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The first 4-chloro-1,3-bis(trimethylsilyloxy)-1,3-diene and its application to the regioselective synthesis of chlorinated arenes

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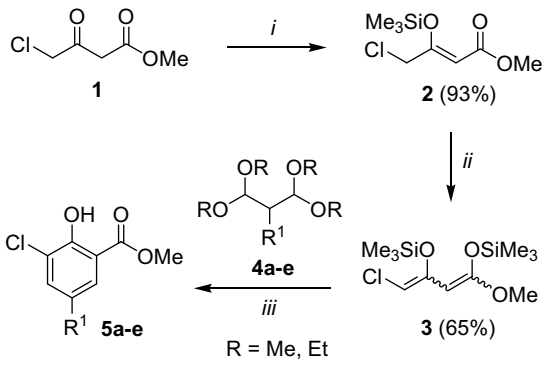
Abstract

Chlorinated phenols, benzophenones, and butenolides are prepared by various one-pot cyclization reactions of the first 4-chloro-1,3-bis(trimethylsilyloxy)-1,3-butadiene.

Keywords: Arenes; Chlorinated products; Cyclizations; Silyl enol ethers

Functionalized chloroarenes are of considerable pharmacological relevance[1] and represent increasingly important building blocks for transition metal-catalyzed cross-coupling reactions.[2] 3-Chlorosalicylates and related compounds are present in a variety of natural products. This includes, for example, dihydronidulin.[3] The spirocyclic griseofulvin[4] and epigriseofulvin[5] have been reported to show clastogenic, cytotoxic and antifungal activity. Polyketide-derived xanthones,[6] geodin[7] and geodin-hydrate-methyl ester[8] show, for example, antibacterial and antifungal activity. 7-Chloro-1-*O*-methylemodin has been reported to exhibit antiviral activity.[9] 3-Chlorosalicylates and related compounds are also present in simple arenes, acetophenones (longissiminone B), benzophenones (chloroisosulochrin, pestalone) and diaryl ethers (methyl chloroasterrate),[10] falconensin B,[11] natural chromones[12] and in 7-chloro-8-hydroxy-6-methoxy-3-methyl-isochroman-1-one.[13]

1,3-Bis(trimethylsilyloxy)-1,3-butadienes (e.g., Chan's diene)[14] represent important synthetic building blocks, which have been used in formal [3+2], [3+3], [4+2] and [4+3] cyclizations and various other transformations.[15,16] Herein, we report what is, to the best of our knowledge, the first synthesis of a chlorinated 1,3-bis(silyloxy)-1,3-butadiene and synthetic applications of this useful building block. The one-pot cyclizations reported herein provide a convenient and regioselective approach to various sterically encumbered, heavily substituted chlorinated products, which are not readily available by other methods. Classic syntheses of chloroarenes, based on direct chlorinations, suffer from many drawbacks, such as low regioselectivities and yields. In fact, the assembly of highly substituted and functionalized arenes can be a difficult task.



Scheme 1. Synthesis of **5a**–**e**. Reagents and conditions: (i) Me_3SiCl, NEt_3, C_6H_6, 20 °C, 72 h; (ii) (1) LDA, THF, −78 °C, 1 h, (2) Me_3SiCl, −78 → 20 °C; (iii) $TiCl_4$, CH_2Cl_2, −78 → 20 °C, 20 h.

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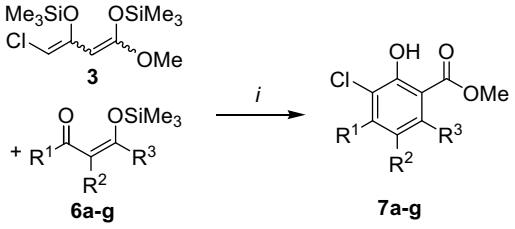
Table 1
Synthesis of 3-chlorosalicylates **5a–e**

4, **5**	R^1	**5**[a] (%)
a	H	30
b	Me	35
c	$CH(Me)_2$	36
d	$(CH_2)_4Me$	52
e	$(CH_2)_6Me$	30

[a] Yields of isolated products.

The silylation of commercially available methyl 4-chloroacetoacetate (**1**) gave 3-silyloxy-2-en-1-one **2** (Scheme 1). 4-Chloro-1-methoxy-1,3-bis(silyloxy)-1,3-butadiene (**3**) was prepared by the deprotonation (LDA) of **2** at −78 °C and subsequent addition of trimethylchlorosilane. Noteworthy, the chloro group proved to be compatible with the reaction conditions. Diene **3** can be stored at −20 °C under inert atmosphere for several weeks. The $TiCl_4$-mediated cyclization of 4-chloro-1,3-bis(silyloxy)-1,3-diene **3** with 1,1,3,3-tetramethoxypropane (**4a**) and 1,1,3,3-tetraethoxypropanes **4b–e**,[17] following a protocol reported by Chan[14] and by us,[18] afforded 3-chlorosalicylates **5a–e**. During the optimization of the reaction, the (high) concentration and the stoichiometry proved to be important parameters.[19] The Me_3SiOTf-catalyzed[20] (0.1 equiv) cyclization of **3** with **4a** also afforded **5a**, albeit, in low yield (see Table 1).

