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Efficient Synthesis of Salicylates by Catalytic [3 + 3] Cyclizations of 1,3-Bis(silyl enol ethers) with 1,1,3,3-Tetramethoxypropane

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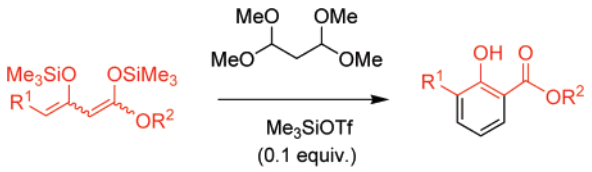

Salicylic acid derivatives were prepared by Me_3SiOTf-catalyzed [3 + 3] cyclization of 1,3-bis(silyl enol ethers) with 1,1,3,3-tetramethoxypropane.

Salicylic acid derivatives are widespread in nature and are of considerable relevance in medicinal chemistry.[1] Synthetic approaches to salicylates mainly rely on the functionalization of phenols by electrophilic substitutions. The preparative scope of this approach is often limited by the formation of regioisomeric mixtures and by the availability of the starting materials. Salicylates are also available by base-mediated cyclization reactions of dimethyl acetone-1,3-dicarboxylate (DMAD) with 1,3-diketones,[2] ynones, and ynals.[3] The scope of these transformations is limited by the fact that a symmetrical, highly activated 1,3,5-tricarbonyl compound has to be employed. Barton et al. reported the synthesis of ethyl 5-ethylsalicylate by cyclization of the dianion of ethyl acetoacetate with 3-(*N*,*N*-dimethylamino)-2-ethylacrolein.[4] Functionalized phenols are also available by [4 + 2] cycloaddition of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene),[5,6] 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (Chan's diene),[7] 1,4-di(methoxy)-1,3-bis(trimethylsilyloxy)-1,3-butadiene (Brassard's diene), or related dienes.[8]

The titanium tetrachloride ($TiCl_4$) mediated formal [3 + 3] cyclization of 1,3-bis(silyl enol ethers)[9] with 3-siloxy-2-en-1-ones provides a convenient approach to a variety of functionalized salicylates.[7a,b,10] In addition, $TiCl_4$-mediated cyclizations of 1,3-bis(silyl enol ethers) with 1,1,3,3-tetramethoxypropane and related bis(acetals) were reported.[7a,b,11,12] All of these transformations rely on the employment of stoichiometric amounts of Lewis acid. Herein, we report what are, to the best of our knowledge, the first *catalytic* [3 + 3] cyclizations of 1,3-bis(silyl enol ethers) with 1,1,3,3-tetramethoxypropane. These reactions provide a convenient approach to a variety of functionalized salicylates under mild conditions. Notably, the products are not directly and readily available by other methods.

The trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) catalyzed condensation of silyl enol ethers with acetals, introduced by Noyori et al.,[13] has found a number of applications in organic synthesis. Recently, we reported the Me_3SiOTf-catalyzed condensation of 1,3-bis(silyl enol ethers) with 1-chloro-2,2-dimethoxyethane[14] and 2-azido-1,1-dimethoxyethane, respectively.[15] The reaction of 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**1a**) with 1,1,3,3-tetramethoxypropane (**2**), in the presence of a catalytic amount of Me_3SiOTf (0.1 equiv), afforded ethyl 2-methoxybenzoate (**3a**) in up to 55% yield (Scheme 1, Tables 1 and 2). During the optimization (Table 1), the workup procedure (10% HCl), the temperature (−78 → 20 °C, 6−12 h; then 20 °C, 2−6 h), and the concentration (ca. 15 mL of CH_2Cl_2 per 1 mmol of **1a**) proved to be important parameters. The use of tetra*ethoxy*propane proved to be unsuccessful. The use of trifluoroacetic acid (rather than Me_3SiOTf) failed to give the desired product.

