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Reductive radical cyclization of cyclic γ-cyanoketones promoted by samarium(II) iodide without photoirradiation

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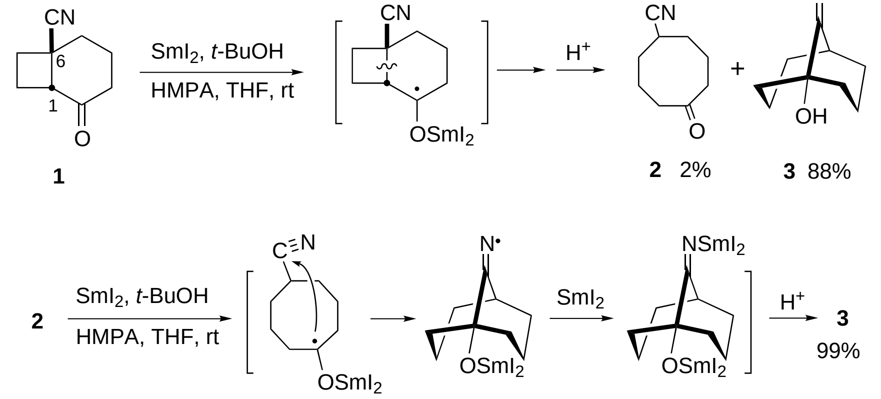
Abstract—Reaction of cyclic γ-cyanoketones with 3 equiv. of SmI_2 in the presence of *t*-BuOH as a proton source in HMPA–THF without photoirradiation gave the desired α-hydroxycycloalkanones along with overreduced ketones after hydrolysis. In the absence of *t*-BuOH, the formation of the overreduced ketones was depressed and the yields of the α-hydroxyketones increased, while the reaction proceeded slowly. © 2001 Elsevier Science Ltd. All rights reserved.

In extension of our study on the development of new skeletal transformations and their application, we have recently found a radical ring-opening reaction of 6-cyanobicyclo[4.2.0]octan-2-one (**1**) promoted by SmI_2 gives 1-hydroxybicyclo[3.3.1]nonan-9-one (**3**) in high yield along with a small amount of 5-cyanocyclooctanone (**2**).[1] Similar treatment of the cyanoketone **2** furnished the hydroxyketone **3** quantitatively. These results suggested that the ketone **3** is produced by intramolecular ketyl-nitrile cyclization of the primary product, the cyanoketone **2**, which is formed through radical-fission of the central cyclobutane bond (C1–C6) of the ketone **1**. The finding prompted us to investigate the intramolecular ketyl-nitrile cyclization of cyclic γ-cyanoketones **4** to α-hydroxycyclopentanones **5** prompted by SmI_2 (Scheme 1). Namely, one-electron reduction of the ketone by SmI_2 forms the ketyl radical **A**, which goes 5-*exo*-*dig* cyclization to produce the iminyl radical **B**. Further reduction by SmI_2 followed by acidic hydrolysis of the samarium species **C** gives the hydroxycyclopentanone. Since a cyanoethyl group can be easily introduced at the α-position of a carbonyl group via the well-documented cyanoethylation, the establishment of this reaction can offer a method for the construction of the five-membered ring utilizing the carbonyl group. There are several examples for ketyl-nitrile cyclization promoted by Zn/TMSCl,[2] by Cp_2TiPh,[3] and by electrochemical reduction.[4] Although a few reports of SmI_2-mediated reaction have also appeared,[5,6] the yields were not satisfactory and the substrates were limited. During this study, Molander and Wolfe reported an efficient method of the ketyl-



Keywords: samarium(II) iodide; γ-cyanoketone; reductive radical cyclization; α-hydroxycycloalkanone.

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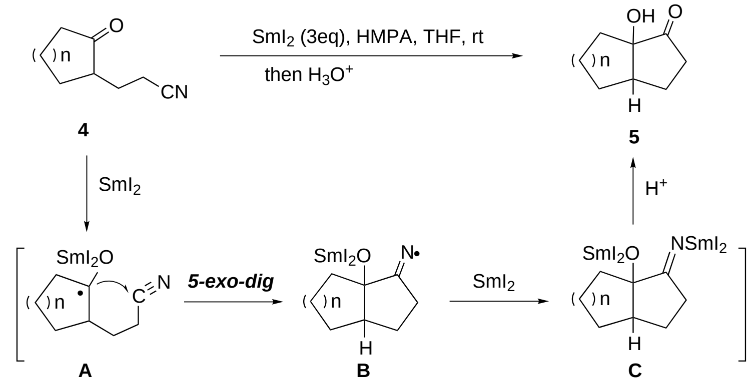


Scheme 1.