The $TiCl_4$-mediated [3+3] cyclization of 4-chloro-1,3-bis(silyloxy)-1,3-diene **3** with 3-silyloxy-2-en-1-ones **6a–g**, prepared by silylation of the corresponding 1,3-diketones, afforded 3-chlorosalicylates **7a–g** (Scheme 2, Table 2). During the optimization, it proved again to be important to carry out the reactions in a highly concentrated solution.[19]



Scheme 2. Synthesis of **7a–g**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78 → 20 °C, 20 h.

Table 2
Synthesis of 3-chlorosalicylates **7a–g**

6, **7**	R^1	R^2	R^3	**7**[a] (%)
a	Me	Me	Me	40
b	Me	H	Me	36
c	Me	Cl	Me	36
d	Et	H	Et	40
e	Me	Et	Me	44
f	Me	H	Ph	42
g	Me	–$(CH_2)_4$–		42[b]

[a] Isolated yields.
[b] Regioisomers.

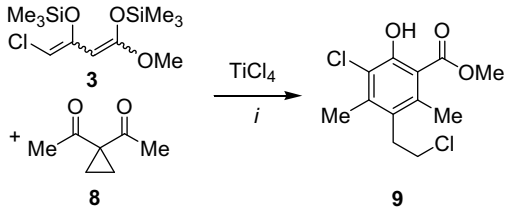
Noteworthy, product **7f** was formed with very good regioselectivity, which can be explained by $TiCl_4$-mediated isomerization of **6f**, conjugate addition by the attack of carbon atom C-4 of **3** onto **6f** and subsequent cyclization.[16]

The $TiCl_4$-mediated reaction of 1,3-bis(silyloxy)-1,3-diene **3** with 1,1-diacetylcyclopropane (**8**) afforded 3-chlorosalicylate **9** (30%) containing a remote chloride function (Scheme 3). The formation of the product can be explained by means of a domino '[3+3]-cyclization-homo-Michael' reaction.[21]

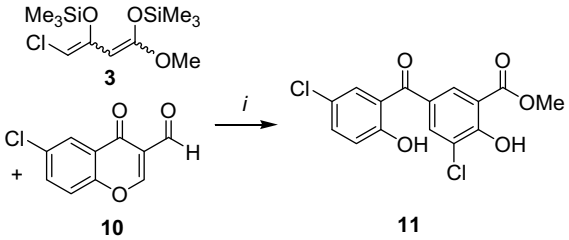
The Me_3SiOTf-catalyzed reaction of 1,3-bis(silyloxy)-1,3-diene **3** with 3-formylchromone (**10**) afforded the chlorinated 2,4′-dihydroxybenzophenone **11** in 33% yield (Scheme 4). The product is formed by a domino 'Michael–retro-Michael–Mukaiyama-Aldol' reaction.[22]

The $TiCl_4$-mediated reaction of 1,3-bis(silyloxy)-1,3-diene **3** with 1-methoxybut-1-en-3-one (**12**) afforded the 3-chlorosalicylate **13** (30%) (Scheme 5). The cyclization proceeded by conjugate addition of carbon atom C-4 of **3** onto **12** and subsequent Mukaiyama-Aldol reaction.

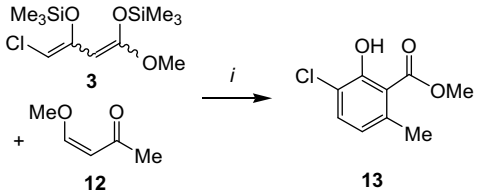
The Me_3SiOTf-catalyzed cyclization of 1,3-bis(silyloxy)-1,3-diene **3** with oxalyl chloride (**14**) afforded the chlorinated γ-alkylidenebutenolide **15** in 55% yield (Scheme 6).



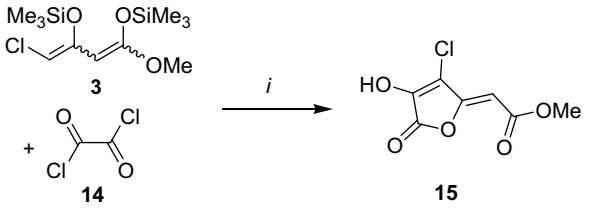
Scheme 3. Synthesis of **9**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78 → 20 °C, 20 h.



Scheme 4. Synthesis of **11**. Reagents and conditions: (i) (1) **10**, Me_3SiOTf (0.3 equiv), 20 °C, 10 min; (ii) **3** (1.3 equiv), CH_2Cl_2, 0 → 20 °C, 12 h; (3) HCl (10%).