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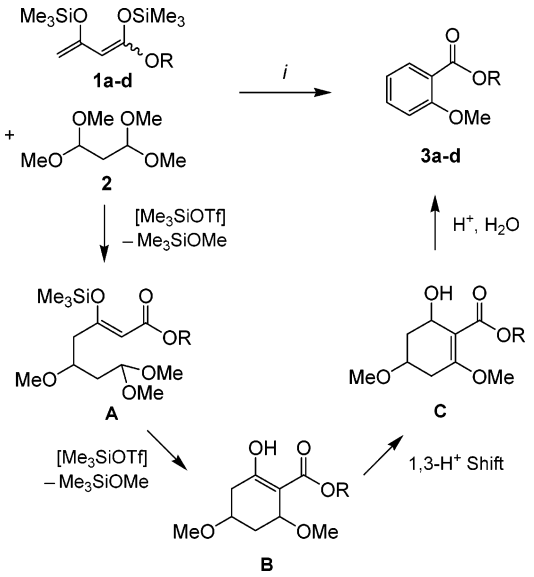
SCHEME 1. Cyclization of 1,3-Bis(silyl enol ethers) 1a−d with 1,1,3,3-Tetramethoxypropane[a]



[a] (i) Me_3SiOTf (0.1 equiv), CH_2Cl_2, −78 → 20 °C; (2) HCl (10%).

TABLE 1. Optimization of the Synthesis of 3a

entry	**1a**/**2**	Me_3SiOTf (equiv)	CH_2Cl_2[a]	workup	% (**3a**)[b]
1	1:1	0.3	2	$NaHCO_3$	32
2	1:1	0.3	15	$NaHCO_3$	35
3	1:1	0.3	15	10% HCl	54
4	1:1	0.3	50	10% HCl	45
5	1:1.1	0.1	15	10% HCl	55

[a] mL (CH_2Cl_2)/mmol (**1a**). [b] Yields of isolated products.

TABLE 2. Synthesis of 3a−d

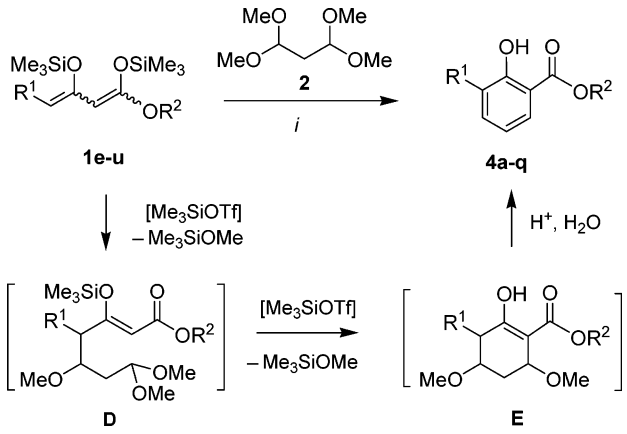
3	R	% (**3**)[a]
a	Et	55
b	Me	32
c	$(CH_2)_2OMe$	30
d	Bn	40

[a] Yields of isolated products

The Me_3SiOTf-catalyzed cyclization of **2** with 1,3-bis(silyl enol ethers) **1a**−**d**, prepared from ethyl, methyl, methoxyethyl, and benzyl acetoacetate, afforded the 2-methoxybenzoates **3a**−**d**. Their formation can be explained by the mechanism depicted in Scheme 1: the Me_3SiOTf-catalyzed attack of the terminal carbon atom of **1** onto **2** gave intermediate **A**. The subsequent Me_3SiOTf-catalyzed cyclization afforded intermediate **B**, which underwent a shift of the double bond to give intermediate **C**. Extrusion of water and methanol from **C** afforded the final product. Notably, the formation of a 2-hydroxybenzoate was not observed, which shows that water rather than methanol was selectively eliminated. This can be explained by the higher steric hindrance of the methoxy compared to the hydroxy group and the better leaving group ability of the latter. The mechanism is supported by the isolation of a small amount of 3,5-dimethoxycyclohexanone. The formation of this side product can be explained by cleavage of the ester group of intermediate **B** and subsequent decarboxylation.

