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A Tandem Reaction Initiated by 1,4-Addition of Bis(iodozincio)methane for 1,3-Diketone Formation

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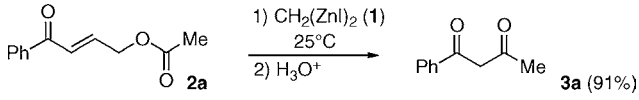
The 1,4-addition of organometallic reagents to α,β-unsaturated ketones has been used as an alternative method for the formation of enolates.[1] Both organometallics and metal hydrides have been used in this transformation.[2] With this method, it is easier to control the regio- and chemoselectivity of enolate formation than with conventional deprotonation using a strong base.[3] The ability of this reaction to tolerate different functional groups is also valuable and permits the coexistence of an additional electrophilic group, such as a ketone or an ester group, in the substrate. This means that the initially formed enolate can be intramolecularly trapped with these electrophiles. Therefore, 1,4-addition is suitable as the first step in an intramolecular tandem reaction.[4,5] In the course of our studies on bis(iodozincio)methane (**1**),[6,7] we considered that the 1,4-addition of **1** to an α,β-unsaturated ketone may simultaneously form two nucleophilic sites in the same molecule, i.e., the zinc enolate and a zinciomethyl group, and that these could trigger a novel tandem reaction.

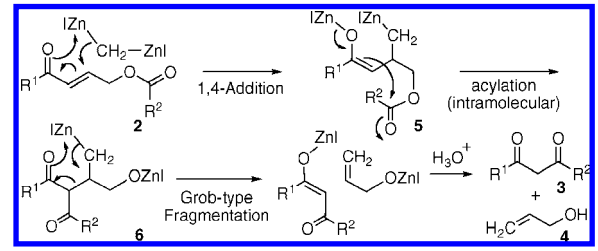
We previously found that the 1,4-addition of **1** to simple enones required a stoichiometric amount of chlorotrimethylsilane and formed the corresponding (*Z*)-silyl enol ethers of β-zinciomethylated ketones.[8] The formation of the silyl enol ether would be undesirable for a tandem reaction, since the sequential reaction by the enolate would be interrupted. To eliminate the need for a silylation reagent, we introduced an acyloxy group at the γ-position of the enone, which is expected to facilitate 1,4-addition by its ability to coordinate to dizinc **1**.[9,10] First, we treated (*E*)-4-acetoxy-1-phenyl-2-buten-1-one[11] (**2a**, 0.5 mmol) with **1** (0.6 mmol, 0.5 M in THF) in THF at 25 °C for 2 h and obtained an unexpected product, 1,3-diketone **3a**, in 91% yield after aqueous workup (Scheme 1).[12]

Scheme 1. Formation of 1,3-Diketone **3a** from **2a**



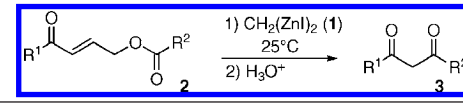
To determine the reaction pathway, we tried the reaction in Scheme 1 with deuterium-labeled bis(iodozincio)methane, $CD_2(ZnI)_2$ (**1-D**);[13] **3a** and 3,3-dideuterio-2-propen-1-ol (**4-D**) were formed quantitatively.[14] On the basis of these observations, the reaction pathway can be explained as shown in Scheme 2. **1** adds to γ-acyloxy-α,β-unsaturated ketone **2** in a 1,4-manner to form zinc enolate **5** with a C−Zn bond. As the second step, enolate **5** reacts with the ester group intramolecularly to form **6**. Finally, Grob-type fragmentation,[15] which is induced by C−Zn bond cleavage, gives the enolate of 1,3-diketone and the zinc alkoxide of allyl alcohol. Thus, treatment of γ-acyloxy-α,β-unsaturated ketones with **1** afforded 1,3-diketones via this unique tandem reaction, which effectively uses two C−Zn bonds of **1** during three sequential steps.

Scheme 2. Plausible Pathway for the Tandem Reaction



Various examples of 1,3-diketone synthesis based on our tandem reaction are shown in Table 1. Aryl enones (R^1 = Ar) produced the corresponding 1,3-diketones **3** in excellent yields (entries 1−10), and alkyl enones (R^1 = alkyl) gave the products in moderate yields (entries 11−14). Notably, intramolecular nucleophilic attack by the zinc enolate on the ester group proceeded smoothly even with sterically hindered substrates such as in entries 3 and 12. Since the substrates **2** can be prepared directly by esterification of the corresponding alcohols, which are easily available according to our reported procedure,[11] this tandem reaction is a general procedure for the preparation of 1,3-diketones.

Table 1. 1,3-Diketone Preparation by the Tandem Reaction of **2**[a]



entry	R^1	R^2	**2**	yield (%)[b]	**3**
1	Ph	Me	**2a**	91	**3a**
2	Ph	*i*-Pr	**2b**	91	**3b**
3	Ph	*t*-Bu	**2c**	81	**3c**
4	Ph	Ph	**2d**	97	**3d**
5	Ph	*p*-$MeOC_6H_4$	**2e**	>99	**3e**
6	Ph	*p*-$CF_3C_6H_4$	**2f**	95	**3f**
7	*p*-Tol	Me	**2g**	92	**3g**
8	*p*-$MeOC_6H_4$	Me	**2h**	84	**3h**
9	*p*-$CF_3C_6H_4$	Me	**2i**	91	**3i**
10	2-naphthyl	Me	**2j**	91	**3j**
11	$PhCH_2CH_2$	Me	**2k**	55	**3k**
12	$PhCH_2CH_2$	*t*-Bu	**2l**	61	**3l**
13	$PhCH_2CH_2$	*p*-$MeOC_6H_4$	**2m**	69	**3m**
14	Me	*p*-$CF_3C_6H_4$	**2n**	51	**3i**

[a] The substrate (**2**, 0.5 mmol) and bis(iodozincio)methane (**1**, 0.6 mmol) were used for the reaction. [b] Determined by ^1H NMR analysis. All of the products were isolated by silica gel column chromatography for the identification.

