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Synthesis of functionalized diaryl selenides by the first [3+3] cyclocondensations of 1,3-bis(silyloxy)-1,3-butadienes with organoselenium compounds

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ABSTRACT

Functionalized diaryl selenides were prepared by the first [3+3] cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with organoselenium compounds (i.e., 2-(phenylselanyl)-3-silyloxy-3-en-1-ones).

Diaryl selenides are of considerable pharmacological relevance, due to their antimicrobial, antitumor, and antioxidant properties. They also play an important role as synthetic reagents (e.g., in the context of elimination reactions based on selenoxide pyrolysis or in the context of radical reactions) and in material sciences (e.g., conductive and supraconductive organic molecules).[1] The synthesis of organoselenium compounds is a demanding task, due to the unstable nature of the products. In addition, most of the methods developed for the synthesis of organosulfur compounds are not applicable to the synthesis of organoselenium compounds. A number of methods have been developed for the preparation of aliphatic organoselenium derivatives. This includes the reaction of a metal selenolate with organic halides, acyl chlorides, epoxides, and enones.[2] However, the synthesis of diaryl selenides from selenide anions with aryl halides is more difficult, due to the low reactivity of the halides. The reaction of halogenated arenes with phenylselenol or benzeneselenolate salts requires the use of a catalyst, ligand and strong base, long reaction times, and harsh reaction conditions.[3] Other syntheses rely on the reaction of diaryl diselenides with organometallic reagents (e.g., organolithiums, Grignard reagents, or cuprates) or organoboronic acids.[4] Unsymmetrical diaryl selenides are also available from (toxic) arylselenyl bromides with aryl lithium derivatives.[5]

The methods listed above, which all rely on the formation of a C–Se bond, often suffer from their low regioselectivity, harsh reaction conditions, and high temperatures. In addition, reduction and formation of diselenides are often observed. Electron-rich arenes and sterically encumbered substrates sometimes react sluggishly or not at all. In addition, the synthesis of the required starting materials, highly functionalized or sterically encumbered halogenated arenes can be a difficult and tedious task.

Our concept to circumvent these problems is based on the development of cyclization reactions of suitable selenium-containing molecules ('building block strategy'). Examples for the application of this strategy to the synthesis of phenylselanyl-substituted carbacycles have only scarcely been reported to date. Stone and co-workers reported the [4+2] cycloaddition of 2-(phenylselanyl)-1,3-butadienes with alkenes and alkynes.[6] Chan and Brownbridge were the first to report[7] the synthesis of salicylates by formal [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes[8] with 3-silyloxy-2-en-1-ones.[9] Herein, we report what is, to the best of our knowledge, the first application of this methodology to the synthesis of organoselenium compounds. The products reported herein, 5-(phenylselanyl)salicylates, can be regarded as functionalized diaryl selenides and have, to the best of our knowledge, not been previously prepared. Symmetrical salicylate-derived diarylselenides are known and have been prepared by reaction of salicylates with (toxic) $SeOCl_2$ and subsequent reduction with zinc.[10] Barton et al. have reported an isolated example of the formation of an unsymmetrical derivative during their study of the oxidation of phenols by benzeneselenic anhydride.[11]

Phenylselanyl-substituted 1,3-diketones **2a**,**b** were prepared by reaction of **1a**,**b** with selenium dioxide and diphenyl diselenide in

