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Samarium-induced iodine-catalyzed reduction of imines: synthesis of amine derivatives

Bimal K. Banik,* Oliwia Zegrocka, Indrani Banik, Linda Hackfeld and Frederick F. Becker *

The University of Texas, M.D. Anderson Cancer Center, Department of Molecular Pathology, Section of Experimental Pathology, 1515 Holcombe Blvd., Houston, TX 77030, USA

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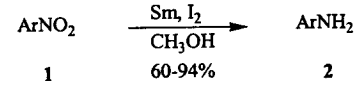
Abstract

Samarium metal induced iodine-catalyzed reduction of the imines towards the synthesis of secondary amines was investigated. The imines derived from aromatic amines produced monoamines whereas imines from arylalkyl amines gave diamines in good yield.

Keywords: samarium metal; reduction; radical; secondary amines.

Synthesis of secondary amines is an important area of research. Recently, several groups have described the synthesis of secondary amines using various reagents.[1] However, the reduction of the imines is still the reaction of choice to produce the secondary amines in reasonably good yield. For example, Lopez and Fu[2] reported the synthesis of secondary amines by tin-catalyzed reduction of imines with polymethylhydrosiloxane.

In a previous publication,[3] we demonstrated a facile synthesis of primary aromatic amines (**2**) by iodine-catalyzed, metallic samarium-induced reduction reactions of aromatic nitro compounds (**1**) in excellent yield (Scheme 1).



Scheme 1.

We[4] have also shown that one of these amines (for example **3**) can be derivatized to anti-tumor agents (for example **5**) by a coupling reaction with an acid (for example **4**, Scheme 2).

Recently, we have decided to test this novel samarium-mediated reduction method on various imines for a projected route to the synthesis of secondary amines. These secondary amines, in turn, could then be used for the required structure–activity study by following our earlier methodology.[4]

* Corresponding authors.

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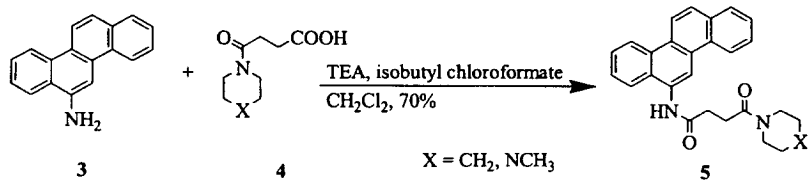
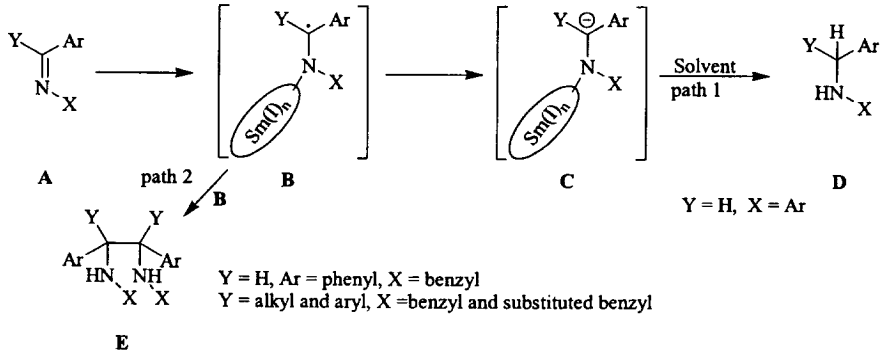


Scheme 2.

Although, the chemistry of SmI_2 is well documented,[5] similar studies of metallic samarium are very limited.[6] During the course of the samarium–iodine induced reaction, we[3] have observed a greater reducing ability of this reagent compared to the commercially available samarium diiodide. The actual reactive species in the Sm–I_2 reaction is not firmly established though Molander[7] suggested that the reagent is solely SmI_2. It has also been claimed[8] that the reactive species is actually SmI_3.

