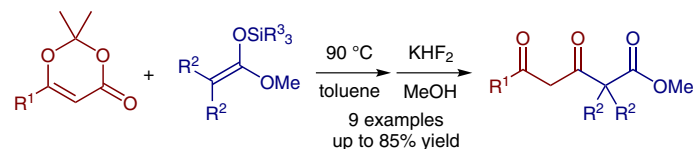


A Mukaiyama–Claisen Approach to 3,5-Diketo Esters

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Dedicated to ‘uncle Peter’, in deep admiration for his marvelous
contributions to chemical synthesis, including *Synlett*.



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Abstract A thermally promoted synthesis of 3,5-diketo esters via a Mukaiyama–Claisen reaction of 4H-1,3-dioxin-4-one derivatives with silyl enolates has been developed. The desired oligocarbonyl compounds were obtained with moderate to good yields.

Key words 3,5-diketo esters, Mukaiyama–Claisen reaction, thermal reaction, silylated nucleophiles

Oligocarbonyl compounds, especially 3,5-diketo ester derivatives, are important building blocks for the synthesis of polyketides and polyols, such as erythromycin A, rosuvastatin, tetracycline and wailupemycin F (Figure 1).^{1–3}

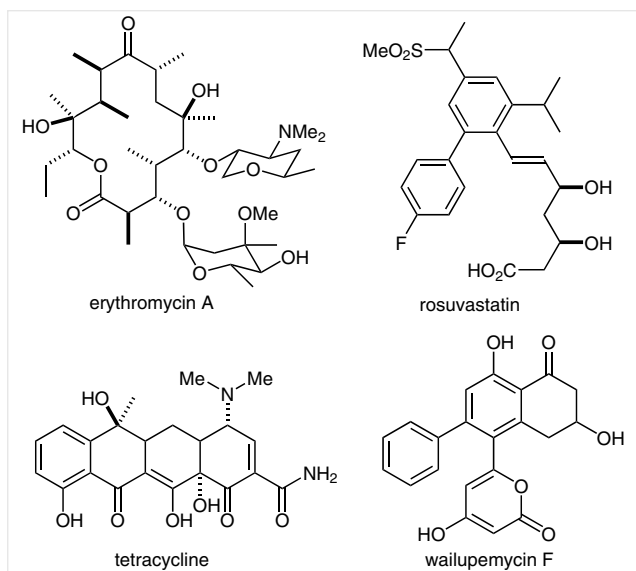
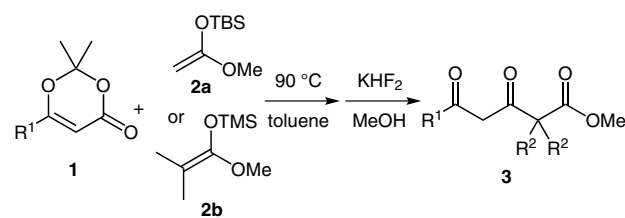


Figure 1 Representative examples of polyketides and polyols

Therefore, approaches towards their synthesis are of interest. Several methodologies have previously been developed to synthesize oligocarbonyl compounds.⁴ Among them, Claisen condensation approaches have proven efficient in building up the carbon backbone. The Langer group recently reported the reaction of silylated nucleophiles with acyl chloride to give 3,5-diketo esters.^{4a–d} Tanabe and co-workers utilized a similar strategy to access analogous 1,3-dicarbonyl compounds.^{4e,f} However, to our knowledge, esters themselves have not been used as electrophiles in Mukaiyama-type Claisen condensations. Notably, 4H-1,3-dioxin-4-one derivatives are useful synthetic equivalents for 1,3-dicarbonyls. In the context of a different study, we have recently described a single example in which a 3,5-diketo ester was accessed by reacting an enol silane with a 4H-1,3-dioxin-4-one derivative.^{5,6} Herein, we explore the generality of this unique transformation and report an improved thermal approach for the synthesis of 3,5-diketo esters via a Mukaiyama–Claisen reaction of 4H-1,3-dioxin-4-one derivatives with silyl ketene acetals.

