# Regioselective Synthesis of 2-(Arylthio)benzoates by the First Catalytic [3+3] Cyclocondensations of 3-(Arylthio)-1-(trimethylsilyloxy)-1,3-butadienes with 1,1,3,3-Tetramethoxypropane

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**Abstract:** 2-(Arylthio)benzoates were regioselectively prepared by the first catalytic [3+3] cyclizations of 3-(arylthio)-1-(trimethylsilyloxy)-1,3-butadienes with 1,1,3,3-tetramethoxypropane.

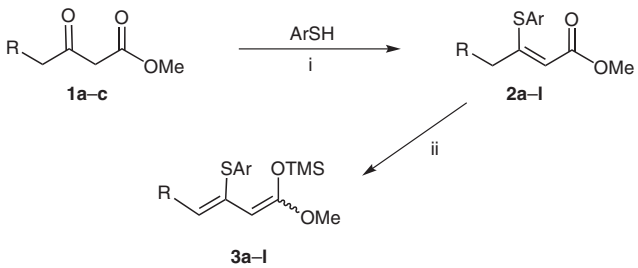
**Key Words:** arenes, cyclizations, diaryl sulfides, regioselectivity, silyl enol ethers

Diaryl sulfides are pharmacologically relevant compounds, which occur in a number of natural products. Prominent examples include the lissoclibadins, dibenzothiophenes, cyclic sulfides, varacins (lissoclinotoxins), and related natural products.[1] Classic syntheses of diaryl sulfides include, for example, reactions of arenes with sulfur[2] or sulfur dichloride,[3] condensations of Grignard or organolithium reagents with chlorophenyl-sulfides,[4] or base-mediated reactions of thiophenols with chloroarenes.[5] The competing formation of polysulfides and low regioselectivities are severe drawbacks of these methods. In contrast, transition-metal-catalyzed[6] and metal-free[7] carbon–sulfur coupling reactions allow the synthesis of diaryl sulfides under relatively mild conditions. However, the scope of this approach is limited by the fact that reactions of sterically encumbered substrates are often difficult or not possible at all. In addition, the synthesis of the starting materials, substituted aryl halides or triflates, can be a difficult task.

A strategy to circumvent these problems relies on the application of a building-block approach using appropriate sulfur-containing substrates in cyclization reactions. Diaryl sulfides have been prepared by cobalt(I)-catalyzed [4+2] cycloaddition of alkynyl sulfides with 1,3-butadienes.[8] Recently, we studied[9] the synthesis of 3- and 5-(arylthio)salicylates by $TiCl_4$-mediated [3+3] cyclizations[10] of 1,3-bis(silyloxy)-1,3-butadienes[11] with 3-(silyloxy)-2-en-1-ones, a method first developed[12] by Chan and coworkers. The $TiCl_4$-mediated cyclocondensation of 1,3-bis(silyloxy)-1,3-butadienes with 1,1,3,3-tetramethoxypropane and 2-alkyl-1,1,3,3-tetraethoxypropanes has also been reported.[12,13] Recently, we have developed a catalytic variant of this reaction using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the catalyst.[14]

Chan et al. reported the synthesis of 2-(phenylthio)benzoates by $TiCl_4$-mediated [3+3] cyclization of 3-(silyloxy)-2-en-1-ones with 3-(arylthio)-1-(trimethylsilyloxy)-1,3-butadienes.[15] Recently, we have studied the $TiCl_4$-mediated domino [3+3]-cyclization–homo-Michael reaction of 3-(arylthio)-1-(trimethylsilyloxy)-1,3-butadienes with 1,1-diacylcyclopropanes.[16] Herein, we communicate a convenient synthesis of 2-(arylthio)benzoates by what are, to the best of our knowledge, the first formal [3+3] cyclocondensations of 3-(arylthio)-1-(trimethylsilyloxy)-1,3-butadienes with 1,1,3,3-tetramethoxypropane. It is important to note that these reactions can be carried out using catalytic amounts of TMSOTf. In contrast to the C–S coupling reactions outlined above, our method relies on the assembly of one of the two arene moieties.

The reaction of β-ketoesters **1a–c** with various thiophenols gave the 3-(arylthio)alkanoates **2a–l** (Scheme 1, Table 1). Deprotonation of **2a–l** (LDA) and subsequent addition of TMSCl afforded the novel 3-(arylthio)-1-(silyloxy)-1,3-butadienes **3a–l** in very good yields.




