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Regioselective synthesis of diaryl sulfides by [3+3] cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-dienes

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Abstract—Functionalized and sterically encumbered diaryl sulfides were prepared based on [3+3] cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-dienes.

Diaryl sulfides are of considerable pharmacological relevance and occur in a number of natural products. These include various dibenzothiophenes,[1] highly cytotoxic lissoclinotoxins (varacins),[2] lissoclibadins (isolated from *Lissoclinum cf. badium*),[3] cyclo(penta-1,4-phenylene sulfide), cyclotetra(*p*-phenylene sulfide),[4] and a number of natural products isolated from *Streptomyces griseus*.[5] Diaryl sulfides have been prepared by thermal reaction of arenes with sulfur.[6] However, these reactions often suffer from low regioselectivity, harsh reaction conditions and formation of polysulfides. Diaryl sulfides are available also by condensation of Grignard or organolithium compounds with chlorophenyl sulfide[7] and by base-mediated reaction of chloroarenes with thiophenols.[8] Some years ago, Chan and co-workers reported[9] the synthesis of salicylates by formal [3+3] cyclization of 1,3-bis(trimethylsilyloxy)-1,3-dienes[10] with 3-siloxy-2-en-1-ones. In recent years, we have reported the application of this method to the synthesis of a variety of functionalized arenes.[11] Chan and Prasad reported the synthesis of 2-(thiophenoxy)benzoates based on [3+3] cyclizations of 1-trimethylsilyloxy-1-methoxy-3-thiophenoxy-1,3-butadiene.[12] Herein, we report what is, to the best of our knowledge, the first synthesis of diaryl sulfides by [3+3] cyclizations of 1,3-bis(silyl enol ethers). These reactions provide a convenient and regioselective approach to sterically encumbered and functionalized diaryl sulfides which are not readily available by other methods. In contrast to the coupling reactions outlined above, our method relies on the assembly of one of the two arene moieties.

The reaction of 3-chloropentane-2,4-dione (**2**) with thiophenols **1a**–**e** afforded, following a known procedure,[13] 3-(thiophenoxy)pentane-2,4-diones **3a**–**e**. Silylation of the latter gave the novel 2-thiophenoxy-3-silyloxy-2-en-1-ones **4a**–**e** (Scheme 1, Table 1). The $TiCl_4$ mediated [3+3] cyclization of **4a**–**e** with 1,3-bis(trimethylsilyloxy)-1,3-dienes **5a**–**d**—readily available from methyl acetoacetate, ethyl 3-oxopentanoate, ethyl 3-oxohexanoate, and ethyl acetoacetate[9]—afforded diaryl sulfides **6a**–**j** (Scheme 1, Table 1).[14] During the optimization of the cyclization reaction, the (high) concentration, the temperature, and the choice of Lewis acid proved to be important parameters. In fact, we have earlier found for related reactions that the use of $SnCl_4$ or $BF_3{\cdot}OEt_2$ resulted in a decrease of yield. No conversion was observed when Me_3SiOTf was employed. All structures were established by spectroscopic methods. The structure of **6a** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[15]

The triethylamine mediated reaction of ethyl 4-chloroacetoacetate with thiophenol (**1a**) afforded ethyl 4-(thiophenoxy)acetoacetate (**7a**),[16] which was transformed in two steps into novel thiophenoxy-substituted 1,3-bis(trimethylsilyloxy)-1,3-diene **9a** (Scheme 2, Table 2). Likewise, **9b** was prepared from ethyl 4-chloroacetoacetate and 4-methoxythiophenol (**1b**). The $TiCl_4$ mediated

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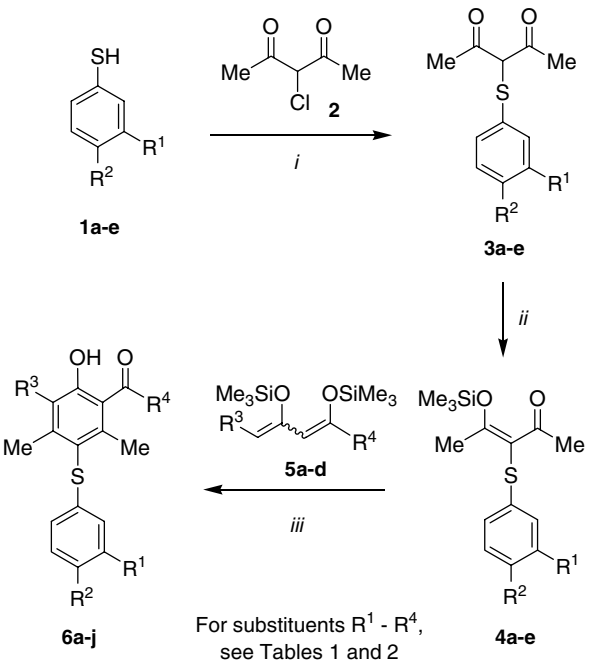


Scheme 1. Synthesis of **6a–j**: Reagents and conditions: (i): C_5H_5N/$C_5H_{11}N$, CH_2Cl_2, MeOH, 0→20 °C, 6 h; (ii): Me_3SiCl, NEt_3, C_6H_6, 20 °C, 72 h; (iii): $TiCl_4$, CH_2Cl_2, −78→20 °C, 20 h.

