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## Organometallic reaction in aqueous media. A samarium induced, efficient, synthesis of homoallyl hydroxylamines and hydrazides

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Abstract—Samarium can be used directly for the allylation of aldonitrones and hydrazones in aqueous media in the presence of  $Bu_4NBr$ .  $\bigcirc$  2001 Elsevier Science Ltd. All rights reserved.

Metal mediated reactions in aqueous media have recently found considerable application in organic synthesis as they offer significant advantages over conventional reactions using dry organic solvents. The addition of an allylic organometallic moiety to a carbon framework is of particular interest and among various metals employed for this purpose,<sup>1</sup> samarium attracts unique attention<sup>2</sup> due to the distinct advantages it offers in comparison with other metals such as Zn, Sn, Mg, Cd and Bi. The main drawbacks of these metals are long reaction times and only reactive halides are found to be effective. The use of samarium<sup>3</sup> is also rapidly increasing because of its advantages (availability, solubility and cost) over the widely-used single-electron transfer reagent, samarium diiodide. Yanada<sup>2c</sup> has studied extensively various reactions mediated by samarium in conjunction with different types of Lewis acids. We have also studied<sup>4</sup> a facile coupling of ketocyanides to 1,2-diketones by this metal in the presence of a catalytic amount of iodine. Kagan et al. have demonstrated<sup>5</sup> and favorably compared the samarium diiodide-mediated Barbier reaction of aldehydes and ketones with other available methods. This method using samarium diiodide is good, but the commerciallyavailable reagent is expensive, and is also moisture- and air-sensitive. As an alternative, this reagent can be prepared in situ in an inert atmosphere under very stringent conditions. In a very recent report<sup>6</sup> for the Barbier type allylation of ketones in the presence of samarium metal, the authors observed the formation of unexpected reductive coupled products (diols) instead of the allylated products. In continuation of our ongoing programme on metal mediated organic transformations,<sup>7</sup> we report herein the first example of samarium mediated allylation of aldonitrones and hydrazones under aqueous conditions using tetrabutylammonium bromide (TBAB) as an additive (Scheme 1).

The 1,3-dipolar cycloaddition reactions of nitrones have been studied extensively, but nitrones also undergo several other reactions which are far less well known. Addition of organomagnesium or organolithium reagents to aldonitrones provides N,N-disubstituted hydroxylamines<sup>8</sup> which can be reduced to secondary amines. These hydroxylamines are synthetically valuable intermediates<sup>9</sup> and can be generated through the allylation of aldonitrones which act as good electrophiles for organometallic additions.<sup>10</sup> Examples of organometallic additions to ketonitrones have also been reported,<sup>11</sup> albeit in cases limited to cyclic nitrones. We have found that various



## Scheme 1.

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Table	1.	Samarium	mediated	allylation	of aldonitrones	1 and	hydrazones 4	
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Entry	Nitrones/ Hydrazones	Products	Reaction time, h	Yield <sup>a</sup> %
1	<b>1a</b> , R¹=Ph R²= Ph	Ph OH 3a	1.5	85
2	<b>1b</b> , R¹= <i>4</i> -CIC <sub>6</sub> H₄ R²= Ph	Ph OH 3b 4-CIC <sub>6</sub> H <sub>4</sub>	2.0	80
3	<b>1c</b> , R¹=3-NO₂C <sub>6</sub> H₄ R²= Ph	Ph OH 3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> 3c	1.5	80
4	1d, R¹= <i>4-</i> CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> R²= Ph	Ph OH 3d 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	1.5	82
5	<b>1e</b> , R¹= √_0 R²= Ph	Ph OH 3e	1.5	80
6	<b>1f</b> , R¹= Ph R²= Me	Me OH 3f	11	61
7	1g, R1= CH₃(CH₂)₃ R²= Ph	Ph OH 3g CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	12	55
8	<b>4a</b> , R=Ph, Ar=Ph	Ph H 5a	5.0	90
9	<b>4b</b> , R=4-CH₃OC <sub>6</sub> H₄, R=Ph	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> NH-NH-Ph H 5b	5.0	85
10	<b>4c</b> , R=4-CIC <sub>6</sub> H₄, Ar=SO₂C <sub>6</sub> H₄CH₃-p	4-CIC <sub>6</sub> H <sub>4</sub> NH-NH-SO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub> H 5c	₃- <i>p</i> 6.0	80
11	<b>4d</b> , R=Ph, Ar=SO₂C <sub>6</sub> H₄CH₃-p	Ph H NH-NH-SO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub> 5d	- <sup>p</sup> 5.5	83
12	<b>4e</b> , R=4-CIC <sub>6</sub> H <sub>4</sub> ,	4-CIC <sub>6</sub> H₄ NH-NH-Ph H 5e	6.0	80
13	Ar=Pn 4f, R= CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> Ar= Ph	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> NH-NH-Ph H 5f	12	60

<sup>a</sup>Yields refer to pure isolated products, fully characterised by <sup>1</sup>H NMR and Ir spectroscopy and by comparison with authentic samples.



