Tandem SmI_2-induced nitrone β-elimination/aldol-type reaction†

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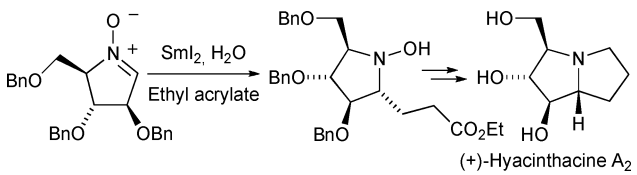
Upon treatment with SmI_2, the carbohydrate-derived nitrones 1a,b undergo a *β*-elimination of the benzyloxy group at C-1, forming original samarium(III) oxy-enamine intermediates. The latter can be reacted with carbonyl compounds to produce aldol-type adducts. The tandem process results in the transformation of a C–O bond into a C–C bond.

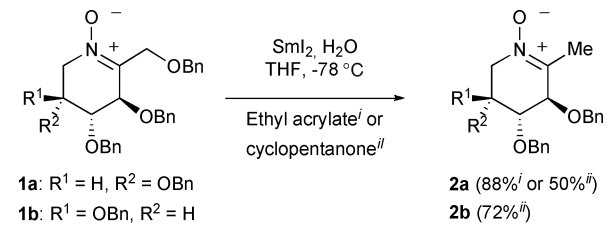
Since its first applications presented by Kagan *et al.* in the early 1980's,[1] SmI_2 has become an essential single-electron reductant for organic chemists.[2] A few years ago, this reagent allowed the chemoselective reductive cross-coupling of nitrones with aldehydes and ketones,[3] with chiral sulfinyl imines,[4] and with α,β-unsaturated esters.[5] As an extension of this last process, the SmI_2-mediated reductive cross-coupling of 5-membered-ring carbohydrate-derived cyclic nitrones[6] with ethyl acrylate was applied to the synthesis of polyhydroxylated pyrrolizidines (Scheme 1).[7]



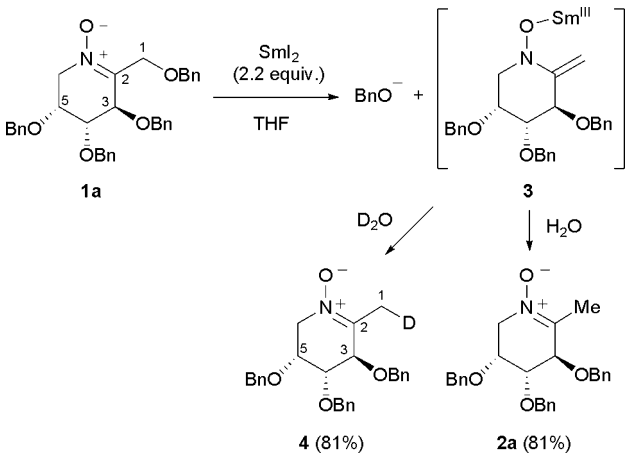
Scheme 1 Synthetic approach towards polyhydroxylated pyrrolizidines using the SmI_2-mediated nitrone *umpolung*.

In continuation of our work in this field, 6-membered ring cyclic nitrones were considered as precursors of indolizidines. Nitrones **1a**,**b** were readily prepared from inexpensive D-fructose and L-sorbose, respectively.[8] However, surprisingly, when these nitrones were treated with SmI_2 using previously described conditions,[7] only the nitrones **2a**,**b** were isolated from the reaction mixtures, whether the electrophilic partner was ethyl acrylate or cyclopentanone (Scheme 2).

