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Synthesis of phthalates and isophthalates by [3+3] cyclizations of 1,3-bis(silyl enol ethers) with 3-(silyloxy)alk-2-en-1-ones

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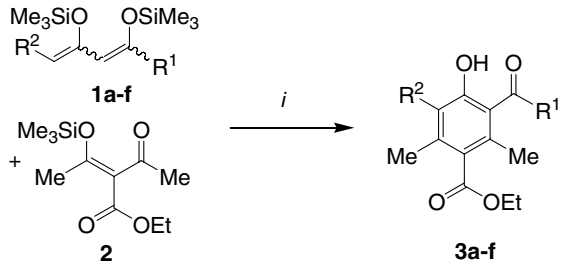
Abstract—3-Hydroxyphthalates and 4-hydroxyisophthalates were prepared by sequential [3+3] cyclization reactions of 1,3-bis(silyl enol ethers) with 2- and 3-alkoxycarbonyl-3-(silyloxy)alk-2-en-1-ones.

Phthalates[1] and isophthalates[2] occur in a number of pharmacologically relevant natural products and represent important synthetic building blocks. The synthesis of these compounds mainly relies on the oxidation of suitable benzene derivatives.[1,2] Some years ago, Chan and co-workers reported[3] an elegant approach to salicylates based on [3+3] cyclizations of 1,3-bis(silyl enol ethers).[4] We have recently reported the application of this methodology to the synthesis of a variety of functionalized arenes.[5] For example, we reported the synthesis of acetophenones by [3+3] cyclization of 1,3-bis(silyl enol ethers) with 2-acetyl-1-(silyloxy)but-1-en-3-one.[5a] Herein, we report, for the first time, the synthesis of 3-hydroxyphthalates and 4-hydroxyisophthalates by [3+3] cyclizations of 1,3-bis(silyl enol ethers) with 3- and 2-alkoxycarbonyl-3-(silyloxy)alk-2-en-1-ones, respectively. The products are not readily available by classic methods.

3-Ethoxycarbonyl-4-(silyloxy)alk-3-en-2-one (**2**) was prepared by silylation of ethyl 2-(acetyl)acetoacetate. The $TiCl_4$ mediated [3+3] cyclization of **2** with 1,3-bis(silyl enol ethers) **1a**–**d** afforded the novel functionalized isophthalates **3a**–**d** in moderate to good yields (Scheme 1, Table 1).[6] The 4-hydroxy-3-acylbenzoates **3e** and **3f** were prepared by cyclization of **2** with 1,3-bis(silyl enol ethers) **1e** and **1f** (available from acetylacetone and benzoylacetone), respectively.



Scheme 1. Synthesis of isophthalates **3a**–**f**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C.

Table 1. Products and yields

3	R^1	R^2	% (3)[a]
a	OMe	H	30
b	OMe	OMe	65
c	OEt	Me	48
d	OEt	Et	50
e	Me	H	40
f	Ph	H	36

[a] Yields of isolated products.

Methyl 4-oxo-2-(silyloxy)pent-2-enoate **4** was prepared by silylation of methyl acetopyruvate. The $TiCl_4$ mediated [3+3] cyclization of **4** with 1,3-bis(silyl enol ethers) **1a**,**b**,**d** afforded the novel functionalized phthalates **5a**–**c** (Scheme 2, Table 2). The 3-hydroxy-2-acylbenzoates **5d** and **5e** were prepared by cyclization of **4** with 1,3-bis(silyl enol ethers) **1e** and **1f**, respectively. Chan and co-workers proposed that [3+3] proceed by conjugate addition of the terminal carbon atom of the 1,3-bis(silyl

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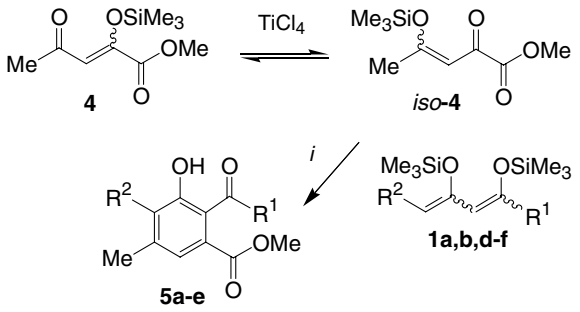

Scheme 2. Synthesis of phthalates **5a**–**e**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C.

Table 2. Products and yields

5	R^1	R^2	% (5)[a]
a	OMe	H	17
b	OMe	OMe	45
c	OEt	Et	22
d	Me	H	34
e	Ph	H	41

[a] Yields of isolated products.

enol ether) onto the 3-(silyloxy)alk-2-en-1-one and subsequent cyclization. The regioselective formation of **5a**–**e** can be explained by $TiCl_4$ mediated isomerization of **4** into *iso*-**4** and subsequent conjugate addition of the terminal carbon atom of the 1,3-bis(silyl enol ether) onto *iso*-**4**. The yield of pure **5a** is relatively low, since the regioisomeric product had to be separated (12% yield). In all reactions, 1,3-dicarbonyl compounds were isolated, which were formed by hydrolysis of the corresponding 1,3-bis-silyl enol ethers **1**. This result shows that the latter was not completely consumed during the reaction, which can be explained by partial decomposition or hydrolysis of silyl enol ethers **2** and **4**.

In conclusion, functionalized phthalates and isophthalates were prepared by [3+3] cyclizations of 1,3-bis(silyl enol ethers) with novel 3-(silyloxy)alk-2-en-1-ones.

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6. Typical procedure for the synthesis of phthalates **3** and isophthalates **5**: To a stirred CH_2Cl_2 solution (2.5 mL) of **2** (305 mg, 1.25 mmol) was added 1,3-bis(trimethylsilyloxy)-1,4-dimethoxy-1,3-pentadiene (**1b**) (363 mg, 1.25 mmol) at −78 °C under argon atmosphere. Subsequently, $TiCl_4$ (0.14 mL, 1.25 mmol) was 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 and the aqueous layer were separated and the latter was extracted (3×) with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-heptane/EtOAc = 9:1) to give **3b** as a yellow oil (230 mg, 65%). Silyl enol ethers **2** and **4** could not be prepared in pure form. They were used as crude material. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.39$ (t, $^3J = 7.3$ Hz, 3H, OCH_2CH_3), 2.23 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.97 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.38 (q, $^3J = 7.3$ Hz, 2H, OCH_2CH_3), 11.30 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.3$, 14.2, 19.8 (CH_3), 52.4, 60.1 (OCH_3), 61.3 (OCH_2CH_3), 111.8, 128.4, 131.7, 134.0, 144.7 (C_{Ar}), 156.1 (C–O), 169.5, 171.7 (O–C=O). IR (neat, cm^{-1}): $\tilde{\nu} = 3422$ (br, w), 2982 (m), 2957 (m), 2939 (m), 2838 (s), 1726 (s), 1683 (s), 1600 (m), 1578 (m). MS (EI, 70 eV): *m*/*z* (%) = 282 (M^+, 35), 250 (93), 237 (23), 222 (100), 205 (26), 194 (43). Anal. Calcd for $C_{14}H_{18}O_6$ (282.29): C, 59.57; H, 6.43. Found: C, 59.65; H, 6.44.