Scheme 2.

aldonitrones and hydrazones derived from aromatic aldehydes undergo allylation when reacted with a stoichiometric quantity of the allylsamarium reagent generated in situ in a  $Bu_4NBr-DMF-H_2O$  system at room temperature.

In a typical procedure, a suspension of samarium powder (1.5 g, 10 mmol), allylbromide (1.2 g, 10 mmol) and TBAB (0.322 g, 1 mmol) was taken in 15 ml DMF-H<sub>2</sub>O (2:1) in a 150 ml round bottom flask and the mixture stirred at room temperature until all the metal dissolved to form a clear solution. To the reaction mixture was then added a solution of aldonitrone 1a (1.97 g, 10 mmol) in DMF. The resulting mixture was stirred for 1.5 h at room temperature. After completion (monitored by tlc) the reaction was quenched with dil. HCl and poured into ice-cold water, followed by extraction with ether  $(3 \times 20)$ ml). The combined ether extract were washed with brine, dried over anhydrous sodium sulphate and the residue obtained thereafter on evaporation of the solvent was subjected to column chromatography using ethyl acetatehexane 1:5 as eluent to afford the pure product **3a** in 85% yield. Similarly, other aldonitrones and hydrazones<sup>12</sup> were reacted, see Table 1. The reactions are generally clean and no trace of an N-allylated product could be detected in the NMR spectra of the crude products. All products were characterized by infrared and <sup>1</sup>H NMR spectroscopy, and by comparison with authentic samples (Scheme 2).

The effect of Bu<sub>4</sub>NBr was found to be remarkable, virtually no allylation occurring in its absence. We tried a number of alkaline metal salts to activate the metal like NaBr, KBr, MgBr<sub>2</sub> and KCl in aqueous media in place of Bu<sub>4</sub>NBr, but found these to be ineffective giving no reaction. However, a 1 M concentration of NH<sub>4</sub>Cl was found to quite effective in activating the samarium to give a good yield of the corresponding homoallylic hydroxylamines and hydrazides. Roughly 0.1 equivalent of Bu<sub>4</sub>NBr was found to be sufficient for these reactions and the use of a large excess did not result in higher yields or better reaction rates. We thus use Bu<sub>4</sub>NBr as the standard additive to activate commercial samarium metal and examined its reaction with a number of aldonitrones and hydrazones. The results are summarised in Table 1. These results reveal the generality of this methodology in terms of structural variations of the nitrone moiety and in each case homoallylic hydroxylamines were isolated in excellent yields within 1.5–2 h (entries 1–7). Furthermore, electron-donating or -withdrawing groups on the aromatic ring did not seen to affect the reaction significantly either in the yield of the product or the rate of the reaction. Moreover, nitro functions were not reduced under the reaction conditions. Thus the nitrone from 3-nitrobenzaldehyde was successfully allylated. Usually, the nitro group is sensitive to reduction by metals and can not be allylated under Barbier conditions.<sup>8</sup> In this sense, the use of TBAB as an activating agent is superior to the use of Al, Fe or NaBH<sub>4</sub> reported previously.<sup>9</sup> Also, allyl iodide was found to be as reactive as allyl bromide, but the reactivity of allyl chloride was found to be much less. Furthermore, the reaction is not equally effective when aliphatic aldonitrone 1g or aliphatic hydrazone 4f were used as substrate. The reaction takes 11-12 h in 55-61% yields only (Table 1). Further, increasing the reaction time gave no significant improvement on the yield and resulted in decomposition of product. Interestingly, when the same experiment was performed with ketone (acetophenone) derived nitrone or hydrazone, the reaction did not yield any allylated product and the starting materials were recovered, after stirring at room temperature for 18-20 h. Moreover, the reaction failed to produce any desired product when THF-H<sub>2</sub>O (3:1) or THF was used as solvent. This indicated that the nature of the solvent is important in the formation of the product in the samarium-induced allylation reaction. Although, the detailed mechanism of the reaction is not clear, it is likely that Bu<sub>4</sub>NBr effects the generation of an active organosamarium reagent.

In conclusion, this simple and easily reproducible technique using samarium under aqueous conditions affords various homoallyl hydrazides and homoallyl hydroxylamines of potentially high synthetic utility in excellent yields and without the formation of any undesirable side products.

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