Regioselective Synthesis of Functionalized Resorcins by Cyclization of 1,3-Bis(trimethylsilyloxy)-1,3-butadienes with 3,3-Dimethoxypentanoyl Chloride

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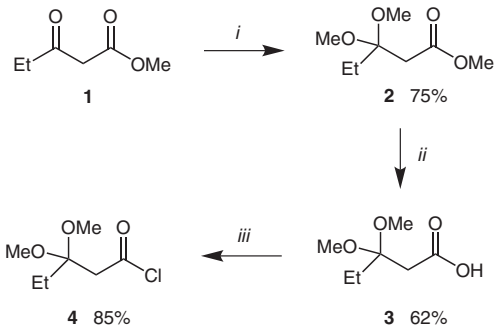
Abstract: Functionalized resorcins are regioselectively prepared by cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3,3-dimethoxypentanoyl chloride. The regioselectivity is controlled by the type of Lewis acid employed.

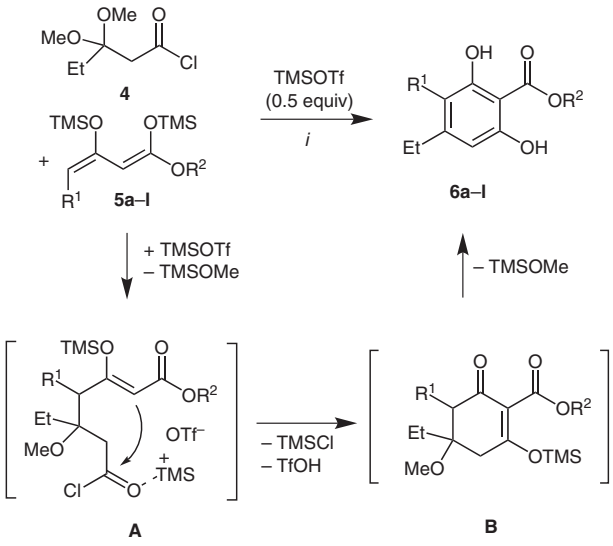
Key words: arenes, cyclizations, regioselectivity, silyl enol ethers

A great variety of pharmacologically important natural products are biosynthetically derived from poly(β-oxo)carboxylic acids (polyketides).[1] Harris and coworkers reported the biomimetic synthesis of various 1,3,5,7-tetracarbonyl compounds and their higher homologues based on condensations of 1,3-dicarbonyl dianions or 1,3,5-tricarbonyl trianions with esters and diesters, Weinreb amides, and salts of β-keto esters.[2] These products are unstable and rapidly undergo an intramolecular aldol condensation to give polyhydroxylated arenes present in many poylyketide-derived natural products. 1,3-Bis(trimethylsilyloxy)-1,3-butadienes can be regarded as electroneutral equivalents of 1,3-dicarbonyl dianions (masked dianions).[3,4] Chan and coworkers were the first to report the reaction of 1-methoxy-1,3-bis(trimethylsiloxy)-1,3-butadiene with acetyl chloride.[5] Salicylates were prepared by Lewis acid mediated [5+1] cyclization of 1-methoxy-1,3,5-tris(trimethylsiloxy)-1,3,5-hexatriene with acid chlorides and imidazolides.[6] We reported on the reaction of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with various acid chlorides.[7,8] γ-Alkylidenebutenolides are available by cyclization of 1,3-bis(silyl enol ethers) with oxalyl chloride[9] and phthaloyl chloride.[10] Recently, we reported the synthesis of new 1,3,5,7-tetracarbonyl compounds by condensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with methyl malonyl chloride.[11] Herein, we report an efficient synthetic approach to functionalized resorcins based on what are, to the best of our knowledge, the first formal [3+3] cyclizations of 1,3-bis(silyl enol ethers) with 3,3-dimethoxypentanoyl chloride.[12]

3,3-Dimethoxypentanoyl chloride was prepared in three steps as shown in Scheme 1. The TMSOTf-catalyzed reaction of **4** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **5a–l**, prepared from the corresponding β-keto esters,[3] afforded the 6-hydroxysalicylates **6a–l** (Scheme 2, Table 1).[13] The best yields were obtained when 0.5 equivalents of TMSOTf were employed. The yield decreased when the amount of TMSOTf was reduced. The use of more Lewis acid (1.0 equiv) did not result in an increase of the yield. The formation of the products can be explained by regioselective attack of the terminal carbon atom of the **5a–l** onto the acetal and subsequent attack from the central carbon onto the acid chloride.



