



## **SmI<sub>2</sub>-Promoted Conjugate Reduction of $\alpha,\beta$ -Unsaturated Esters and Ketones Studied in Comparison with Mukaiyama-Michael Reaction of Ketene Silyl Acetal**

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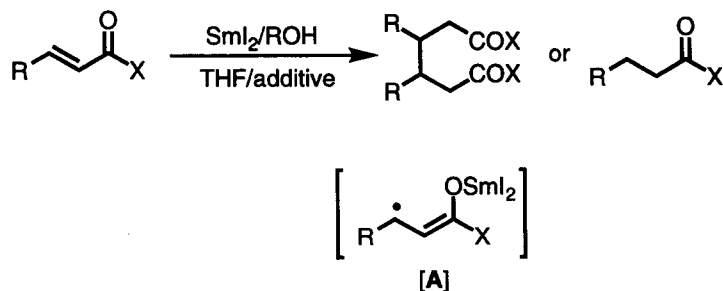
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**Abstract:** SmI<sub>2</sub>-promoted conjugate reduction of  $\alpha,\beta$ -unsaturated esters and ketones proceeds in a manner quite similar to Mukaiyama-Michael reaction of ketene silyl acetal. The more substituted esters are reduced more preferentially than the less substituted ones. The substrates with a 12 or 16 membered-ring structure undergo reduction smoothly. On the other hand, the 6-membered substrates completely fail to react under the same conditions. These results indicate generation of intermediate enolate radicals to be a key step for the conjugate reduction. © 1997 Elsevier Science Ltd.

Inanaga et al. reported that hydrodimerization of  $\alpha,\beta$ -unsaturated esters and amide was effectively promoted by SmI<sub>2</sub>-THF-HMPA in the presence of proton sources (Scheme 1).<sup>1</sup> When HMPA was replaced by N,N-dimethylacetamide (DMA), conjugate reduction occurred.<sup>2</sup> The analogous reduction was also reported by Alper et al.<sup>3</sup> It was suggested that the reactions were initiated by formation of enolate radical species A.<sup>1</sup>

**Scheme 1**

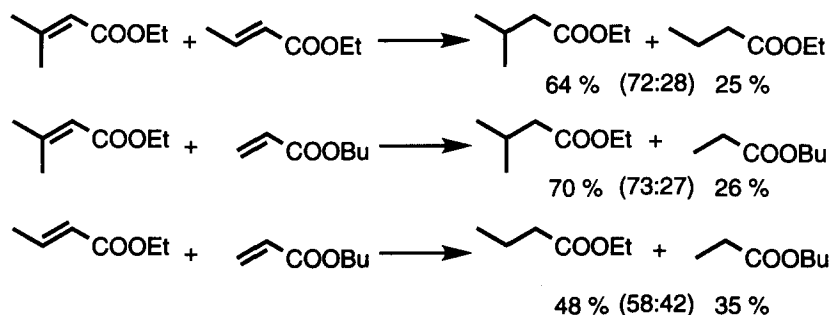


Previously, we disclosed that Mukaiyama-Michael reaction of ketene silyl acetal proceeds by an electron transfer process where metal enolate radicals having a structure quite similar to A are key intermediates.<sup>4,7</sup> The radical character of the reaction was supported by competition reactions in which the more substituted ketene silyl acetals reacted faster than the less substituted ones. Furthermore, in the preceding paper, generation of

the enolate radical has proved to be difficult with 3-methyl-2-cyclohexenone but easy with macrocyclic enones.<sup>8</sup> Consequently, if the intermediacy of the enolate radical in  $\text{SmI}_2$ -promoted conjugate reduction is true, the reaction should undergo the similar effects from  $\beta$ -substituents and ring strain.

First, to confirm the radical character of the  $\text{SmI}_2$ -promoted conjugate reduction, we conducted competition reaction between acyclic  $\alpha,\beta$ -unsaturated esters (Scheme 2). Apparently, ethyl 3,3-dimethylacrylate was reduced more preferentially than ethyl crotonate and butyl acrylate. The difference between monomethyl and unsubstituted compounds was small. The analogous tendency had also been observed in the Mukaiyama-Michael reaction.<sup>7</sup>

**Scheme 2<sup>a)</sup>**

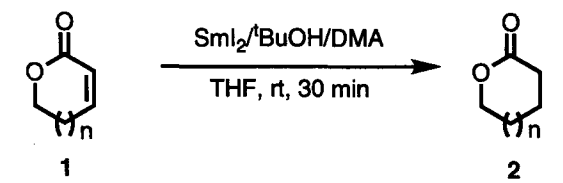


<sup>a)</sup> Reaction conditions: esters 0.2 mmol;  $\text{SmI}_2$  (2.5 equiv); <sup>t</sup>BuOH (2.0 equiv) DMA (0.5 ml); THF (3 ml); rt; 30 min. Yields were determined by GLC.

