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Regioselective Synthesis of 5-Alkylsalicylates, 5-Alkyl-2-hydroxy-acetophenones, and 5-Alkyl-2-hydroxy-benzophenones by [3 + 3] Cyclization of 1,3-Bis(silyl enol ethers) with 2-Alkyl-1,1,3,3-tetraethoxypropanes

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A variety of 5-alkylsalicylates, 5-alkyl-2-hydroxy-acetophenones, and 5-alkyl-2-hydroxy-benzophenones was regioselectively prepared by $TiCl_4$ mediated formal [3 + 3] cyclization of 1,3-bis(silyl enol ethers) with 2-alkyl-1,1,3,3-tetraethoxypropanes.

Functionalized phenols, such as salicylates, 2-hydroxy-acetophenones, or 2-hydroxy-benzophenones, represent important building blocks in organic[1] and medicinal[2] chemistry. The classic approach to functionalized acetophenones relies on multistage reactions starting with phenol. However, this approach can suffer from several drawbacks, such as low regioselectivity. For example, 5-ethyl-2-hydroxy-acetophenone is available by acylation and Fries rearrangement of phenol (formation of regioisomers),[3] reduction of the acetyl group,[4] and a second Fries rearrangement.[5] A second strategy for the synthesis of functionalized phenols relies on the Diels−Alder reaction of alkynes with appropriate 1,3-dienes (such as furans or fulvenones) and subsequent oxidation.[6] For example, methyl 5-ethylsalicylate is available by Diels Alder cycloaddition of 2-ethylfuran with methyl propiolate.[7] However, 2-alkylfurans are not readily available, and methyl propiolate is rather expensive. The formal [3 + 3] cyclization of 1,3-bis(silyl enol ethers)[8] with 1,3-dielectrophiles provides convenient access to substituted arenes.[9] Notably, most of these reactions rely on the employment of 3-silyloxyalk-2-en-1-ones as 1,3-dielectrophilic building blocks and allow the synthesis of 4,6-di- and 4,5,6-trisubstituted derivatives. Chan et al. reported the synthesis of methyl salicylate by the cyclization of 1-methoxy-1,3-bis-(trimethylsilyloxy)-1,3-butadiene with 1,1,3,3-tetramethoxypropane.[10] Herein, we wish to report a significant extension of this reaction by what are, to the best of our knowledge, the first [3 + 3] cyclizations of 1,3-bis(silyl enol ethers) with 2-alkyl-1,1,3,3-tetraethoxypropanes. These reactions allow a convenient and regioselective synthesis of salicylates, 2-hydroxy-acetophenones, and 2-hydroxy-benzophenones containing an alkyl chain located at carbon atom C-5. In contrast to the functionalization of benzene derivatives by electrophilic substitutions or by palladium(0)-catalyzed cross-coupling reactions, our approach relies on the formation of the benzene moiety. From a preparative viewpoint, substituted phenols can be regioselectively prepared, and the synthesis of functionalized benzene derivatives as starting materials is not required.

The general procedure for the formation of the known 2-alkyl-1,1,3,3-tetraethoxypropanes requires three steps as depicted in Scheme 1. In the first step, commercially available aldehydes **1a**−**h** were reacted with triethyl orthoformate in dry ethanol to give the appropriate acetals **2a**−**h** under acid catalysis (1 drop of concd H_2SO_4).[11] Following the procedure of Nerdel et al.,[12] the enol ethers **3a**−**h** were prepared by the elimination of EtOH from acetals **2a**−**h**. The next step involves the $BF_3{\cdot}OEt_2$ mediated reaction of these enol ethers with triethyl orthoformate to give the respective 2-alkyl-1,1,3,3-tetraethoxypropanes **4a**−**h**.[13] The synthesis of all precursors and intermediates was previously reported.[11−14]

1,3-Bis(silyl enol ethers) **5a**−**e** were prepared, as reported in the literature, from pentane-2,4-dione,[15] benzoylacetone,[15] heptane-3,5-dione,[16] methyl acetoacetate,[17] and ethyl acetoac-

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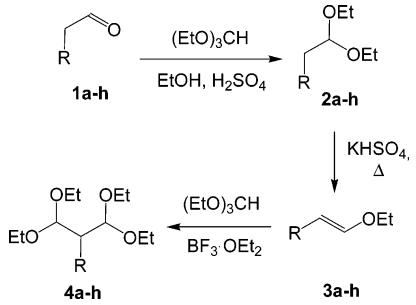
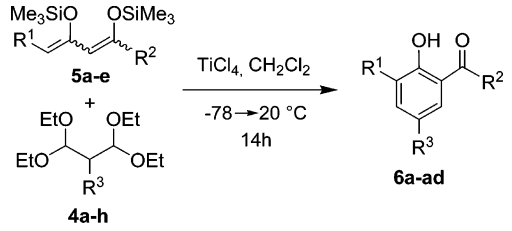
SCHEME 1. Preparation of Bis(acetals) 4a−h



