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Synthesis of 1,3-diketones through ring-opening of ketoketene dimer β-lactones

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ABSTRACT

The reaction of ketoketene dimers with organolithium reagents afforded 1,3-diketones in good to excellent yields, and with good diastereoselectivity in some cases.

The single step conversion of esters to ketones is a potentially useful reaction in complex molecule synthesis. However, there are few examples of such one-step transformations in the literature.[1–5] Typically, the reactions of organolithium and Grignard reagents with esters form ketones initially, which being more electrophilic than esters, undergo a second nucleophilic addition to give tertiary alcohols.[1,2] While a few dimethylketene dimer ring-openings are known, ring-openings of ketoketene dimers derived from unsymmetrical ketoketenes have not been studied due to a paucity of general methods for their preparation.[3–12] Interestingly, the reaction of dimethylketene dimer **1a** with simple Grignard reagents (EtMgX, *i*-PrMgX, *t*-BuMgX, and PhMgBr) was reported to provide 1,3-diketones in modest yields (5–50%), while a single example involving PhLi as the nucleophile favored retro-aldol product **5a** (80%) after double addition.[4,5] Retro-aldol products presumably arise from decomposition of the intermediate **3a** during the reaction (Scheme 1) or alternatively through decomposition of the derived β-hydroxyketone during aqueous work-up.[4,10]

In addition, a handful of modest yielding ketone forming reactions (21–71%) from the reaction of β-lactones (derived from aldehydes) with organometallics are known.[13–16]

Access to 1,3-diketones from ketoketene dimers would be a desirable reaction as 1,3-diketones are important organic compounds and are found in many natural products and pharmacologically active compounds, and moreover have been widely used as intermediates in synthesis.[17] The most popular method for 1,3-diketone synthesis rely on the use of a modification of the Claisen condensation (acylation of a ketone by an ester in the presence of an alkoxide or metal hydride base) or on the use of LDA to preform an enolate from a ketone followed by C-acylation through reaction with an acyl chloride.[17–21] More recently a milder soft enolization protocol has been introduced.[19] However most of these methods have disadvantages with respect to competing side reactions (e.g., O-acylation or bis-acylation) or limited substrate scope (e.g., tetrasubstituted enolates not being tolerated).[18]

Our group has recently developed a general method for the stereoselective dimerization of ketoketenes to give a range of ketoketene dimer β-lactone products in good to excellent yields and with excellent diastereoselectivity favoring the *Z*-isomer (Scheme 2).[3,22]

With the aim of utilizing our ketoketene dimers in the synthesis of interesting molecules possessing a quaternary stereogenic center, we initiated the development of organometallic-mediated ring-opening reactions of our β-lactones.[3] We initially investigated the reaction of methylphenylketene dimer **1b** with excess *n*-BuLi (2 equiv) in THF at −78 °C and were surprised to find that 1,3-diketone **6b** (88%, dr = 86:14), derived from single addition, was obtained as the major product rather than retro-aldol product **5b** (Scheme 3).[4,5] Interestingly, relatively few studies have investigated diastereoselectivity in 1,3-diketone formation.[23]

Although quenching the reaction with excess water after warming from −78 °C to room temperature led to good diastereoselectivity (dr = 86:14), we subsequently found that slightly higher diastereoselectivity could be obtained when the reaction was quenched with water (93%, dr = 89:11) or acetic acid (72%, dr = 90:10) at −78 °C.[24]

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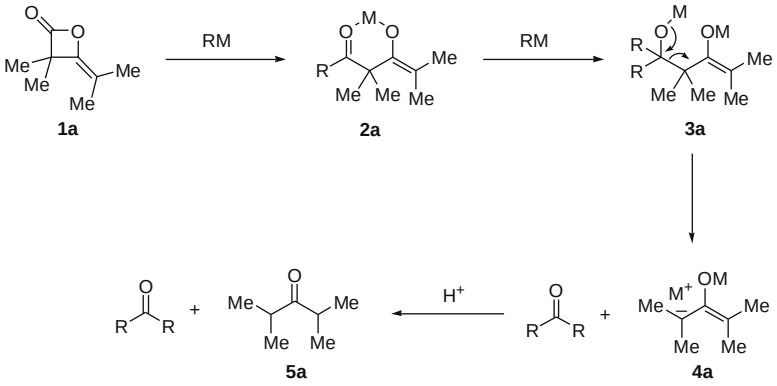
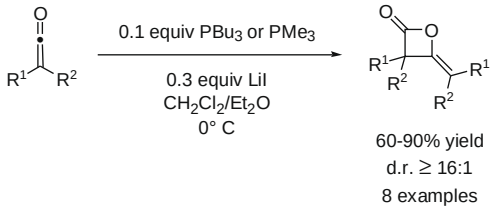
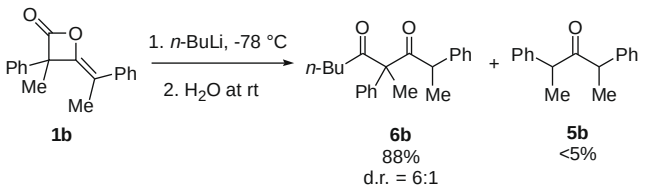


Scheme 1. Formation of retro-aldol products from dimer **1a**.