The Me_3SiOTf-catalyzed cyclization of 1,3-bis(silyl enol ether) **1e**, prepared from ethyl 3-oxopentanoate, afforded ethyl 3-methylsalicylate (i.e., ethyl 3-methyl-2-hydroxybenzoate) (**4a**)

SCHEME 2. Cyclization of 1,3-Bis(silyl enol ethers) 1e-u with 1,1,3,3-Tetramethoxypropane[a]



[a] (i) (1) Me_3SiOTf (0.1 equiv), CH_2Cl_2, −78 → 20 °C; (2) HCl (10%).

TABLE 3. Synthesis of 4a−q

1	**4**	R^1	R^2	% (**4**)[a]
e	**a**	Me	Et	45
f	**b**	Et	Et	40
g	**c**	*n*-Bu	Me	60
h	**d**	*i*-Bu	Me	45
i	**e**	*n*-Hex	Et	50
j	**f**	*n*-Hept	Me	59
k	**g**	*n*-Oct	Et	56
l	**h**	*n*-Dec	Et	54
m	**i**	$(CH_2)_6Cl$	Me	67
n	**j**	$(CH_2)_2CH{=}CH_2$	Me	63
o	**k**	CH_2Ph	Me	57
p	**l**	$(CH_2)_3Ph$	Me	61
q	**m**	OMe	Me	32
r	**n**	OH	Et	27[b]
s	**o**	PhS	Et	52
t	**p**	4-$(MeO)C_6H_4S$	Et	42
u	**q**	4-MeC_6H_4S	Et	40

[a] Yields of isolated products. [b] From **1r** (R^1 = O-*t*-Bu).

(Scheme 2, Table 3). Notably, the formation of ethyl 5-methyl-2-methoxybenzoate was *not* observed. The formation of **4a** can be explained, in analogy to the formation of **3a**−**d**, by attack of **1e** onto **2** to give intermediate **D** and subsequent cyclization to give **E** (which correspond to intermediates **A** and **B** shown in Scheme 1). Intermediate **E** undergoes a rapid extrusion of two molecules of methanol (rather than a shift of the double bond as discussed for the formation of **3a**−**d**). The change of the mechanism can be explained by the fact that the presence of the substituent R^1 seems to enhance the rate of the elimination of methanol from intermediate **E**. This can be rationalized by the assumption that the protonation and cleavage of the hydroxy group is sterically hindered by the presence of the neighboring methyl group, which results in selective elimination of methanol rather than water.

The Me_3SiOTf catalyzed cyclization of **2** with 1,3-bis(silyl enol ethers) **1f**−**u** afforded the salicylates **4b**−**q**. The cyclization of **2** with 1,4-di(methoxy)-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**1q**) gave salicylate **4m** containing a protected and a nonprotected hydroxy group. Ethyl 3-hydroxysalicylate (**4n**) was prepared from 1-ethoxy-4-(*tert*-butoxy)-1,3-bis(trimethylsiloxy)-1,3-butadiene (**1r**). The *tert*-butyl group was cleaved during the reaction. The Me_3SiOTf-catalyzed cyclization of **2** with 1,3-bis(silyl enol ethers) derived from 1,3-diketones (e.g., acety-

lacetone and benzoylacetone) proved to be unsuccessful (formation of complex mixtures). Most salicylates **3a**−**d** and **4a**−**q** were isolated in only moderate yields. This can be explained by the fact that not all of the 1,3-bis(silyl enol ether) was converted into product. Some amount of the corresponding β-ketoester, formed by hydrolysis of unreacted 1,3-bis(silyl enol ether) during the aqueous workup, was isolated as a side product.

In conclusion, a variety of salicylates were prepared by Me_3-SiOTf-catalyzed formal [3 + 3] cyclization of 1,3-bis(silyl enol ethers) with 1,1,3,3-tetramethoxypropane. The use of 1,3-bis-(silyl enol ethers) **1a**−**d**, containing no substituent at carbon atom C-4, resulted in the formation of 2-methoxybenzoates **3a**−**d**. The best yield was obtained for salicylate **3a**. The yields depend on the quality of the silyl enol ether and on the handling of each individual experiment. 2-Hydroxy- rather than 2-methoxybenzoates were generally formed when 1,3-bis(silyl enol ethers) **1e**−**u**, containing a substituent located at carbon atom C-4, were employed. The best yields were obtained for alkyl-, ω-chloroalkyl-, ω-phenylalkyl-, and thiophenoxy-substituted 1,3-bis(silyl enol ethers) **1g**,**i**−**p**,**s**. Most salicylates **3a**−**d** and **4a**−**q** were obtained in only moderate yields. However, the method reported provides a new and convenient approach to salicylates under mild conditions which is complementary to known syntheses of salicylates.