The formation of nitrones **2a**,**b** from **1a**,**b** can be explained by a SmI_2-reduction of the C–N double bond, followed by elimination of the benzyloxy group at C-1. This elimination would parallel the known SmI_2-promoted elimination occurring in α-heterosubstituted carbonyl compounds.[9] The latter has been generally admitted to involve two sequential single-electron transfers from SmI_2 to a carbonyl group to produce a dianion, which undergoes *β*-elimination to form a samarium enolate.[10] It is likely that a similar process occurs when nitrones **1a**,**b** react with samarium diiodide. An original samarium(III) oxy-enamine intermediate **3** would be formed, which would then react with water, either in the reaction medium or upon quenching (Scheme 3).[11] This mechanistic hypothesis was probed by unambiguous deuterium incorporation at C-1 (forming nitrone **4**) when the reaction was performed in the presence of deuterium oxide.[12]



Scheme 2 Unexpected reactivity of nitrones **1a**,**b** under SmI_2-promoted reductive coupling conditions.



Scheme 3 Mechanism of formation of nitrones **2** and **4**.

Recently, side-products resulting from *β*-elimination have also been found in SmI_2-induced reactions of two α-alkoxy-substituted nitrones, by the group of Fišera.[13] However, to the best of our knowledge, the reactivity of anionic enamine equivalents from nitrones (*i.e.* **3**) is completely unknown. We thus decided to explore the utility of the herein-described SmI_2-induced *β*-elimination in nitrones for regioselective functionalization. A single report on nitrone cross-aldol alkylation exists in the literature.[14] The method (catalysed by L-proline) was applied only to highly electrophilic carbonyl partners and modest yields were reported. If intermediate **3** was capable of reacting with electrophiles instead of H_2O or

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† Electronic supplementary information (ESI) available: Experimental procedures for the preparation of compounds **2** and **4–11**, characterization of compounds **2** and **4–11** including copies of their ^1H and ^{13}C NMR spectra, and a copy of the ESI mass spectrum for compound **4**. See DOI: 10.1039/b910486k

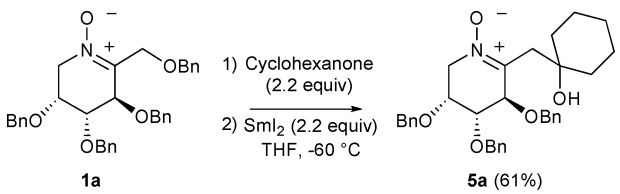
Table 1 SmI_2-mediated reaction of nitrones **1a**,**b** with electrophiles[a]

Entry	Nitrone **1a**,**b**	Electrophile	Coupling product (% Yield)[b]	dr[c]	Nitrone **2a**,**b** (% Yield[b])
1	**1a**	Cyclohexanone	**5a** (53)	–	**2a** (38)
2	**1b**	Cyclohexanone	**5b** (60)	–	**2b** (20)
3	**1a**	Cyclopentanone	**6a** (63)	–	**2a** (24)
4	**1a**	3-Pentanone	**7a** (31)	–	**2a** (52)
5	**1a**	Cyclohexane carboxaldehyde	**8a** (77)	7:3	**2a** (14)
6	**1a**	Benzaldehyde	**9a** (56)	9:1	**2a** (16)
7	**1a**	Ethyl glyoxylate	**10a** (40)	1:1	**2a** (52)
8	**1a**	Ethyl trifluoromethylpyruvate	**11a** (27)	1:1	**2a** (28)
9	**1a**	Allyl bromide	**12a** (0)	–	**2a** (50)

[a] Grignard conditions, see ESI.† [b] Isolated yields. [c] From NMR spectra of crude reaction mixtures.

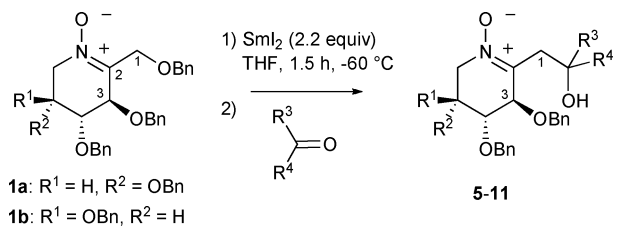
D_2O, tandem β-elimination/alkylation reactions could be effected, resulting in the selective replacement of a C–O bond by a C–C bond.