Scheme 1 Synthesis of **4**. *Reagents and conditions*: (*i*) $HC(OMe)_3$ (6.0 equiv), Amberlite IR 120$^+$; (*ii*) NaOH, H_2O, 12 h, 20 °C; (*iii*) $(COCl)_2$, C_6H_6, 2 h, reflux.



Scheme 2 Synthesis of **6a–l**. *Reagents and conditions*: (*i*) TMSOTf (0.5 equiv), CH_2Cl_2, –78 °C to 20 °C.

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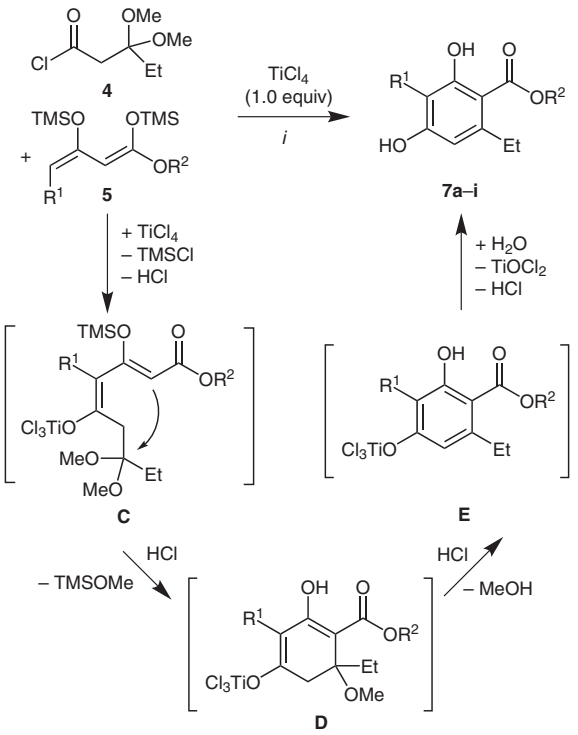
Table 1 Synthesis of **6a–l**

5, **6**	R^1	R^2	Yield of **6** (%)[a]
a	H	Me	43
b	H	Et	47
c	H	*i*-Pr	56
d	H	CH_2Ph	52
e	H	$(CH_2)_2OMe$	38
f	Me	Me	35
g	Et	Et	60
h	*i*-Bu	Me	40
i	*n*-Pr	Me	40
j	*n*-Bu	Et	50
k	Bn	Me	36
l	MeO	Me	34

[a] Yields of isolated products.

The $TiCl_4$-mediated reaction of **4** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **5** afforded the 4-hydroxysalicylates **7a–i** (Scheme 3, Table 2).[14] The formation of products **7** can be explained by regioselective attack of the terminal carbon atom of the 1,3-bis(trimethylsilyloxy)-1,3-butadiene onto the acid chloride and subsequent attack of the central carbon atom onto the acetal.



Scheme 3 Synthesis of **7a–i**. *Reagents and conditions*: (*i*) 1) $TiCl_4$ (1.0 equiv), CH_2Cl_2, –78 °C to 20 °C; 2) H_2O.

Table 2 Synthesis of **7a–i**

5	**7**	R^1	R^2	Yield of **7** (%)[a]
5a	**7a**	H	Me	61
5b	**7b**	H	Et	40
5d	**7c**	H	CH_2Ph	34
5e	**7d**	H	$(CH_2)_2OMe$	40
5f	**7e**	Me	Me	65
5h	**7f**	*i*-Bu	Me	66
5m	**7g**	*n*-Hex	Me	52
5n	**7h**	*n*-Hept	Me	57
5o	**7i**	*n*-Oct	Et	53

[a] Yields of isolated products.