SCHEME 2. Synthesis of 6a−ad



etate, respectively.[17] The $TiCl_4$ mediated cyclization of bis(acetals) **4b**−**h** with bis(silyl enol ethers) **5a** and **5b**, prepared from methyl and ethyl acetoacetate, afforded the 5-alkylsalicylates **6a**−**g** (Scheme 2and Table 1). The cyclization of bis(acetals) **4a**−**h** with bis(silyl enol ether) **5c**, prepared from acetylacetone, afforded 5-alkyl-2-hydroxy-acetophenones **6h**−**p**. 5-Alkyl-2-hydroxy-benzophenones **6q**−**w** were prepared from bis(silyl enol ether) **5d**, which was prepared from benzoylacetone. The reaction of bis(acetals) **4a**−**c** and **4e**−**h** with bis(silyl enol ether) **5e**, prepared from heptane-3,5-dione, gave 5-alkyl-2-hydroxy-3-methyl-propiophenones **6x**−**ad**.

The formation of product **6a** can be explained by the $TiCl_4$ mediated generation of an oxonium ion from bis(acetal) **4a**, attack of the terminal carbon atom of 1,3-bis(silyl enol ether) **5a** onto the oxonium ion, and extrusion of trimethylchlorosilane to give intermediate **A** (Scheme 3). Activation of the second acetal group and subsequent cyclization via the central carbon atom of the 1,3-dicarbonyl moiety afforded intermediate **B**. Aqueous workup, using hydrochloric acid (10%), resulted in the elimination of 2 equiv of ethanol to give the final product **6a**.

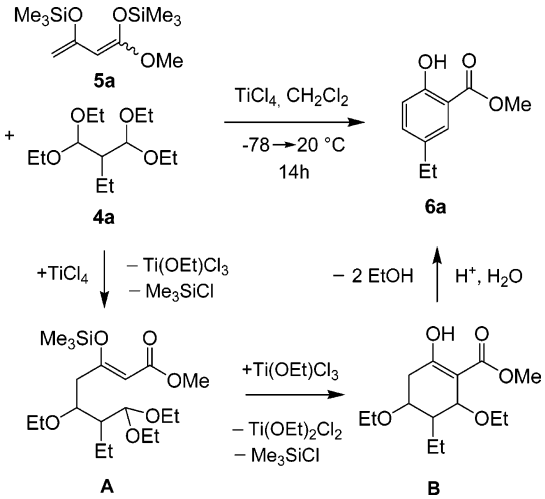
Products **6a**−**ad** were isolated in the range of 22−63% yield. The low yields can be explained by decomposition and hydrolysis of the starting materials and by side reactions, such as $TiCl_4$ mediated oxidative dimerization of the 1,3-bis(silyl enol ether). The best protocol for the cyclizations is similar to the typical procedure previously reported for related [3 + 3] cyclizations.[9] The stoichiometry of the starting materials and reagents played an important role. In contrast to other [3 + 3] cyclizations, the best results were obtained when an excess of

TABLE 1. Synthesis of 6a−ad

4	5	6	R^1	R^2	R^3	% (**6**)[a]
b	**a**	**a**	H	OMe	Et	51
c	**b**	**b**	H	OEt	*n*-Pr	50
d	**b**	**c**	H	OEt	*i*-Pr	36
e	**a**	**d**	H	OMe	*n*-Bu	35
f	**b**	**e**	H	OEt	*n*-Pent	36
g	**a**	**f**	H	OMe	*n*-Hex	34
h	**b**	**g**	H	OEt	*n*-Hept	34
a	**c**	**h**	H	Me	Me	55
b	**c**	**i**	H	Me	Et	36
c	**c**	**k**	H	Me	*n*-Pr	58
d	**c**	**l**	H	Me	*i*-Pr	22
e	**c**	**m**	H	Me	*n*-Bu	36
f	**c**	**n**	H	Me	*n*-Pent	45
g	**c**	**o**	H	Me	*n*-Hex	54
h	**c**	**p**	H	Me	*n*-Hept	45
a	**d**	**q**	H	Ph	Me	48
b	**d**	**r**	H	Ph	Et	31
c	**d**	**s**	H	Ph	*n*-Pr	55
e	**d**	**t**	H	Ph	*n*-Bu	43
f	**d**	**u**	H	Ph	*n*-Pent	43
g	**d**	**v**	H	Ph	*n*-Hex	34
h	**d**	**w**	H	Ph	*n*-Hept	54
a	**e**	**x**	Me	Et	Me	61
b	**e**	**y**	Me	Et	Et	40
c	**e**	**z**	Me	Et	*n*-Pr	51
e	**e**	**aa**	Me	Et	*n*-Bu	38
f	**e**	**ab**	Me	Et	*n*-Pent	54
g	**e**	**ac**	Me	Et	*n*-Hex	32
h	**e**	**ad**	Me	Et	*n*-Hept	63

[a] Isolated yields.