[3+3] cyclization of **9a** and **9b** with 1,1,3,3-tetramethoxypropane afforded diaryl sulfides **10a** and **10b**, respectively.

The [3+3] cyclization of 1,3-bis(trimethylsilyloxy)-1,3-dienes **9a** and **9b** with 3-silyloxy-2-en-1-ones **11a** and **11b**—prepared from pentane-2,4-dione and heptane-3,4-dione—afforded diaryl sulfides **12a** and **12b**, respectively (Scheme 3, Table 3). Bis(diaryl sulfides) **12c** and **12d** were prepared by cyclization of **9a** and **9b** with 2-thiophenoxy-3-silyloxy-2-en-1-one **4a**, respectively.

In conclusion, we have reported the synthesis of functionalized and sterically encumbered diaryl sulfides by [3+3] cyclizations of 4-thiophenoxy-1,3-bis(trimethylsilyloxy)-1,3-dienes with 3-siloxy-2-en-1-ones and 1,1,3,3-tetramethoxypropane and by [3+3] cyclization of 1,3-bis(trimethylsilyloxy)-1,3-dienes with 2-thiophenoxy-3-siloxy-2-en-1-ones.

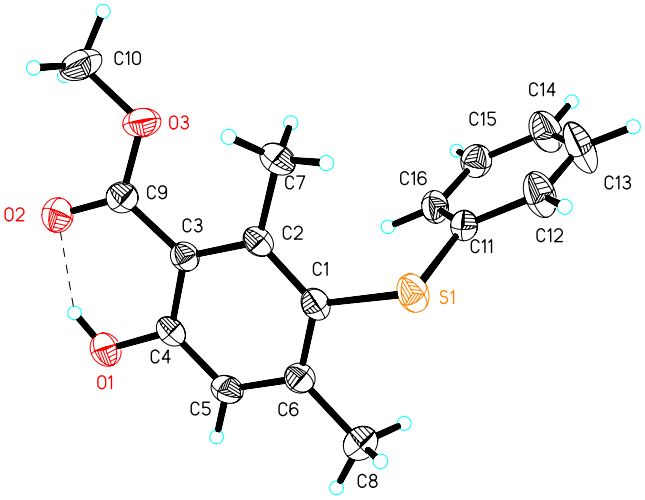
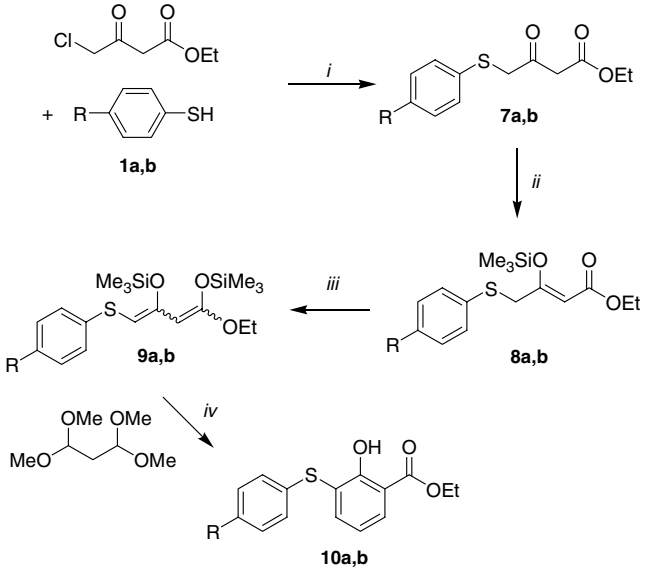


Figure 1. ORTEP plot of **6a**.



Scheme 2. Synthesis of **10a**,**b**: Reagents and conditions: (i): NEt_3, CH_2Cl_2, 30 min, 0 °C; (ii): Me_3SiCl, NEt_3, C_6H_6, 20 °C, 72 h; (iii): (1) LDA, THF, −78 °C, 1 h, (2) Me_3SiCl, −78→20 °C; (iv): $TiCl_4$, CH_2Cl_2, −78→20 °C, 20 h.

