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First Example of Samarium Diiodide-Promoted Sequential Cyclization and Ring-Expansion Reactions of α-Bromomethyl Cyclic β-Keto Esters to Homologated γ-Keto Esters

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Abstract: SmI_2 reductions of some aromatic as well as aliphatic α-bromomethyl cyclic β-keto esters produced one-carbon homologated γ-keto esters in modest to good yields.

Various examples of reductive transformations of organic functional groups promoted by samarium diiodide (SmI_2) have been reported since Kagan's introduction of this reagent to synthetic organic reactions.[1,2] For example, carbonyl groups are reversibly reduced to ketyls, and reduction of carbon-halogen bonds undergoes dissociative electron transfer to give carbon radicals.[3] Therefore, the intramolecular Barbier reaction is intriguing since the substrates possess both carbonyls and carbon-halogen bonds. Despite the apparent mechanistic complexity due to the possibility of competitive reduction of carbonyls and carbon-halogen bonds,[4] there have been many successful synthetic applications which often demonstrated excellent chemo- and stereoselectivity.[2] Thus, we became interested in SmI_2 reductions of α-haloalkyl cyclic β-keto esters which have been subjected to free radical reactions to give the homologated γ-keto esters.[5] Although many examples of intramolecular samarium Barbier reactions have been reported,[2] to the best of our knowledge, there is no previous example of a cyclization and ring-expansion sequence promoted by SmI_2. Therefore, we decided to investigate the samarium diiodide reduction of some α-bromomethyl cyclic β-keto esters (Chart 1 and Table 1).

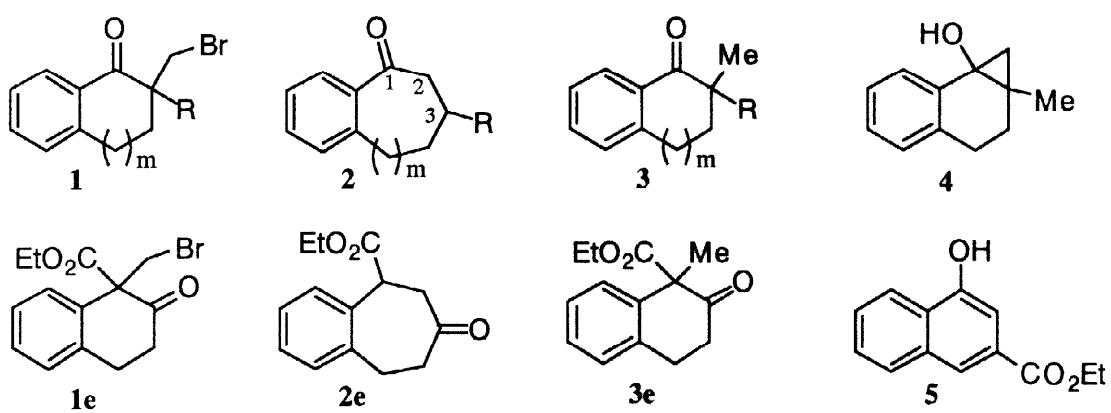

Chart 1

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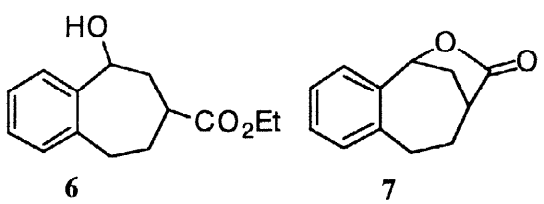
Table 1. SmI_2 Reductions of α-Bromomethyl Benzocyclic β-Keto Esters and Related Ketone.[a)]

Entry	1	m	R	R'OH[b)]	HMPA[c)]	Conv. %	Yields / % 2	3	4	5
1	**1a**	1	CO_2Et	0	0	>99	65	<2	-	-
2	**1b**	1	Me	0	0	100	0	0	98	-
3	**1c**	2	CO_2Et	0	0	100	71	0	-	-
4	**1d**	0	CO_2Et	0	4	100	12	0	-	10
5	**1d**	0	CO_2Et	MeOH, 2	4	>99	29	<1	-	<1
6	**1d**	0	CO_2Et	*t*-BuOH, 2	4	97	35	3	-	2
7	**1e**	-	-	MeOH, 20	0	100	90	0	-	-

a) **1** (0.50 mmol), SmI_2 (2.2 equiv. *vs.* **1**), THF (12.5 ml), room temp., 30 min (see ref. 6). b) equiv. *vs.* **1**. c) equiv. *vs.* SmI_2.

