

# First oxidative cyclization of 1,3-bis(trimethylsilyloxy)buta-1,3-dienes

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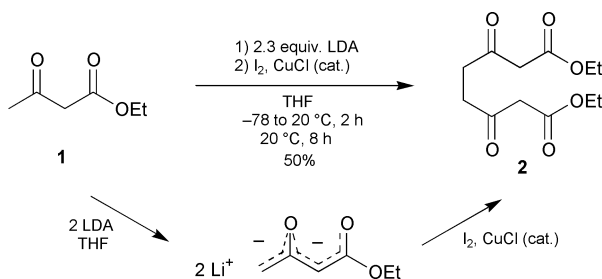
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The first oxidative cyclizations of 1,3-bis(trimethylsilyloxy)buta-1,3-dienes, electroneutral 1,3-dicarbonyl dianion synthons, result in regioselective formation of functionalized 1,4-dihydroquinones.

The development of new, preparatively useful single-electron-transfer (SET) reactions is of considerable current interest. Although SET-oxidations of monoanions have been extensively studied,<sup>1</sup> little is known about dianion oxidations.<sup>2</sup> Herein, we wish to report, to the best of our knowledge, the first oxidative cyclizations of 1,3-bis(trimethylsilyloxy)buta-1,3-dienes which represent electroneutral 1,3-dicarbonyl dianion synthons.<sup>3</sup> This methodology provides a direct, mild and regioselective synthesis of 2,3-acceptor-substituted 1,4-dihydroquinones which can be regarded as products of a formal oxidative cyclization of 1,3-dicarbonyl dianions.<sup>4</sup> These products, which have been previously prepared by multi-step syntheses under drastic conditions,<sup>5</sup> represent useful intermediates in organic synthesis. 2,3-Acceptor-substituted 1,4-dihydroquinones are present in a variety of polyketide-derived natural products, such as *dericamycin A* and the related *fredericamycin A*,<sup>5a</sup> or prominent enediynes, such as *calicheamicin*, *esperamicin*, *neocarzinostatin* chromophore or *dynemicin A*.<sup>6a</sup> Simple 1,4-dihydroquinone-2,3-dicarbonyl derivatives have proven biologically active against murine tumors.<sup>6b</sup>

Oxidation of the dianion<sup>7,8</sup> of ethyl acetoacetate with iodine or bromine in the presence of catalytic amounts of copper(I) chloride has been reported to afford the open-chain dimerization product **2** rather than a cyclization product (Scheme 1).<sup>9</sup> The use of 1,2-dibromoethane, CuCl<sub>2</sub> and Cu(OTf)<sub>2</sub> as the oxidizing agents resulted in formation of complex mixtures. The main problem associated with the oxidative cyclization of dianions is the fact that, due to electrostatic repulsion, dimerization of the radical anionic intermediates is slow and many side-reactions, such as deprotonation of the solvent (THF), can occur.

