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# A CONVENIENT SAMARIUM-INDUCED REDUCTION OF FERROCENYL IMINES

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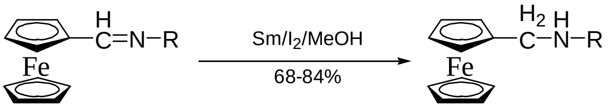
Abstract – Samarium metal induced reduction of the ferrocenyl imines to the ferrocenyl amines in excellent yield has been developed.

Ferrocene containing organic molecules has shown considerable biological activities.[1] Of particular, these types of compounds have shown potent medicinal properties, including for the treatment of iron deficiency anaemia and as β-lactam antibiotics.[2] The aromaticity, stability and low toxicity of ferrocene make it a suitable candidate in drug design. In addition, ferrocene with different types of unsaturated chain has recently turned attention.[3] Amino compounds bound to ferrocene might be useful in structure-activity study of different types of biologically active compounds. This paper describes a facile synthesis of various types of ferrocenylamines (**2**) by samarium metal induced reduction of ferrocenyl imines (**1**).

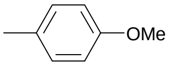
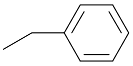
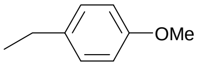
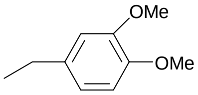
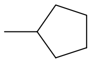
The reductive amination of carbonyl compounds with primary and secondary amines is one of the most widely investigated methods for the synthesis of amines.[4-6] Many reagents have been discovered for this purpose. Of them Borch reduction, sodium borohydride-acetic acid or aqueous sulfuric acid, sodium cyanoborohydride, titanium isopropoxide-sodium borohydride were found to be most effective.[4] However, sodium cyanoborohydride is a toxic reagent and it's use raises the risk of residual cyanide in the product. To overcome the problem, zinc borohydride was used in the reductive alkylations of amines.[5] In spite of application of reductive amination reaction in amine synthesis, only two examples using acylferrocene as the substrate are known. For example, synthesis of *N,N*-dialkylferrocenylamines has been reported by a reductive amination method.[6] The lability of ferrocenylalkylamines to acedolysis restricts the use of protic or Lewis acids mediated reductive amination procedures. In continuation of our study on samarium metal-induced organic reactions,[7] we envision that this metal can be used directly in the reduction of ferrocenyl imines. This paper demonstrates the successful realization of such an objective for the synthesis of several ferrocenylamines by samarium-induced reduction of ferrocenyl imines in good yield (Scheme 1, **1** to **2**).

**Scheme 1**



**1** **2**

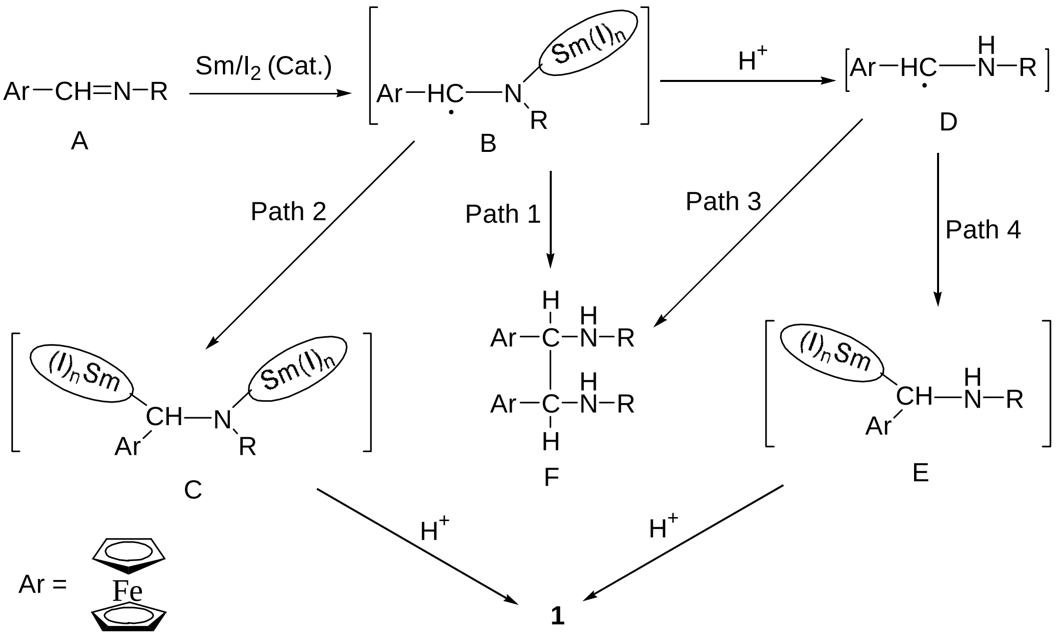
**Table 1**: Reduction of ferrocenyl imines (**1**) to amines (**2**).

