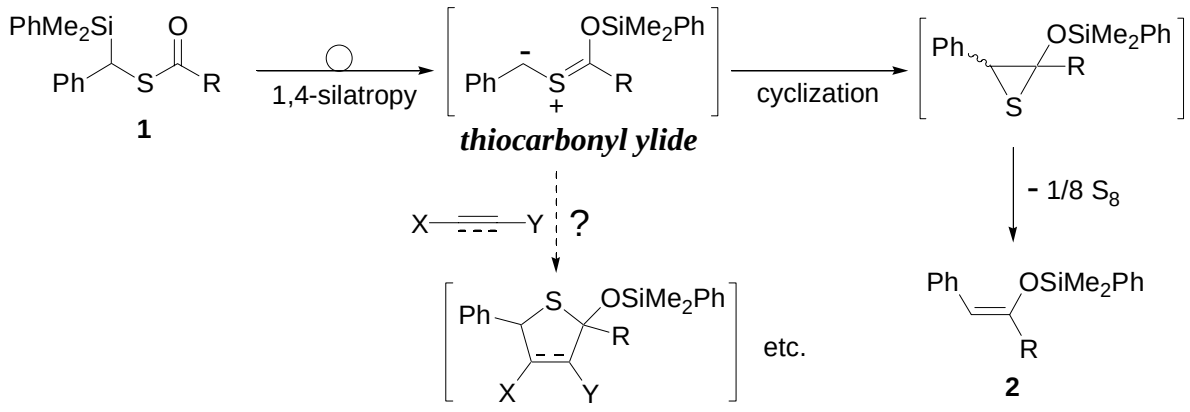
Abstract – The cycloaddition of *S*-α-(dimethylphenylsilyl)benzyl acylates (**1**) with acetylenic dipolarophiles *via* 1,4-silatropy proceeded readily to afford thiophene derivatives. The reaction of thioesters (**1**) with 1-diethylamino-1-propyne (**A**), an electron-rich acetylenic dipolarophile, 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.

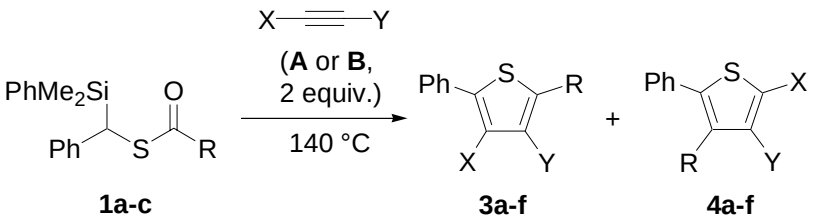


Scheme 1. Generation of Thiocarbonyl Ylides and Cycloaddition with Dipolarophiles

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 ºC 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



1a-c **3a-f** **4a-f**

a : R = Ph
b : R = *p*-$MeOC_6H_4$
c : R = *p*-$NO_2C_6H_4$

A : X = NEt_2, Y = Me
B : X = Y = CO_2Me

a : R = Ph, X = NEt_2, Y = Me
b : R = *p*-$MeOC_6H_4$, X = NEt_2, Y = Me
c : R = *p*-$NO_2C_6H_4$, X = NEt_2, Y = Me
d : R = Ph, X = Y = CO_2Me
e : R = *p*-$MeOC_6H_4$, X = Y = CO_2Me
f : R = *p*-$NO_2C_6H_4$, X = Y = CO_2Me