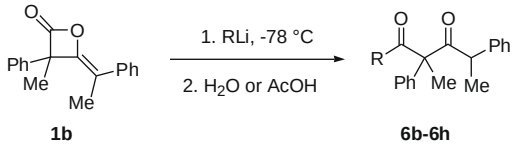


Scheme 2. Phosphine-catalyzed dimerization of ketoketenes.



Scheme 3. Reaction of *n*-BuLi with ketoketene dimer **1b**.

Table 1
Ring-opening of **1b** with various RLi to afford **6b–h**[a]



Entry	R	Yield % of **6**	dr[b] of **6**	Compound
1	*n*-Bu	93	89:11 (90:10)[c]	**6b**
2	*t*-Bu	80	85:15[c]	**6c**
3	*s*-Bu	72	87:13[c]	**6d**
4	Et	>99[d]	77:23	**6e**
5	Me	21[e]	80:20	**6f**
6	Ph	70[e]	58:42	**6g**
7	MeO	99	62:38	**6h**

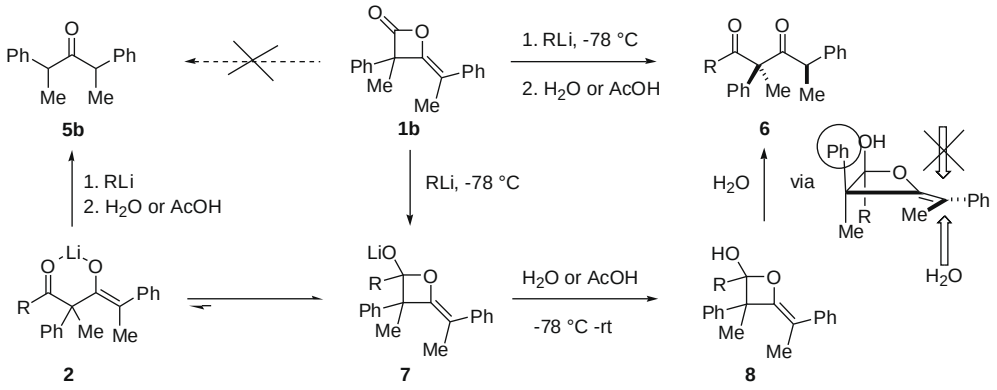
[a] Yields are isolated yields.
[b] Diastereomeric ratio (dr) as determined by GC–MS or ^{1}H NMR analysis.
[c] Quenched with AcOH (2 equiv).
[d] Contains 10% **5b**.
[e] Conversion to 6 as determined by GC–MS analysis. The rest of the product mixture was accounted for by **5b**.

Employing our optimized conditions (2 equiv RLi, −78 °C, and H_2O or acetic acid quench at −78 °C) we then investigated the reaction of methylphenylketene dimer **1b** with a variety of commercially available and in situ-prepared organolithium reagents (Table 1).[25] A THF solution of MeOLi was generated in situ, through the reaction of *n*-BuLi with methanol in THF (Table 1, entry 7). In most cases, single addition of the organolithium reagent occurred to give the corresponding 1,3-dicarbonyl compounds **6b–h** cleanly with moderate to good diastereoselectivity (dr up to 90:10). The poor conversion of **1b** to 1,3-diketone **6f** when MeLi is the nucleophile is presumably due to intermediate **2** (Scheme 4) readily undergoing a second addition of MeLi. We speculate that the transition state for equilibration of **7** to **2** is of lower energy when R = Me than when R = *n*-Bu or *t*-Bu, due to reduced steric interactions in the transition state leading to **2f**, and consequently this would mean that **2f** rather than **7f** is favored at equilibrium. Therefore in reactions involving MeLi, the formation of double addition-derived retro-aldol product **5b**, rather than 1,3-diketone **6**, is favored.

The reaction of other ketoketene dimers (**1c–e**) with various alkyllithium reagents was also investigated (Table 2). While ring-opening of ethylphenylketene dimer **1c** proceeded less cleanly, ring-opening reactions of methyl-4-tolylketene dimer **1d** and methyl-6-methoxy-2-naphthylketene dimer **1e** gave similar yields to those of **1b**. In some cases, the crude products obtained from alkyllithium ring-opening of **1d** contained 5–10% retro-aldol product **5d**, as determined by GC–MS and ^{1}H NMR analysis, most likely formed through the mechanism outlined in Scheme 1.

