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The first example of samarium diiodide-promoted intramolecular ketone–ester coupling of ketones tethering acyloxyalkyl side chains producing 2-hydroxy cyclic hemiacetals

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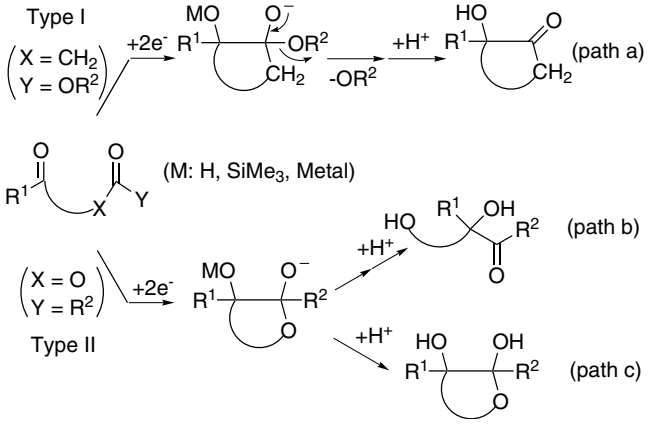
Abstract—The reaction of samarium diiodide with some cyclic and acyclic ketones tethering acyloxyalkyl side chains produced 2-hydroxy cyclic hemiacetals in moderate to good yields, in which an intramolecular addition of samarium ketyl radicals to distant ester carbonyls would be involved.

Samarium diiodide (SmI_2)[1]-promoted intramolecular coupling reactions of ketone carbonyls with other functional groups to produce various carbocycles and heterocycles.[2] Although there have been several examples of intramolecular ketone–ester coupling reactions under various electron transfer conditions,[3] the reaction of keto ester substrates using SmI_2 as a reductant has been less explored.[4] In these examples, a common structure in the substrates is an alkoxycarbonyl-substituted ketone ($X = CH_2$, $Y = OR^2$ in Scheme 1, named Type I) and it was commonly proposed that an intramolecular addition of either ketyl radicals or ketyl-derived carbanions to distant ester carbonyls followed by the release of alkoxy anions would occur to produce 2-hydroxy cyclic ketones (path a).

Recently, we discovered novel examples of SmI_2-promoted intramolecular ketone–ester coupling of certain types of cyclic keto esters, also categorized in Type I, and the following rearrangements giving ring-expansion products.[5] On the other hand, the SmI_2 reductions of ketones tethering acyloxyalkyl side chains ($X = O$, $Y = R^2$ in Scheme 1, named Type II) are unprecedented.[6] Therefore, it should be interesting to investigate the SmI_2-promoted intramolecular ketone–ester coupling reaction of such substrates, and to find out whether the expected cyclic intermediates undergo a carbon–oxygen bond cleavage to give dihydroxy ketones (path b), or are protonated to give cyclized products (path c). In this paper, we will report our preliminary results and discussion on the reactions of some aromatic ketones tethering acyloxyalkyl side chains with SmI_2, in which the expected intramolecular ketone–ester coupling did occur to produce 2-hydroxy cyclic hemiacetals in moderate to good



Scheme 1.

Keywords: Samarium diiodide; Intramolecular ketone ester coupling; Cyclic hemiacetals.
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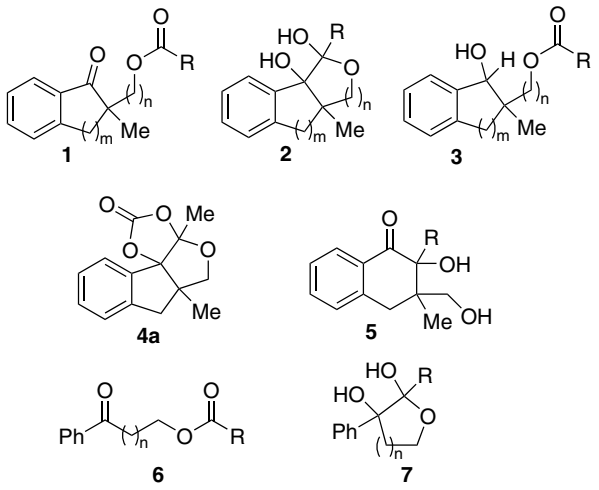


Chart 1.