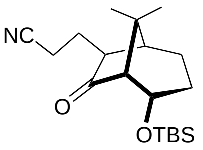
nitrile cyclization using SmI_2 activated by irradiation of visible light.[7] We wish to report here a systematic study of ketyl-nitrile cyclization of cyclic γ-cyanoketones promoted by SmI_2 without photoirradiation.[8]

Reactions of various γ-cyanoketones **4** with 3 equiv. of SmI_2 were carried out in the presence or absence of 3 equiv. of *t*-BuOH in HMPA (20 equiv.)[9] and THF at room temperature, and the results are summarized in Table 1.[10] Reaction of γ-cyanoethylcyclopentanone **4a** in the presence of *t*-BuOH gave hydroxybicyclo[3.3.0]octan-2-one (**5a**) in 41% yield along with the overreduced ketone **6a** in 11% yield (Table 1, entry 1). Since the deoxygenated ketone **6a** is considered to be formed from the iminyl species **C** by protonation and subsequent dehydration followed by 1,4-reduction of the resulting α,β-unsaturated imine **D** (Scheme 2), we carried out the reaction of **4a** in the absence of *t*-BuOH as a proton source. Consequently, the yield of **5a** increased to 77% and the formation of **6a** was depressed, although the reaction time was prolonged (entry 2). A similar tendency was also observed in the case of cyanoethylcyclohexanone **4b** (entries 3 and 4). Without *t*-BuOH, the 5-6 fused hydroxyketone **5b** was obtained in 82% yield. Reactions of the higher homologues **4c** and **4d** furnished the 5-7 fused compounds **5b** and **6b**, and the 5-8 fused ketones **5c** and **6c** in good yields as a mixture of *cis*- and *trans*-fused diastereomers along with overreduced ketones, respectively (entries 5 and 6). The yields of α-hydroxyketones are higher than those obtained by Zn/TMSCl,[2] Cp_2TiPh,[3] and electrochemical reductions,[4] and are also comparable to those prepared by SmI_2-photoactivation.[7]

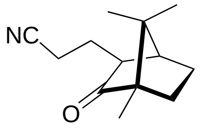
In the case of ketone **4e** having an ester group at the α-carbon, the desired α-hydroxyl ketone **5e** was obtained as the sole product even in the presence of *t*-BuOH (entry 7).[11] However, the higher homologue **4f** did not give the desired product on using 4 equiv. of SmI_2 and 4 equiv. of *t*-BuOH (entry 8).

Like electrochemical reactions,[4] the diquinane cyanoketones **4g** and **4h**, prepared by cyanoethylation of **6a**, also gave the linearly fused triquinane ketones **5g** and the angularly fused triquinane ketone **5h** in moderate yields, respectively (entries 9 and 10).

The γ-cyanoketones **4i** and **4j**, which did not produce the hydroxyketones by electrochemical ketyl-nitrile cyclization,[4] gave the 5-5-6 and 5-6-6 fused ketones **5i** and **5j** in good yields, respectively (entries 11 and 12). In the case of the more hindered substrate, α,α-dimethylcyclopentanone derivative **4k**, the cyclized product **5k** was obtained in 94% yield based on the consumed starting material, though the conversion was 51% (entry 13). Reactions of the bridged bicyclic ketones **4l** and **4m** did not afford the cyclopentane ring-fused products probably due to the severe steric hindrance, but gave the corresponding alcohols by reduction of the carbonyl group.

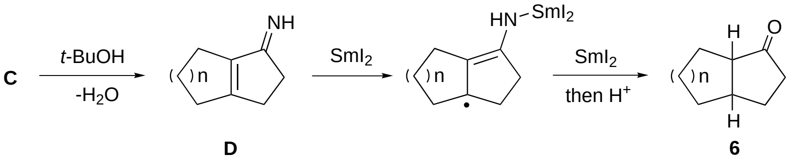


4l



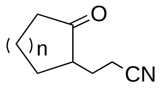
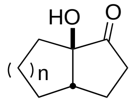
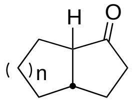
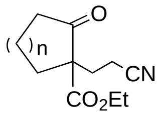
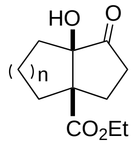
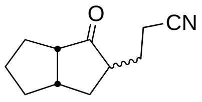
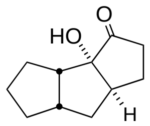
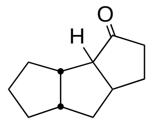
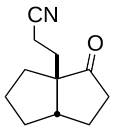
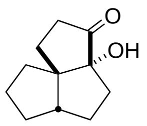
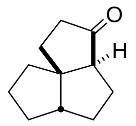
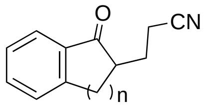
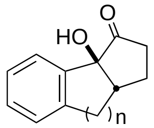
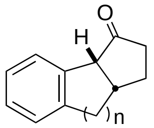
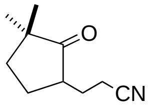
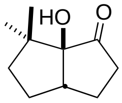
4m

