

## INTRAMOLECULAR REDUCTIVE CYCLIZATION OF ALDEHYDES AND KETONES WITH ALKYNES PROMOTED BY SAMARIUM(II) IODIDE

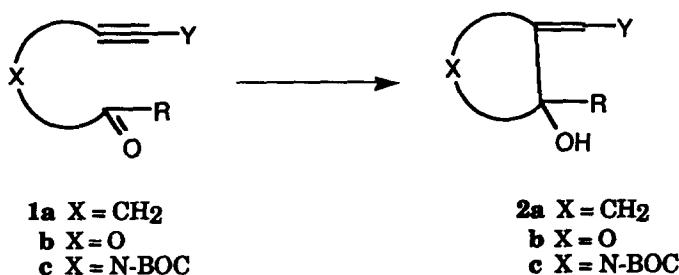
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**Summary:** *Samarium(II) iodide mediated intramolecular reductive coupling of carbonyl groups and alkynes in the presence of HMPA and *t*-BuOH was successfully performed to provide cyclized products. Some cyclic compounds containing a heteroatom such as oxygen or nitrogen were also efficiently prepared by this coupling reaction.*

Samarium(II) iodide has gained increasing popularity as a powerful reagent in organic synthesis.<sup>1,2</sup> Recent investigations extended the versatility of this reagent to various synthetic transformations in inter- as well as intramolecular mode. Reductive coupling reaction<sup>3-5</sup> is one of the most actively investigated areas in recent years. There is, however, no systematic investigation reported on samarium(II) iodide-promoted intramolecular coupling reaction of aldehydes and ketones with alkynes. Despite the apparent similarity between the free radical addition to unsaturated carbon-carbon bonds and the reductive coupling promoted by samarium(II) iodide, no example except one brief examination by Molander<sup>5</sup> on the coupling of ketones with alkynes in intramolecular manner has been reported.<sup>6</sup>

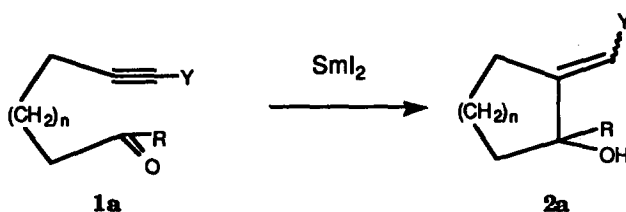
We have been interested in the intramolecular ketone (or aldehyde)-alkyne coupling reaction promoted by samarium(II) iodide and wish to report here the successful coupling reactions to generate functionalized cyclic products as shown in the following equation.



A typical experimental procedure is as follows. To a solution of ethyl 7-oxooct-2-ynoate

(1a, R = CH<sub>3</sub>, Y = CO<sub>2</sub>Et, n = 1; 182 mg, 1.0 mmol)(entry 14 in Table 1) in THF (50 mL), HMPA (2.5 mL), and t-BuOH (190  $\mu$ L, 2.0 mmol) was added a THF solution of SmI<sub>2</sub> (0.1 M, 20 mL) at 0 °C with stirring under nitrogen atmosphere. The solution was stirred at 0 °C for ca. 10 min. After addition of saturated aqueous NaHCO<sub>3</sub> solution(10 mL) the usual workup followed by purification (flash chromatography on silica gel) afforded 1-methyl-2-[(E)-(ethoxycarbonyl)methylene]cyclopentanol (138 mg, 75%). Addition of HMPA turned out to be crucial to achieve reasonable yields.<sup>7</sup> The results for the reductive cyclization of 1a are summarized in Table 1.

