

Synthesis of functionalized 4-chlorophenols and 1,4-dihydroquinones by [3+3] cyclization of 1,3-bis-silyl enol ethers with 2-chloro- and 2-acyloxy-3-(silyloxy)alk-2-en-1-ones

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Abstract—Functionalized 4-chlorophenols and 1,4-dihydroquinones were prepared by [3+3] cyclization of 1,3-bis-silyl enol ethers with 2-chloro- and 2-acyloxy-3-(silyloxy)alk-2-en-1-ones.
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1,4-Dihydroquinones and 4-chlorophenols occur in a number of natural products, for example, in the natural product belamcandol A.^{1–3} They have found many technical and medicinal applications and represent important synthetic building blocks. 2-Alkoxyacetyl- and 2-acyl-1,4-dihydroquinones also occur in natural products, for example, in methoxymicareic acid (Chart 1);⁴ 2-alkoxyacetyl- and 2-acyl-4-chlorophenols are found, for example, in the natural product chloratranorin (Chart 2).¹ Some years ago, Chan and co-workers reported an elegant approach to salicylates based on [3+3] cyclizations^{5,6} of 1,3-bis-silyl enol ethers;⁷ the latter can be regarded as electroneutral equivalents of 1,3-dicarbonyl dianions. Herein, we report the synthesis of functionalized 4-chlorophenols and 1,4-dihydroquinones by what are, to the best of our knowledge, the first [3+3] cyclizations of 1,3-bis-silyl enol ethers with novel 2-chloro- and 2-acyloxy-3-(silyloxy)alk-2-en-1-ones, respectively. These transformations are of synthetic usefulness, since they offer a convenient approach to mono-protected 1,4-dihydroquinones without the need of regioselective protective group manipulations. Likewise, the functionalized 4-chlorophenols prepared are not readily available by other methods, since the classic approach, based on aromatic chlorinations, suffers from low regioselectivities and yields.

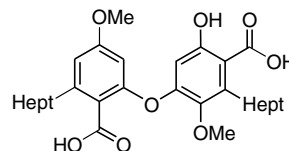


Chart 1. Methoxymicareic acid.

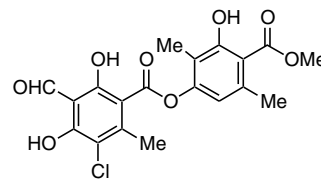
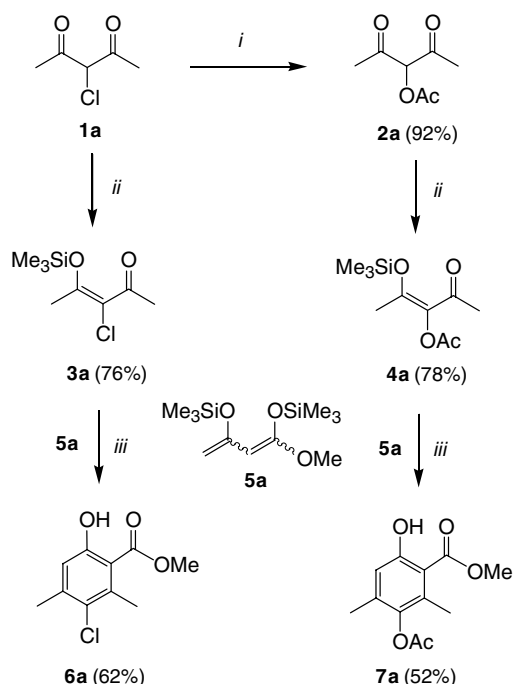


Chart 2. Chloratranorin.

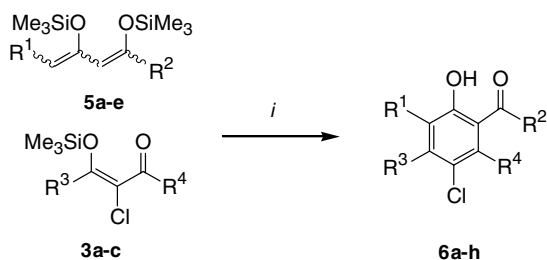
2-Chloro-1,3-diketones, such as **1a**, are readily available by reaction of 1,3-diketones with *N*-chlorosuccinimide (NCS).⁸ The reaction of **1a** with sodium acetate afforded, following a known procedure,⁹ 2-acetoxypentane-2,4-dione (**2a**). The reaction of **1a** with Me₃SiCl/NEt₃ afforded 2-chloro-3-(silyloxy)alk-2-en-1-one **3a**.¹⁰ Likewise, the novel 2-acetoxy-3-(silyloxy)alk-2-en-1-one **4a** was prepared from **2a**. The TiCl₄ mediated [3+3] cyclization of **3a** with 1,3-bis-silyl enol ether **5a** afforded the desired 4-chlorosalicylate **6a** without extrusion of the chloride group (Scheme 1). The cyclization of **5a** with 2-acetoxy-3-(silyloxy)alk-2-en-1-one **4a** was equally successful and gave the desired 4-acetoxysalicylate **7a**

