



## First synthesis of 4-(arylsulfonyl)phenols by regioselective [3+3] cyclocondensations of 1,3-bis(silyloxy)-1,3-butadienes with 2-arylsulfonyl-3-ethoxy-2-en-1-ones

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### ABSTRACT

The formal [3+3] cyclization of 1,3-bis(silyloxy)-1,3-butadienes with readily available 2-arylsulfonyl-3-ethoxy-2-en-1-ones resulted in regioselective formation of 4-(arylsulfonyl)phenols.

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4-(Arylsulfonyl)phenols are of considerable pharmacological relevance. This includes antibacterial activity,<sup>1</sup> inhibition of phospholipidase A<sub>2</sub>,<sup>2</sup> inhibition of catechol O-methyltransferase,<sup>3</sup> inhibition of dihydropteroate synthase of *Escherichia coli*,<sup>4</sup> hypolipidemic activity,<sup>5</sup> cytotoxicity against HeLa cells and the antipicornavirus,<sup>6</sup> neuropeptide Y<sub>1</sub> receptor binding activity,<sup>7</sup> anti-HIV activity,<sup>8</sup> anticholesteremic activity,<sup>9</sup> binding to human muscarinic M<sub>1</sub> and M<sub>2</sub> receptors,<sup>10</sup> histamine H<sub>3</sub>-receptor antagonistic activity,<sup>11</sup> antiprotozoal activity,<sup>12</sup> binding to neuroblastoma cells,<sup>13</sup> binding to the human cannabinoid CB<sub>1</sub> receptor,<sup>14</sup> and inhibition of the main protease of the recombinant SARS coronavirus.<sup>15</sup>

Diaryl sulfones are available by oxidation of diaryl sulfides. For example, 4-(phenylsulfonyl)anisole has been prepared by oxidation of 4-(phenylthio)anisole with hydrogen peroxide.<sup>16</sup> An alternative approach to this compound relies on the aluminum(III)chloride-mediated reaction of anisole with phenylsulfonic acid chloride.<sup>17</sup> However, this approach suffers from the formation of a regioisomeric mixture, which is difficult to be separated. The reaction of phenol with benzenesulfonic acid has been reported to give 4-(phenylsulfonyl)phenol.<sup>18</sup> However, no yield was given, and the reaction required harsh conditions (240 °C). Recently, an

efficient approach to 4-(phenylsulfonyl)phenol, based on the CuI/proline-mediated reaction of aryl iodides with sodium benzenesulfinate, has been reported.<sup>19</sup> 4-(Phenylsulfonyl)anisole has been prepared by Suzuki reaction of 4-methoxybenzeneboronic acid with phenylsulfonic acid chloride.<sup>20</sup> Recently, its synthesis by Cu(OAc)<sub>2</sub>-catalyzed reaction of 4-methoxybenzeneboronic acid with sodium benzenesulfinate in the presence of 1,10-phenanthroline and oxygen has been reported.<sup>21</sup> All of these reactions rely on the coupling of two arene moieties. The application of these reactions to the synthesis of sterically encumbered or functionalized products can be difficult in some cases. In addition, the synthesis of the required starting materials, functionalized arenes, can be a tedious task.

Chan and coworkers were the first to report<sup>22</sup> the TiCl<sub>4</sub>-mediated [3+3] cyclization<sup>23</sup> of 1,3-bis(trimethylsilyloxy)-1,3-butadienes<sup>24</sup> with 3-silyloxy-2-en-1-ones, which allows a convenient synthesis of salicylates. In recent years, the application of this methodology to the synthesis of various functionalized arenes has been reported.<sup>23</sup> Herein, we report, for the first time, the synthesis of 4-(arylsulfonyl)phenols by [3+3] cyclocondensations of 1,3-bis(silyloxy)-1,3-butadienes with 2-arylsulfonyl-3-ethoxy-2-en-1-ones. These reactions allow a convenient and regioselective access to functionalized 4-(arylsulfonyl)phenols, which are not readily available by other methods. In contrast to the C–S coupling reactions that are outlined above, the method reported herein

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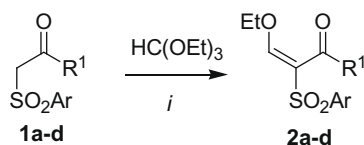
E-mail address: [peter.langer@uni-rostock.de](mailto:peter.langer@uni-rostock.de) (P. Langer).

involves the formation of one of the two arene moieties by formation of two C–C bonds.