As noted above, enolate formation by a 1,4-addition can be performed selectively and can tolerate various functional groups. Therefore, we can obtain enolates with an additional reactive functional group, such as a ketone or an ester. In the second step of the tandem reaction, the intramolecular addition of the enolate

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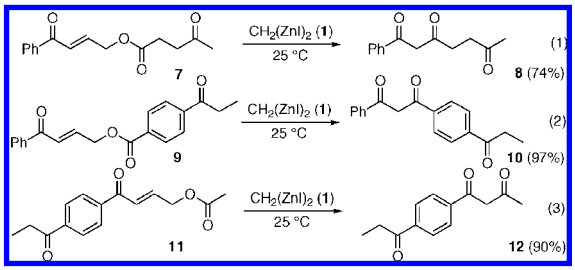
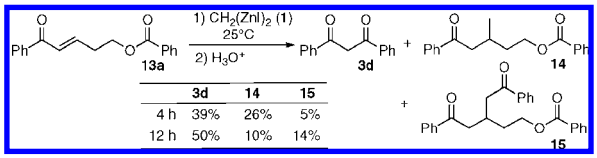
to the ester group should also proceed selectively even in the presence of another ketone group, since it proceeds preferentially in a 5-exo-trigonal manner[16] (Scheme 2). As shown in Scheme 3, substrates that contained another ketone group were examined with our tandem reaction. During the reaction, the extra ketone group remained intact. Treatment of the substrates **7**, **9**, and **11** with **1** gave the corresponding triketones **8**, **10**, and **12** selectively in good to excellent yields.

Scheme 3. Preparation of Triketones by the Tandem Reaction



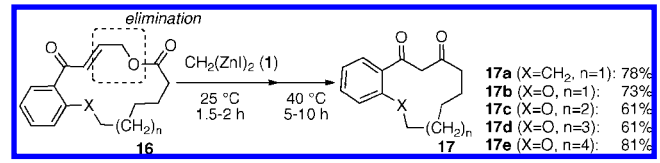
In view of the mechanism of this tandem reaction starting from γ-acyloxy-α,β-unsaturated ketone **2** as shown in Scheme 2, δ-acyloxy-α,β-unsaturated ketone **13** may also be a suitable substrate to give 1,3-diketone **3**. In the latter case, the enolate initially formed from **13** should react intramolecularly with the ester group in a 6-exo-trigonal manner and release homoallyl alcohol by Grob-type fragmentation. As shown in Scheme 4, 5-benzoyloxy-1-phenylpent-2-en-1-one (**13a**) was treated with **1**. While the corresponding γ-acyloxy-α,β-unsaturated ketone 4-benzoyloxy-1-phenylbut-2-en-1-one (**2d**) was transformed into **3d** exclusively (Table 1, entry 4), **13a** gave a mixture of **3d**, **14**, and **15**. The product **14** was obtained by protonolysis of the enolate, which was formed by the 1,4-addition of **1** to **13a**; product **15** was obtained by intermolecular 1,4-addition of the enolate to **13a**, which was followed by Grob-type fragmentation. After a prolonged reaction period, the yield of **3d** was improved to 50%, but the production of **14** and **15** could not be avoided. Therefore, in this novel tandem reaction, γ-acyloxy-α,β-unsaturated ketone **2** is more suitable as a substrate than **13**.

Scheme 4. Reaction of δ-Benzoyloxy-α,β-unsaturated Ketone **13a** with Bis(iodozincio)methane (**1**)



In addition to the selectivity shown in Scheme 3, a characteristic feature of this method is the elimination of three atoms in the last step of the tandem reaction. When this reaction is applied to a lactone, it is transformed into a cyclic 1,3-diketone via ring contraction with the elimination of three atoms. As shown in Scheme 5, 14-membered lactone **16a** (X = CH_2, $n = 1$) was treated with **1** at 25 °C for 2 h and at 40 °C for 5 h. At 25 °C, β-methylated product **18**, which resulted from the 1,4-addition of **1**, was formed as the sole product after aqueous workup. In this transformation, the 1,4-addition of **1** to **16a** proceeded at 25 °C, and the subsequent intramolecular nucleophilic attack required heating to 40 °C, since intramolecular addition of the enolate in a 5-exo-trigonal manner across the ring structure proceeded along with formation of the more strained ring. Other lactones **16b**−**e** were also converted to the corresponding 1,3-diketones **17b**−**e** via ring contraction under the same conditions.

Scheme 5. Preparation of Cyclic 1,3-Diketones **17** from Lactones **16** via Ring Contraction by the Tandem Reaction



Thus, we have demonstrated a novel tandem reaction initiated by bis(iodozincio)methane (**1**) that affords various types of 1,3-diketones efficiently and selectively, accompanied by the elimination of three atoms. The reaction consists of three sequential steps: 1,4-addition of **1** to the enone, intramolecular addition to the ester group, and Grob-type fragmentation. The two nucleophilic sites, i.e., the zinc enolate and a zinciomethyl group, that were introduced by the 1,4-addition of *gem*-dizinc **1** induced the intramolecular addition and Grob-type fragmentation, respectively. Further mechanistic investigations are now underway, and we suppose that the two addition reaction steps in our tandem reaction would be promoted in a cooperative manner by the two zinc atoms, which can act as Lewis acids.

Supporting Information Available: Experimental procedures and spectroscopic and analytical data for the substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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