

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

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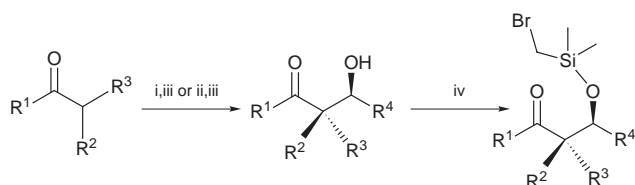
A new SmI_2 -promoted intramolecular reductive cyclization of β -(α -bromo siloxy) carbonyl compounds is reported.

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 electron 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}

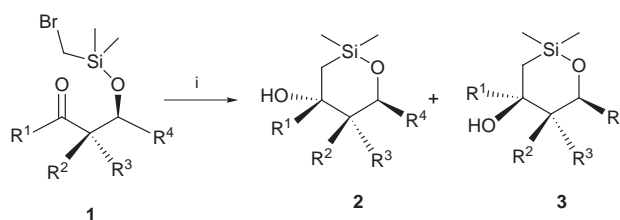
Intramolecular cyclizations of β -(α -bromo siloxy) alkenes or alkynes or vinyl bromo siloxy derivatives *via* a free radical process by treatment with Bu_3SnH gave various useful cyclic silyl ethers¹¹ with high degrees of regio-, chemo- and stereoselectivity; the reaction products are potentially useful 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 ¹³C 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, $\text{ClMe}_2\text{SiCH}_2\text{Br}$, 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 ¹³C 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	<i>c</i> -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	$-(\text{CH}_2)_4-$	H	H	Ph	10	>99:1	74
1l	H	$-(\text{CH}_2)_4-$	Ph	Ph	10	>99:1	69
1m	$-(\text{CH}_2)_3-$	H	H	Ph	10	>99:1	80
1n	$-(\text{CH}_2)_3-$	H	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.

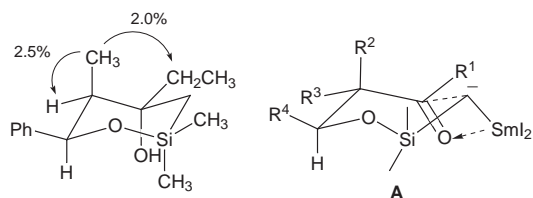
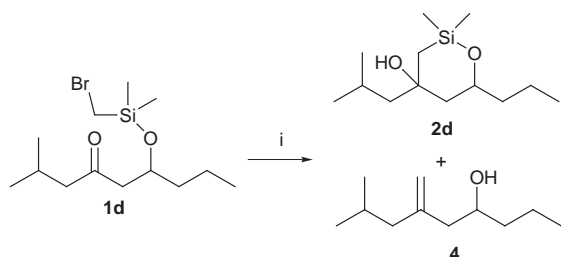


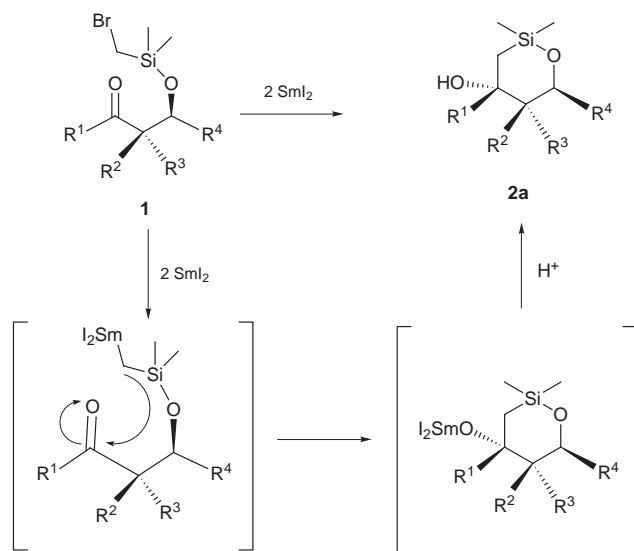
Fig. 1 NOE correlations of β -hydroxy cyclic silyl ether.



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 processes; 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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