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Samarium diiodide-promoted intramolecular ketone–ester coupling reaction: novel cyclization and ring expansion pathway

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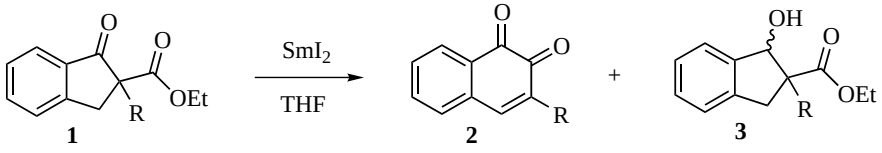
Abstract—When ethyl 2-substituted-1-indanone-2-carboxylates were treated with samarium diiodide (SmI_2), ring expansion products such as 3-substituted-1,2-naphthoquinones were isolated. Alcohols were also obtained as the mixture of *cis*- and *trans*-isomers of hydroxy and ester substituents. A reaction mechanism involving intramolecular addition of samarium ketyl radicals to ester substituents followed by ring expansion was proposed for the formation of the one-carbon homologated products. Similarly, reaction of ethyl 1-substituted-2-oxo-1-cyclopentanecarboxylates with SmI_2 produced 3-substituted-2-hydroxy-2-cyclohexenones along with the corresponding alcohols.

Samarium diiodide (SmI_2) has been recognized as a most useful single-electron reductant in synthetic organic chemistry since its application was first reported by Kagan and co-workers.[1,2] SmI_2-promoted intramolecular reductive coupling reactions of ketone carbonyls with other functional groups, for example, formyl, chloro acyl, cyano, olefinic, haloalkyl substituents have been extensively investigated to achieve the construction of various carbocycles by Molander and other chemists.[2,3] The involvement of ketyl radicals has been often proposed as the key intermediates in these reactions.[3,4] Similarly, ketone–ester coupling reactions would be expected to occur since such reactions are already known under the other electron transfer conditions.[5] In fact, a SmI_2-promoted intramolecular ketone–ester coupling reaction was recently reported.[6] However, one may not expect that ester substituents readily react with samarium ketyl radicals when other reactive functional groups co-exist in the same molecules. In this communication, we will report that SmI_2 could promote novel ketone–ester coupling followed by ring expansion reactions of ethyl 2-substi-

Table 1. Reaction of various ethyl 2-substituted-1-indanone-2-carboxylates with SmI_2



1 **2** **3**

Exp.	1	R	Conv. (%)	Yield (%)	
				2	3 (*cis*:*trans*)
1	**1a**	$(CH_2)_3Br$	95	60	14 (9:5)
2	**1b**	Me	100	44	41 (1:1)
3	**1c**	$(CH_2)_2CH_3$	100	54	19 (2:1)
4	**1d**	CH_2Ph	100	60	10 (8:5)
5	**1e**	$CH_2CH{=}CH_2$	99	60	24 (8:5)
6	**1f**	$(CH_2)_3CN$	100	55	28 (6:5)

Keywords: samarium diiodide; β-ketoester; samarium ketyl radical; ketone–ester coupling; ring expansion; 1,2-naphthoquinone.