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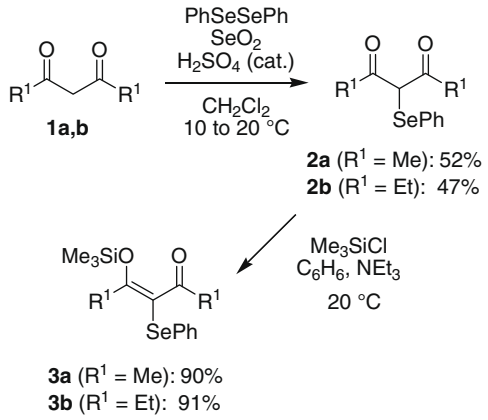
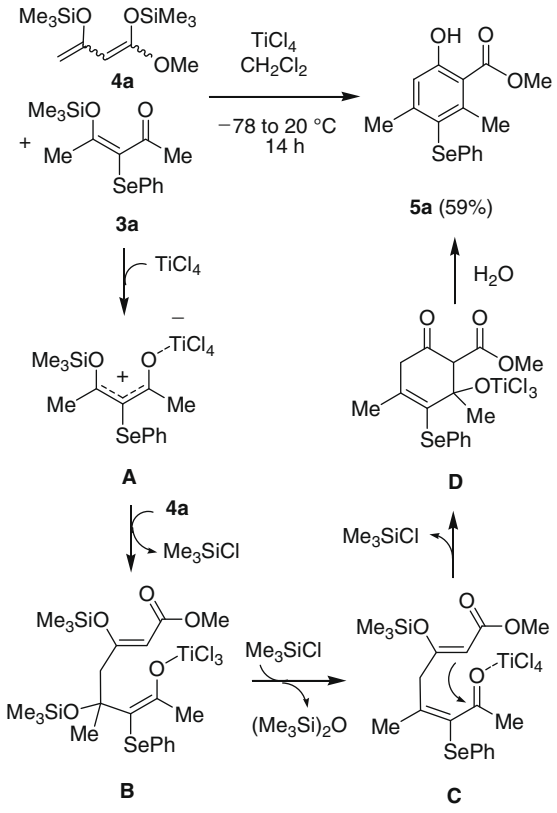


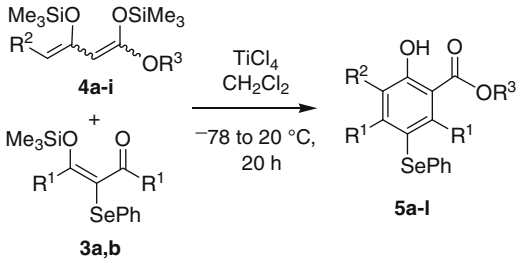
Scheme 1. Synthesis of **3a**,**b**.

the presence of catalytic amounts of sulfuric acid (Scheme 1). The synthesis of **2a** has been previously reported.[12] The silylation of **2a**,**b** with chlorotrimethylsilane afforded the novel 3-silyloxy-2-en-1-ones **3a**,**b**. 1,3-Bis(silyloxy)-1,3-butadienes **4a–i** were prepared as previously reported.[7,13,14]

The $TiCl_4$-mediated cyclization of **3a** with **4a** afforded the diaryl selenide **5a** (Scheme 2). The best yield was obtained when the reaction was carried out in a highly concentrated solution.[15] The formation of **5a** can be explained by reaction of **3a** with $TiCl_4$ to give allylic cation **A**. The attack of the terminal carbon atom of **4a** onto **A** resulted in the formation of intermediate **B**. The elimination of hexamethyldisiloxane (intermediate **C**) and subsequent cyclization gave intermediate **D**. The elimination of titanium hydroxide and aromatization resulted in the formation of product **5a**.



Scheme 2. Possible mechanism of the formation of **5a**.



Scheme 3. Synthesis of **5a**–**l**.

The $TiCl_4$-mediated cyclization of enones **3a**,**b** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **4a–i** afforded the highly functionalized diaryl selenides **5a–l** in 46–70% yield (Scheme 3, Table 1). The structures of all compounds were established by spectroscopic methods. The structure of **5b** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[16]

In conclusion, we have reported a new and convenient synthesis of various functionalized unsymmetrical diaryl selenides containing a salicylate substructure.

Table 1
Synthesis of **5a**–**l**

3	4	5	R^1	R^2	R^3	% (**5**)[a]
a	**a**	**a**	Me	H	Me	59
a	**b**	**b**	Me	H	$(CH_2)_2OMe$	57
a	**c**	**c**	Me	H	CH_2Ph	46
a	**d**	**d**	Me	Me	Me	68
a	**e**	**e**	Me	Et	Me	70
a	**f**	**f**	Me	*n*Bu	Me	69
a	**g**	**g**	Me	*n*Hex	Me	62
a	**h**	**h**	Me	*n*Hep	Me	62
a	**i**	**i**	Me	*n*Oct	Me	59
b	**a**	**j**	Et	H	Me	56
b	**b**	**k**	Et	H	$(CH_2)_2OMe$	55
b	**d**	**l**	Et	Me	Me	61

[a] Yields of isolated products.