Table 1. Synthesis of **6a–j**

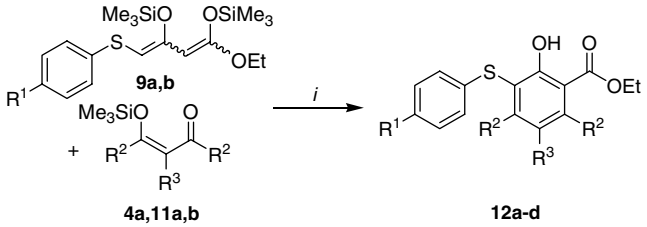
3,4	5	6	R^1	R^2	R^3	R^4	% (3)[a]	% (4)[a]	% (6)[a]
a	**a**	**a**	H	H	H	OMe	72	81	48
a	**b**	**b**	H	H	Me	OEt			40
a	**c**	**c**	H	H	Et	OEt			40
b	**d**	**d**	H	OMe	H	OEt	33	90	43
b	**b**	**e**	H	OMe	Me	OEt			35
b	**c**	**f**	H	OMe	Et	OEt			38
c	**a**	**g**	H	Br	H	OMe	28	79	36
d	**b**	**h**	H	Me	Me	OEt	81	92	33
e	**a**	**i**	OMe	H	H	OMe	73	81	32
e	**b**	**j**	OMe	H	Me	OEt			30

[a] Yields of isolated products.

Table 2. Synthesis of **10a**,**b**

7–10	R	% (**7**)[a]	% (**8**)[a]	% (**9**)[a]	% (**10**)[a]
a	H	80	84	89	31
b	OMe	81	78	85	30

[a] Yields of isolated products.



Scheme 3. Synthesis of **12a**–**d**: Reagents and conditions: (i): $TiCl_4$, CH_2Cl_2, −78→20 °C, 20 h.

Table 3. Synthesis of **12a**–**d**

4a,11	9	12	R^1	R^2	R^3	% (**12**)[a]
11a	**a**	**a**	H	Me	H	48
11b	**b**	**b**	OMe	Et	H	35
4a	**a**	**c**	H	Me	PhS	34
4a	**b**	**d**	OMe	Me	PhS	34

[a] Yields of isolated products.

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14. *General procedure for the synthesis of diaryl sulfides* **6a**–**j**, **10a**,**b**, and **12a**–**d**: To a dichloromethane solution (2 mL/mmol) of **4**, **11**, or 1,1,3,3-tetramethoxypropane (1.0 mmol) and of **5** or **9** (1.0 mmol) was added $TiCl_4$ (1.0 mmol) at −78 °C. The solution was allowed to warm to ambient temperature within 20 h. To the solution was added a saturated solution of $NaHCO_3$ (15 mL). The organic and the aqueous layer were separated and the latter was extracted with diethyl ether (3 × 20 mL). The filtrate was concentrated in vacuo and the residue was purified by chromatography (silica gel, EtOAc/*n*-heptane = 1:4). *Synthesis of methyl 4,6-dimethyl-5-(thiophenoxy) salicylate* (**6a**): Starting with 3-(silyloxy)alk-2-en-1-one **4a** (200 mg, 0.71 mmol), 1,3-bis(silyl enol ether) **5a** (185 mg, 0.71 mmol), and $TiCl_4$ (0.08 mL, 0.71 mmol), **6a** was isolated as a colorless solid (99 mg, 48%), mp 77 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 6.89 (d, 2H, $J = 8.2$ Hz, ArH), 6.76 (s, 1H, ArH), 6.91 (s, 1H, ArH), 7.05 (br t, 1H, $J = 7.2$ Hz, ArH), 7.18 (br t, 1H, $J = 7.4$ Hz, ArH), 11.17 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 2.7, 52.3, (CH_3), 112.4 (C), 117.7 (CH), 122.7 (C), 124.6 (CH), 125.2 (2C, CH), 128.9 (2C, CH), 138.2, 147.1, 151.4, 162.5, 171.8 (C); IR (KBr): $\tilde{\nu} = 3061$ (m), 2954 (m), 1663 (s), 1478 (s), 1360 (s), 1233 (s), 1187 (m), 1024 (m), 947 (w), 740 (s), 690 (m), 629 (w) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%): 288.1 (M^+, 57), 256.1 (100), 185.1 (7), 91 (6). Elemental Anal. Calcd (%) for $C_{16}H_{16}O_3S$ (288.08): C, 66.64; H, 5.59. Found: C, 66.81; H, 5.68.
15. CCDC 632304 contains all crystallographic details of this publication which are available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; Fax: (+44)1223 336 033; or deposit@ccdc.cam.ac.uk.
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