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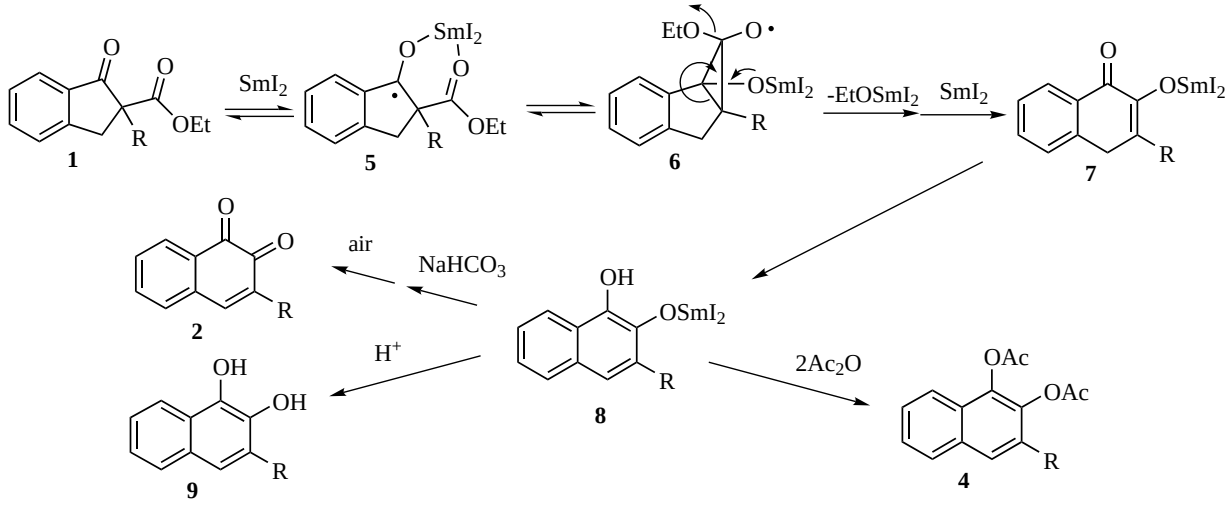
tuted-1-indanone-2-carboxylates as well as ethyl 1-substituted-2-oxo-1-cyclopentanecarboxylates. Surprisingly, carbon–bromine bond, carbon–carbon double bond, and cyano substituent in these substrates did not react and remained in the products.

When ethyl 2-(3-bromopropyl)-1-indanone-2-carboxylate **1a**[7] was treated with 2.2 equiv. of SmI_2 under N_2 atmosphere for 30 min in THF, an unexpected orange-colored solid was isolated.[8] On the basis of its spectral data indicating that bromopropyl side chain still existed, it was identified as 3-(3-bromopropyl)-1,2-naphthoquinone **2a**.[9] Alcohols **3a**[10] were also obtained as a mixture of *cis*- and *trans*-isomers of hydroxy and ester substituents. The observation suggests that the ketone carbonyl part of **1a** is first reduced by SmI_2, and that the formed samarium ketyl radical reacts not with the carbon–bromine bond but with the ester substituent. We soon realized that this novel rearrangement similarly occurred for the reactions of other indanone derivatives **1**[8] with SmI_2 (Table 1). Further interesting aspects are pointed out in Table 1. The ratio of **2** to **3**[10] changed depending on the change of substituent R:bulky R increased the relative yield of **2** (see entries 2, 3, and 4). Unactivated olefin seems to be a tolerable substituent for the reaction (entry 5).[3i] Again surprisingly, a nitrile group was inert under the reaction conditions (entry 6).[3f,g,h]

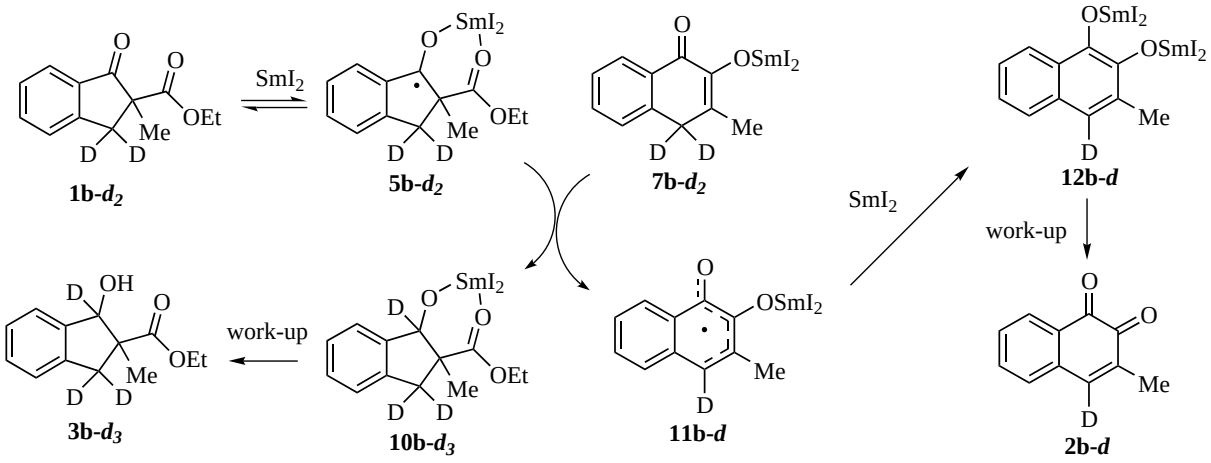
In order to gain more information on the reaction mechanism, several experiments using **1b** with SmI_2 were conducted. In the above experiments,[8] when the reaction flasks were opened and saturated $NaHCO_3$ was added to the reaction mixtures, the color of the solutions gradually changed from colorless to orange which indicated the formation of **2**. On the other hand, addition of 1N HCl to the resulting reaction mixture of **1b** with SmI_2 did not cause the color change to orange and gave a crude mixture whose ^1H NMR indicated the existence of 1,2-dihydroxy-3-methylnaphthalene **9b**.[11] When the reaction mixture was treated with acetic anhydride (4 equiv.) for 12 h, 1,2-diacetoxy-3-methylnaphthalene **4b**[12] was isolated in 42% yield along with **3b** (6%) and the acetate of **3b** (27%) without the formation of **2b**.