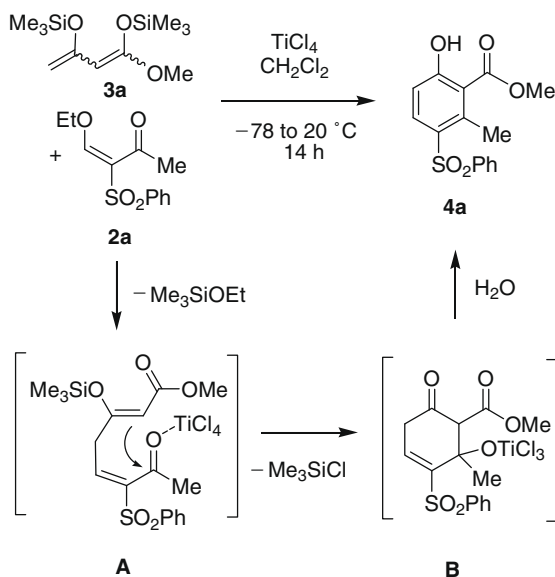
1,3-Bis(silyloxy)-1,3-butadienes **3a–g** were prepared from the corresponding  $\beta$ -ketoesters in two steps.<sup>22</sup> 2-Arylsulfonyl-3-ethoxy-2-en-1-ones **2a–d** were prepared, following a known procedure,<sup>25</sup> by reaction of  $\beta$ -ketosulfones **1a–d** with triethyl orthoformate and acetic anhydride (Scheme 1).

The  $\text{TiCl}_4$ -mediated cyclization of **2a** with **3a** afforded the novel 4-(arylsulfonyl)phenol **4a** in up to 80% yield (Scheme 2). The best yield was obtained when the reaction was carried out, in a highly concentrated solution.<sup>26</sup> It is worth to be noted that the cyclization proceeded with excellent regioselectivity. The formation of product **4a** might be explained by  $\text{TiCl}_4$ -mediated attack of the terminal carbon atom of **3a** onto **2a** to give intermediate **A**, cyclization via the central carbon (intermediate **B**) and subsequent aromatization.

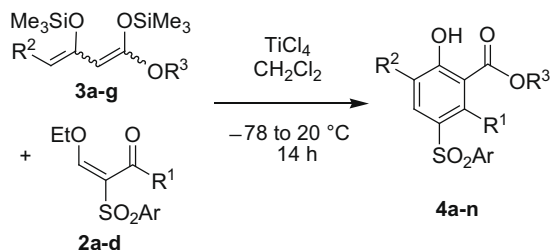
The formal [3+3] cyclization of 2-arylsulfonyl-3-ethoxy-2-en-1-ones **2a–d** with 1,3-bis(silyloxy)-1,3-butadienes **3a–g** afforded the 4-(arylsulfonyl)phenols **4a–n** in 45–80% yield (Scheme 3, Table 1). The aryl groups located at the sulfonyl group of enones **2** have



**Scheme 1.** Synthesis of **2a–d**. Reagents and conditions: (i) **1a–d** (1.0 equiv),  $\text{HC(OEt)}_3$  (1.2 equiv),  $\text{Ac}_2\text{O}$ , reflux, 2 h.