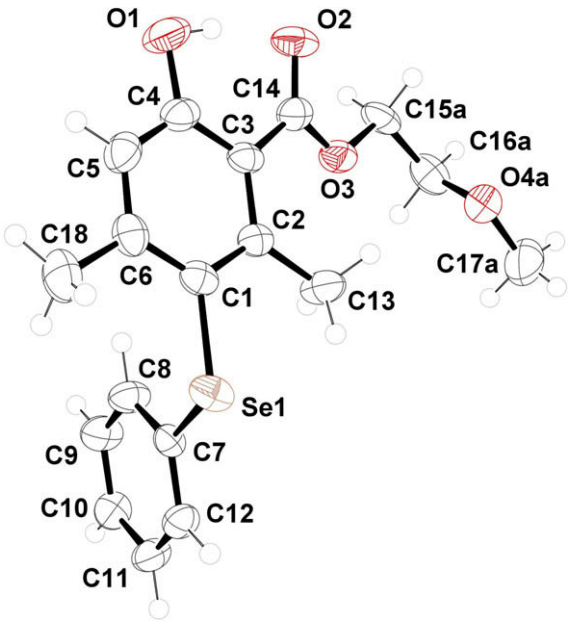


Figure 1. Crystal structure of **5b** (50% probability level).

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14. Nguyen, V. T. H.; Bellur, E.; Appel, B.; Langer, P. *Synthesis* **2006**, 2865.
15. *Typical procedure for the synthesis of diaryl selenides* **5a–I**. To a CH_2Cl_2 solution (5 mL) of **3a** (491 mg, 1.5 mmol) and **4a** (429 mg, 1.65 mmol) was added dropwise $TiCl_4$ (0.18 mL, 1.6 mmol) at −78 °C. The reaction mixture was allowed to warm to 20 °C for 6–12 h. After stirring for additional 2–6 h at 20 °C, hydrochloric acid (10%, 20 mL) was added. The organic and the aqueous layers were separated and the latter was extracted with dichloromethane (3×25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes/ethyl acetate) to give **5a** as a colorless oil (297 mg, 59%). *Methyl 6-hydroxy-2,4-dimethyl-3-(phenylselanyl)benzoate* (**5a**): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.34 (s, 3H, CH_3), 2.66 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 6.75 (s, 1H, CH_{Ar}), 6.94–6.98 (m, 2H, $2CH_{Ar}$), 7.05–7.14 (m, 3H, $3CH_{Ar}$), 10.91 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.4, 25.7 (CH_3), 52.3 (OCH_3), 112.2 (CCO_2CH_3), 117.3 (CH_{Ar}), 123.1 (C_{Ar}), 125.5 (CH_{Ar}), 128.18, 129.2 ($2CH_{Ar}$), 133.4, 146.6, 151.2 (C_{Ar}), 162.4 (COH), 171.7 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3054 (w), 2950 (w), 2922 (w), 2852 (w), 1730 (w), 1689 (w), 1656 (s), 1631 (m), 1593 (m), 1475 (m), 1375 (w), 1348 (s), 1298 (s), 1223 (s), 1186 (s), 1125 (s), 1101 (s), 1064 (s), 1020 (m), 997 (m), 947 (w), 858 (w), 801 (m), 731 (s), 688 (m), 664 (m), 589 (m). MS (GC-MS, 70 eV): *m/z* (%): 338 (16), 337 (15), 336 (M^+, 79), 334 (40), 333 (15), 332 (15), 306 (21), 305 (23), 304 (100), 303 (17), 302 (52), 301 (23), 300 (20), 224 (25), 196 (15), 195 (12), 168 (13), 167 (21), 165 (10), 152 (11), 119 (12), 91 (25), 77 (12), 65 (13), 51 (10). HRMS (EI): Calcd for $C_{16}H_{16}O_3Se$: 336.02592; found: 336.025935.
16. CCDC-743731 contains all crystallographic details of this publication and is 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.