Keywords: Cyclization; Dihydroquinones; Phenols; Silyl enol ethers.

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Scheme 1. Synthesis of **5a**. Reagents and conditions: (i) NaOAc, DMSO, 3 h, 20 °C; (ii) Me₃SiCl, NEt₃, C₆H₆, 20 °C, 3 d; (iii) TiCl₄, CH₂Cl₂, -78→20 °C, 20 h.



Scheme 2. Synthesis of **6a-h**. Reagents and conditions: (i) TiCl₄, CH₂Cl₂, -78→20 °C, 20 h.

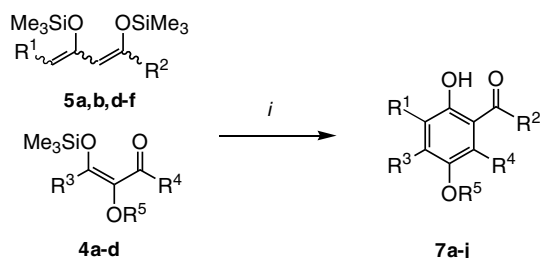
without extrusion of the acetoxy group or cleavage of the acetyl group.

The reaction of 2-chloro-3-(silyloxy)alk-2-en-1-one **3a** with **5b** and **5c**, prepared from acetylacetone and benzoylacetone, afforded the 2-acetyl- and 2-benzoyl-4-chlorophenols **6b** and **6c**, respectively (Scheme 2 and Table 1). The cyclization of **3a** with **5d** and **5e**, prepared

Table 1. Products and yields

6	R ¹	R ²	R ³	R ⁴	Yield (%) ^a
a	H	OMe	Me	Me	62
b	H	Me	Me	Me	50
c	H	Ph	Me	Me	44
d	Me	OEt	Me	Me	55
e	Et	OEt	Me	Me	56
f	H	OMe	Et	Et	52
g	Et	OEt	Et	Et	54
h	Me	OEt	Ph	Me	51

^a Isolated yields.



Scheme 3. Synthesis of **7a-j**. Reagents and conditions: (i) TiCl₄, CH₂Cl₂, -78→20 °C, 20 h.

from ethyl 3-oxopentanoate and ethyl 3-oxohexanoate, gave the 4-chlorosalicylates **6d** and **6e**. The cyclization of **5a** and **5e** with **3b**, prepared from 4-chloroheptane-3,5-dione (**1b**), afforded **6f** and **6g**. The cyclization of **5d** with **3c**, prepared from 3-chlorobenzoylacetone (**1c**), resulted in regioselective formation of **6h**.

The reaction of 2-acetoxy-3-(silyloxy)alk-2-en-1-one **4a** with 1,3-bis-silyl enol ether **5b** afforded the 2-acetyl-4-(acetoxy)phenol **7b** (Scheme 3 and Table 2). The cyclization of **4a** with **5d** and **5e** gave the methyl- and ethyl-substituted 4-(acetoxy)salicylates **7c** and **7d**. The cyclization of **4a** with **5f**, prepared from methyl 4-(methoxy)acetoacetate, afforded the salicylate **7e** containing one free and two orthogonally protected hydroxyl groups. The cyclization of **5a,d** with **4b**, prepared from 4-(acetoxy)heptane-3,5-dione (**2b**), gave the 4-(acetoxy)salicylates **7f,g**. The cyclization of **5d** with **4c**, prepared from 3-(acetoxy)benzoylacetone (**2c**), resulted in regioselective formation of **7h**. The cyclization of 1,3-bis-silyl enol ethers **5a,e** with 3-(benzoyloxy)acetylacetone (**4d**) afforded the *O*-benzoyl-protected 1,4-dihydroquinones **7i,j**.

First results indicate that 1,4-dihydroquinones **7** can be readily deprotected and oxidized to the corresponding functionalized 1,4-quinones. The free hydroxy group can be functionalized by Suzuki reaction via the corresponding enol triflates.