**Scheme 2.** Possible mechanism of the formation of **4a**.

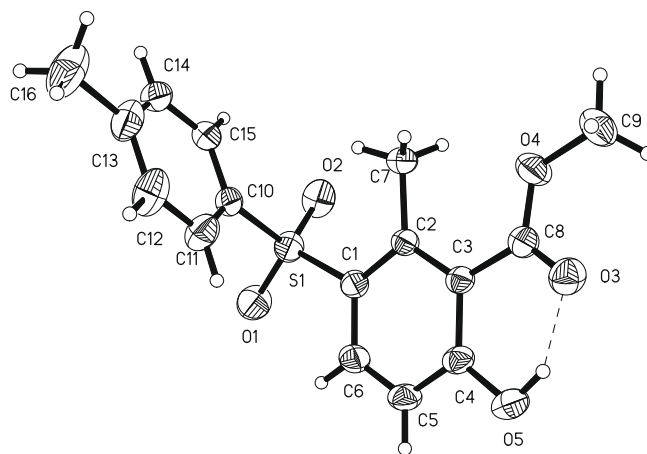


**Scheme 3.** Synthesis of **4a–n**.

**Table 1**  
Synthesis of **4a–n**

2	3	4	Ar	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	% <sup>a</sup>
<b>a</b>	<b>a</b>	<b>a</b>	Ph	Me	H	Me	80
<b>a</b>	<b>b</b>	<b>b</b>	Ph	Me	<i>n</i> Bu	Me	76
<b>a</b>	<b>c</b>	<b>c</b>	Ph	Me	<i>n</i> Hept	Me	75
<b>b</b>	<b>a</b>	<b>d</b>	4-MeC <sub>6</sub> H <sub>4</sub>	Me	H	Me	57
<b>b</b>	<b>d</b>	<b>e</b>	4-MeC <sub>6</sub> H <sub>4</sub>	Me	Me	Me	65
<b>b</b>	<b>b</b>	<b>g</b>	4-MeC <sub>6</sub> H <sub>4</sub>	Me	<i>n</i> Bu	Me	65
<b>b</b>	<b>c</b>	<b>h</b>	4-MeC <sub>6</sub> H <sub>4</sub>	Me	<i>n</i> Hept	Me	60
<b>b</b>	<b>e</b>	<b>f</b>	4-MeC <sub>6</sub> H <sub>4</sub>	Me	<i>n</i> Oct	Me	59
<b>c</b>	<b>a</b>	<b>i</b>	4-ClC <sub>6</sub> H <sub>4</sub>	Me	H	Me	47
<b>c</b>	<b>d</b>	<b>j</b>	4-ClC <sub>6</sub> H <sub>4</sub>	Me	Me	Me	48
<b>c</b>	<b>f</b>	<b>k</b>	4-ClC <sub>6</sub> H <sub>4</sub>	Me	Et	Et	47
<b>c</b>	<b>g</b>	<b>l</b>	4-ClC <sub>6</sub> H <sub>4</sub>	Me	<i>n</i> Hex	Me	50
<b>c</b>	<b>e</b>	<b>m</b>	4-ClC <sub>6</sub> H <sub>4</sub>	Me	<i>n</i> Oct	Me	52
<b>d</b>	<b>a</b>	<b>n</b>	4-MeC <sub>6</sub> H <sub>4</sub>	4-(O <sub>2</sub> N)C <sub>6</sub> H <sub>4</sub>	H	Me	45

<sup>a</sup> Yields of isolated products.



**Figure 1.** Ortep plot of **4d** (30% probability level).

some influence on the yields. The best yields were obtained for products **4a–c** derived from phenyl-substituted enone **2a**. In contrast, the presence of a substituent located at carbon atom C-4 of the 1,3-bis(silyloxy)-1,3-butadiene has no significant effect on the yield. Products **4a–m**, derived from enones **2a–c**, contain a methyl group located at carbon C-3 of the phenol moiety. Product **4n**, containing an aryl group located at C-3, was prepared from enone **2d**. The yield was slightly lower than the yield of **4d** (which also contains, like **4n**, a tosyl group located at C-4). All products were formed with excellent regioselectivity.

