Reductive intramolecular cyclization of α-bromo silyl ethers mediated by samarium diiodide

H. S. Park, I. S. Lee, D. W. Kwon and Y. H. Kim*

Department of Chemistry, Korea Advanced Institute of Science and Technology, Taejon 305 - 701 Korea. E-mail:kimyh@sorak.kaist.ac.kr

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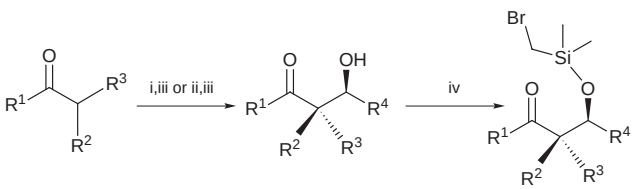
A new SmI_2-promoted intramolecular reductive cyclization of β-(α-bromo siloxy) carbonyl compounds is reported.

In the last decade, SmI_2 has become one of the most developed reagents in organic synthesis due to the oxophilicity of samarium metal and its powerful one election donor reactivity with various functional groups.[1] Reductions, reductive cyclizations or coupling reactions using SmI_2 have been intensively studied. In particular, intramolecular reductive cyclizations have brought noticeable results in the formation of highly functionalized carbocycles[1,2] and heterocycles.[1,3] Barbier type reactions,[1c,4] Reformatsky type reactions,[1c,5] pinacolic coupling reactions[1c,6] and ketone-olefin coupling reactions[1b,c,7] have been investigated for intramolecular reductive cyclization. Aryl radical cyclization,[8] halide induced cyclization,[1b,c,9] and sequence cyclization[1a,10] have also been reported. Of these reactions, Barbier type reactions give excellent results for cyclization with high stereoselectivity.[1c]

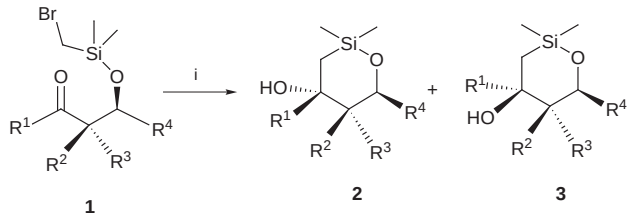
Intramolecular cyclizations of β-(α-bromo siloxy) alkenes or alkynes or vinyl bromo siloxy derivatives *via* a free radical process by treatment with Bu_3SnH gave various useful cyclic silyl ethers[11] with high degrees of regio-, chemo- and stereoselectivity; the reaction products are potentially useful intermediates which can be converted to triols by Tamao oxidation.[12]

Although many attempts have been made to construct functionalized carbocycles or heterocycles by ring closure of a ketyl radical or anion with a ketene or alkyne, there is no reported example of radical or anion cyclization of β-(α-bromo siloxy) carbonyl derivatives mediated by SmI_2. Matsuda and co-workers examined cyclization of β-(α-bromo siloxy) carbonyl derivatives in sugar moieties, and demonstrated that no cyclization occurred.[13]

We were intrigued by the possibility of another Barbier type reaction, this time with β-(α-bromo siloxy) carbonyl substrates using SmI_2. The β-(α- bromo siloxy) carbonyl substrates were prepared *via* two steps as shown in Scheme 1. The ketones were condensed with aldehydes or ketones under typical aldol conditions.[14] For the preparation of α-substituted aldol products, Bu^n_2BOTf was used and the *erythro* product was obtained as the major product. The resulting β-hydroxy ketone was treated with bromomethyl(dimethyl)chlorosilane in the presence of pyridine at 0 °C to provide the desired product **1** in excellent yields as shown in Scheme 1. Their structures were identified by ^1H and ^{13}C NMR and mass spectroscopy.



Scheme 1 *Reagents and conditions*: i, LDA, THF, −78 °C; ii, Bu^n_2BOTf, Pr^i_2NEt, THF, −78 °C; iii, R^4CHO, −78 °C; iv, $ClMe_2SiCH_2Br$, pyridine, CH_2Cl_2, 0 °C.



Scheme 2 *Reagents and conditions*: i, SmI_2 (2 equiv.), HMPA (4 equiv.), THF, −78 °C.

Here we describe a new intramolecular reductive cyclizations of β-(α-bromo siloxy) carbonyl compounds **1** with SmI_2 in the presence of HMPA to **2**, as shown in Scheme 2.

In order to generalize the cyclization of β-(α-bromo siloxy) carbonyl substrates, both acyclic (**1a–j**) and cyclic substrates (**1k–n**) were subjected to the cyclizations under the optimized reaction conditions [SmI_2 (2.2 equiv.), HMPA (4 equiv.), THF, −78 °C]. The results obtained are summarized in Table 1.