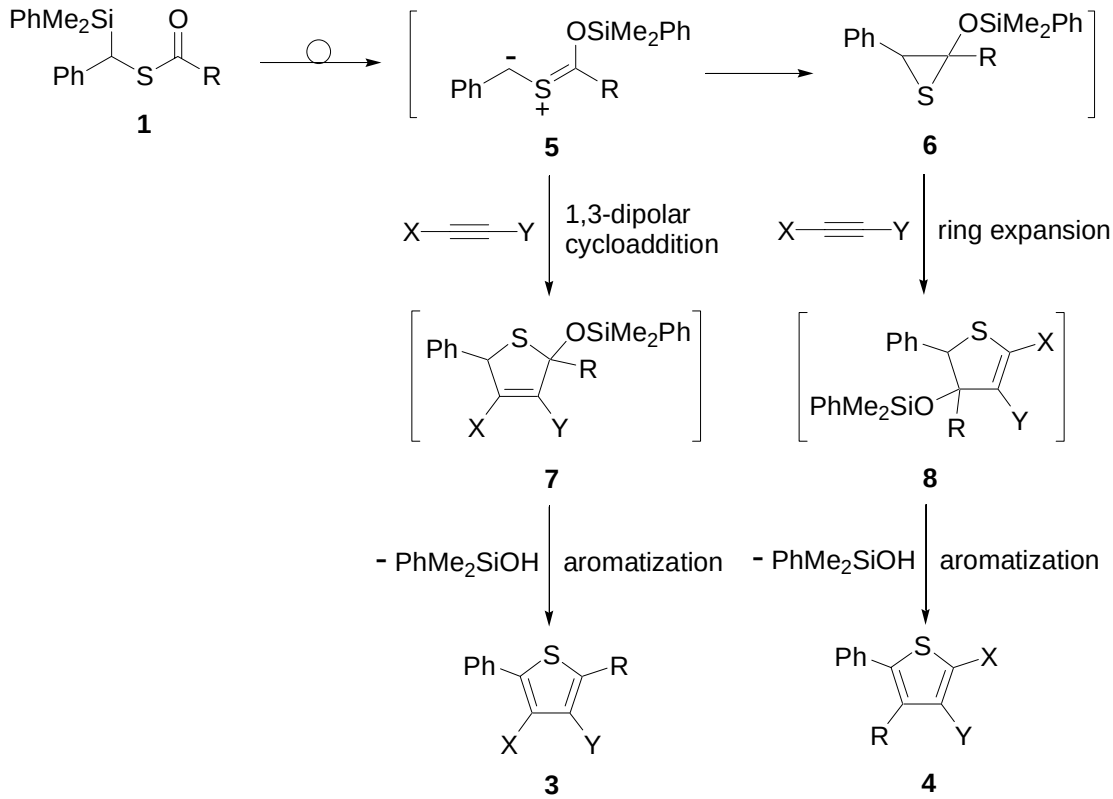
Run	Substrate	Dipolarophile	Solvent	Time (h)	Yield (%)[a]	Ratio[a]
1	**1a**	**A**	PhH	26	75	53/47 (**3a** / **4a**)
2	**1a**	**A**	THF	25	48	63/37 (**3a** / **4a**)
3	**1b**	**A**	PhH	40	51	35/65 (**3b** / **4b**)
4	**1c**	**A**	PhH	4	47	57/43 (**3c** / **4c**)
5	**1a**	**B**	PhH	50	54	**4d** only
6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

[a] Determined by ^1H NMR spectral analysis. [b] Benzyl *p*-methoxyphenyl ketone was obtained in 32% yield. [c] Enol silyl ether (**2**) (R = *p*-$NO_2C_6H_4$, 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 α-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.[8] 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[9] 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.

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5. Structures of **1a-c**,[4] **2**,[4] and **4a**[6] were determined by comparison of their ^{1}H and ^{13}C NMR spectra with known, published data. The structures of **3a-f** and **4b-f** were determined by spectroscopic analysis (^{1}H, ^{13}C NMR, IR, HRMS, NOE experiments etc., and/or X-Ray crystal structure analysis). Selected spectroscopic data are as follows.

3a : ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.02 (t, 6H, *J* = 7.2 Hz, NCH_2CH_3), 2,24 (s, 3H, thiophene-CH_3), 3.02 (q, 4H, *J* = 7.2 Hz, NCH_2CH_3), 7.3 – 7.6 (m, 10H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.3, 14.4 (NCH_2CH_3 and thiophene-CH_3), 47.2 (CH_2CH_3), 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 $C_{21}H_{23}NS$, 321.1551, Found

321.1552.