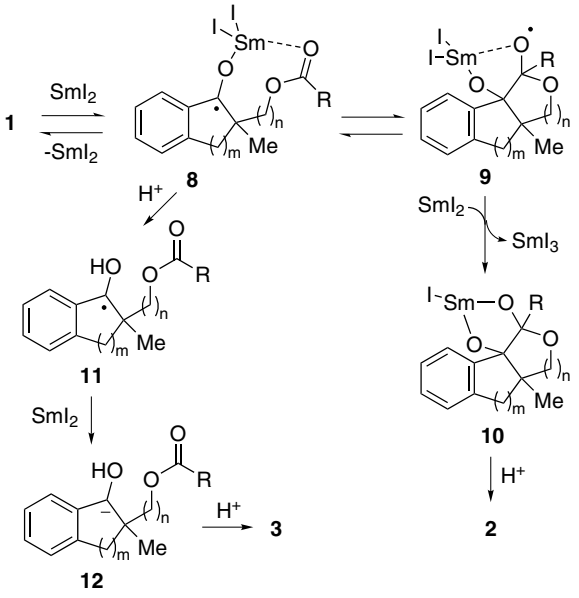
yields. The representative keto ester substrates and products are shown in Chart 1.

We first examined the reaction of cyclic keto esters **1** with SmI_2, and the results are summarized in Table 1.[7] Regardless of the presence or absence of *t*-BuOH, cyclic hemiacetals **2** were obtained in moderate to good yields. The stereochemistry of 1,2-dihydroxy groupings in **2** was assigned as the cis-configuration, which is consistent with the observation that the treatment of **2a** with dimethyl carbonate gave cyclic carbonate **4a**.[8,9] Interestingly, when the reaction solution of **1a** and SmI_2 in the absence of *t*-BuOH was worked-up after 24 h, dihydroxy tetralone derivative **5a** was isolated (48%) instead of **2a**.[10] It should be also noted that the addition of an excess amount of *t*-BuOH (20 equiv) still produced **2a** as a major product (entry 3), while a large excess of *t*-BuOH (100 equiv) decreased the yield of **2a** and resulted in the formation of alcohol **3a** (10%) (entry 4). On the other hand, the addition of MeOH (20 equiv) completely suppressed the formation of **2a** and gave **3a** in a low yield (14%). Substituent R of the ester moiety in **1** was found to influence the reaction progress. For example, the yield of **2c** from phenyl ester **1c** was better than that of **2a** (compare entry 7 to entry 1), and the yield of **2d** from formyl ester **1d** was significantly increased (compare entry 9 to entry 1). This tendency was also observed in the reactions of other substrates. For example, the reaction of **1e** produced six-membered cyclic hemiacetal **2e** (entry 11); however, the reaction of the corresponding methyl ester (R = Me, $m = 1$, $n = 2$, not shown) produced a rather complex mixture in which the expected cyclic product did not exist. Also, in the reactions of acyclic keto ester substrates **6** with SmI_2, methyl ester **6a** (R = Me, $n = 1$) afforded a complex mixture from which no **7a** was isolated, and, however, formyl esters **6b** (R = H, $n = 1$) and **6c** (R = H, $n = 2$) gave **7b** (40%) and **7c** (40%), respectively.

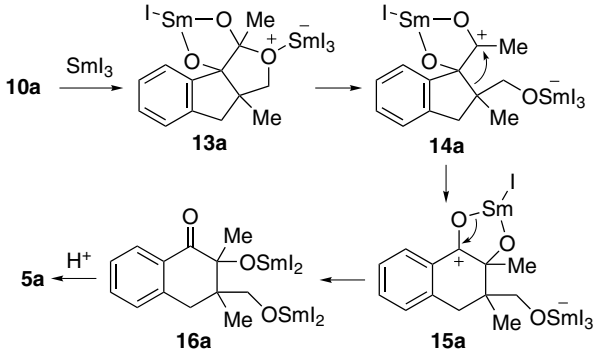
Table 1. SmI_2 reductions of keto-ester **1**

Entry	1	R	*m*	*n*	*t*-BuOH (equiv vs **1**)	Conv of **1** (%)	Yield of **2** (%)
1	**1a**	Me	1	1	0	100	52
2	**1a**	Me	1	1	2	100	64
3	**1a**	Me	1	1	20	95	57
4	**1a**	Me	1	1	100	83	30
5	**1b**	Me	2	1	0	100	63
6	**1b**	Me	2	1	2	100	44
7	**1c**	Ph	1	1	0	100	61
8	**1c**	Ph	1	1	2	90	52
9	**1d**	H	1	1	0	100	77
10	**1d**	H	1	1	2	100	82
11	**1e**	H	1	2	0	100	65
12	**1e**	H	1	2	2	100	62