Thus, the ketyl-nitrile cyclization using SmI_2 proceeds efficiently without photoirradiation to give the corresponding hydroxycylopentanones in high yields, unlike the report of Molander et al.[7] It may be reasonably presumed that use of 3 equiv. of SmI_2 and enhancement



Scheme 2.

Table 1. Reductive radical cyclization of γ-cyanoketones promoted by SmI_2

entry	cyanoketone	*t*-BuOH	time (h)	product and % isolated yield	
					
1	**4a** n = 1	3 eq	2	**5a** 41[a]	**6a** 11
2		–	16	**5a** 77	**6a** 4
3	**4b** n = 2	3 eq	0.5	**5b** 73	**6b** 17[b]
4		–	17	**5b** 82	**6b** 4[b]
5	**4c** n = 3	–	24	**5c** 80[c]	**6c** 14[d]
6	**4d** n = 4	–	22	**5d** 74[e]	**6d** 18[f]
					
7	**4e** n = 1	3 eq	3	**5e** 73	
8	**4f** n = 4[g]	4 eq	4.5	**5f** –	
					
9	**4g**[h]	–	90	**5g** 43[a]	**6g** 12[i]
					
10	**4h**	3 eq	3	**5h** 58	**6h** 29
					
11	**4i** n = 1	–	17	**5i** 58[a]	**6j** 13
12	**4j** n = 2	–	22	**5j** 71	**6j** 5
					
13	**4k**	–	20	**5k** 48 (94 based on conversion)[a]	

[a] The starting material was recovered, for **4a**: 21%, for **4g**: 17%, for **4i**: 16%, for **4k**: 49%. [b] A 16 : 84 mixture of diastereomers. [c] The *cis*- and *trans*-fused products were obtained in 68% and 12% yields. [d] A 1 : 1 mixture of diastereomers. [e] The *cis*- and *trans*-fused products were obtained in 49% and 25% yields. [f] A 62 : 38 mixture of diastereomers. [g] 4 equiv. of SmI_2 was used. [h] A 7 : 3 mixture of the *cis* and *trans* diastereomers, and 6 equiv. of SmI_2 was used. [i] A 9 : 1 mixture of *anti* and *syn* diastereomers.

of the reactivity of SmI_2 by addition of HMPA[9] raise the concentration of the ketyl **A** and, therefore, that of the iminyl radical **B**. Using more than 3 equiv. of SmI_2 increases the formation of an overreduced product such as **6**, and using a lesser amount of SmI_2 decreases the conversion of the reaction.

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10. All new compounds gave satisfactory spectral data and high-resolution mass spectra. General experimental procedure is as follows: A mixture of Sm metal (mesh type, 99.9%, 496 mg, 3.3 mmol), purchased from High Purity Chemicals Co., Ltd., and 1,2-diiodoethane (846 mg, 3 mmol) was placed in a flask, which was purged with nitrogen. Dry THF (30 mL, distilled freshly under a nitrogen atmosphere) was added with a syringe through a rubber septum. The mixture was stirred at rt for 3–5 h until a dark-blue solution formed. The 0.1 M SmI_2–THF solution was added with a syringe at rt to a stirred mixture of γ-cyanoketone (1.0 mmol) and HMPA (3.48 mL, 20 mmol) in dry THF (20 mL). If necessary, *t*-BuOH (0.29 mL, 3.00 mmol) was placed in the flask before the SmI_2 solution was added. The mixture was stirred at rt under a nitrogen atmosphere until the deep-purple color faded to an opaque gray. H_2O (30 mL) was added and the mixture was stirred for another 3 h. Then 5% HCl (5 mL) was added and the mixture was extracted with ether. The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine, and dried ($MgSO_4$). The solvent was evaporated in vacuo to give the crude products, which were purified by flash chromatography on silica gel.
11. Formation of the α,β-unsaturated imine **D** is impossible in this case.