4a : ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.11 (t, 6H, *J* = 7.1 Hz, NCH_2CH_3), 1.96 (s, 3H, thiophene-CH_3), 3.01(q, 4H, *J* = 7.1 Hz, NCH_2CH_3), 7.1 – 7.3 (m, 10H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.1, 13.6 (NCH_2CH_3 and thiophene-CH_3), 51.4 (NCH_2CH_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 ($CDCl_3$) δ 1.01 (t, 6H, *J* = 7.0 Hz, NCH_2CH_3), 2.20 (s, 3H, thiophene-CH_3), 3.01 (q, 4H, *J* = 7.0, NCH_2CH_3), 3.85 (s, 3H, OCH_3), 6.95 (br d, 2H, *J* = 8.9 Hz, 3-H and 5-H of $C_6H_4OCH_3$), 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 $C_6H_4OCH_3$); ^{13}C NMR ($CDCl_3$) δ 14.4 (NCH_2CH_3 and thiophene-CH_3), 47.3 (NCH_2CH_3), 55.3 (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 (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, $CDCl_3$) δ 1.10 (t, 6H, *J* = 7.0 Hz, NCH_2CH_3), 1.95 (s, 3H, thiophene-CH_3), 3.00 (q, 4H, *J* = 7.0 Hz, NCH_2CH_3), 3.82 (s, 3H, OCH_3), 6.85 (br d, 2H, *J* = 8.6 Hz, 3-H and 5-H of $C_6H_4OCH_3$), 7.14 – 7.17 (m, 5H, Ph), 7.10 (br d, 2H, *J* = 8.6 Hz, 2-H and 6-H of $C_6H_4OCH_3$); ^{13}C NMR (270 MHz, $CDCl_3$) δ 13.2, 13.7 (NCH_2CH_3 and thiophene-CH_3), 51.4 (NCH_2CH_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 ($CDCl_3$) δ 1.02 (t, 6H, *J* = 7.0 Hz, NCH_2CH_3), 2.28 (s, 3H, thiophene-CH_3), 3.01 (q, 4H, *J* = 7.0, NCH_2CH_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 $C_6H_4NO_2$), 7.61 (br d, 2H, *J* = 7.0 Hz, 3-H and 5-H of $C_6H_4NO_2$); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.9 (NCH_2CH_3 and thiophene-CH_3), 47.3, (NCH_2CH_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 $C_{21}H_{22}N_2O_2S$ 366.1401, Found 366.1405.

4c : ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.10 (t, 6H, *J* = 7.1 Hz, NCH_2CH_3), 1.95 (s, 3H, thiophene-CH_3), 3.02 (q, 4H, *J* = 7.0 Hz, NCH_2CH_3), 7.08 – 7.18 (m, 5H, Ph), 7.35 (br d, 2H, *J* = 8.9 Hz, 2-H and 6-H of $C_6H_4NO_2$), 8.61 (br d, 2H, *J* = 8.9 Hz, 3-H and 5-H of $C_6H_4NO_2$); ^{13}C NMR (270 MHz, $CDCl_3$) δ 13.2,

13.6 (NCH_2CH_3 and thiophene-CH_3), 51.4 (NCH_2CH_3), 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 $C_{21}H_{22}N_2O_2S$ 366.1401, Found 366.1411.

4d : ^{1}H-NMR (270 MHz, $CDCl_3$) δ 3.75 (s, 3H, $COOCH_3$), 3.90 (s, 3H, $COOCH_3$), 7.2 – 7.3 (m, 10H, Ar); ^{13}C NMR (68 MHz, $CDCl_3$) δ 52.6, 52.7 ($COOCH_3$), 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 ($COOCH_3$); Anal. Calcd for $C_{20}H_{16}O_4S$: C, 68.16; H 4.57; S, 9.09. Found: C, 67.80; H, 4.63; S, 8.93.

4e : ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.77 (s, 3H, $COOCH_3$), 3.79 (s, 3H, OCH_3), 3.90 (s, 3H, $COOCH_3$), 6.81 (br d, 2H, *J* = 8.7 Hz, 3-H and 5-H of $C_6H_4OCH_3$), 7.12 (br d, 2H, *J* = 8.7 Hz, 2-H and 6-H of $C_6H_4OCH_3$), 7.18 – 7.27 (m, 5H, Ph); ^{13}C NMR (270 MHz, $CDCl_3$) δ 52.5, 52.7 ($COOCH_3$), 55.1 (OCH_3), 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 ($COOCH_3$); EI-MS *m*/*z* : 382 (M^+, 100), 351 (20); HRMS Calcd for $C_{21}H_{18}O_5S$ 382.0875, Found 382.0882.

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