



Regioselective radical ring-opening reaction of bicyclo[4.2.0]octan-2-ones promoted by samarium(II) iodide

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Abstract—Radical ring-opening reactions of bicyclo[4.2.0]octanones, its C6 alkyl derivatives, and tricyclic ketones promoted by SmI₂ gave cyclohexanones via fission of the external cyclobutane bond. The CO₂Me, CN, and phenyl derivatives led to the production of the eight-membered ring compounds through cleavage of the central cyclobutane bond. Using this regioselective reaction, the synthesis of (±)-acorenone was achieved. © 2003 Elsevier Science Ltd. All rights reserved.

Samarium(II) iodide (SmI₂) has become increasingly important in organic synthesis because it can be used under mild and neutral conditions and functions as a one electron reductant.¹ Although the radical ring-closure reactions promoted by SmI₂ are well-documented, detailed information on the chemistry of radical ring-opening reactions promoted by SmI₂ is not available.² Recently we reported on the new and high-efficient skeletal rearrangement of bicyclo[4.2.0]octan-2-ones to bicyclo[4.2.1]nonanones and the use of this rearrangement as a pivotal step in the total synthesis of (±)-tetramethylmediterraneanol B.³ In an extension of these studies, we now report a systematic study of the radical ring opening of bicyclo[4.2.0]octan-2-ones **1a–n**, as promoted by SmI₂. We disclose here a remarkable effect of the C6 substituent on the regioselective radical ring-opening of cyclobutyl ketones and the application of this reaction to the synthesis of (±)-acorenone (**16**).

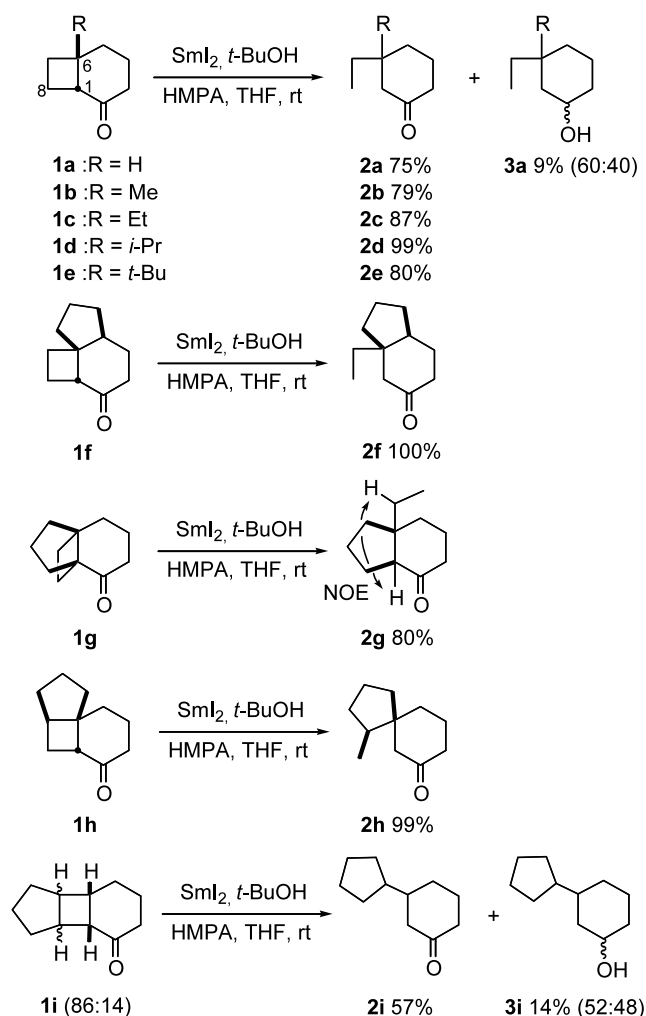
The reaction of bicyclo[4.2.0]octan-2-one **1a** with SmI₂, *t*-BuOH, and HMPA in THF gave the cyclohexanone **2a** and the over-reduced alcohol **3a** via fission of the external bond (C1–C8) (Scheme 1).⁴ In the case of ketones **1b–e**, which contain an alkyl group at C6, 3,3-disubstituted cyclohexanones **2b–e** were selectively

obtained in high yields regardless of the nature of the alkyl substituent. Moreover, reactions of tricyclic ketones **1f–i**, which have a cyclopentane ring fused on the bicyclo[4.2.0] unit, gave different types of carbocyclic compounds **2f–i**, respectively, via the cleavage of the external C1–C8 bond.