Under optimized conditions both aliphatic and α,β -unsaturated 4H-1,3-dioxin-4-one derivatives could be employed in the thermally promoted Mukaiyama–Claisen reaction. Simply treating compounds **1** with an excess of silyl ketene acetals **2a** or **2b**, gave the corresponding 3,5-diketo esters in good yields after desilylation (Table 1). Using an *N*-Boc carbamate containing substrate, the corresponding tricarbonyl products **3a** and **3b** were obtained in 85% and 78% yield, respectively. With an *O*-TBS protected substrate, the reactions proceeded smoothly, giving **3c** and **3d** in 85% and 84% yield, respectively. Reactions involving a conjugated alkenyl substrate required higher temperature (110 °C), and the corresponding products **3e** and **3f** were obtained in 61% and 73% yield, respectively. Using the simple, methyl-substituted substrate, the desired tricarbonyl compounds **3g** and **3h** were obtained in 73% and 75% yield, respectively.

Table 1 Substrate Scope of the Mukaiyama–Claisen Reaction

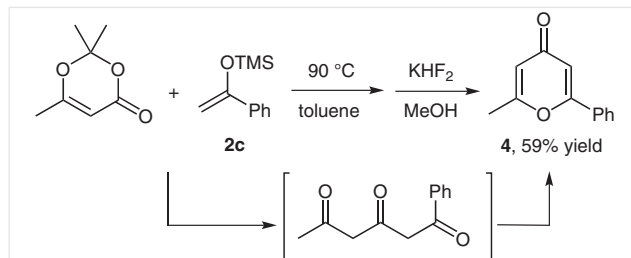
Entry ^a	Product	Yield (%)
1	3a 	85
2	3b 	78
3	3c 	85
4	3d 	84
5 ^b	3e 	61
6 ^b	3f 	73
7	3g 	73
8	3h 	75

^a Reactions were carried out with **1** (0.1 mmol) and **2** (0.4 mmol) in toluene (1 mL) for 4–5 h at 90 °C.

^b Reactions were carried out at 110 °C.

Interestingly, when a silyl enol ether (**2c**) was explored as the nucleophile, an intramolecular cyclization was observed and 2-methyl-6-phenyl-4*H*-pyran-4-one (**4**) was isolated in 59% yield (Scheme 1). Presumably, under these conditions, a triketone is initially formed and subsequently undergoes cyclization to heterocycle **4**.⁷

In summary, a thermally promoted synthesis of 3,5-diketone esters via a Mukaiyama–Claisen reaction of 4*H*-1,3-dioxin-4-one derivatives with silylated enolate nucleophiles has been developed.⁸ The desired oligocarbonyl compounds were obtained in good yields. This methodology may find applications in the synthesis of bioactive polyketides or polyols.

**Scheme 1** Intramolecular cyclization observed using silyl enol ether **2c** as nucleophile

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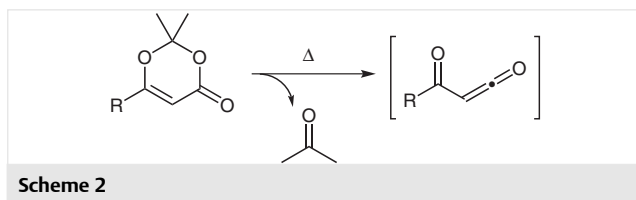
Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0034-1380145>.

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- (6) An acyl ketene intermediate has recently been proposed in thermal reactions of 4*H*-1,3-dioxin-4-ones (Scheme 2):



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- (8) A cooling-finger-capped Schleck tube with a stirring bar was charged with the corresponding 4*H*-1,3-dioxin-4-one derivative **1** (0.1 mmol), silylated nucleophile **2** (0.4 mmol), and anhydrous toluene (1 mL). The resulting mixture was heated to 90 °C or 110 °C for 4–5 h until full consumption of the starting material was observed (monitored by TLC). The solvent was removed under reduced pressure, MeOH (1 mL) and KHF₂ (10 equiv) were added, and the reaction mixture was stirred at r.t. for 10 min. After filtering through a thin layer of Celite, the residue was purified by column chromatography (isohexanes–EtOAc, 5:1 to 1:1).