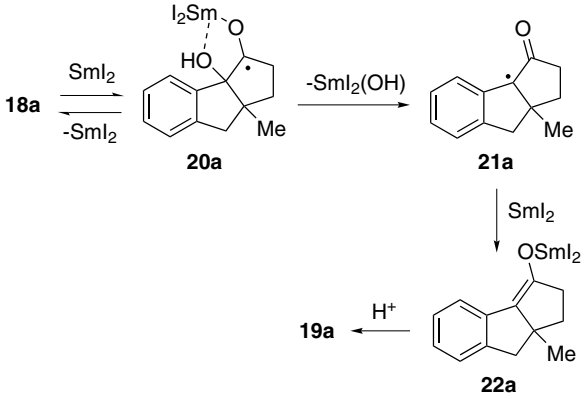
On the basis of the above results and our related studies,[5] a plausible reaction mechanism for the reaction of **1** with SmI_2 is proposed in Scheme 2. The single electron transfer from SmI_2 to ketone carbonyl of **1** gives samarium ketyl radical **8**, which undergoes intramolecular addition to ester carbonyl. The chelation interaction between the samarium center coordinated with ketyl and ester carbonyl in **8** would be expected similarly to other related cases,[11] which is consistent with the *cis*-diol structures of **2** described above. The formed oxy radical **9** is reduced by another equivalent of SmI_2 to give cyclic dialkoxide **10**, which is protonated to give **2**. If **8** is intercepted by a proton donor, the protonated ketyl **11** is formed. Then, **11** is reduced by SmI_2 and subsequently protonated to give **3**.[12] This sequence is a well-recognized process for the SmI_2-promoted conversion of ketones to alcohols in the presence of proton donors.[1,2] Therefore, it was rather surprising to find that **2** was still obtained in the presence of *t*-BuOH (100 equiv). Among the possible rationalizations would be that this intramolecular ketyl–ester coupling competitively proceeds to protonation of ketyl. Therefore, choosing a suitable, appropriately acidic, proton donor and adjusting its quantity to be added are important to obtain cyclic hemiacetals.



Scheme 2.



Scheme 3.



Scheme 4.

It should be also necessary to rationalize the formation of **5a**. A plausible mechanism is proposed in Scheme 3. The existing Lewis acidic samarium ion(III) perhaps catalyzes this rearrangement. Namely, the opening of the tetrahydrofuran ring in **13a** proceeds to give tertiary carbocation **14a**. Following 1,2-carbon shift[13] in **14a** produces benzyl cation **15a**, which is converted to **16a**. The fact that the corresponding rearrangement products **5b–d** were not obtained or were obtained in quite low yields clearly suggests that these cationic rearrangements would be sensitive to the nature of the substituent (R) and the size of the fused ring.[14]

In order to investigate the influence of the structure of the ester moieties, we briefly conducted reactions of δ-keto esters **17** as well as keto carbonates **23**, which have not been previously subjected to SmI_2 reduction (Chart 2).[4,5] In the reaction of **17a** ($m = 1$) with SmI_2, **18a** (39%) along with **19a** (9%) were obtained. The production of **19a** must be rationalized by the assumption that the initially formed **18a** is further reduced by SmI_2. In fact, when **18a** was treated with SmI_2, **19a** was obtained in a good yield (79%). A plausible reaction pathway for this transformation, which is related to SmI_2-promoted reduction of α-heterosubstituted ketones,[15] is presented in Scheme 4. Again notably, the addition of *t*-BuOH (2 equiv) did not suppress ketone–ester coupling but significantly increased the yield of **19a** (32%) without the isolation of **18a**. In the reaction of **17b** ($m = 2$), **18b** and **19b** were isolated in 48% and 17% yields, respectively, while only **19b** (38%) was obtained upon the addition of *t*-BuOH. On the other hand, SmI_2 reduction of **23a** ($m = 1$) produced 2-hydroxy γ-lactone **24a** (56%) while the addition of *t*-BuOH (2 equiv) did not greatly affect the yield of **24a** (66%). Moreover, the reaction of **23b** ($m = 2$) with SmI_2 produced **24b** in an excellent yield (96%).

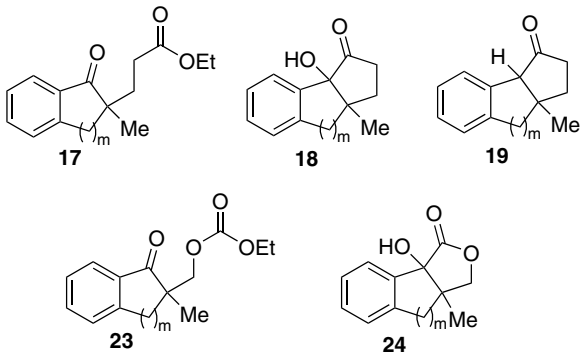


Chart 2.