Formation of two stereoisomers is possible; one is the *syn* isomer, which has the R^3 and OH groups pointing in the same direction, and the other is *anti* isomer, which has the R^3 and OH groups pointing in opposite directions. As a result the *syn* isomer **2** was obtained together with trace amount of the *anti* isomer **3**. The configuration of **2** (**2f**) was identified by ^1H and ^{13}C NMR and NOE experiments (Fig. 1) and mass spectroscopy. The *syn* isomer conformation obtained could be explained by steric hindrance in the transition state. In the four possible transition states, conformation **A** seems to be the most favorable due to steric effects, as suggested by Molander.[9]

In the absence of HMPA, the yield of **2** is low and desilylated aldol products were obtained as the major product. *Erythro* or *threo* cyclohexanone substrates gave the corresponding *erythro* or *threo* products respectively in good yields. The substrate **1d** gave the desired cyclized product **2d** (44%) together with olefin

Table 1 Cyclization of siloxy derivatives using SmI_2[a]

Substrate	R^2	R^1	R^3	R^4	*t*/min	Ratio **2**:**3**	Yield (%)[b]
1a	H	Ph	H	Et	10	> 99:1	61
1b	H	Ph	H	Pr	15	> 99:1	75
1c	H	Me	H	Pr	30	> 99:1	72
1d	H	Pr^i	H	Pr	30	> 99:1	44[c]
1e	H	Me	H	c-Hex	30	> 99:1	57
1f	Me	Et	H	Ph	30	95:5	65 (15)[d]
1g	Me	Et	K	Pr	30	90:10	67
1h	Me	Et	H	Bu^t	30	95:5	62
1i	Me	Ph	H	H	15	92:8	71
1j	Me	Ph	H	Ph	10	95:5	35
1k	$-(CH_2)_4-$		H	Ph	10	> 99:1	74
1l	H		$-(CH_2)_4-$	Ph	10	> 99:1	69
1m	$-(CH_2)_3-$		H	Ph	10	> 99:1	80
1n	$-(CH_2)_3-$		H	Et	30	> 99:1	63

[a] All reactions were carried out using SmI_2 (2.2 equiv.) in THF and HMPA (4 equiv.) at −78 °C. [b] Isolated yields. [c] Eliminated olefin was obtained in *ca.* 20% yield. [d] The reaction was carried out in the absence of HMPA.

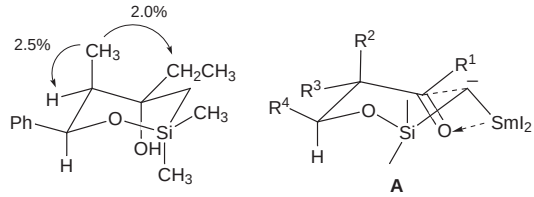
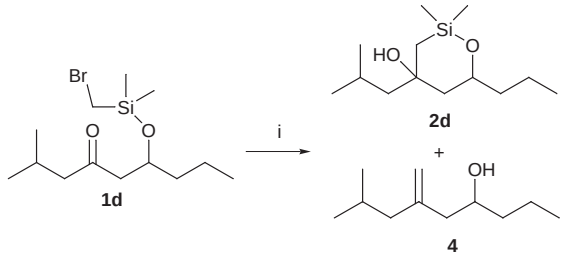


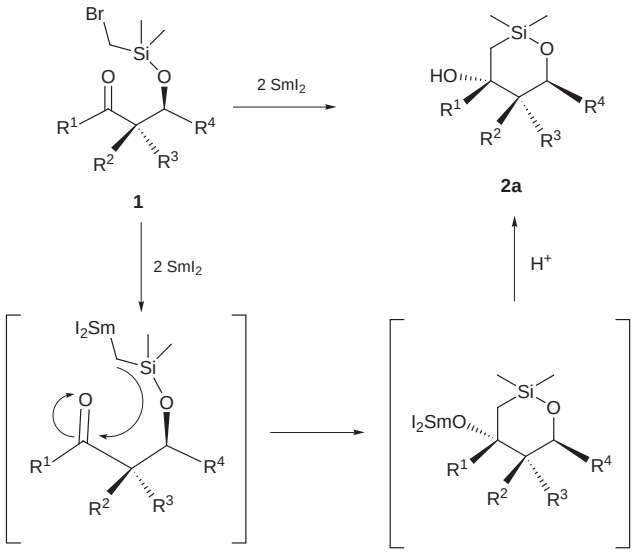
Fig. **1** NOE correlations of β-hydroxy cyclic silyl ether.



Scheme 3 *Reagents and conditions*: i, SmI_2 (2.2 equiv.), HMPA (4 equiv.), THF, −78 °C.

4 (20%) which is formed by elimination of the siloxy moiety as shown in Scheme 3.

In the reaction mechanism, there are two possible process; a radical–radical coupling process and a samarium Grignard-type anion process (Scheme 4). In the radical–radical coupling reaction, 2 equiv. of SmI_2 generates both a ketyl radical and an alkyl radical which couple each other. On the other hand, the organosamarium Grignard-type species, which could be generated from an alkyl radical by one more electron transfer from SmI_2, could add to the carbonyl group. Since the reactivity of primary alkyl bromides with SmI_2 is higher than that of carbonyl groups, it can be considered that the organosamarium Grignard-type process is more favorable.



Scheme 4

The α-effect of the silicon moiety may also help to promote the organosamarium pathway. Most of the reactions gave the reduced aldol products in *ca*. 20% yield as a side product. Formation of the aldol side product also supports the organosamarium pathway. If the reaction occurs *via* a diradical pathway, the carbonyl moiety might be reduced to a β-OH moiety. However, only the desilylated aldol products (up to 20%) were obtained and confirmed.

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