In conclusion, functionalized resorcins were prepared by cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3,3-dimethoxypentanoyl chloride. The regioselectivity depends on the type of Lewis acid employed. The regioselectivity might be explained based on the HSAB principle. The acid chloride is selectively activated by the 'hard' Lewis acid $TiCl_4$. In contrast, TMSOTf is known to readily activate ketals and acetals, but not ketones and aldehydes.[7,15] On the other hand, acid chlorides are readily activated by TMSOTf.[3,7,9] The observed selectivity in favor of the activation of the ketal (rather than the acid chloride) might again be explained based on the HSAB principle.

Acknowledgment

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(12) (a) Some years ago, an isolated example of the cyclization of a protected β-keto ester was reported, see ref. 12b. In the case of **2**, this reaction failed to give the desired product (formation of a complex mixture). An isolated reaction of a 1,3-dioxolan-protected β-keto acid chloride was also reported by Chan and Chaly. However, in our hands, the use of the dioxolan group proved to be disadvantageous in order to isolate the desired product in pure form. (b) Chan, T. H.; Chaly, T. *Tetrahedron Lett.* **1982**, *23*, 2935.
(13) **Typical Procedure for the Synthesis of 6a-l**
To a CH_2Cl_2 solution (8 mL) of 1,3-bis(trimethylsilyloxy)-1-methoxy-1,3-butadiene (**5a**, 860 mg, 3.32 mmol) and of **4** (660 mg, 3.65 mmol) was dropwise added TMSOTf (0.3 mL, 1.66 mmol, 0.5 equiv) at –78 °C. The reaction mixture was allowed to warm to 20 °C during 6–12 h. After stirring for additional 2–6 h at 20 °C, HCl (10%, 25 mL) was added. The organic and the aqueous layers were separated and the latter was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($NaSO_4$), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (SiO_2, heptanes–EtOAc) to give **6a** as yellow solid (280 mg, 43%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (t, 3 H, *J* = 7.6 Hz, CH_3), 2.48 (q, 2 H, *J* = 7.5 Hz, CH_2), 3.99 (s, 3 H, OCH_3), 6.28 (s, 2 H, CH_{Ar}), 9.54 (s, 2 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_3), 29.2 (CH_2), 52.7 (OCH_3), 97.7 (C), 107.8 (CH), 154.6,164.5, 169.8 (C). IR (KBr): 3427 (s), 2960 (s), 1670 (s), 1571 (s), 1377 (m), 1257 (s), 1103 (s), 1040 (m), 949 (m), 846 (s)799 (s), 738 (s), 613 (s), 531 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 196.0(35) [M$^+$], 164.0(100), 136.0(21), 121.0(27). Anal. Calcd for $C_{10}H_{12}O_4$ (196.07): C, 61.22; H, 6.16. Found: C, 61.32; H, 6.11.
(14) **Typical Procedure for the Synthesis of 7a–i**
To a CH_2Cl_2 solution (5 mL) of 1,3-bis(trimethylsilyloxy)-1-methoxy-1,3-butadiene (500 mg, 1.91 mmol) and of **4** (385 mg, 2.11 mmol) was added dropwise $TiCl_4$ (0.21 mL, 1.91 mmol) at –78 °C. The reaction mixture was allowed to warm to 20 °C during 6–12 h. After stirring for additional 2–6 h at 20 °C, a sat. aq solution of $NaHCO_3$ (20 mL) was added. The organic and the aqueous layers were separated and the latter was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried ($NaSO_4$), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (SiO_2, heptane–EtOAc) to give **7a** as a yellow solid (230 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, 3 H, *J* = 7.5 Hz, CH_3), 3.28 (q, 2 H, *J* = 7.5 Hz, CH_2), 4.01 (s, 3 H, OCH_3), 6.08 (s, 1 H, CH_{Ar}), 6.78 (s, 1 H, CH_{Ar}), 12.06 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8 (CH_3), 28.8 (CH_2), 52.7 (OCH_3), 110.5, 116.0, 155.0, 166.0, 167.6, 170.5, 179.9. IR (KBr): 3427 (s), 2960 (s), 1670 (s), 1571 (s), 1377 (m), 1257 (s), 1103 (s), 1040 (m), 949 (m), 846 (s), 799 (s), 738 (s), 613 (s), 531 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 196.0(37) [M$^+$], 164.0(100), 136.0(26), 121.0(27). HRMS (EI): *m/z* calcd for $C_{10}H_{12}O_4$ [M]$^+$: 196.072572; found: 196.07301.
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