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Synthesis of functionalized acetophenones by [3 + 3] cyclizations of 1,3-bis-silyl enol ethers with 2-acetyl-3-silyloxyalk-2-en-1-ones

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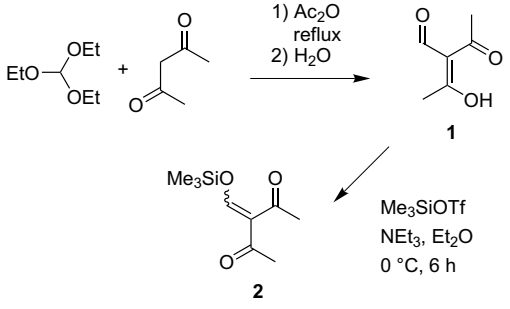
Abstract—The $TiCl_4$ mediated cyclization of 1,3-bis-silyl enol ethers with 2-acetyl-1-silyloxybut-1-en-3-one and 3-acetyl-4-silyloxypent-3-en-2-one, readily prepared from 3-formyl(acetylacetone) and triacetylmethane, afforded a variety of functionalized acetophenones.

Functionalized acetophenones are of considerable interest as synthetic building blocks and occur in a number of natural product analogues.[1] Some years ago, Chan and co-workers reported an elegant synthesis of salicylates by [3 + 3] cyclization of 1,3-bis-silyl enol ethers—electrneutral 1,3-dicarbonyl dianion equivalents[2,3]—with 1,1,3,3-tetramethoxypropane or 3-silyloxyalk-2-en-1-ones.[4] Herein, we wish to report the application of this methodology to the synthesis of functionalized acetophenones by [3 + 3] cyclizations of 1,3-bis-silyl enol ethers with 2-acetyl-3-silyloxyalk-2-en-1-ones.

3-Formylacetylacetone (**1**) was prepared according to a literature procedure by reaction of acetylacetone with triethyl orthoformate and acetic anhydride.[5] It was assumed for a long time that **1** exists as 3-(hydroxymethylidene)acetylacetone.[5,6] However, it was later shown that **1** mainly resides as 3-formyl-2-hydroxypent-2-en-4-one.[7,8] Reactions of **1** have only scarcely been reported in the literature.[5,8] Our first experiments related to the silylation of **1** were unsuccessful as the reaction of **1** with Me_3SiCl/NEt_3 resulted in the formation of a complex mixture. In contrast, treatment of an ether solution of **1** with Me_3SiOTf/NEt_3[9] afforded the 2-acetyl-1-silyloxybut-1-en-3-one **2** in 85% yield (Scheme 1). The synthesis of **2** has, to the best of our knowledge, not yet been reported and proceeded by regioselective silylation of the formyl rather than the acetyl group.



Scheme 1. Synthesis and silylation of **1**.

The $TiCl_4$ mediated [3 + 3] cyclization of 3-(silyloxymethylidene)acetylacetone (**2**) with 1,3-bis-silyl enol ether **3a**, readily available from methyl acetoacetate, afforded the functionalized acetophenone **4a** in reasonable yield (Scheme 2).[10] The regioselective formation of the product can be explained based on general observations reported by Chan:[3,4] conjugate addition of the terminal carbon atom of **3a** onto **2** gave intermediate **A** and subsequent cyclization and aromatization afforded the final product. The regioselective conjugate addition can be explained by coordination of the 1,3-diketo moiety of **2** with $TiCl_4$, which enhances the electrophilicity of the carbon atom attached to the silyloxy group.[4] Transmetallation and formation of a titanium enolate cannot be excluded.

Keywords: Acetophenones; Cyclizations; Regioselectivity; Silyl enol ethers.
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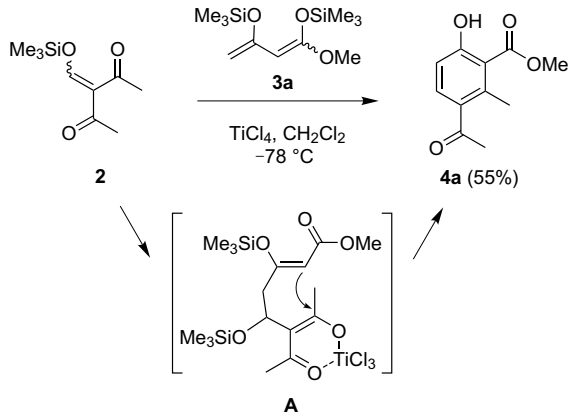
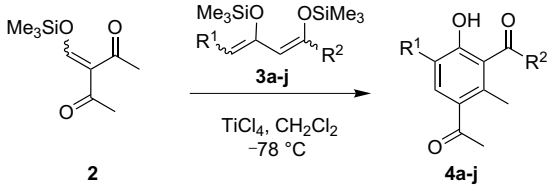


Scheme 2. Synthesis of salicylate **4a**.