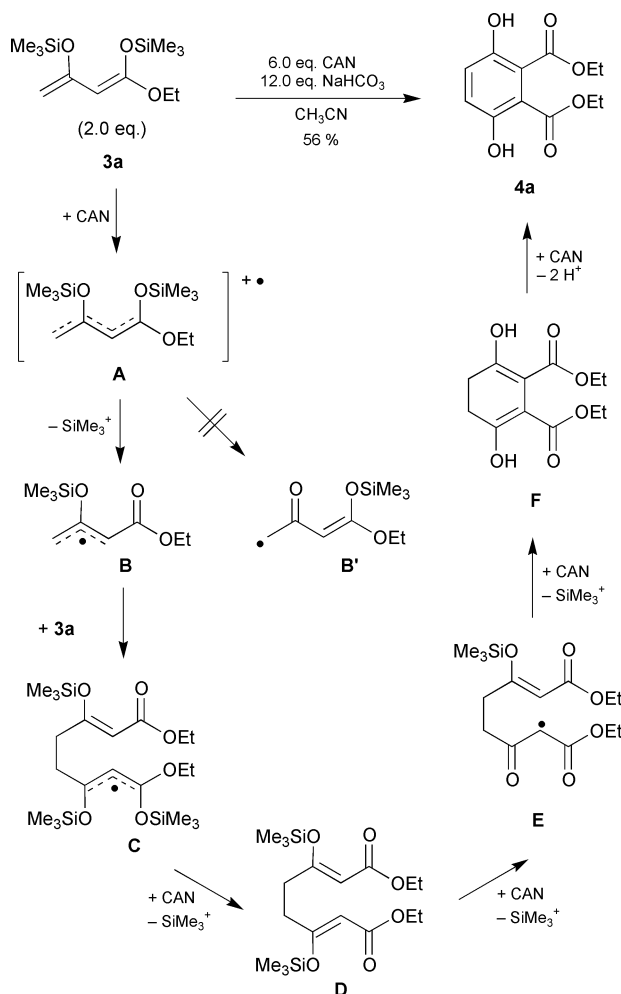
Our concept to overcome these problems was to study the oxidative dimerization of 1,3-bis(trimethylsilyloxy)buta-1,3-dienes **3**.<sup>10</sup> Slow addition of an acetonitrile solution of CAN to an acetonitrile solution of NaHCO<sub>3</sub> and diene **3a**<sup>3c</sup> resulted in formation of the ester-substituted 1,4-dihydroquinone **4a**, however, in only low yield. Much to our satisfaction, employment of an inverse addition protocol resulted in an increase of the yield. Optimal yields (up to 56%) were obtained when an acetonitrile solution of **3a** (2 eq.) was slowly added to a solution of CAN (6 eq.) and NaHCO<sub>3</sub> (12 eq.) at -45 °C.†



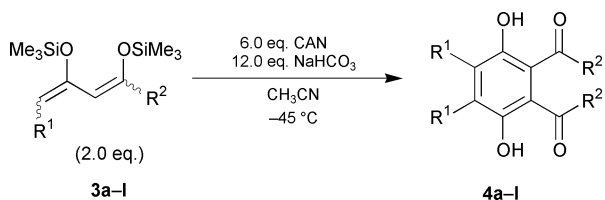
Scheme 1

Formation of **4a** can be explained by the following working hypothesis (Scheme 2): SET-oxidation of **3a** affords the radical cation **A**. Formation of a ceric enolate, supported by the chelating nature of the two oxygen atoms, can not be excluded.<sup>11</sup> Cleavage of the Si–O bond and NaHCO<sub>3</sub>-assisted extrusion of a silyl-cation results in formation of radical **B** which subsequently attacks the terminal carbon atom of a second molecule of **3a** to give intermediate **C**. Radical **B** should be more stable than the isomeric, cross-conjugated radical **B'**. Oxidation and extrusion of the second silyl group affords intermediate **D**. Oxidation of the latter and extrusion of the third silyl group results in formation of intermediate **E**. Cyclization, oxidation and extrusion of the fourth silyl group affords intermediate **F** which is subsequently oxidized to give the final product **4a**.

The 'head–head' regioselectivity may be rationalized by considering that attack at the  $\gamma$ -position of radical **B** leads to the most stabilized carbonyl conjugated  $\alpha$ -silyloxy radical **C**. Radical **C** is probably formed through a transition state less



Scheme 2



Scheme 3

**Table 1** Oxidative cyclization of 1,3-bis(trimethylsilyloxy)buta-1,3-dienes **3**

<b>4</b>	R <sup>1</sup>	R <sup>2</sup>	yield (%) <sup>a</sup>
<b>a</b>	H	OEt	56
<b>b</b>	H	OMe	55
<b>c</b>	H	O( <i>i</i> -Pr)	52
<b>d</b>	H	O(CH <sub>2</sub> ) <sub>2</sub> OMe	54
<b>e</b>	H	O( <i>i</i> -Bu)	54
<b>f</b>	H	O( <i>t</i> -Bu)	26
<b>g</b>	H	OCH <sub>2</sub> Ph	41
<b>h</b>	H	Me	28
<b>i</b>	Me	OMe	38
<b>j</b>	Et	OEt	41
<b>k</b>	OMe	OMe	29
<b>l</b>	CO <sub>2</sub> Me	Me	18