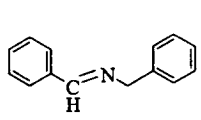
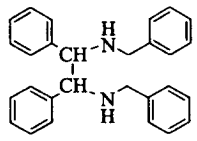
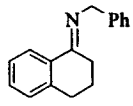
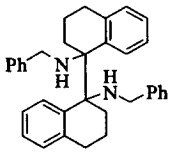
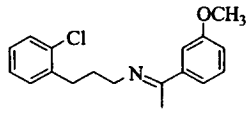
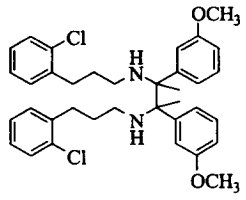
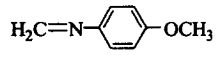
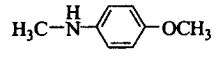
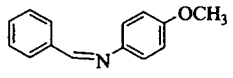
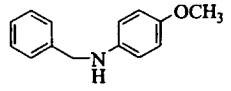
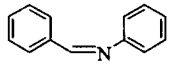
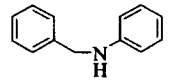
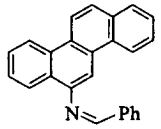
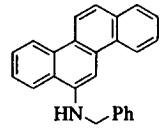
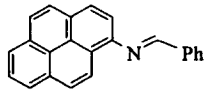
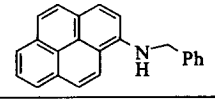
Reaction of various imines with samarium metal and iodine using methanol as the solvent was accomplished and useful selectivity was observed. We discovered that the nature of the final products depend on the structures of the starting imines and from a series of experiments, a generalization could be made. Thus, imines from the polyaromatic amines (Table 1, entries 7 and 8) and aniline derivatives (Table 1, entries 4 to 6) gave monomeric secondary amines whereas imines from arylalkyl amines (Table 1, entries 1 to 3) gave dimeric products. This is in contrast with the SmI_2-mediated reaction of the imines from which a mixture of dimeric products (*dl* and *meso*) was obtained.[9–11] The formation of the dimeric structures by SmI_2-mediated reaction was explained by postulating a one electron transfer mechanism across the C=N bond and subsequent coupling of the two carbon radical as was observed during the pinacol type[12] of reactions.

Although, the reactive species formed by the reaction between samarium metal and iodine (SmI_2 or SmI_3 or any other iodo–samarium complex), cannot be identified at this time, the final distribution of products can be tentatively explained by postulating two competing pathways resulting in the generation of the reduction product (Scheme 3, path 1) or the dimeric product (Scheme 3, path 2). Mechanistically, the formation of the monoamine (**D**) can be explained by the second electron transfer to the initially formed radical (**B**) to generate the dianion (**C**) and then protonation of (**C**) by the solvent. This process could be due to the presence of the electron releasing substituent at the nitrogen (entries 4–8) which can change the reduction potential of the radical anion (**B**) so that second electron transfer becomes the only path. Alternatively, the radical (**B**) in the polyaromatic system prevents self-coupling due to steric considerations. Increased congestion around the carbon radical inhibits the C–C bond formation. The basis for the formation of monoamines with simpler aromatic amines and diamines (path 2, **E**, radical–radical coupling) with aryl alkyl amines is not clearly understood at this time. Experiments with



Scheme 3.

Table 1
Reduction of the imines with Sm/I_2

Entry	Starting Imines	Product Amines	Yield	Time and Condition
1			52% meso : dl 9 : 1	RT, 30min
2			66% meso : dl 4 : 1	RT, 30min
3			42% meso : dl 9 : 1	RT, 30min
4			61%	RT, 30min
5			55%	RT, 30min
6			58%	RT, 30min
7			70%	overnight reflux
8			65%	overnight reflux

MeOD and CD_3OD are planned to give us a better understanding of the mechanism of this reduction method. These results indicate that the nature of the products by samarium induced iodine catalyzed reduction of the imines depends entirely on the substituent present at the *N*- of the imines.

A representative procedure is as follows: To the imine (1.5 mmol) in methanol (1.5 mL) was added samarium metal (4 mmol) and iodine (20 mol%). The suspension was stirred at room temperature or reflux under argon atmosphere, see Table 1. Water (2 mL) and dichloromethane (10 mL) was added to the reaction mixture and filtered. The organic layer was collected, washed with sodium thiosulfate solution (5%, 5 mL), water (5 mL), dried with sodium sulfate, evaporated and the product was purified by column chromatography on silica gel using ethyl acetate–hexanes as the eluent. All the new compounds were characterized by spectroscopic data.

In conclusion, we have shown an entirely new samarium mediated reduction method of the imines to amino derivatives in good yield.

Acknowledgements

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