The preparative scope was studied by systematic variation of the substituents of the 1,3-bis-silyl enol ether (Scheme 3, Table 1). The cyclization of **2** with **3b** and **3c**, derived from ethyl and benzyl acetoacetate, afforded the acetophenones **4b** and **4c** (Scheme 2). The cyclization of **2** with 2,4-bis(trimethylsilyloxy)-1,3-pentadiene (**3d**) afforded **4d**. Starting with 1,3-bis-silyl enol ethers **3e**–**h**, containing a substituent at the terminal carbon atom, afforded the methyl-, ethyl-, butyl- and allyl-substituted acetophenones **4e**–**h**, respectively. The cyclization of **2** with **3i**–**j** afforded the methoxy- and ethoxy-substituted acetophenones **4i**–**j**, respectively.

The cyclization of 1,3-bis-silyl enol ether **3a** with known[11] 3-acetyl-4-silyloxypent-3-en-2-one (**5**), prepared by treatment of triacetylmethane with Me_3SiOTf, afforded the functionalized acetophenone **6** (Scheme 4).

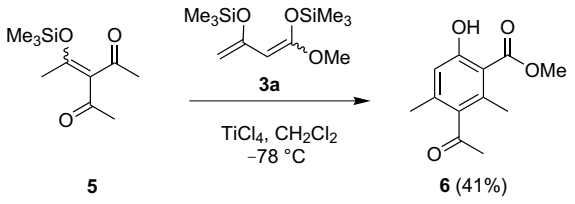


Scheme 3. Synthesis of salicylates **4a**–**j**.

Table 1. Products and yields

4	R^1	R^2	%[a]
a	H	OMe	55
b	H	OEt	40
c	H	OBn	33
d	H	Me	35
e	Me	OMe	72
f	Et	OEt	60
g	Bu	OMe	77
h	Allyl	OEt	74
i	OMe	OMe	35
j	OEt	OEt	30

[a] Yields of isolated products.



Scheme 4. Synthesis of salicylate **6**.

Acknowledgements

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References and notes

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10. *General procedure for the preparation of salicylates* **4**: To a stirred CH_2Cl_2 solution (4.5 mL) of 3-(silyloxymethylidene)acetylacetone (**2**) (206 mg, 1.03 mmol) was added $TiCl_4$ (0.13 mL, 1.18 mmol) at −78 °C under argon atmosphere in the presence of molecular sieves (4 Å) (0.4 g). Then 1,3-bis(trimethylsiloxy)-1-methoxy-1,3-pentadiene **3e** (418 mg, 1.52 mmol) was added. The temperature of the reaction mixture was allowed to rise to 20 °C during 20 h and was stirred for another 4 h. After addition of CH_2Cl_2 (50 mL) and removal of the molecular sieves, a saturated aqueous solution of $NaHCO_3$ (20 mL) was poured into the reaction mixture. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). Subsequently, an aqueous solution of HCl (10%, 10 mL) was added to the aqueous layer, which again was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexane/ethyl acetate = 10:1) to give **4e** (164 mg, 72%) as colourless crystals; $R_f = 0.51$ (hexane/ethyl acetate = 3:1); IR (KBr, cm^{-1}): $\tilde{\nu} = 3222$, (s, br), 3015 (m), 3001 (m), 2951 (m), 1733 (s), 1646 (s), 1560 (s), 1480 (m), 1439 (s), 1382 (m), 1362 (s), 1303 (s), 1244 (s), 1210 (s), 1149 (s), 1065 (m); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 11.31$ (s, 1H, OH), 7.47 (s, 1H, ArH), 3.98

(s, 3H, OCH_3), 2.57 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 2.25 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 201.85, 172.09, 161.70, 138.37, 134.64, 132.33, 123.77, 113.85, 52.36, 30.38, 19.76, 15.71; MS (EI, 70 eV): *m/z* (%) = 223.0 ($[M + 1]^+$, 6), 222.0 (M^+, 49), 191.0 (23), 190.0 (84), 175.0 (100), 161.9 (24), 91 (23); Anal. Calcd for $C_{12}H_{14}O_4$: C 64.85, H 6.35; found: C 64.94, H 6.28.

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