We have reported a new approach to the functionalized 4-chlorophenols and 1,4-dihydroquinones based on [3+3] cyclizations of 1,3-bis-silyl enol ethers with novel 2-chloro- and 2-acyloxy-3-(silyloxy)alk-2-en-1-ones.

Table 2. Products and yields

7	R ¹	R ²	R ³	R ⁴	R ⁵	Yield (%) ^a
a	H	OMe	Me	Me	Ac	52
b	H	Me	Me	Me	Ac	55
c	Me	OEt	Me	Me	Ac	55
d	Et	OEt	Me	Me	Ac	54
e	OMe	OMe	Me	Me	Ac	50
f	H	OMe	Et	Et	Ac	51
g	Me	OEt	Et	Et	Ac	73
h	H	OMe	Ph	Me	Ac	43
i	Et	OEt	Ph	Me	Ac	37
j	H	OMe	Me	Me	Bz	55
k	Et	OEt	Me	Me	Bz	46

^a Isolated yields.

Currently, we study the preparative scope and synthetic applications of these transformations.

General procedure for the synthesis of 4-chloro- and 4-hydroxysalicylates: To a CH_2Cl_2 solution (15 mL) of 1,3-bis-silyl enol ether **5** (7.67 mmol) and 3-(silyloxy)alk-2-en-1-one **3** or **4** (7.67 mmol) was added TiCl_4 (7.67 mmol) at -78°C under argon atmosphere. The temperature of the reaction mixture was allowed to rise to 20°C during 20 h and, subsequently, a saturated aqueous solution of NaHCO_3 (20 mL) was added. The organic layer was separated and extracted with diethyl ether (3×30 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-heptane/EtOAc).

Compound 6a: Starting with **5a** (2.00 g, 7.67 mmol), **3a** (1.58 g, 7.67 mmol) and TiCl_4 (0.85 mL, 7.67 mmol), **6a** was isolated as a colourless solid (1.01 g, 62%), mp $59-60^\circ\text{C}$; ^1H NMR (250 MHz, CDCl_3): $\delta = 2.35$ (s, 3H, CH_3), 2.60 (s, 3H, CH_3) 3.96 (s, 3H, OCH_3), 6.76 (s, 1H, ArH), 10.83 (s, 1H, OH); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 19.90$, 21.90, 52.36 (CH_3), 111.96 (C), 117.41 (CH), 126.82, 137.92, 143.63, 159.98, 171.39 (C); IR (KBr): $\tilde{\nu} = 3426$ (w), 3000 (w), 2952 (s), 2874 (m), 1663 (s), 1603 (s), 1564 (s), 1449 (s), 1381 (m), 1358 (s), 1310 (s), 1229 (s), 1190 (s), 1104 (m), 943 (m) cm^{-1} ; MS (EI, 70 eV): *m/z* (%): 214 (M^+ , 88), 184 (100), 154 (61), 91 (64); elemental analysis: calcd (%) for $\text{C}_{10}\text{H}_{11}\text{O}_3\text{Cl}$ (214.65): C 55.95, H 5.16; found: C 55.97, H 5.12. All compounds were characterized by spectroscopic methods and gave correct elemental analyses and/ or high resolution mass data.

Compound 7e: Starting with **5f** (600 mg, 2.06 mmol), **4a** (476 mg, 2.06 mmol) and TiCl_4 (0.22 mL, 2.06 mmol), **7e** was isolated as a colourless solid (263 mg, 50%), mp $68-72^\circ\text{C}$; ^1H NMR (250 MHz, CDCl_3): $\delta = 2.10$ (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 11.16 (s, 1H, OH); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 10.86$, 15.42, 20.76, 52.71, 60.66 (CH_3), 111.62, 127.23, 131.57, 140.88, 145.31, 154.41, 169.54, 172.19 (C); IR (KBr): $\tilde{\nu} = 3501$ (w), 3009 (w), 2960 (w), 2937 (w), 1753 (s), 1660 (s), 1440 (s), 1352 (s), 1214 (s), 1071 (m), 1041 (m), 806 (m) cm^{-1} ; GC-MS (EI, 70 eV): *m/z* (%): 268 (M^+ , 10), 226 (17), 194 (100), 165 (38), 67 (46); HRMS

(EI, 70 eV): calcd for $\text{C}_{13}\text{H}_{16}\text{O}_6$ (M^+): 268.0941; found: 268.0942.

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