Regioselective Synthesis of 2-Arylthio-4-methoxybenzoates by Formal [3+3] Cyclocondensations of 3-Arylthio-1-trimethylsilyloxybuta-1,3-dienes with 3-Oxo-orthoesters

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Abstract: A variety of 2-arylthio-4-methoxybenzoates are regioselectively prepared by the first formal [3+3] cyclocondensations of 3-arylthio-1-trimethylsilyloxybuta-1,3-dienes with 3-oxo-orthoesters.

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

Diaryl sulfides are of pharmacological importance and are found in many natural products. This includes, for example, the lissoclibadins, dibenzothiophenes, cyclic sulfides, varacins (lissoclinotoxins), and related natural products.[1] Diaryl sulfides are available by reaction of arenes with sulfur[2] or sulfur dichloride,[3] by condensation of organometallic reagents with chlorophenylsulfides[4] or by base-mediated reactions of thiophenols with chloroarenes.[5] However, the competing formation of polysulfides and the (in several cases) low regioselectivities are severe drawbacks of these classic synthetic approaches. In recent years, a number of transition-metal-catalyzed[6] and metal-free[7] carbon–sulfur coupling reactions have been developed which allow the formation of diaryl sulfides under mild conditions. However, 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 and tedious task.

An alternative approach to diaryl sulfides is based on the use of sulfur-containing building blocks in cyclization reactions. Hilt and coworkers reported a convenient approach to diaryl sulfides by cobalt(I)-catalyzed [4+2] cycloaddition of alkynyl sulfides with 1,3-butadienes.[8] Recently, we have studied[9] the synthesis of 3- and 5-(arylthio)salicylates by $TiCl_4$-mediated formal [3+3] cyclizations[10] of 1,3-bis(silyloxy)buta-1,3-dienes[11] with 3-silyloxy-2-en-1-ones.[12] 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 1-methoxy-3-phenylthio-1-trimethylsilyloxybuta-1,3-diene.[13] We have recently reported the synthesis of 5-chloroethyl-2-(arylthio)benzoates by $TiCl_4$-mediated domino '[3+3] cyclization–homo-Michael' reaction of 3-arylthio-1-trimethylsilyloxybuta-1,3-dienes with 1,1-diacylcyclopropanes.[14] Recently, we have studied the synthesis of 4-methoxysalicylates by cyclization of 1,3-bis(silyloxy)buta-1,3-dienes with 3-oxo-orthoesters.[15] Herein, we report a convenient synthesis of 2-arylthio-4-methoxybenzoates by what are, to the best of our knowledge, the first [3+3] cyclocondensations of 3-oxo-orthoesters with 3-arylthio-1-trimethylsilyloxybuta-1,3-dienes. This method provides a regioselective approach to a wide range of novel diaryl sulfides which are not readily available by other methods. In contrast to the C–S coupling reactions outlined above, our method relies on the assembly of one of the two arene moieties.

The known 3-oxo-orthoesters **1a**,**b** were prepared, following literature procedures, by condensation of 1,1-dichloroethene with acetyl and propionyl chloride, respectively, and subsequent reaction of the 3,3,3-trichloro-ketones thus formed with methanol.[16] The known 3-arylthio-1-trimethylsilyloxybuta-1,3-dienes **2a–i** were prepared, again according to the literature, from methyl acetoacetate, methyl 3-oxopentanoate, and various thiophenols in two steps.[13,17]

The $TiCl_4$-mediated cyclization of **1a** with 3-phenylthio-1-trimethylsilyloxybuta-1,3-diene **2a** resulted in regioselective formation of the 2-phenylthio-4-methoxybenzoate **3a** (Scheme 1).[18] The formation of 2-phenylthio-6-methoxybenzoate, a regioisomer of **3a**, was not observed. The best yields were obtained when a stoichiometric ratio of **2a**/**1a**/$TiCl_4$ = 1.0:1.5:1.5 was used, and when the reaction was carried out in a fairly concentrated solution [*c* (**1a**) = 0.33 M].

The formation of **3a** can be explained by $TiCl_4$-mediated attack of the terminal carbon atom of diene **2a** onto the orthoester to give intermediate **A**, subsequent cyclization by attack of the central carbon atom of **2a** onto the carbonyl group (intermediate **B**), aromatization (intermediates **C** and **D**) and hydrolysis upon aqueous workup. Alternatively, the cyclization might proceed by $TiCl_4$-mediated extrusion of methanol from **1a** to give 4,4-dimethoxybut-3-en-2-one. Attack of the terminal carbon atom of **2a** onto the latter (conjugate addition) and subsequent cyclization would lead to the final product. This process would follow a mechanism earlier suggested for the cyclization of

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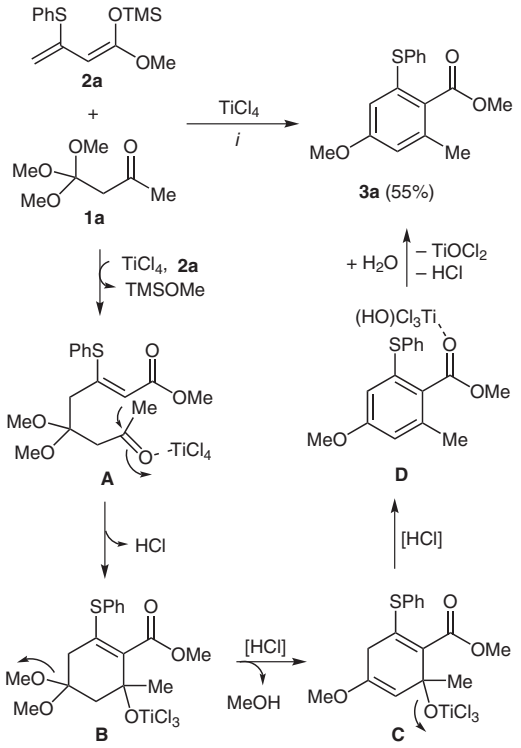
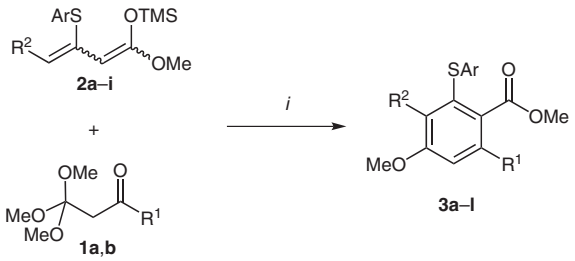