**Table 1. Intramolecular Reductive Coupling of Aldehydes and Ketones with Alkynes**



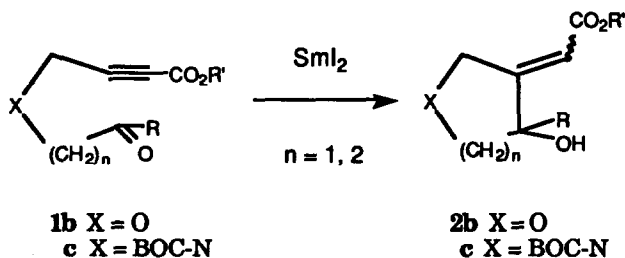
Entry	Y	R	n	Yield	(E/Z)
1	H	H	1	30%	-
2	H	CH <sub>3</sub>	1	55%	-
3	H	H	2	N.R. <sup>a</sup>	-
4	H	CH <sub>3</sub>	2	N.R. <sup>a</sup>	-
5	SiMe <sub>3</sub>	H	1	0% <sup>b</sup>	-
6	SiMe <sub>3</sub>	CH <sub>3</sub>	1	56%	<i>E</i> only
7	SiMe <sub>3</sub>	H	2	0% <sup>b</sup>	-
8	SiMe <sub>3</sub>	CH <sub>3</sub>	2	N.R. <sup>a</sup>	-
9	Ph	H	1	34%	(2.4/1)
10	Ph	CH <sub>3</sub>	1	71%	<i>E</i> only
11	Ph	H	2	52%	(2/1)
12	Ph	CH <sub>3</sub>	2	54%	<i>E</i> only
13	CO <sub>2</sub> Et	H	1	65%	<i>E</i> only
14	CO <sub>2</sub> Et	CH <sub>3</sub>	1	75%	<i>E</i> only
15	CO <sub>2</sub> Et	H	2	60%	(3/2)
16	CO <sub>2</sub> Et	CH <sub>3</sub>	2	72%	<i>E</i> only

<sup>a</sup> Starting material was recovered. <sup>b</sup> A mixture of various products was obtained.

The effect of the substituents at the terminal site of alkyne was examined. Unexpectedly unactivated alkynes were cyclized to give five-membered rings albeit in low yields (entries 1 and 2). However, no reaction took place in the attempted six-membered ring formation (entries 3 and 4). In the case of trimethylsilyl substituted alkynes (entries 5 - 8), cyclization proceeded only with methyl 5-(trimethylsilyl)-4-pentynyl ketone (entry 6).<sup>5</sup>

The major difference from the reported results<sup>5</sup> was observed in the reaction with activated alkynes. It is easily expected that the presence of electron-withdrawing group at the terminal site of alkyne could facilitate the coupling. The cyclization proceeded in reasonable yields with phenyl and ethoxycarbonyl substituted alkynes (entries 9 - 16) supporting this expectation. Ketones generally provided slightly better yields than aldehydes, and it is noteworthy that *E* stereoisomers were isolated in all cases (entries 6, 10, 12, 14, and 16). Stereochemistry of the products was determined either by the independent synthesis of cyclized products (entries 13 and 15) or by the analysis of <sup>1</sup>H NMR spectra. The cyclization to form six-membered rings was also successful in the reaction of activated alkynes (entries 11, 12, 15, and 16) in contrast to the cases with unactivated alkynes (entries 3, 4, 7, and 8).

**Table 2. Intramolecular Reductive Coupling of Carbonyl Groups and Alkynes for the Preparation of Heterocyclic Compounds**



Entry	n	X	R	R'	Yield*
a	1	O	H	Et	61%
b	2	O	H	Et	60%
c	1	O	CH <sub>3</sub>	Et	70%
d	2	O	CH <sub>3</sub>	Et	64%
e	1	BOC-N	H	Me	53%
f	2	BOC-N	H	Me	54%
g	1	BOC-N	CH <sub>3</sub>	Me	62%
h	2	BOC-N	CH <sub>3</sub>	Me	58%

\* Only *E* isomers were observed.

Despite the increasing number of reports on the usefulness of samarium(II) iodide in organic synthesis, applications to the preparation of heterocycles have been rather limited. In the present study, samarium(II) iodide promoted reductive coupling reaction has been extended to the synthesis of cyclic compounds containing a heteroatom such as oxygen or nitrogen (X=O or BOC-N) (Table 2). Based upon the previously obtained substituent effects (Table 1), only alkoxy carbonyl substituted alkynes (Y= CO<sub>2</sub>Me or CO<sub>2</sub>Et) were examined. Various substrates examined produced cyclic compounds in good yields (Table 2). In our reductive coupling reactions six-membered ring formation also proceeded successfully (entries b, d, f, and h) and only *E* isomers were obtained in all cases.

In summary, it has been demonstrated that the samarium(II) iodide promoted intramolecular reductive coupling reaction between alkynes and carbonyl groups such as aldehydes and ketones is a synthetically useful and general method to provide functionalized cyclic compounds. Further studies on the optimization of this reductive cyclization as well as on the synthetic applications are under investigation.

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5. Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236.
6. Molander and Kenny studied a few examples on the samarium(II) iodide promoted intramolecular reductive coupling reactions involving cyclization of  $\beta$ -ketoesters substituted with an alkyne and apparently encountered with little success. Their results are in contrast with ours reported here.
7. For the importance of HMPA for the generation of ketyls and their addition to olefins, see Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, *30*, 2837.