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# $SmI_2$-mediated nitrile aldol reaction

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## Abstract

The $SmI_2$-mediated coupling of α-bromoacetonitrile and α-bromopropionitrile with aliphatic ketones and aldehydes produces β-hydroxynitriles in good yields. Reactions typically proceed with little diastereoselectivity, but selectivity enhancement occurs with the addition of tetra-*n*-hexylammonium bromide. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* samarium; nitriles; aldol reactions; coupling reactions.

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In the last two decades, lanthanides have been increasingly used in organic synthesis to successfully replace traditional organometallic reagents.[1] Among them, samarium(II) reagents have proven to be the most useful due to their high reduction potential and to the fact that samarium iodide ($SmI_2$), the samarium reagent of choice, is fairly soluble in common organic solvents such as THF and acetonitrile. Reactions of $SmI_2$ include the selective reduction of aldehydes in the presence of ketones,[2] the reduction of α,β-unsaturated carbonyl compounds to the saturated derivatives,[3] the reduction of alkyl halides,[4] Barbier-type reactions,[5] Reformatsky reactions[5] and pinacol couplings.[6]

The nitrile aldol reaction is an important synthetic tool in organic chemistry, allowing the introduction of a latent amino, carboxyl or other derived functionality into an organic molecule. Traditionally, the reaction is carried out through the deprotonation of a nitrile followed by addition to an aldehyde or ketone through a nucleophilic attack. The procedure has the disadvantage of being harsh on sensitive acidic functional groups present in the substrate. Although the coupling of an α-halonitrile with a carbonyl by $SmI_2$ would appear to provide a mild pathway to a nitrile aldol product, very few examples of this reaction have appeared in the literature. In 1993, Corey and Wu reported the $SmI_2$-induced intramolecular coupling of an α-chloronitrile with a ketone as a key step in the synthesis of paeoniflorin.[7] The cyclization produced a four-membered ring, proceeded in excellent yield, and provided the core substructure of paeoniflorin.

To our knowledge, no general study of the $SmI_2$-mediated bimolecular coupling of an α-halonitrile and carbonyls has been carried out. We initiated the reaction in Scheme 1. All reactions were carried out using the samarium Barbier procedure.[8,9] All attempts to carry out the reaction using the samarium

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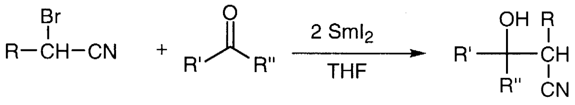
Grignard procedure[8] failed. The $SmI_2$-mediated reaction of bromoacetonitrile and 2-bromopropionitrile with a series of ketones and aldehydes is contained in Table 1. The reaction provides good yields in reactions utilizing aliphatic ketones or aldehydes. The reaction is fast in all cases with substrates reacting completely in less than 30 min at room temperature. Aromatic aldehydes and ketones do not react with the α-halonitriles in the presence of $SmI_2$. In these cases, reduction of the carbonyl to an alcohol occurs instead because aryl ketones and aldehydes are readily reduced with $SmI_2$. The yield of the reactions are dependent on the way $SmI_2$ is prepared. Preparation of $SmI_2$ from a slight excess of Sm metal and molecular iodine provides approximately 5–10% higher yields in the coupling reactions compared to commercially available $SmI_2$.



Scheme 1.

Table 1
Yields of coupling products

| **Substrate** | **bromoacetonitrile Yield**[a] | **2-bromopropionitrile Yield**[a] |
|---|---|---|
| 3-pentanone | 87% | N/A |
| heptanal | 81% | N/A |
| cyclohexanone | 85% | 83% |
| 2-methylcyclohexanone | 75% | 80% |
| 4-*tert*-butyl-cyclohexanone | 70% | 73% |
| (-)-menthone | 72% | 76% |
| pinacolone | 83% | N/A |
| benzaldehyde | NR | N/A |
| acetophenone | NR | N/A |

[a] **GC yield**

The diastereoselectivity of the nitrile aldol reaction has been studied extensively. Previous studies have described very good diastereoselectivity for the reaction of lithiated acetonitrile and propionitrile with substituted cyclohexanones and cyclohexenones.[10] In the present case, the diastereoselectivity was not very good. Reactions at low temperatures (−78°C) provided no increase in selectivity. Molander reported that the addition of HMPA to the $SmI_2$-mediated cyclization of olefinic ketones significantly enhanced the diastereoselectivity of the reaction.[11] We employed both HMPA and 1,1,3,3-tetramethylurea (TMU) as additives to the $SmI_2$ promoted coupling of α-bromoacetonitrile and (−)-menthone in order to enhance the diastereoselectivity of the reaction. Unfortunately, only acetonitrile and unreacted menthone were recovered from the reaction. An alternative additive, tetra-*n*-hexylammonium bromide (THAB) was used in the coupling reaction. Surprisingly, THAB provided a 6:1 ratio of diastereomers.[12]

The nitrile aldol reaction mediated by $SmI_2$ provides an alternative method for introducing a nitrile into an organic molecule. The only limitation resides in the fact that $SmI_2$, a powerful reductant, will readily reduce activated carbonyls such as aromatic aldehydes and ketones, therefore the method is limited to aliphatic substrates, which are not as easily reduced.

## Acknowledgements

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9. *Experimental details*: the α-halonitrile (0.6 mmol) and the carbonyl compound (0.5 mmol) were dissolved in THF (3 mL) in an oven-dried, 25 mL round-bottomed flask fitted with a septum, a magnetic stir bar, and connected to an $N_2$ line. A solution of $SmI_2$ in THF (0.1 M, 12 mL, 1.2 mmol) was added. The solution was stirred for 30 min. The mixture was diluted with ether and washed with a saturated solution of sodium thiosulfate (3×5 mL), then brine (3×5 mL) and dried over $MgSO_4$. The crude product was analyzed by GC/MS. Column chromatography on silica gel (hexane:ethyl acetate, 5:1 as eluant) yielded the pure product.
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12. The ratio of diastereomers was determined by GC. The stereochemistry of the major isomer remains to be determined.