SCHEME 3. Possible Mechanism for Formation of 6a



the 1,3-bis(silyl enol ether) was employed. The use of the Lewis acid trimethylsilyl-trifluoromethanesulfonate (Me_3SiOTf) rather than $TiCl_4$ proved to be unsuccessful. The high concentration of the solution (only 2 mL of solvent per 1 mmol of starting material) proved to be a very important parameter. The yields significantly decreased when the reactions were carried out in more dilute solutions. To guarantee a complete elimination of ethanol from intermediate **B**, hydrochloric acid (10%) was used for the aqueous workup. A general trend for the influence of the substitution pattern on the yield was not observed. The yields seem to mainly depend on the quality of the starting materials, reagents, and solvent and on the handling of each individual experiment.

In conclusion, a general method for the synthesis of 5-alkylsalicylates, 5-alkyl-2-hydroxy-acetophenones, and 5-alkyl-2-

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hydroxy-benzophenones by [3 + 3] cyclization of 1,3-bis(silyl enol ethers) with 2-alkyl-1,1,3,3-tetraethoxypropanes, based on an initial finding of Chan et al., was reported.

Experimental Section

Experimental details, analytical data, and spectra of compounds **6a**−**ad** can be found in the Supporting Information. All cyclization reactions were carried out in Schlenk tubes under an argon atmosphere using dried solvents and freshly distilled $TiCl_4$. The appropriate acetals, enol ethers, and substituted 1,1,3,3-tetraethoxypropanes were prepared as described in the literature.[11−14] For ^1H and ^{13}C NMR spectroscopy, the deuterated solvents indicated were used. Mass spectrometric (MS) data were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane), or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60−200 mesh) was used. Melting points are uncorrected.

General Procedure for the Synthesis of 6a−ad. To a CH_2Cl_2 solution (5 mL) of 1,3-bis(silyl enol ether) **5a**−**e** (2 equiv) and of the respective 2-alkyl-1,1,3,3-tetraethoxypropane **4a**−**h** (1 equiv) was added $TiCl_4$ (1 equiv) at −78 °C under argon atmosphere. The temperature of this mixture was allowed to rise to 20 °C during 14 h, and subsequently, an aqueous HCl solution (10%, 10 mL) was added. The organic layer was separated, and the residue was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by column cromatography (silica gel, *n*-heptane/EtOAc = 50:1 to 20:1).

5-Ethyl-salicylic Acid Methylester (6a). Following the general procedure, the starting materials 2-diethoxymethyl-1,1-diethoxybutane (**4b**) (0.500 g, 2.01 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**5a**) (1.11 g, 4.04 mmol), and $TiCl_4$ (0.22 mL, 2.01 mmol) in CH_2Cl_2 (4 mL) yielded **6a** as a yellow syrup (186 mg, 51%). R_f = 0.4 (*n*-heptane/EtOAc = 2:1). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3206 (w), 2964 (m), 1680 (s). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.21 (t, 3H, ^3J = 7.6 Hz, CH_2CH_3), 2.58 (q, 2H, ^3J = 7.6 Hz, CH_2CH_3), 3.94 (s, 3H, OCH_3), 6.91 (d, 1H, $^3J_{3,4}$ = 8.5 Hz, H-3), 7.30 (dd, 1H, $^3J_{3,4}$ = 8.5 Hz, $^4J_{4,6}$ = 2.2 Hz, H-4), 7.65 (d, 1H, $^4J_{4,6}$ = 2.2 Hz, H-6), 10.58 (s, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 15.7, 27.9, 52.2, 112.0, 117.4, 128.4, 134.9, 135.6, 159.7, 170.6. MS (EI, 70 eV): *m*/*z* (%) = 180 (M^+, 40), 148 (100), 133 (79), 105 (16), 91 (12), 77 (17), 32 (49). HRMS (EI, 70 eV): calcd. for $C_{10}H_{12}O_3$ (M^+): 180.0781; found: 180.0783.

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Supporting Information Available: General experimental procedures, including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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