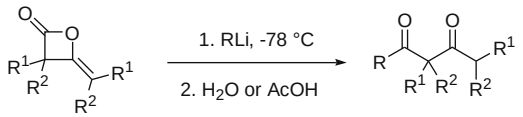
On the basis of the results obtained in these experiments we postulate that the reaction involves a stabilized lithium lactol tetrahedral intermediate **7** (Scheme 4). **7** is stable at −78 °C and only collapses to give 1,3-diketone **6** when water (or another proton source) is added at −78 °C and the reaction is allowed to warm to ambient temperature. Good diastereoselectivity (Table 1, entries 1–3, and Table 2, entry 2) in 1,3-diketone formation presumably arises from protonation of the less sterically hindered π-face of **8** (the face not blocked by the 4° center Ph substituent) to give the *anti*-diastereomer as the major diastereomer (see Scheme 4 for a plausible stereochemical model).[26] In those cases where lower diastereoselectivity (Table 1, entries 6 and 7) is obtained we presume that tetrahedral intermediate **7** is less stable (due to the R = MeO or Ph substituent) than **2** and hence that the acyclic enolate intermediate **2** is favored under the reaction conditions. Protonation of acyclic lithium enolate **2** would be expected to proceed with poor diastereoselectivity due to reduced diastereocontrol associated with the conformational flexibility of **2** and the similar sizes of the Ph and RC═O substituents at the 4° center, in comparison with that expected from the conformationally rigid cyclic intermediate **8**.[27]

Tentative support for the intermediacy of **7** was obtained from the following control experiments: Firstly, reaction of **1b** with 1 equiv of MeOLi, followed by 2 equiv *n*-BuLi, led to the formation of ca. 30% double addition-derived retro-aldol product **5b** (Scheme 4). This implies that the non-cyclic lithium enolate intermediate **2** from this reaction does not significantly contribute to 1,3-diketone



Scheme 4. Proposed mechanism for the formation of 1,3-diketone **6**.

Table 2
Ring-opening of **1c–e** with various RLi to afford **6i–n**[a]



1c-1e **6i-6n**

Entry	R^1	R^2	R	Yield % of **6**	dr[b] of **6**	Compound
1	Ph	Et	*n*-Bu	73[c]	n.d.	**6i**
2	4-MePh	Me	*n*-Bu	78[d]	85:15	**6j**
3	4-MePh	Me	*t*-Bu	83	76:24	**6k**
4	4-MePh	Me	*s*-Bu	90[d]	60:40	**6l**
5	6-MeO-2-Naphthyl	Me	*n*-Bu	96	70:30	**6m**
6	6-MeO-2-Naphthyl	Me	*t*-Bu	94	67:33	**6n**

[a] Yields are isolated yields.
[b] Diastereomeric ratio (dr) as determined by GC–MS or ^{1}H NMR analysis.
[c] Conversion as determined by GC–MS analysis.
[d] Contains 5–10% retro-aldol product **5d**.

formation. Secondly, when **6b** was exposed to 4 equiv *n*-BuLi, ca. 25% **5b** was obtained after quenching with water. This again suggests that the 1,3-diketone forming reaction primarily involves **7** as opposed to the lithium enolate **2**. Finally, reaction of **1b** with MeOLi provided β-ketoester **6h** (Table 1, entry 7) in excellent yield, but with poor diastereoselectivity (dr = 62:38) after an aqueous quench, and so it must involve quenching of a significantly different intermediate to that for **6b**, which was obtained in a dr of 90:10.

When toluene was used as the solvent, lower conversion to **6b** (ca. 25%) was obtained and an elevated level of **5b** was obtained (ca. 20%). This suggests that the polarity of the solvent is critical to stabilization of the intermediate **7**, and hence formation of **6**.

In conclusion, we have described an efficient method for the conversion of ketoketene dimers to 1,3-diketones with moderate to good diastereoselectivity. We are currently carrying out further mechanistic investigations of this reaction and exploring its application in drug molecule synthesis.

Acknowledgments

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Supplementary data

Supplementary data (Detailed experimental procedures and characterization data for **6b–n**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.158.

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24. The dr's for **6b** were determined by GC–MS analysis and were found to be reproducible over three injections.
25. A typical procedure for the reaction of ketoketene dimers **1** with alkyllithiums is as follows: Ketoketene dimer **1** (0.61 mmol) was dissolved in THF (4.8 mL), and *n*-butyllithium (2.5 M in hexane, 0.48 mL, 1.20 mmol) was added dropwise over 5 min at −78 °C. After 15 min the reaction was quenched by adding water (2 mL) at −78 °C. The quenched reaction was then warmed up to room temperature, brine (8 mL) and CH_2Cl_2 (5 mL) were added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and the

combined organics were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford the desired 1,3-diketone **6** as a colorless oil in the yields given in Tables 1 and 2. All 1,3-diketones were characterized by GC–MS, IR, ^1H NMR, ^{13}C NMR and HRMS analyses.

26. The relative stereochemistry of 1,3-diketones **6** remains to be determined and this is the subject of current studies.

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