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# Samarium(II) iodide reduction of isoxazolidines

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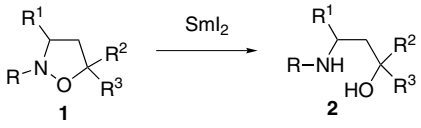
**Abstract**—$SmI_2$ was used as reducing agent for the N–O bond cleavage in isoxazolidines. The procedure revealed is general and particularly useful for the transformation of 5-spirocyclopropane isoxazolidines to the corresponding β-aminocyclopropanols, a troublesome transformation with other known reagents.


Samarium(II) iodide has found a widespread use as a reducing agent.[1] Several functional groups are easily reduced by this reagent while the radical intermediates produced in the process gave access to an important series of new reactions.[2] Particularly efficient is the reduction of the N–O bond which has found application in the reduction of nitrocompounds,[3] hydroxylamines and hydroxamic acids,[4] 1,2-oxazine,[5] isoxazoles[6] and isoxazolines.[7] Furthermore this reactivity has found an interesting application in a traceless release strategy for solid-phase synthesis.[8] Even if the use of $SmI_2$ for the reduction of isoxazolidinyl derivatives appears a logic consequence, there are only two examples of the use of $SmI_2$ for the reduction of an isoxazolidinone derivative[9] and of isoxazolidines fused with a heterocyclic ring.[10] This is probably due to the availability of a large number of reduction procedures for these compounds which allowed the N–O bond reduction in the presence of the most common functional groups and reaction conditions. Nevertheless, the development of new N–O bond reduction procedures is still useful since modern organic synthesis always requires more selective and mild procedures to cope with the simultaneous assembly of reacting functional groups on the same molecule.

During our ongoing research for the synthetic exploitation of 5-spirocyclopropane isoxazolidines it was needed to transform these compounds into the corresponding β-aminocyclopropanols through the reduction of the N–O bond (Scheme 1, $R^2$–$R^3$ = –$CH_2$–$CH_2$–).[11] This is, generally, a very simple and straightforward transformation, but the presence of a spirofused cyclopropyl ring next to the oxygen atom made this reaction troublesome. As a matter of fact several of the most common reagents used in the literature for the reduction of the N–O bond were tested, like $H_2$/Pd/C,[12] Zn/$H^+$,[13] Zn/$Cu(OAc)_2$,[14] $Mo(CO)_6$,[15] In,[16] but all invariably failed to afford the expected aminoalcohol. Only the use of $Pd(OH)_2$/C and $H_2$ afforded aminoalcohols **19** and **20** in acceptable yields.[11] However the extension of this methodology to other substrates failed. We presume that the difficulties encountered in this transformation were due to the scarce stability of the final product. Cyclopropane derivatives are known to be very reactive both under acidic and basic conditions,[17] as well as under reducing conditions,[18] leading to open chain products. On the other hand the same 5-spirocyclopropane isoxazolidines are thermally labile since they easily undergo thermal rearrangement to afford, as main product, tetrahydropyridones.[19] We decided, then, to verify the use of $SmI_2$ as a reducing agent, considering the mild reaction condition usually needed. Furthermore the use of $SmI_2$ on cyclopropane substituted substrates posed some interesting questions about the reactivity of the intermediate radicals that are known to be formed in this kind of reaction.[1,2] Examples are reported in the



1 2

**Scheme 1.**

*Keywords*: Samarium iodide; Reduction; Isoxazolidine.
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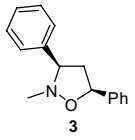
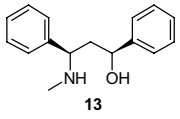
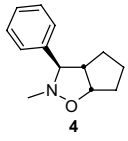
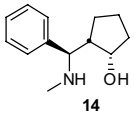
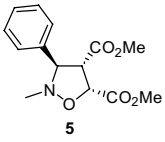
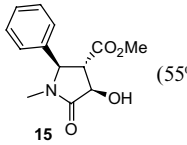
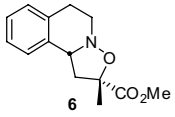
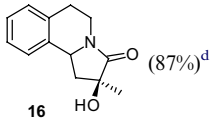
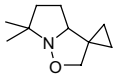
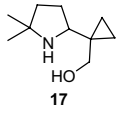
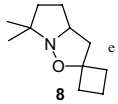
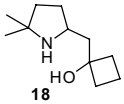
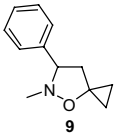
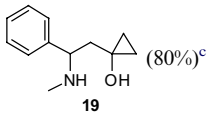
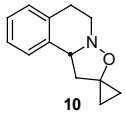
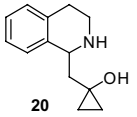
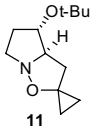
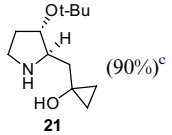
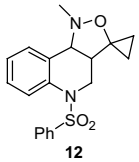
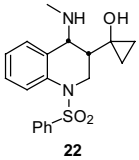
literature of cyclopropane ring cleavage in reaction of bromo-substituted cyclopropanes with $SmI_2$[20] as well as in the reduction of cyclopropyl ketones.[21]

$SmI_2$ has never been used as a general reducing agent with isoxazolidines besides the two cited examples,[9,10] for this reason the reaction was initially tested on isoxazolidines lacking the spirofused cyclopropane ring, to verify its general applicability and to tune the reaction conditions (Scheme 1).