On the basis of the observations made, a plausible mechanism for this novel cyclization and ring expansion reaction is proposed in Scheme 1. Single electron transfer from SmI_2 to the ketone carbonyl of **1** gives the ketyl radical **5**. Subsequent ketyl radical cyclization, which might be reversible, gives the cyclopropoxy radical **6**. Opening of the cyclopropane ring of **6** liberating the ethoxy anion, followed by reaction with another equivalent of SmI_2, yields the α-keto enolate **7**. This ring-opening is accelerated by the bulky substituent R since some steric repulsion between R and $OSmI_2$ substituents in **6** is expected (see Table 1). The enolate **7** tautomerizes to naphthoxide **8**. Protonation of **8** gives **9** while **8** may be readily oxidized by air to produce **2** under the basic conditions. On the other hand, **8** is sequentially acetylated by acetic anhydride to give **4** as an isolable product.

We next paid our attention to the mechanism for the formation of **3**. Reaction of **1b** with SmI_2 in the presence of *t*-BuOH (20 equiv.) produced only **3b** (61%, *cis*:*trans* = 1:4) without the formation of **2b** and **9b**. In this case, the ketyl radical **5b** is probably protonated and the formed carbon radical is reduced by SmI_2 followed by protonation to give **3b**. Indeed, when *t*-BuOH was replaced by *t*-BuOD, high deuterium incorporation at C_1 position of **3b** (98%-*d*) was observed. However, this mechanism can not rationalize the formation of **3** in the reactions described above since no proton donors such as alcohols were added.[8] Another possibility that **3** are produced through an aqueous work-up[13] is also unlikely since the treatment of the resulting reaction mixture of **1b** and SmI_2 with D_2O gave **3b** containing almost no deuterium. Therefore, we hypothesized that some sources of either hydrogen atom or proton may exist in the reaction system. It was then discovered that reaction of 3,3-dideuterio **1b**-d_2 with SmI_2 resulted in marked deuterium incorporation



Scheme 1.



Scheme 2.

at C_1 position of **3b** (70%-*d*). This observation suggests that a reaction mechanism such as Scheme 2 in which samarium ketyl radical **5b**-d_2 abstracts hydrogen atom from the enone **7b**-d_2 would be in part operating. If this explanation is correct, samarium ketyl radicals more efficiently generated than **5b** would predominantly react with **7b** to increase the formation of **2b**, and then would decrease the formation of **3b**. This indeed happened when benzophenone (0.6 mmol) was added to the reaction of **1b** (0.5 mmol) and SmI_2 (2.4 mmol), yielding 87% of **2b** without the formation of **3b** along with benzhydrol (54%) and benzpinacol (31%).[14]

Since it is supposed that the facile conversion from **8** to **2** is driven by the formation of a stable 1,2-naphthoquinone structure, the corresponding conversion is not expected to occur in the reaction of aliphatic substrates such as ethyl 1-substituted-2-oxo-1-cyclopentanecarboxylates **13** with SmI_2. In fact, 3-substituted-2-hydroxy-2-cyclohexenones **14**,[15] the enol forms of the α-diketones, were isolated in good yields (62% for 95% conv. of **13a**, 79% for 93% conv. of **13b**; 65% for 100% conv. of **13d**) (Scheme 3). The corresponding alcohols **15**[16] were also obtained (**15a**: 14%, **15b**: 13%, **15d**: 23%).

