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Synthesis of 3,5-dioxoalkanoates, 3,5-dioxopimelates and 2,4-dioxoadipates by acylation of 1,3-bis-silyl enol ethers

Stefanie Reim,[a,b] Van Thi Hong Nguyen,[a] Uwe Albrecht[a] and Peter Langer[b,c,*]

[a]*Institut für Chemie und Biochemie, Universität Greifswald, Soldmannstr. 16, 17487 Greifswald, Germany*
[b]*Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany*
[c]*Leibniz-Institut für Organische Katalyse an der Universität Rostock e. V. (IfOK), Albert-Einstein-Str. 29a, 18059 Rostock, Germany*

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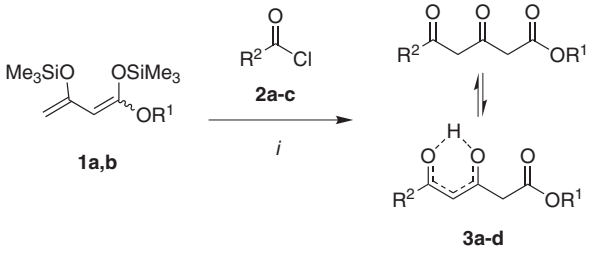
Abstract—3,5-Dioxoalkanoates, 3,5-dioxopimelates and 2,4-dioxoadipates were prepared by acylation of 1,3-bis-silyl enol ethers with carboxylic chlorides, methyl 3-chloro-3-oxopropanoate and ethyl 2-chloro-2-oxoacetate, respectively.

Poly(β-oxocarboxylic acids) occur in a variety of antibiotic natural products (polyketides) and represent important starting materials for the stereoselective synthesis of polyols.[1] Some years ago, Harris and co-workers developed elegant, biomimetic syntheses of poly-β-ketones and polyketides based on reactions of 1,3-dicarbonyl dianions with carboxylic esters and diesters.[2] From a structural viewpoint, 3,5-dioxopimelates are closely related to tetraketides. Despite their potential synthetic usefulness, 3,5-dioxopimelates have only rarely appeared in the literature so far: Robertson and Sandrock reported the synthesis of diethyl 2,2-diethyl-3,5-dioxopimelate by reaction of ethyl 3-chloro-3-oxo-2,2-dimethylpropionate with diethyl acetone-1,3-dicarboxylate.[3] Parent (unsubstituted) 3,5-dioxopimelates have not been prepared by this approach. Recently, the first approach to parent dimethyl 3,5-dioxopimelate has been reported by Kiegel et al.: the reaction of acetone, malonyl dichloride and ketene afforded a bis(dioxinone) which was transformed into the desired product by methanolysis (44% yield over two steps).[4] Herein, we report a new and convenient one-step synthesis of substituted and unsubstituted 3,5-dioxopimelates based on the acylation of 1,3-bis-silyl enol ethers, masked 1,3-dicarbonyl dianions,[5,6] with methyl 3-chloro-3-oxopropionate. In addition, we report what are, to the best of our knowledge, the first syntheses of parent (unsubstituted) 2,4-dioxoadipates by reaction of 1,3-bis-silyl enol ethers with ethyl 2-chloro-2-oxoacetate.[7]

Based on exploratory work of Chan and Brownbridge,[8] we first studied the reaction of 1,3-bis-silyl enol ethers with simple carboxylic chlorides.[9,10] The reaction of 1,3-bis-silyl enol ether **1a**, prepared from ethyl acetoacetate, with acetyl chloride (**2a**) afforded ethyl 3,5-dioxohexanoate (**3a**)[8] in up to 40% yield (Scheme 1, Table 1).



Scheme 1. Acylation of β-ketoester derived 1,3-bis-silyl enol ethers: Reagents and conditions: (i) CH_2Cl_2, −78 → 20 °C.

Table 1. Products and yields

3	R^1	R^2	Keto/enol[a]	Yield[b] (%)
a	Et	Me	2:1	40
b	$(CH_2)_2OMe$	Me	2:3	50
c	Et	Et	1:4	48
d	Et	Ph	0:1	66

[a] Determined by ^1H NMR ($CDCl_3$).
[b] Yields of isolated products.