<sup>a</sup> Isolated yields.

energetic than that leading to the respective unconjugated  $\alpha$ -silyloxy radical (by attack of the central carbon atom of intermediate **B** onto **3a**), assuming the addition step possesses a substantial product-like character. This suggestion is supported by the regioselectivity observed for the alkoxy radical catalyzed auto-oxidation of 1,4-dienes.<sup>12</sup> It is noteworthy, that the open-chain dimer **2** was isolated as a side-product in low yield. This result supports the assumption that bis-silyl enol ether **D** represents an intermediate of the reaction.

In order to study the preparative scope of our new cyclization reaction, the substituents of the 1,3-bis(trimethylsilyloxy)buta-1,3-dienes were systematically varied (Table 1). Oxidation of the dienes derived from ethyl-, methyl-, iso-propyl-, methoxyethyl-, iso-butyl-, *tert*-butyl- and benzyl acetoacetate afforded the corresponding ester-substituted 1,4-dihydroquinones **4a–g** with very good regioselectivities. Dimerization of the diene derived from acetylacetone afforded 2,3-diacetyl-1,4-dihydroquinone (**4h**). Oxidation of the 1,3-bis(trimethylsilyloxy)buta-1,3-dienes derived from methyl 3-oxopentanoate and ethyl 3-oxohexanoate afforded the 1,4-dihydroquinones **4i–j** containing two ester groups at carbons C-2 and C-3 and two alkyl groups at carbons C-5 and C-6. Oxidation of the 1,3-bis(trimethylsilyloxy)buta-1,3-diene derived from methyl 4-methoxyacetoacetate resulted in formation of the highly functionalized 1,4-dihydroquinone **4k**. Reaction of the diene derived from methyl 3,5-dioxohexanoate afforded the highly functionalized 1,4-dihydroquinone **4l**.

In summary, we have developed the first oxidative cyclizations of 1,3-bis(trimethylsilyloxy)buta-1,3-dienes which represent electroneutral 1,3-dicarbonyl dianion synthons. Currently, we are studying the mechanism and preparative scope of the new transformation.

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## Notes and references

† Preparation of 1,4-dihydroquinone **4a**. To a thoroughly degassed CH<sub>3</sub>CN solution (25 ml) of NaHCO<sub>3</sub> (15.3 mmol, 12 eq., 1.29 g) and CAN (7.65

mmol, 6 eq., 4.20 g) was slowly added a CH<sub>3</sub>CN solution (2 ml) of 1,3-bis(trimethylsilyloxy)buta-1,3-diene **3a** (2.55 mmol, 2 eq., 0.7 g) at –45 °C. The temperature of the reaction mixture was allowed to rise to 20 °C during 2 h. After stirring for 1 h at 20 °C a saturated aqueous solution of brine was added, the organic layer was separated and the aqueous layer was repeatedly extracted with ether. The combined organic extracts were dried (MgSO<sub>4</sub>), filtered and the solvent of the filtrate was removed *in vacuo*. The residue was purified by column chromatography (silica gel, ether–petrol ether = 1 : 1; (CDCl<sub>3</sub>, 250 MHz)  $\delta_{\text{H}}$  1.34 (t, 6 H, *J* = 7, CH<sub>3</sub>), 4.34 (q, 4 H, *J* = 7, OCH<sub>2</sub>), 7.07 (s, 2 H, CH), 8.85 (s, 2 H, OH); (CDCl<sub>3</sub>, 62.5 MHz)  $\delta_{\text{C}}$  13.98, 62.01, 112.66, 123.83, 152.29, 168.98; MS (70 eV) 254 (22, M<sup>+</sup>), 208 (40), 180 (100), 162 (58); *Anal.* calcd. for C<sub>12</sub>H<sub>14</sub>O<sub>6</sub>: C, 56.69; H, 5.55. Found: C, 56.42; H, 5.68. All compounds were characterized by spectroscopic methods and gave correct elemental analyses and/or high resolution mass spectra.

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