| Entry | R | Time (h) | Yield (%) |
|---|---|---|---|
| 1 |  | 2.5 | 70 |
| 2 |  | 2 | 73 |
| 3 |  | 2 | 81 |
| 4 |  | 3 | 84 |
| 5 | $—(CH_2)_3—Me$ | 2 | 80 |
| 6 | $—(CH_2)_7—Me$ | 2 | 69 |
| 7 | $—(CH_2)_8—Me$ | 2 | 72 |
| 8 |  | 2.5 | 68 |

Several ferrocenyl imines (**1**) were prepared easily by refluxing the commercially available ferrocenecarboxaldehyde in benzene with the corresponding amines using Dean Stark water separator. Reaction of **1** by samarium metal (4 eqivalent) in iodine (20 mol%) at room temperature in the presence of methanol was investigated and the products were found to be monoamines (**2**) in all the cases. This observation is interesting since earlier a similar samarium iodide-mediated reduction of various aldimines produced diamines instead of monoamines.[8] In addition, this reaction is very convenient for the synthesis of these types of compounds. The remarkable features include the success with aromatic amine (Entry 1), aryl-alkyl amines (Entries 2-4) and aliphatic amines (Entries 5-8) in moderate yield (68-84%).

The mechanism of the samarium-induced reaction of ferrocenyl imines deserves some special attraction. Previously, the formation of the dimeric products by samarium diiodide-mediated reaction was explained by postulating a one electron transfer mechanism across the C=N bond and subsequent coupling of the two carbon radical.[8] From the preliminary data, we are unable to identify the reactive species formed by the reaction between samarium metal and catalytic amounts of iodine in our experiment. By following our

**Scheme 3**



earlier hypothesis,[7a] we can explain the final distribution of products by postulating four competing pathways resulting in the generation of the reduction product (Scheme 3, paths 2 and 4) or the dimeric product (Scheme 3, paths 1 and 3). Single electron transfer to A by samarium generates ion-radical B. Second electron transfer to the initially formed B generates the dianion C and then protonation of the dianion C results the monoamine. Protonation of the ion-radical B and then electron transfer-protonation could also be involved (D→E, path 4). Based on the nature of the product, we believe the path (B→C) or (B→D→E) is facilitated in this present investigation. This reflects a tremendous role of the cyclopentadienyliron in the present study. However, the exact way how this clopentadienyliron can stabilize the carbanions C and E is not known to us at this time. Alternatively, as a result of severe steric crowding, the ion-radical B prevents self-coupling (B→F). Increased congestion around the carbon radical inhibits the C-C bond formation. The adamantyl system and imines with bulkier polyaromatic system also support the above mechanism.[7] Since with adamantyl and polyaromatic systems, monoamines were the only products. Recently, low-valent titanium was efficiently used for the reductive dimerization of imines.[9] In contrast to our observation, no monoamine formation was reported in this investigation. Reductive coupling of aldimines to vicinal diamines by indium under aqueous conditions was investigated.[10] Convenient reduction of aldimines to a mixture of monoamines and diamines by zinc powder in aqueous alkali was also studied.[11] Therefore, mechanistically our samarium-induced reduction of ferrocenyl imines is completely different than the existing methods.[8-11] The reactive species is not known at this time. However, involvement of catalytic amounts of samarium diiodide by the reaction of samarium metal and catalytic amounts of iodine is speculated. The generated samarium diiodide could be reduced by samarium metal to monovalent samarium species. Use of 20 mol% or excess samarium diiodide alone is not suitable for the synthesis of monoamines described here. It has been demonstrated in a recent elaborate study on the electronic conjugation pathways in ferrocenyl imines that the electron density around C=N bond is not differed too much by the presence of aromatic or aliphatic group.[12] Thus, our present study demonstrates a unique role of the ferrocene moiety in controlling the product distribution. These results indicate that the nature of the products by samarium-induced iodine-catalyzed reduction of the ferrocenyl imines depends on the substituent present at the N- and also at the C-of the imines. Electronic effects and steric effects of the imines are both responsible in deciding the product distribution and their yield. In the present investigation, presence of electron deficient iron is found to control the reaction course and stabilizes the transition state (paths 2 and 4) of the reaction.

In conclusion, we have shown a new general method of samarium-mediated reduction of the ferrocenyl imines to ferrocenylamino derivatives.[13] Considering the mildness and neutral reaction conditions of this procedure, this method should provide an easy access to several chiral ferrocenyl amines with high enantiomeric excess.

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13. A representative procedure is as follows: To the imine (1.5 mmol) in methanol (5 mL) was added samarium metal (4 mmol) and iodine (20 mol%). The suspension was stirred at room temperature under argon atmosphere. Water (2 mL) and dichloromethane (10 mL) were added to the reaction mixture and the mixture 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.