Keywords: Acid chlorides; Acylation; Polyketides; Regioselectivity; Silyl enol ethers.
* Corresponding author. Tel.: +49 381 4986410; fax: +49 381 4986412; e-mail: peter.langer@uni-rostock.de

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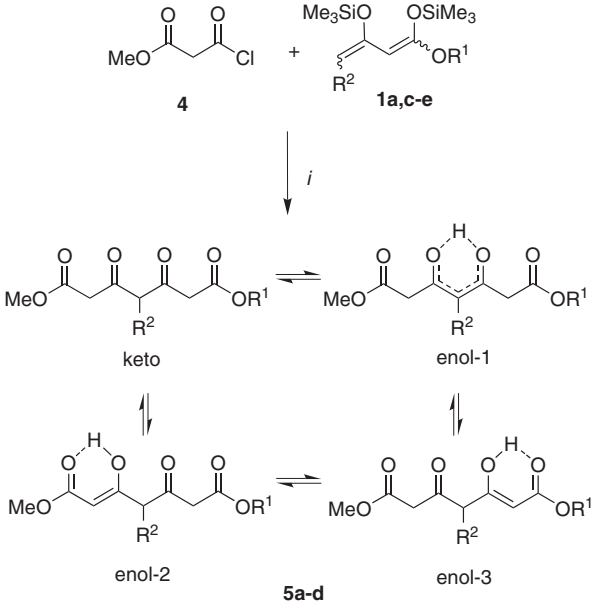
During the optimization of this reaction, the following parameters proved to be important: (a) the *absence* of any Lewis acid (the use of Me_3SiOTf resulted in decomposition), the temperature, the concentration and the stoichiometry.[11] The reaction of **1b** with acetyl chloride gave **3b**. The condensation of **1a** with propionyl chloride (**2b**) afforded **3c**. Ethyl 3,5-dioxo-5-phenylpentanoate (**3d**) was prepared by reaction of **1a** with benzoyl chloride (**1c**). The methodology reported herein competes well with known procedures for the synthesis of **3a**[12] and **3d**.[13] The synthesis of **3b** and **3c** has, to the best of our knowledge, not yet been reported.

The reaction of 1,3-bis-silyl enol ether **1c**, prepared from methyl acetoacetate, with methyl 3-chloro-3-oxopropionate (**4**) afforded dimethyl 3,5-dioxopimelate (**5a**) in up to 40% yield (Scheme 2, Table 2). In this reaction, the *presence* of Me_3SiOTf (0.4 equiv) proved to be important.[14] The reaction of **4** with **1a** afforded **5b**. The condensation of **4** with **1d** and **1e**, prepared from methyl 3-oxopentanoate and ethyl 3-oxohexanoate, afforded the 3,5-dioxopimelates **5c** and **5d**, respectively. Symmetrical 3,5-dioxopimelate **5a** mainly resides in the form of enol-1. Unsymmetrical **5b** also mainly resides in the form of enol-1; besides, a small amount of keto tautomer is present. For symmetrical **5c**, containing a methyl group at carbon C-4, three tautomers are present. Four tautomers are present for unsymmetrical 4-ethyl-3,5-dioxopimelate **5d**. Products **5a–d** are stable, since two terminal ester groups are present and, thus, no intramolecular aldol cyclization can occur to give a stable benzene derivative. Intramolecular Claisen condensation and over-addition (by attack of the 1,3-bis-silyl enol ether onto the product) are possible side reactions and may account for the moderate yields.

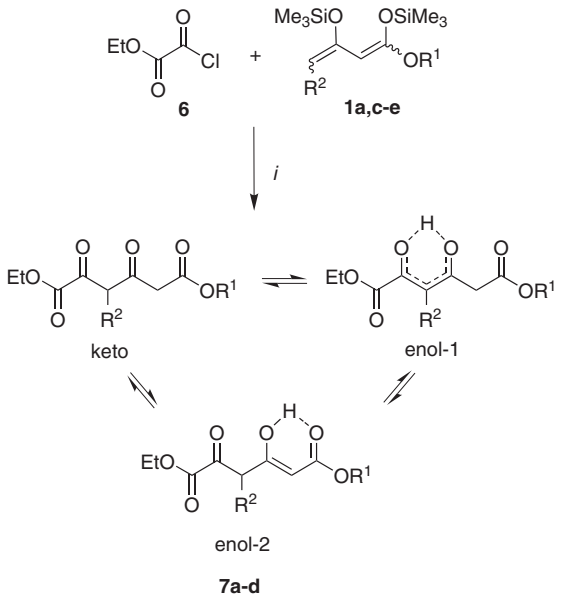
The reaction of 1,3-bis-silyl enol ether **1c** with ethyl 2-chloro-2-oxoacetate (**6**), in the presence of Me_3SiOTf (0.4 equiv), afforded dimethyl 2,4-dioxoadipate (**7a**) in 50% yield (Scheme 3, Table 3). Likewise, the reaction of **6** with **1a** and **1d**,**e** afforded the 2,4-dioxoadipates **7b–d**. 2,4-Dioxoadipate **7a** resides as a mixture of keto/enol-1 tautomers. Three tautomers were observed for **7b–d**.