Experimental Section

General Comments. All solvents were dried by standard methods, and all reactions were carried out under an inert atmosphere. For ^{1}H and ^{13}C NMR spectra, the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O), or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60−200 mesh) was used. Melting points are uncorrected.

Typical Procedure for the Synthesis of Salicylates 3 and 4. To a CH_2Cl_2 solution (100 mL) of 1,3-bis(trimethylsilyloxy)-1-ethoxy-1,3-butadiene (2.00 g, 7.28 mmol) and of 1,1,3,3-tetramethoxypropane (1.32 mL, 8.01 mmol, 1.1 equiv) was dropwise added TMSOTf (0.11 mL, 0.73 mmol, 0.1 equiv) at −78 °C. The reaction mixture was warmed to 20 °C during 6−12 h. After the mixture was stirred for 2−6 h at 20 °C, an aqueous solution of HCl (10%, 50 mL) was added. The organic and aqueous layers were separated, and the latter was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptane/ethyl acetate).

Ethyl 2-Methoxybenzoate (3a). Starting with 1,3-bis(silyl enol ether) **1a** (2.00 g, 7.28 mmol), 1,1,3,3-tetramethoxypropane **2** (1.32 mL, 8.01 mmol, 1.1 equiv), and TMSOTf (0.11 mL, 0.73 mmol, 0.1 equiv), **3a** was obtained as a yellow oil (720 mg, 55%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.1 Hz, 3H, CH_3), 3.89 (s, 3 H, OCH_3), 4.35 (q, J = 7.1 Hz, 2H, OCH_2), 6.95−6.99 (m, 2H, Ar), 7.43−7.47 (m, 1H, Ar), 7.78 (dd, J = 7.8, 1.8 Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 56.0, 60.8, 112.0, 120.1, 120.5, 131.5, 133.3, 159.0, 166.1; IR (neat, cm^{-1}) $\tilde{\nu}$ = 1725 (s), 1601 (m), 1491 (s), 1436 (s), 1302 (s), 1252 (s), 1080 (m); MS (EI, 70 eV) m/z 180 (M^+, 24), 135 (100), 105 (20), 92 (20), 77 (38); HRMS (EI) calcd for $C_{10}H_{12}O_3$ 180.078678, found 180.07919.

Ethyl 2-Hydroxy-3-methylbenzoate (4a). Starting with 1,3-bis-(silyl enol ether) **1e** (2.00 g, 6.93 mmol), 1,1,3,3-tetramethoxypropane **2** (1.20 mL, 7.62 mmol, 1.1 equiv), and TMSOTf (0.11 mL, 0.69 mmol, 0.1 equiv), **4a** was obtained as a yellow oil (570 mg, 45%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, 3 H, J = 5.3 Hz, OCH_3), 2.13 (s, 3 H, CH_3), 4.25 (q, 2 H, J = 5.3 Hz, OCH_2), 6.63 (t, 1 H, J = 5.7 Hz, ArH), 7.16 (dd, 1 H, J = 1.5, 7.8 Hz, ArH), 7.56 (dd, 1 H, J = 1.2, 5.5 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 15.5, 61.2, 111.8, 118.3, 126.4, 127.3, 136.2, 160.0, 170.6; IR (neat, cm^{-1}) $\tilde{\nu}$ 3397 (m), 2985 (s), 1670 (s), 1616 (m), 1435 (m), 1290 (s), 1250 (s), 1148 (s), 1083 (s), 1027 (m), 879 (w), 755 (s); GC−MS (EI, 70 eV): m/z (%): 180.1 (M^+, 61), 134,1 (100), 106.1 (95), 77.1 (31); HRMS (EI) calcd for $C_{10}H_{12}O_3$ 180.077698, found 180.07810.

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Supporting Information Available: Experimental procedures, compound characterization, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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