Scheme 5. Synthesis of **13**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78 → 20 °C, 20 h.



Scheme 6. Synthesis of **15**. Reagents and conditions: (i) Me_3SiOTf (0.3 equiv), CH_2Cl_2, −78 → 20 °C, 20 h.

The formation of this product can be explained by the attack of carbon atom C-4 of **3** onto **14** and subsequent regioselective cyclization via the neighboured oxygen atom of **3**.[23] The exocyclic double bond was formed with high *Z*-diastereoselectivity (due to the steric influence of the chlorine atom).

In conclusion, a variety of highly substituted chlorinated arenes and hetarenes were regioselectively prepared by one-pot cyclizations of the first 4-chloro-1,3-bis(trimethylsilyloxy)-1,3-butadiene. The products are not readily available by other methods.

Acknowledgement

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19. *General procedure for the synthesis of salicylates* **5** *and* **7**: To a stirred CH_2Cl_2 solution of **3** (1.0 equiv) was added 1,1,3,3-tetraalkoxypropane **4a–e** (0.5 equiv) or 3-(silyloxy)alk-2-en-1-one **6a–g** (1.0 equiv) at −78 °C under argon atmosphere. Subsequently, $TiCl_4$ (1.0 equiv) was dropwise added. The temperature of the reaction mixture was allowed to rise to 20 °C during 20 h. The solution was poured into an aqueous solution of HCl (10%). The organic layer was separated and the aqueous layer was repeatedly extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography (silica gel, *n*-heptane/EtOAc) to give salicylates **5** or **7**. *Methyl 3-chloro-2-hydroxybenzoate* (**5a**): Starting with **3** (0.590 g, 2.0 mmol), 1,1,3,3-tetramethoxypropane (**4a**) (0.164 g, 1.0 mmol) and $TiCl_4$ (0.22 mL, 2.0 mmol) in CH_2Cl_2 (2 mL), **5a** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 20:1) as a yellow oil (0.074 g, 36%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.96$ (s, 3H, OCH_3), 6.83 (t, $^3J = 8.0$ Hz, 1H, CH), 7.54 (dd, $^2J = 1.7$ Hz, $^3J = 6.3$ Hz, 1H, CH), 7.76 (dd, $^2J = 1.7$ Hz, $^3J = 6.3$ Hz, 1H, CH), 11.33 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 52.7$ (OCH_3), 113.6 (C_{Ar}), 119.2 (CH), 122.2 (C_{Ar}), 128.4, 135.8 (CH), 157.3 (COH), 170.3 (*C*$OOCH_3$). IR (ATR, cm^{-1}): $\tilde{\nu} = 3090$ (w), 2955 (w), 2926 (w), 2853 (w), 1732 (w), 1675 (s), 1607 (m), 1438 (s), 1322 (s), 1282 (m), 1252 (s), 1197 (s), 1176 (s), 1151 (s), 1073 (m). MS (GC–MS, 70 eV): *m/z* (%) = 188 ($[M]^+$, [^{37}Cl], 11), 186 ($[M]^+$, [^{35}Cl], 33), 156 (34), 154 (100). Anal. Calcd for $C_{10}H_{11}ClO_3$ (214.65): C, 55.96; H, 5.17. Found: C, 55.72; H, 5.32. *Methyl 3-chloro-2-hydroxy-4,5,6-trimethylbenzoate* (**7a**): Starting with **3** (0.442 g, 1.5 mmol), 3-methyl-4-(trimethylsilyloxy)pent-3-en-2-one (**6a**) (0.279 g, 1.5 mmol) and $TiCl_4$ (0.16 mL, 1.5 mmol) in CH_2Cl_2 (3 mL), **7a** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 20:1) as a yellow oil (0.129 g, 38%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.17$ (s, 3H, CH_3), 2.38 (s, 6H, CH_3), 3.95 (s, 3H, OCH_3), 10.58 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.4$, 18.0, 18.9 (CH_3), 52.3 (OCH_3), 113.0, 119.9, 128.0, 135.8, 140.7 (C_{Ar}), 153.9 (COH), 171.5 (*C*$OOCH_3$). IR (ATR, cm^{-1}): $\tilde{\nu} = 2957$ (w), 2922 (w), 2851 (w), 1732 (m), 1660 (m), 1593 (w), 1496

(w), 1439 (m), 1333 (m), 1314 (m), 1257 (s), 1232 (s), 1198 (s), 1160 (s), 1077 (s), 1010 (s). MS (GC–MS, 70 eV): m/z (%) = 230 ([M]$^+$, [^{37}Cl], 8), 228 ([M]$^+$, [^{35}Cl], 24), 198 (35), 197 (28), 196 (100). HRMS (EI): calcd for $C_{11}H_{13}ClO_3$ ([M]$^+$, [^{35}Cl]) 228.05477, found: 228.05463.

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