**Scheme 1** Synthesis of **3a–l** (for substituents and yields, see Table 1). *Reagents and conditions*: (i) $P_4O_{10}$, $CH_2Cl_2$, 20 °C, 18 h; (ii) 1. LDA, THF, –78 °C, 1 h; 2. TMSCl, –78 to 20 °C, 14 h.

The reaction of 3-(phenylthio)-1-(silyloxy)-1,3-butadiene **3a** with 1,1,3,3-tetramethoxypropane (**4**), in the presence of catalytic amounts of TMSOTf, afforded the 2-(phenylthio)benzoate **5a** (Scheme 2).[17] The best yields were obtained when 0.1 equivalents of Lewis acid were used. The use of 0.2 or 1.0 equivalents of TMSOTf did not result in an increase of the yield. The yields decreased when less than 0.1 equivalents of Lewis acid were employed. The use of 1.0 equivalent of $TiCl_4$ proved to be possible,

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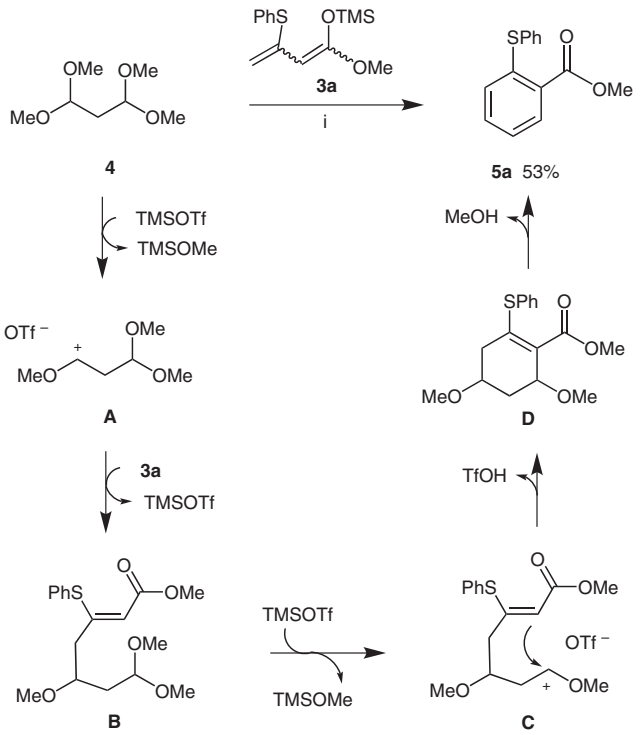
**Table 1** Synthesis of **5a–l**

| 2, 3, 5 | R | Ar | Yield of **2** (%)[a] | Yield of **3** (%)[a] | Yield of **5** (%)[a] |
|---|---|---|---|---|---|
| **a** | H | Ph | 84 | 83 | 53 |
| **b** | H | 4-$MeC_6H_4$ | 85 | 88 | 53 |
| **c** | H | 3-$MeC_6H_4$ | 82 | 82 | 54 |
| **d** | H | 4-$FC_6H_4$ | 80 | 80 | 47 |
| **e** | H | 4-$ClC_6H_4$ | 87 | 84 | 51 |
| **f** | H | 3-$ClC_6H_4$ | 80 | 86 | 51 |
| **g** | H | 2-Naph | 75 | 78 | 33 |
| **h** | Me | Ph | 81 | 87 | 50 |
| **i** | Me | 4-$MeC_6H_4$ | 82 | 85 | 46 |
| **j** | Me | 4-$FC_6H_4$ | 34 | 82 | 44 |
| **k** | Et | Ph | 84 | 83 | 50 |
| **l** | Et | 4-$MeC_6H_4$ | 83 | 84 | 52 |

[a] Isolated yields.

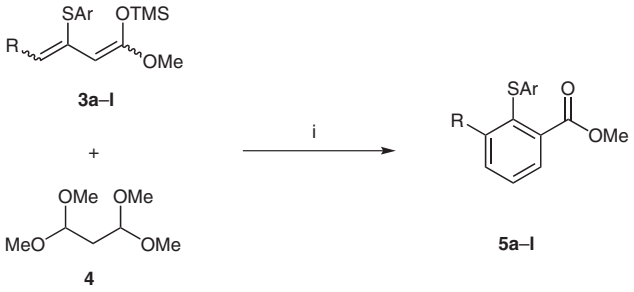



**Scheme 2** Possible mechanism of the formation of **5a**. *Reagents and conditions*: (i) 1. TMSOTf (0.1 equiv), $CH_2Cl_2$, –78 to 20 °C, 20 h; 2. HCl, $H_2O$.