In order to examine the substituent effect at C6, we carried out reactions of ketones **1j** and **1k** having an electron withdrawing group such as CO₂Me and CN in a similar manner. Interestingly, the reaction of the ester-ketone **1j**, using MeOH as a proton source instead of *t*-BuOH, gave the cyclooctanols **4j** (18%) and the lactone **5** (55%), along with the recovered ketone **1j** (17%) (Scheme 2).⁵ The products **4j** and **5** were derived through fission of the central cyclobutane bond (C1–C6) followed by over-reduction and the subsequent lactonization of **4j**. In the case of the cyanoketone **1k**, the fission of the central bond was also observed. With 4 equiv. of SmI₂, cyclooctanone **6k** was obtained as a minor product, along with bicyclo[3.3.1]nonanone **7** in 81% yield. The fact that the isolated cyanoketone **6k** was quantitatively converted to the α-hydroxyketone **7** under the same conditions, suggests that the hydroxyketone **7** is produced by the reaction of **6k** with another SmI₂ during the course of the reaction.⁵ Moreover, the phenylketone **1l** also gave cyclooctane derivatives **4l**, **6l**, and **8**, and bicyclo[3.3.0]octanol **9**. As the amount of SmI₂ was increased and the reaction time prolonged, the yields of ketone **6l** and dimeric compound **8** decreased.

Keywords: bicyclo[4.2.0]octanones; radical ring opening; samarium(II) iodide; regioselectivity; acorenone.

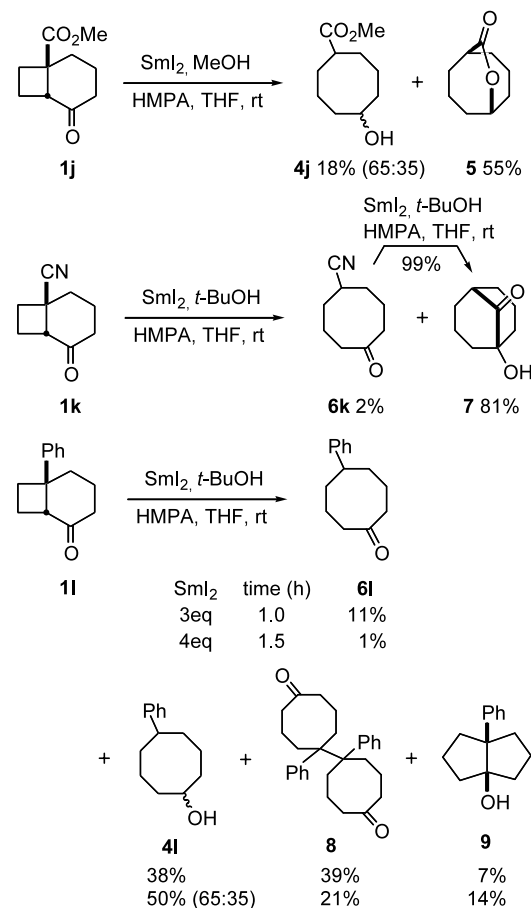
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Scheme 1.

A plausible reaction path is shown in Scheme 3. A one electron transfer from SmI_2 to ketone **1** generates the cyclobutylcarbinyl radical **10**. There are two pathways available for the radical **10** to react. In the case of $\text{R} = \text{H}$, alkyl, and tricyclic ketones **1a–i**, fission of the external cyclobutane bond (path a) produces the radical intermediate **11**. The over-reduction of the ketone **2** leads to the alcohol **3**. On the other hand, carbomethoxy-, cyano-, and phenyl-ketones **1j–l** gave the radical **12** via cleavage of the central cyclobutane bond (path b). In a similar manner, another one electron transfer followed by protonation of the organosamarium **13** leads to the cyclooctanone **6**. Radical dimerization of **12** gives the product **8**. Transannular cyclization of **13** (path c) yields the alcohol **9**. The over-reduction of **6** also leads to the alcohol **4** via the radical **14**. In the case of carbomethoxy-ketone **1j**, an intramolecular esterexchange reaction proceeds to give the lactone **5**. In the case of $\text{R} = \text{CN}$, the radical **14** undergoes an intramolecular ketyl-nitrile cyclization predominantly (path d) followed by protonation and subsequent hydrolysis to give the α -hydroxyketone **7**.⁶