In order to investigate this possibility, a solution of nitrone **1a** was treated with 2.2 equiv. SmI_2 at –60 °C, in the presence of excess (2.2 equiv.) cyclohexanone (Barbier conditions, see Scheme 4). Encouragingly, the corresponding alkylated nitrone **5a** was obtained in 61% yield, establishing the validity of the approach. However, when benzaldehyde was used as the electrophile, its pinacolic homo-coupling was found to be a major side-reaction (quant.), and nitrone **1a** was recovered unreacted.



Scheme 4 SmI_2-induced tandem β-elimination/alkylation of nitrone **1a** under Barbier conditions.

To broaden the scope of the process, the reactions were next conducted under the so-called Grignard conditions: the nitrone was pre-treated with SmI_2 until total disappearence of the starting material (1.5 h at –60 °C or 6 h at –78 °C), then the electrophile was added (Scheme 5, Table 1).[15] In these conditions, the reaction of nitrone **1a** with cyclohexanone afforded the expected product **5a** in a moderate yield of 53% (entry 1). The related L-sorbose-derived nitrone **1b**, under the same conditions, afforded the adduct **5b** in 60% yield (entry 2). In both cases, the main side product was nitrone **2a** or **2b**, respectively, resulting from undesired protonation of the oxy-enamine intermediates in the reaction mixtures. When the reaction was performed in d8-THF, no deuterium incorporation occurred, ruling out the participation



Scheme 5 SmI_2-induced reaction of nitrones **1a**,**b** with electrophiles under Grignard conditions.[15]

of the solvent in the formation of **2** (**4** was not detected). The addition of HMPA, DMPU, or NiI_2 to the reaction mixtures did not improve the yields of the alkylation products, in contrast to the advantageous effect of these additives for alkylation of samarium enolates.[9]

Nitrone **1a**, was also converted to products **6a–11a** by reaction with various ketones and aldehydes, including the highly reducible benzaldehyde and ethyl glyoxylate (Entries 3–8). However, its reaction with allyl bromide was unsuccessful (entry 9).

When prochiral electrophiles were used, various degrees of diasteroselectivity were observed. Adduct **9a** was obtained from the reaction of nitrone **1a** with benzaldehyde, with excellent stereoselectivity (dr = 9:1, entry 6). From cyclohexane carboxaldehyde, ethyl glyoxylate, or ethyl trifluoromethylpyruvate, lower diastereoselectivities were observed (dr = 7:3 to 1:1, entries 5, 7, 8).

Remarkably, in none of these reactions were products arising from alkylation at C-2 of the nitrones detected, contrasting with the previously described SmI_2-induced reductive coupling reactions of nitrones with aldehydes and ketones.[3] The good conversions of nitrones **1a**,**b** evidence their high propensity to undergo reduction by SmI_2, and subsequent regioselective β-elimination. It appears that the other "allylic" benzyloxy group (at the C-3 position, on the ring) cannot adopt a suitable orientation for its elimination to proceed. The yields of the carbonyl-compound-trapping reactions, however, are lowered by the formation of nitrones **2a**,**b** as byproducts, despite our efforts to eliminate proton sources from the reaction mixtures.[16]

In conclusion, a novel type of regioselective alkylation of nitrones in the presence of SmI_2 is presented, which complements the previously known reactions of nitrones, such as nucleophilic additions, 1,3-dipolar cycloadditions and reductive coupling reactions.[17] The extension of this aldol-type reaction to other α-heterosubstituted nitrones and the trapping of different classes of electrophiles will be useful to delineate the scope and limits of this reaction.

Acknowledgements

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11 Using only one equivalent of SmI_2 led to 45% conversion of nitrone **1** to **2**, suggesting that two equivalents of SmI_2 are needed to complete the reaction. In addition, benzyl alcohol was produced (from NMR analysis of the crude reaction mixture).

12 See ESI† for ESI-MS and NMR data.

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15 Typical procedure: see ESI†.

16 For reproducible results, co-evaporation of the starting nitrone several times with toluene, use of THF dried over molecular sieves, and thorough purge of the reaction media using Schlenk techniques were essential. Addition of proton sponge to the reaction mixtures did not improve the yields in alkylation products.

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