but again did not increase the yield. The workup procedure (diluted HCl), the temperature (–78 to 20 °C, 20 h), and the concentration (ca. 2 mL of $CH_2Cl_2$ per 1 mmol of **3a**) proved to be important parameters during the optimization. The high concentration is a significant difference to the procedure reported[14] for the TMSOTf-catalyzed cyclization of 1,3-bis(silyloxy)-1,3-butadienes with **4**. The use of tetraethoxypropane rather than **4** proved to be unsuccessful. The use of trifluoroacetic acid or triflic acid (rather than TMSOTf) failed to give the desired product.

The formation of **5a** can be explained by TMSOTf-catalyzed formation of oxonium cation **A**, attack of the terminal carbon atom of **3a** onto **A** to give intermediate **B**, TMSOTf-catalyzed formation of oxonium cation **C**, cyclization to give intermediate **D**, and subsequent aromatization by extrusion of methanol. The suggested mechanism has not been experimentally proved.

The cyclization of dienes **3a–l** with **4** afforded the 2-(arylthio)benzoates **5a–l** in moderate yields (Scheme 3, Table 1). Comparable yields were obtained for products **5d–f**, which are derived from dienes containing an electron-withdrawing halogen atom located at the arylthio group, and for products **5a–c**, which are derived from dienes containing an electron-rich arylthio group. In addition, no decrease of the yield was observed for products **5h–l** derived from dienes **3h–l** containing a methyl or ethyl group located at carbon atom C4 of the diene, compared to products **5a–g** derived from unsubstituted dienes **3a–g**.




**Scheme 3** Synthesis of **5a–l**. *Reagents and conditions*: (i) 1. TMSOTf (0.1 equiv), $CH_2Cl_2$, –78 to 20 °C, 20 h; 2. HCl, $H_2O$.

In conclusion, we have reported a convenient approach to 2-(arylthio)benzoates by the first catalytic [3+3] cyclizations of 3-(arylthio)-1-(trimethylsilyloxy)-1,3-butadienes with 1,1,3,3-tetramethoxypropane. The scope and applications of this methodology are currently studied in our laboratory.

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(17) **Typical Experimental Procedure**

To a $CH_2Cl_2$ solution (2 mL/mmol of **3**) of **3** (1.5 mmol) and of 1,1,3,3-tetramethoxypropane (1.0 mmol) was added TMSOTf (0.1 mmol) at –78 °C. The solution was allowed to warm to 20 °C within 20 h. To the solution was added a diluted aq solution of HCl (15 mL). The organic and the aqueous layer were separated, and the latter was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography.

**Methyl 2-(Phenylthio)benzoate (5a)**

Starting with 1,1,3,3-tetramethoxypropane (0.33 mL, 2.0 mmol), **3a** (843 mg, 3.0 mmol), TMSOTf (0.036 mL, 0.2 mmol), and $CH_2Cl_2$ (4 mL), **5a** was isolated as a highly viscous colourless oil (275 mg, 53%). $^1$H NMR (250 MHz, $CDCl_3$): δ = 3.66 (s, 3 H, $OCH_3$), 6.75 (dd, 1 H, $^3J$ = 7.20, $^4J$ = 1.87 Hz, ArH), 7.06 (ddd, 1 H, $^3J$ = 7.20, $^4J$ = 1.87, $^5J$ = 0.92 Hz, ArH), 7.16 (m, 2 H, ArH), 7.36 (m, 3 H, ArH), 7.48 (m, 2 H, ArH). $^{13}$C NMR (62 MHz, $CDCl_3$): δ = 52.1 ($OCH_3$), 124.2 (ArCH), 126.7 (C), 127.4, 129.0 (ArCH), 129.7 (2C, ArCH), 131.1, 132.2 (ArCH), 124.6 (C), 135.5 (2C, ArCH), 143.1, 166.8 (C). IR (neat): ν = 3056 (w), 2948 (w), 1711 (s), 1585 (m), 1562 (m), 1433 (s), 1246 (s), 1189 (m), 1056 (s), 738 (s), 688 (s)530 (m) cm$^{-1}$. GC-MS (EI, 70 eV): *m/z* (%) = 244 (100), 213 (76), 184 (55), 152 (16), 139 (10), 108 (8). HRMS (EI): *m/z* calcd for $C_{14}H_{12}O_2S$ [M$^+$]: 244.05525; found: 244.05570.