Linking the bicyclo[4.2.0] unit to an appropriate unsat-

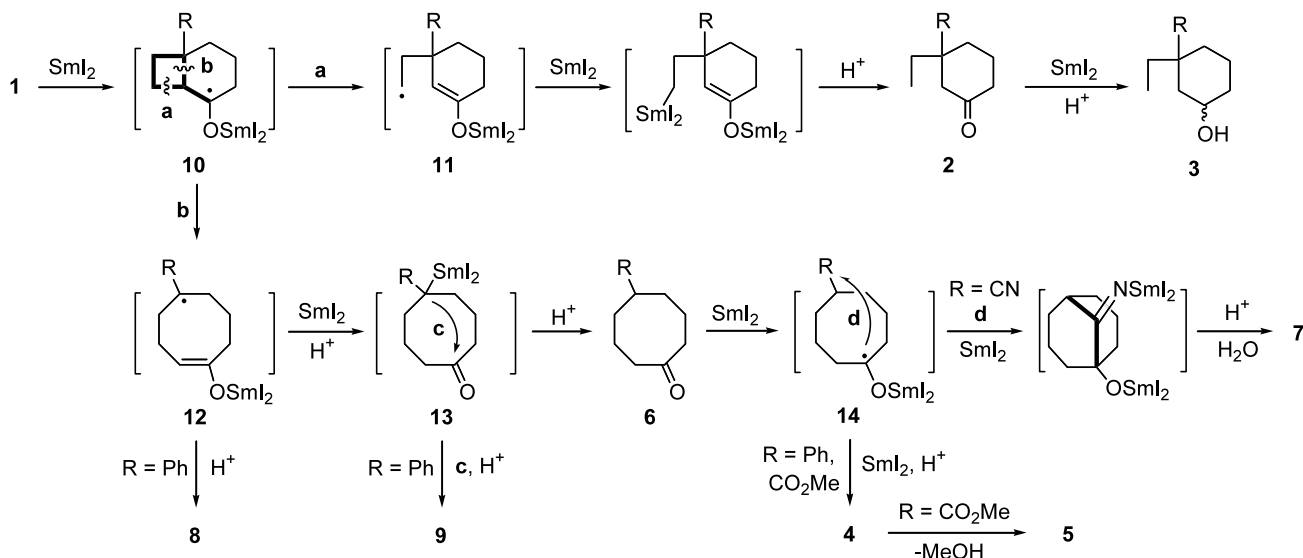


Scheme 2.

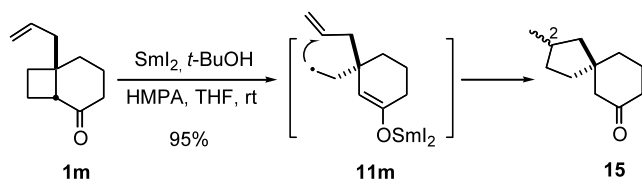
urated side chain, a cyclization via the radical **11** or **12** would be feasible as a secondary step. A favored process could be the well-known 5-*exo* cyclization of 5-hexenyl radicals.⁷ Treatment of the ketone **1m** bearing an allyl group at C6 with SmI_2 as described above gave the expected spiro[4.5]decanone **15** in 95% yield as a 62:38 mixture of C2 methyl epimers, suggesting the intermediacy of the radical **11m** (Scheme 4).

Finally, we demonstrate that the ring-opening reaction shown above is applicable to the synthesis of the sesquiterpene, (\pm)-acorenone (**16**). A similar reaction of the cyclobutane derivative **1n**⁸ with SmI_2 gave the ketone **2n** in 99% yield (Scheme 5). Since the transformation of **2n** to **16** has been established previously,⁹ a formal total synthesis of (\pm)-acorenone (**16**) was accomplished.

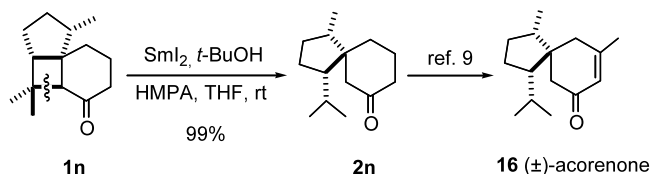
In summary, we found that the regioselective radical ring-opening reactions of bicyclo[4.2.0]octanones are promoted by SmI_2 , and the selectivity of the reaction is controlled by the C6 substituent, while the reason governing the regioselectivity is not clear at present. The radical reaction was applied to the selective synthesis of (\pm)-acorenone (**16**). The elucidation of factors that control the regioselectivity is currently in progress in our laboratory.



Scheme 3.



Scheme 4.



Scheme 5.

Acknowledgements

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- All new compounds gave satisfactory spectral data and high-resolution mass spectra. General experimental procedure is as follows: under an atmosphere of argon, Sm metal (99.9%, 423 mg, 1.66 mmol) and a magnetic stirring bar were placed in a two-necked 50 mL flask and equipped with a septum inlet. After the flask was flame-dried in vacuo, 1,2-diiodoethane (423 mg, 1.50 mmol) was placed in the flask, which was then purged with argon. THF (15 mL) was added via a syringe through the rubber septum with stirring. The mixture was stirred at room temperature for 3–5 h until a dark blue 0.1 M THF solution of SmI₂ was formed. The SmI₂–THF solution was added by cannular transfer at room temperature to a mixture of ketone **1** (0.5 mmol), *t*-BuOH or MeOH (2.0 mmol), and HMPA (1.78 mL, 10 mmol) in dry THF (20 mL) with stirring. Once the addition was complete, the deep purple color faded to an opaque gray. After 30 min, the reaction mixture was quenched with MeOH. 1N HCl was added to

dissolve the samarium salts. The aqueous portion was extracted with ether (four times), and the combined organic layers were washed with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$, saturated aqueous NaHCO_3 , and brine. The extracts were dried (MgSO_4), filtered, and concentrated under reduced pressure. The crude products were purified by silica gel chromatography.

5. Similar reaction using *t*-BuOH gave a complex mixture of products including a small amount of **4j** (2%) and **5** (2%) at low conversion (54% recovery of **1j**). Using EtOH, the ethyl ester instead of the methyl ester **4j** was obtained in

25% yield due to transesterification, along with **5** (20%).

6. This finding prompted us to investigate the intramolecular ketyl-nitrile cyclization of cyclic γ -cyanoketones: Kakiuchi, K.; Fujioka, Y.; Yamamura, H.; Tsutsumi, K.; Morimoto, T.; Kurosawa, H. *Tetrahedron Lett.* **2001**, 42, 7595.
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