As expected the reduction of simple isoxazolidines efficiently afforded the corresponding aminoalcohols or lactams (Table 1). The reaction proceeded despite the steric hindrance (entries 4 and 6) and proved selective also towards benzylic substitution (entries 1–3). Such selectivity was already demonstrated in precedent examples.[4] The presence of a spirocyclopropane group on the C4 position of the isoxazolidinyl ring, as in isoxazolidine **7**, is compatible with the reaction conditions (entry 5). The synthesis of compound **18** demonstrated the stability of a four-membered cyclic ring adjacent to the oxygen atom. In any case, except for entry 3, the yields are comparable, if not higher, with precedent methods.[12–16] The low yield for compound **15** was ascribed to a partial hydrolysis of the ester group in the basic work-up. The reduction of isoxazolidines **9–12** was then examined using the reaction conditions tuned before. Every 5-spirocyclopropane isoxazolidine tested afforded the corresponding aminoalcohol in good to excellent yield (see entries 7–10).[25] The presence of the spirocyclopropane ring in the final aminoalcohols was easily determined by $^1H$ and $^{13}C$ NMR spectroscopy due to the high field resonance typical of both hydrogen atoms ($\delta$ 0.8–0.3 ppm) and carbon atoms ($\delta$ 13–5 ppm) of the cyclopropane ring.

This successful transformation suggests some considerations about the reaction mechanism. It is well known that $SmI_2$ act as a single electron donor affording, in the first step, radical anion species such as **24**.[1] However the isolation of the aminoalcohol with the cyclopropyl group suggests the formation of the alkoxysamarium species **26** stabilizing the intermediate radical anion

**Table 1.** $SmI_2$ reduction of some representative isoxazolidines[a]

| Entry | Isoxazolidine | Product (yield) | Entry | Isoxazolidine | Product (yield) |
|---|---|---|---|---|---|
| 1 |  **3** |  (95%)[b] **13** | 2 |  **4** |  (98%)[b] **14** |
| 3 |  **5** |  (55%)[c] **15** | 4 |  **6** |  (87%)[d] **16** |
| 5 |  **7** |  (80%)[c] **17** | 6 |  [e] **8** |  (90%) **18** |
| 7 |  **9** |  (80%)[c] **19** | 8 |  **10** |  (70%)[c] **20** |
| 9 |  **11** |  (90%)[c] **21** | 10 |  **12** |  (95%)[c] **22** |

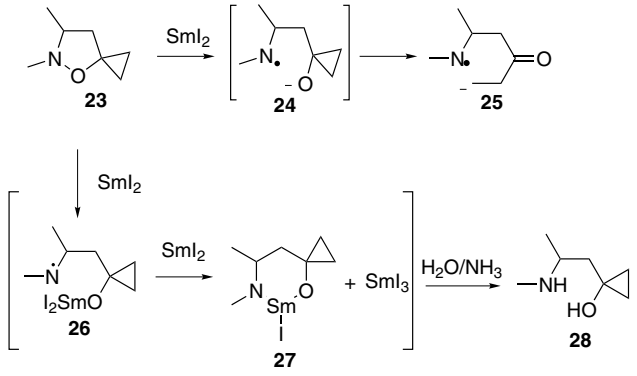
[a] General procedure: a 100 mL Schlenck flask charged with the isoxazolidine (0.5 mmol) was added, under nitrogen atmosphere, with 17.5 mL of a commercial 0.1 M THF solution of $SmI_2$ (3.5 equiv) at rt. The resulting blue solution was stirred for 2 h. A 1 M solution of $NH_3$ in MeOH (8.5 mL) was added and left under stirring for 20 min. Finally 17 mL of water were added and the resulting solution was brought to pH 9 by addition of a 1 M solution of NaOH. The mixture was then saturated with $Na_2S_2O_3$ and extracted with diethyl ether ($3 \times 15$ mL). The organic phase was then dried with $Na_2SO_4$, filtered and concentrated to afford the crude product.

[b] See Ref. 22.

[c] See Ref. 25.

[d] See Ref. 23.

[e] See Ref. 24.




**Scheme 2.**

which otherwise would easily rearrange to afford **25** (Scheme 2).

The formation of Sm(III) alcoholate are documented in the literature[1] and are in accord with the Lewis acid properties of Sm(III). Subsequently a second equivalent of $SmI_2$ should reduce the nitrogen centred radical forming the chelate complex **27**. The presence of $NH_3$ solution in the work-up procedure is necessary to hydrolyze such complexes which otherwise are extracted in the organic phase.

In conclusion $SmI_2$ revealed a selective and mild reagent for the reduction of isoxazolidines and solved the synthetic problem of a general and efficient reduction of spirocyclopropane isoxazolidines affording also an alternative and general synthetic method for the synthesis of β-aminocyclopropanols.[17a]

## Acknowledgements

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25. All new compounds were fully characterized. Compound **19**: $R_f$ ($CH_2Cl_2$–$CH_3OH$ 14:1); $^1H$ NMR: $\delta$ 7.42–7.22 (m, 5H); 3.87 (dd, $J$ = 10.5, 2.9 Hz, 1H); 2.38 (dd, $J$ = 14.2, 10.5 Hz, 1H); 2.32 (s, 3H); 1.35 (dd, $J$ = 14.2, 2.9 Hz, 1H); 0.84–0.72 (m, 2H), 0.52–0.27 (m, 2H). $^{13}C$ NMR: $\delta$ 128.0 (d, 2C); 127.9 (s); 126.6 (d, 2C); 125.8 (d); 64.5 (d); 55.6 (s); 43.4 (t); 32.8 (q); 12.7 (t); 12.1 (t).