Scheme 1 Possible mechanism of the formation of arene **3a**. *Reagents and conditions*: *i*: 1) $TiCl_4$ (1.0 equiv), CH_2Cl_2, –78 °C to 20 °C, 20 h; 2) HCl (10%).

1,3-bis(trimethylsilyloxy)buta-1,3-dienes with 3-alkoxy- and 3-silyloxy-2-en-1-ones.[10,12]

The $TiCl_4$-mediated cyclization of 3-oxo-orthoesters **1a**,**b** with 3-arylthio-1-trimethylsilyloxybuta-1,3-dienes **2a–i** afforded the novel 2-arylthio-4-methoxybenzoates **3a–l** (Scheme 2, Table 1). A wide range of products could be successfully prepared. Various substituents can be introduced at carbon atoms C3 and C6 of the benzoate moiety (substituents R^1 and R^2) and at the arylthio group. The moderate yields can be explained by partial hydrolysis of the starting materials and $TiCl_4$-mediated oxidative dimerization of the diene. In some reactions a small amount of hydrolyzed starting material was recovered.



Scheme 2 Synthesis of arenes **3a–l**. *Reagents and conditions*: *i*: 1) $TiCl_4$ (1.0 equiv), CH_2Cl_2, –78 °C to 20 °C, 20 h; 2) HCl (10%).

In conclusion, we have reported a convenient and regioselective synthesis of a variety of 2-arylthio-4-methoxybenzoates by formal [3+3] cyclocondensations of 3-arylthio-1-trimethylsilyloxybuta-1,3-dienes with 3-oxo-orthoesters. The scope and applications of this methodology are currently studied in our laboratory.

Table 1 Synthesis of **3a–l**

1	2	3	R^1	R^2	Ar	Yield of **3** (%)[a]
1a	**2**	**3a**	Me	H	Ph	55
1a	**2b**	**3b**	Me	H	3-MeC_6H_4	50
1a	**2c**	**3c**	Me	H	3-ClC_6H_4	46
1a	**2d**	**3d**	Me	H	4-MeC_6H_4	51
1a	**2e**	**3e**	Me	H	4-EtC_6H_4	45
1a	**2f**	**3f**	Me	H	4-FC_6H_4	40
1a	**2g**	**3g**	Me	H	4-ClC_6H_4	46
1a	**2h**	**3h**	Me	Me	Ph	37
1a	**2i**	**3i**	Me	Me	4-EtC_6H_4	35
1b	**2c**	**3j**	Et	H	3-ClC_6H_4	37
1b	**2d**	**3k**	Et	H	4-MeC_6H_4	38
1b	**2g**	**3l**	Et	H	4-ClC_6H_4	40

[a] Isolated yields.

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(18) **General Experimental Procedure**
To a CH_2Cl_2 soln (3 mL/mmol of **1**) of **2** (1.5 mmol) and **1** (2.25 mmol) was added $TiCl_4$ (2.25 mmol) at –78 °C. The solution was allowed to warm to 20 °C within 20 h. To the solution was added HCl (10%, 25 mL). The organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo, and the residue was purified by chromatography (SiO_2, EtOAc–*n*-heptane = 1:9).

4-Methoxy-6-methyl-2-(3-tolylsulfanyl)benzoic Acid Methyl Ester (3b)

Starting with **1a** (2.25 mmol), **2b** (1.5 mmol), and $TiCl_4$ (2.25 mmol), **3b** was isolated as a yellow oil (226 mg, 50%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.25 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 3.69 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 6.57–7.39 (m, 6 H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 20.4 (CH_3), 21.2 (CH_3), 51.9 (OCH_3), 55.2 (CH_3O), 114.1, 114.5, (CH_{Ar}), 126.9, 128.3 (C), 129.4, 131.5, 132.1, 133.0 (CH_{Ar}), 138.3, 139.1, 140.1, 146.9, 168.8 (C). IR (KBr): ν = 2998 (w), 2947 (w), 2834 (w), 2735 (w), 2570 (w), 1724 (s), 1589 (s), 1564 (m), 15560 (m), 1471 (m), 1426 (m), 1380 (w), 1302 (m), 1264 (s), 1217 (s), 1187 (m), 1136 (s), 1090 (s), 1047 (s), 998 (m), 960 (m), 776 (s), 691 (s), 608 (m). MS (EI): *m/z* (%) = 302 (100) [M$^+$], 272 (11), 271 (61), 270 (21), 269 (86), 256 (18), 255 (49),228 (17), 227 (13), 184 (15), 121 (3), 91 (4), 65 (5). HRMS (EI): *m/z* calcd for $C_{17}H_{18}O_2O_3S$ [M$^+$]: 302.09712; found: 302.097152.