When we first conducted the reaction of **1a** with SmI_2, the ring-expanded ketone **2a** was obtained with a small amount of simply debrominated ketone **3a** (entry 1 in Table 1).[6,7] In the presence of MeOH (20 equiv. *vs.* **1a**), further reduction of **2a** was observed to give the corresponding alcohol **6** (27%) and the lactone **7** (10%) along with 8% of **2a** and 27% of recovered **1a**. Therefore, the deuterium labeling experiment was performed by the addition of a deuterium source to the resulting mixture of **1a** and SmI_2. Then, we found that the ratio of deuterium incorporated at C_3 of **2a** was about 76% independent of the kind of deuterium source (D_2O and MeOD), which would suggest that the samarium enolate is the plausible precursor of **2a**. The samarium enolate seems to be rather unstable since the yield of **2a** was significantly reduced (24%) after 24 h. However, it was indicated that HMPA could prevent the decomposition of the samarium enolate by the fact that 63% of **2a** was isolated when **1a** was treated with SmI_2 for 30 min followed by 24 h stirring with HMPA (4 equiv. *vs.* SmI_2). Thus, when the resulting mixture of **1a** and SmI_2 was treated with HMPA followed by allyl iodide (5 equiv. *vs.* **1a**) for 24 h, 31% of C_3-allylated ring-expanded ketone **8a** was isolated along with 24% of **2a**. Interestingly, when the ethoxy carbonyl substituent was replaced by methyl, 98% of the cyclopropanol **4** was isolated in the reaction of **1b** with SmI_2 (entry 2). Similarly, when **1c** was treated with SmI_2, 71% of **2c** was isolated (entry 3). A deuterium labeling experiment using MeOD revealed that 89% of hydrogen at C_3 of **2c** was deuterated. Allylation product **8c** was also obtained in 56% yield along with 5% of **2c**.



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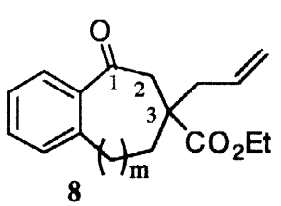

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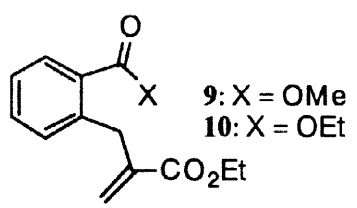
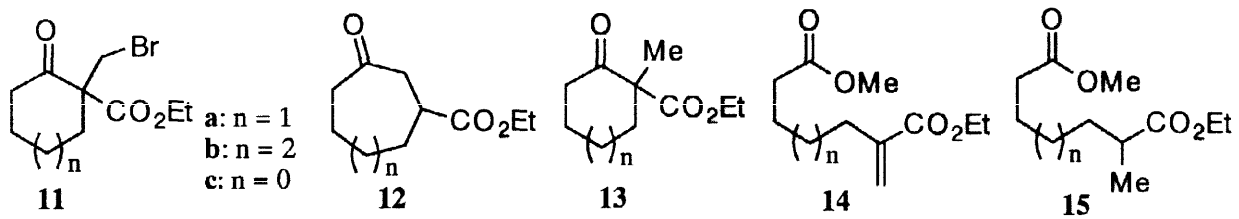


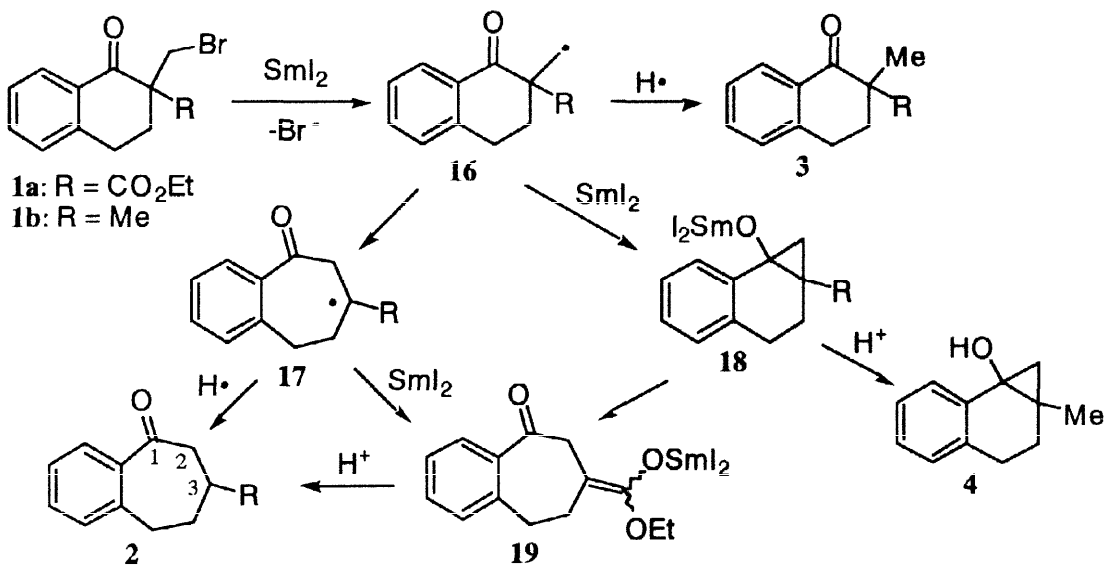
Unexpectedly, the reaction of **1d** with SmI_2 afforded a complicated mixture containing **2d** as a minor component whose isolation was not succesful. When the reaction was conducted in the presence of HMPA, **5**[8] (10%) as well as **2d** (12%) were isolated (entry 4). Eventually, we found that both HMPA and a proper proton source such as MeOH and *t*-BuOH were necessary to prevent the formation of **5** and to increase the

yields of **2d** (entry 5 and 6). The modest yields of **2d** are partly due to the ring opening of **1d** to give **9** (16%) and **10** (6%), respectively. The origin of ethoxide to produce **10** is unclear for the reaction with *t*-BuOH.