In conclusion, we have first demonstrated that the reactions of some cyclic and acyclic ketones tethering acyloxyalkyl side chains with SmI_2 promote novel intramolecular addition of samarium ketyl radicals to ester carbonyls, and thus provide a new entry to synthesize 2-hydroxy cyclic hemiacetals, which are structurally related to bioactive natural products.[16] Also, some keto carboxylates as well as keto carbonates were found to undergo SmI_2-promoted intramolecular ketone–ester coupling reactions.

Acknowledgments

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7. *A typical experiment*: A THF solution (1.0 mL) of indanone **1a** (0.50 mmol) was added dropwise under N_2 during 3 min to the THF solution (11.0 mL) of SmI_2 (1.10 mmol) and *t*-BuOH (0.9 mL, 1.0 mmol) at room temperature. The reaction mixture was stirred for 30 min followed by quenching with 0.1 M HCl (10 mL), and was stirred under air for 10 min. The resulting mixture was extracted with Et_2O (30 mL × 3), and then the organic layer was washed with saturated aqueous $NaHCO_3$, $Na_2S_2O_3$, and NaCl (30 mL), and dried over $MgSO_4$. The residue obtained by the concentration of the extract was separated by thin-layer chromatography on silica gel (EtOAc/benzene = 1:6) to give **2a** (0.32 mmol, 64%). *The spectral data of* **1a** *and* **2a**. Compound **1a**: IR (neat) 1750, 1720, 1240 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.79–7.76 (m, 1H), 7.66–7.60 (m, 1H), 7.49–7.37 (m, 2H), 4.25 (m, 2H), 3.28 (d, $J = 17.0$ Hz, 1H), 2.93 (d, $J = 17.0$ Hz, 1H), 1.91 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.9, 172.8, 154.4, 137.6, 137.1, 129.6, 128.6, 126.4, 70.3, 50.9, 40.1, 23.2, 22.8. Compound **2a**: IR (neat) 3412, 1118 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.34–7.15 (m, 4H), 3.90 (d, $J = 8.8$ Hz, 1H), 3.80 (d, $J = 8.8$ Hz, 1H), 3.08 (d, $J = 16.3$ Hz, 1H), 2.88 (d, $J = 16.3$ Hz, 1H), 1.25 (s, 3H), 1.15 (s, 3H), two hydroxy peaks did not appear; ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.5, 142.4, 128.8, 126.7, 125.2, 124.5, 104.8, 92.6, 76.2, 52.8, 45.9, 25.3, 19.4. Reactions of other substrates **1**, **6**, **17**, and **20** with SmI_2 were performed in essentially the same manner as the above-described procedure. These substrates and products **2**, **3**, **7**, **18**, **19**, and **21** were satisfactorily characterized by their ^1H NMR, ^{13}C NMR, and IR data.
8. *Spectral data of* **4a**: IR (neat) 1802, 1092 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.38–7.21 (m, 4H), 4.11 (d, $J = 9.7$ Hz, 1H), 3.87 (d, $J = 9.7$ Hz, 1H), 3.09 (d, $J = 16.0$ Hz, 1H), 2.92 (d, $J = 16.0$ Hz, 1H), 1.30 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 152.4, 141.2, 134.8, 130.4, 127.7, 125.4, 124.5, 115.5, 101.4, 75.0, 55.7, 43.3, 22.0, 17.6.
9. Also, the cis-configuration of dihydroxy substituents of **2c** was demonstrated by X-ray crystallography. The details will be reported in a full paper.
10. *The spectral data of* **5a**: IR (neat) 3452, 1686 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.02–7.98 (m, 1H), 7.60–7.51 (m, 1H), 7.39–7.21 (m, 2H), 4.15 (d, $J = 11.2$ Hz, 1H), 3.45 (d, $J = 11.2$ Hz, 1H), 2.95 (d, $J = 17.6$ Hz, 1H), 2.66 (d, $J = 17.6$ Hz, 1H), 1.39 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.5, 140.3, 134.5, 129.6, 129.2, 127.6, 126.9, 79.5, 68.8, 43.3, 37.1, 21.2, 17.2. In the cases of **1b**–**d**, prolonged reactions did not significantly change the product distributions. For example, **2b**–**d** were still major products, 55%, 58%, and 55%, respectively. And only small amounts of **5c** (4%) and **5d** (5%) were isolated.
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