Acknowledgements

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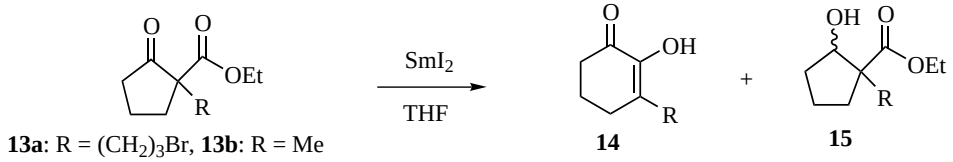

13a: R = $(CH_2)_3Br$, **13b**: R = Me
13d: R = CH_2Ph

Scheme 3.

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7. Indanone **1a** was prepared by NaH-promoted bromopropylation at the C_2 position of ethyl 1-indanone-2-carboxylate which was obtained by the ethoxy carbonylation of 1-indanone. Other indanones **1** were similarly synthesized.
8. Typical experimental procedure: A THF solution (1 mL) of indanone **1a** (0.5 mmol) was added dropwise under N_2 during 3 min to the THF solution (11 mL) of SmI_2 (1.1 mmol) at room temperature. The reaction mixture was stirred for 30 min, and then it was quenched with saturated aqueous $NaHCO_3$ solution (5 mL), and the solution was stirred under air for 10 min. The solution was extracted with Et_2O (3×20 mL), 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 crude reaction mixture obtained by the concentration of the extract was separated by column chromatography on silica gel (EtOAc:benzene = 1:6) to give naphthoquinone **2a** and alcohol **3a**. Reactions of other indanones **1** with SmI_2 were performed in the same manner.
9. Physical and spectral data of **2a**: Orange needles, mp 97–98°C (C_6H_6/n-C_6H_{14}); IR (KBr) 1690, 1664, 1584 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.06 (dd, $J=8$, 8 Hz, 1H), 7.63 (dd, $J=8$, 8 Hz, 1H), 7.45 (dd, $J=8$, 8 Hz, 1H), 7.33–7.27 (m, 2H), 3.46 (t, $J=6$ Hz, 2H), 2.63 (t, $J=7$ Hz, 2H), 2.19–2.05 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.9, 179.0, 142.0, 138.5, 136.0, 135.0, 130.6, 130.0 (2C), 129.4, 33.0, 30.8, 28.2. Other 1,2-naphthoquinones **2** including known **2b**, mp 121–122°C (observed); mp 121–122°C (lit. Takuwa, A.; Naruta, Y.; Soga, O.; Maruyama, K. *J. Org. Chem.* **1984**, *49*, 1857–1864) were similarly identified.
10. Identification of **3** were achieved by the comparison of the spectral data with those of the products obtained by the $NaBH_4$ reduction of **1**.
11. Diagnostic peaks of **9b** were observed in ^1H NMR of the reaction mixture of **1b**, **3b** and **9b**: δ 7.92 (d, 1H), 7.65 (d, 1H), 2.40 (s, 3H). Several attempts to isolate pure **9b** were not successful since concomitant conversion of **9b** to **2b** always occurred.
12. Physical and spectral data of **4b**: Colorless needles, mp 149–150°C (C_2H_5OH); IR (KBr) 1762 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.76–7.73 (m, 2H), 7.60 (s, 1H), 7.46–7.41 (m, 2H), 2.42 (s, 3H), 2.35 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.4, 170.2, 141.2, 139.5, 134.2, 132.2, 129.4, 128.9, 128.3 (2C), 128.2, 123.1, 22.5 (2C), 18.9.
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15. Physical and spectral data of **14b**: Colorless solid, mp 38°C; IR (KBr) 3416, 1670, 1644 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.10 (s, 1H), 2.49 (t, $J=6$ Hz, 2H), 2.36 (t, $J=6$ Hz, 2H), 2.03–1.91 (m, 2H), 1.91 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.2, 145.8, 132.8, 37.8, 32.5, 24.3, 19.0. **14a** and **14d** were similarly identified.
16. Identification of **15** were achieved by the comparison of the spectral data with those of the products obtained by the $NaBH_4$ reduction of **13**.