The results with cyclic  $\alpha,\beta$ -unsaturated esters<sup>9)</sup> are shown in Table 1. A clear distinction was observed between the 6- and 16-membered cyclic homologs: the latter reacted smoothly to give **2** in quantitative yield while no reaction occurred at all with the former.

Next, the reduction of  $\alpha,\beta$ -unsaturated ketones was investigated. The ketone was treated with  $\text{SmI}_2$  in the presence of <sup>t</sup>BuOH or MeOH in THF/DMA or HMPA at room temperature for 30 min (the detailed reaction conditions are given in Table 2). The reaction mixture was combined with water and extracted with dichloromethane. The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. The residue was purified by column chromatography on silica gel. It should be noted that the conjugate reduction always took place irrespective of additives although hydrodimerization had occurred with the  $\alpha,\beta$ -unsaturated esters in the presence of HMPA.<sup>10</sup> As in the case of the unsaturated lactones revealed above, no reaction took place with the 6-membered enone which was recovered quantitatively after attempted reaction (entries 1 and 2). On the other hand, the 12- and 15-membered enones underwent clean reduction to give saturated ketones **4** in good yields (entries 3-6).

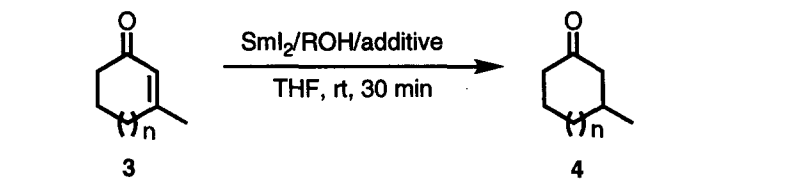
Table 1. SmI<sub>2</sub>-Promoted Conjugate Reduction of  $\alpha,\beta$ -Unsaturated Lactones of Different Ring Size.



n	yield (%) of 2 <sup>a)</sup>	recovery (%) of 1 <sup>a)</sup>
1	0	85
11	88	0

<sup>a)</sup> Isolated yield after column chromatography.

Table 2. SmI<sub>2</sub>-Promoted Conjugate Reduction of  $\alpha$ -Enones of Different Ring Size.



entry	n	react. conditn. <sup>a)</sup>	yield (%) of 4 <sup>b)</sup>	recovery (%) of 3 <sup>b)</sup>
1	1	A	0	96
2		B	0	91
3	7	A	82	0
4		B	87	0
5	10	A	80	0
6		B	89	0

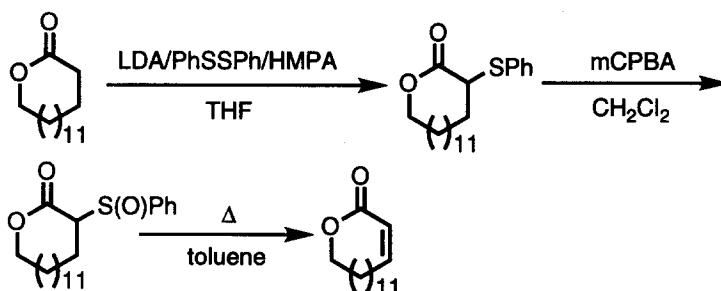
<sup>a)</sup> Reaction conditions: A: ketone (0.2 mmol), SmI<sub>2</sub> (0.4 mmol), MeOH (0.4 mmol), HMPA (0.4 ml), THF (0.4 ml); B: ketone (0.2 mmol), SmI<sub>2</sub> (0.5 mmol), <sup>t</sup>BuOH (0.4 mmol), DMA (0.5 ml), THF (3 ml).

<sup>b)</sup> Isolated yield after column chromatography.

As a result, it is strongly supported that the  $\text{SmI}_2$ -promoted conjugate reduction is initiated by oxidative addition of  $\text{SmI}_2$  to generate the enolate radical on the following basis. First, the more substituted the substrates, the more readily they are reduced. This is consistent with the well-recognized idea that the more substituted the carbon center, the more stable the resulting radical. Next, macrocyclic lactone and enones undergo smooth reduction while no reaction occurs with the 6-membered analogs at all. The rotation of  $\alpha,\beta$ -carbon-carbon bond facilitates to generate the radical species leading to localization of the spin density on the  $\beta$ -carbon. These results are quite similar to those observed in Mukaiyama-Michael reaction of ketene silyl acetals in all respects. In other words, the electron transfer mechanism of this reaction has found support from the samarium chemistry.

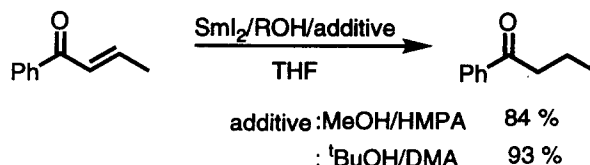
### References and Notes

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- The macrocyclic lactone was prepared as follows:



Cf: Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, 98, 4887.

- This is also the case for the acyclic enone.



(Received in Japan 11 January 1997; revised 10 February 1997; accepted 14 February 1997)