The reaction of 1,3,5-tris-silyl enol ether **8**[15] with **6** resulted in the formation of phthalate **9** (Scheme 4). The formation of **9** can be explained by attack of the terminal carbon of **8** onto **6** and subsequent Mukaiyama aldol reaction and aromatization ([5+1] cyclization).[15]

In summary, we have reported a convenient synthesis of 3,5-dioxoalkanoates, 3,5-dioxopimelates and 2,4-dioxoadipates by acylation of 1,3-bis-silyl enol ethers with carboxylic chlorides, methyl 3-chloro-3-oxopropionate and ethyl 2-chloro-2-oxoacetate, respectively.



Scheme 2. Synthesis of **6a–d**: Reagents and conditions: (i) TMSOTf (0.4 equiv), CH_2Cl_2, −78 → 20 °C.



Scheme 3. Synthesis of **7a–d**: Reagents and conditions: (i) TMSOTf (0.4 equiv), CH_2Cl_2, −78 → 20 °C.

Table 2. Products and yields

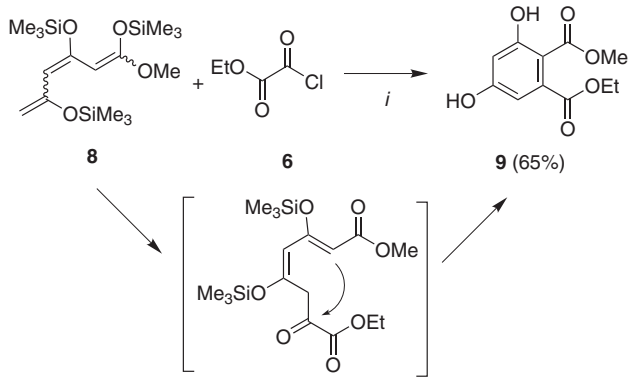
5	R^1	R^2	Keto/enol-1/enol-2/enol-3[a]	Yield[b] (%)
a	Me	H	1:10:0[c]	40
b	Et	H	1:6:0:0	23
c	Me	Me	2:2:1[c]	20
d	Et	Et	2:1:1:1	37

[a] Determined by ^1H NMR ($CDCl_3$).
[b] Yields of isolated products.
[c] Enol-2 and enol-3 are identical.

Table 3. Products and yields

7	R^1	R^2	Keto/enol-1/enol-2[a]	Yield[b] (%)
a	Me	H	1:5:0	50
b	Et	H	1:6:3	47
c	Me	Me	1:2:1	45
d	Et	Et	2:5:1	33

[a] Determined by ^1H NMR ($CDCl_3$).
[b] Yields of isolated products.



Scheme 4. [5+1] Cyclization of 1,3,5-tris-silyl enol ether **8** with **6**: (i) 0.4 equiv TMSOTf, CH_2Cl_2, $-78 \rightarrow 20$ °C.

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14. *Typical procedure for the synthesis of 3,5-dioxopimelates* (**5a–d**): To a CH_2Cl_2 solution (100 mL) of 1,3-bis(trimethylsilyloxy)-1-methoxy-1,3-butadiene (5.20 g, 20.0 mmol) was added **4** (1.36 g, 10.0 mmol) and TMSOTf (0.45 g, 2.0 mmol) at -78 °C under argon atmosphere. The solution was allowed to warm to 20 °C within 6 h and was stirred at this temperature for 12 h. To the solution was added a saturated aqueous solution of NH_4Cl (30 mL). The organic and the aqueous layers were separated and the latter was extracted with ether (3×30 mL). The combined organic layers were extracted with a saturated aqueous solution of NaCl, dried ($NaSO_4$), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-hexane/EtOAc = 3:1) to give **5a** as a yellow oil (868 mg, 40%, keto/enol = 1:10). Compound **5a**: ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 3.38$ (s, 2H, CH_2), 3.75 (s, 3H, OCH_3), 5.75 (s, 1H, CH), 14.80 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 44.05$ (CH_2), 52.51 (OCH_3), 100.91 (CH), 167.04 (C), 167.69 (C), 170.57 (C), 185.76 (C). IR (KBr): $\tilde{\nu} = 3468$ (w), 3178 (w), 3108 (w), 3008 (w), 2960 (m), 2859 (w), 1741 (s), 1629 (w), 1441 (m), 1409 (m) cm^{-1}. MS (CI): 217 ($[M+H]^+$, 100). All new compounds gave correct elemental analyses and/or high resolution mass data. Products **5b–d** were prepared by employment of **1a**,**d**,**e** (3.0 mmmol), **4** (3.3 mmol) and TMSOTf (1.2 mmol).
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