The structures of all products were confirmed by spectroscopic methods. The structure of **4d** was independently confirmed by X-ray crystal structure analysis (Fig. 1).<sup>27</sup>

In conclusion, we have reported a convenient and regioselective synthesis of 4-(arylsulfonyl)phenols by what are, to the best of our knowledge, the first formal [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes with 2-arylsulfonyl-3-ethoxy-2-en-1-ones. The reactions are easy to be carried out and the starting materials are readily available. We currently study the preparative scope of the methodology and applications to the synthesis of pharmacologically active products.

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- General procedure for the synthesis of 4-(arylsulfonyl)phenols **4a–n**: To a CH<sub>2</sub>Cl<sub>2</sub> solution (2 mL) 1 mmol of **2a–d** were added **3a–g** (1.1 mmol) and, subsequently, TiCl<sub>4</sub> (1.1 mmol) at 78 °C. The temperature of the solution was allowed to warm to 20 °C during 14 h with stirring. To the solution was added hydrochloric acid (10%, 20 mL) and the organic and the aqueous layer were separated. The latter was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes/EtOAc) to give **4a–n**.  
Methyl 6-hydroxy-2-methyl-3-tosylbenzoate (**4d**): Starting with **2a** (0.402 g, 1.5 mmol) and **3a** (0.429 g, 1.65 mmol), **4d** was isolated (0.274 g, 57%) as a yellowish solid (0.274 g, 57%), mp 109–110 °C. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>): δ 2.28 (s, 3H, CH<sub>3</sub>Ar), 2.47 (s, 3H, CH<sub>3</sub>), 3.81 (s, 3H, OCH<sub>3</sub>), 6.87 (d, <sup>3</sup>J = 8.4 Hz, 1H, Ar), 7.14–7.17 (m, 2H, Ar), 7.35–7.58 (m, 2H, Ar), 8.22 (d, <sup>3</sup>J = 8.7 Hz, 1H, Ar), 11.03 (s, 1H, OH). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ 19.0, 21.5 (2 × CH<sub>3</sub>), 52.7 (OCH<sub>3</sub>), 115.1 (CCO<sub>2</sub>CH<sub>3</sub>), 115.6 (CH<sub>Ar</sub>), 127.3 (2 × CH<sub>Tol</sub>), 129.6 (2 × CH<sub>Tol</sub>), 131.8 (C<sub>Ar</sub>SO<sub>2</sub>), 135.2 (CH<sub>Ar</sub>), 138.9 (C<sub>Ar</sub>CH<sub>3</sub>), 142.6 (C<sub>Tol</sub>SO<sub>2</sub>), 143.8 (C<sub>Tol</sub>CH<sub>3</sub>), 165.2 (COH), 171.0 (CO). IR (KBr, cm<sup>-1</sup>): ν = 3072 (w), 3029 (w), 2953 (w), 2922 (w), 2852 (w), 1715 (w), 1673 (m), 1592 (m), 1574 (m), 1495 (w), 1435 (m), 1348 (m), 1300 (m), 1286 (m), 1218 (m), 1188 (m), 1155 (m), 1142 (s), 1109 (m), 1081 (m), 1040 (w), 1018 (w), 997 (m), 939 (m), 848 (w), 815 (m), 759 (w), 709 (m), 692 (m), 649 (m), 597 (w), 587 (m), 565 (m), 549 (m), 533 (s). GC–MS (EI, 70 eV): m/z (%) = 320 ([M]<sup>+</sup>, 34), 289 (27), 288 (100), 271 (23), 269 (18), 256 (9), 255 (48), 224 (16), 223 (20), 222 (17), 181 (10), 152 (11), 149 (12), 121 (12), 105 (10), 91 (19), 77 (22), 65 (20), 51 (14). HRMS (EI): Calcd for C<sub>16</sub>H<sub>16</sub>O<sub>5</sub>S ([M]<sup>+</sup>): 320.07130; found: 320.071076. All products gave correct elemental analyses and/or HRMS data.
- CCDC-699679 contains all crystallographic details of this publication and is available free of charge at [www.ccdc.cam.ac.uk/conts/retrieving.html](http://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.