The reaction of **1e** with SmI_2 produced **2e** in low yield (27%). We then suspected that the samarium enolate decomposed before converting to **2e**. If so, an efficient trapping of the samarium enolate was expected to improve the yield of **2e**. Indeed, when SmI_2 was added into **1e** in the presence of MeOH, the yield of **2e** was significantly increased (entry 7). Since **2e** is a non-conjugated ketone which is considered to be less reactive than an aromatic one like **2a**, further reduction of **2e** by SmI_2 would not be a serious concern. This information is particularly encouraging when the SmI_2-promoted method is applied to other aliphatic substrates. Then, we conducted the SmI_2 reductions of bromomethyl keto esters **11a**, **11b** and **11c** in the presence of MeOH. In the reaction of **11b**, the corresponding ring-expanded ketone **12b** was obtained in 89% yield. On the other hand, the yields of **12a** and **12c** were modest; 44% and 39%, respectively, due to the substantial ring opening of **11a** and **11c** by the methoxide anion to give **14a** (8%) and **14c** (16%) together with their reduced forms **15a** (15%) and **15c** (9%). Debrominated-ketones **13** could not be isolated.



The mechanistic scheme is represented for the reaction of **1a** and **1b** with SmI_2 (Scheme 1). Single-electron transfer to **1** from SmI_2 would produce the carbon radical **16**.[9] The sequence for the radical cyclization and ring-expansion (**16**→**17**) is already known.[5,12] The formed radical **17** abstracts hydrogen to give **2**; however, this route appears to be a minor one since the deuteration percent at C_3 of **2** was found to be relatively high. This would indicate the existence of the route from **17** to **19**. Another possibility must be the reduction of **16** by SmI_2 which affords cyclopropoxide **18**. Subsequent ring-opening of **18** gives **19**. The



Scheme 1

conversion of **18** to **19** appears to be assisted by the electron-withdrawing ethoxy carbonyl. Indeed, in the case of **1b**, the cyclopropanol **4** was isolated in high yield.

In summary, we have found SmI_2 was able to promote the conversion of α-bromomethyl cyclic β-keto esters to the corresponding one-carbon homologated γ-keto esters in modest to good yields. Although the scope and limitation were not fully established,[13] this method could be complementary to the traditional free radical method.[14]

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6. General experimental procedure for the reaction of **1** with SmI_2: A THF solution (1.5 ml) of **1** was added into a 0.1M THF solution (11ml) of SmI_2 under N_2. The order of addition of the solutions was reversed for the reactions of **1e** and **11a-c**. The resulting mixture was stirred for 30 min at room temperature followed by saturated $NaHCO_3$. For deuteration and allylation, the mixture was stirred for a further period after addition of appropriate electrophiles. Crude reaction products were separated by silica gel column chromatography and TLC.

7. Compounds **1a**, **1c**, **1e**, **2a**, **2c**, **2e**, **3a**, **3c**, **3e**, **11a-c**, **12a-c**, and **13a-c** are known.[5] The structures of other compounds were determined by their IR and NMR data.

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9. Aromatic carbonyls are easily reduced by SmI_2; on the other hand, the reduction of alkyl bromides does not proceed smoothly by SmI_2 in the absence of HMPA.[1,10] Therefore, the reaction of **1** would be initiated by single-electron transfer (SET) from SmI_2 to the ketone carbonyl giving ketyl. Since it is proposed that ketyls could irreversibly reduce the distant carbon-halogen bonds via intramolecular single-electron transfer,[11] the formation of **16** from the initially formed ketyl would be expected.

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13. SmI_2 reductions of other substrates such as ethyl α-bromoethyl, α-bromopropyl, α-bromopropenyl, and α-bromobutenyl-1-tetralone-2-carboxylates were also conducted. However, no ring expansion products were obtained.

14. We independently conducted free radical reactions of representative **1** with Bu_3SnH : a benzene solution (100ml) of **1a** (0.50 mmol), Bu_3SnH (1.0 equiv. *vs.* **1a**), and AIBN (0.10 equiv. *vs.* **1a**) was refluxed under N_2 for 6 h. The reaction solution was subjected to DBU workup[15] followed by silica gel column chromatography and TLC to give **2a** (68%) and **3a** (10%). Similarly, **2c/3c** (19/27%), **2d/3d** (63/8%), **2e/3e** (72/10%) were obtained. The yields of **2c** and **2d** (>60%) were greater than the reported values while the yield of **2b** is similarly low to that in the previous report:[5c] **2a** (39%), **2c** (25%), **2e** (51%).

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