SHORT PAPER

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Samarium-mediated iodine-catalysed reductive amination of the adamantyl methyl ketone†

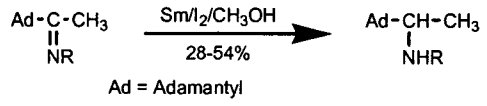
Bimal K. Banik*, Oliwia Zegrocka, and Frederick F. Becker

The University of Texas, M.D. Anderson Cancer Center, Department of Molecular Pathology, Box 89,1515 Holcolmbe Blvd. Houston, TX 77030, USA

Adamantyl amines were prepared by samarium-metal induced iodine-catalysed reduction of the imines in a one-pot operation.

Synthesis and biological evaluation of amines have been the subject of extensive investigations.[1] The reductive amination[2] of aldehydes and ketones is the most widely studied reaction used for the synthesis of amines. Various hydride donors, such as sodium borohydride, sodiun cyanoborohydride and zinc borohydride have been used for this purpose.[3] To overcome the problems associated with the use of these reagents, Bhattacharyya[4] demonstrated similar transformations with titanium isopropoxide and sodium borohydride. In an elegant study, he showed that biologically active adamantyl amines can be prepared by a direct reductive amination reaction using titanium isopropoxide and borohydride reagents. Indirect synthesis [5] of such adamantyl amines has also been reported. The reagents, particularly sodium cyanoborohydride used in some of these reports are extremely toxic. For this reason, a method to accomplish these reactions under relatively mild conditions would be useful.

Recently, we[6] have demonstrated a facile reduction of aromatic nitro compounds and imines to the amino derivatives by samarium mediated, iodine-catalysed reactions. During the reduction of imines by this method, we observed that the formation of monoamines or diamines depends on the substituent present at the nitrogen of the imines. Thus arylalkyl imines produced diamines and arylaryl imines gave monoamines. We explained the mechanism of the formation of these monoamines and diamines as based on the electron releasing property of the aromatic moiety and also steric considerations.[6b] In order to gain a more complete mechanistic insight into this novel reduction method and to apply this method to prepare biologically active compounds, we became interested in the reduction study of adamantyl imines Scheme 1. This paper demonstrates the synthesis of several racemic adamantyl amines by reductive amination reaction mediated by samarium-iodine and also establishes our earlier hypothesis on the mechanistic path of this reduction reaction (Scheme 1).



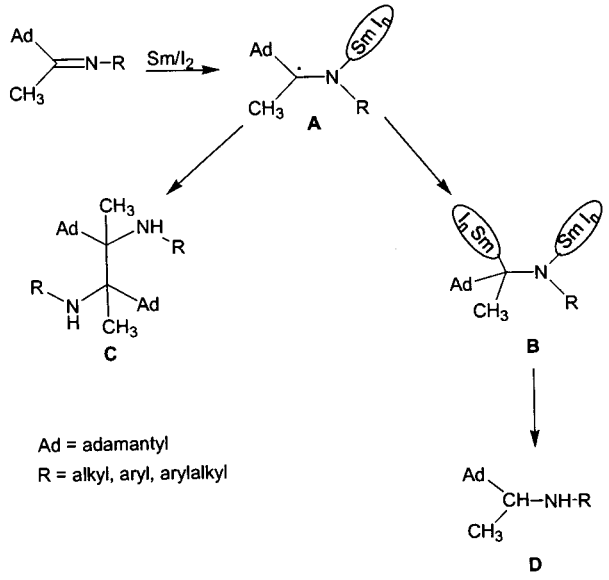
Scheme 1

The synthesis of several imines with adamantyl methyl ketone was carried out with a wide variety of amines. For example, aromatic amine (entry 1 and 8), aryl-alkyl amine (entry 3), aliphatic cyclic amine (entry 4), aliphatic open chain amine (entry 5 and 6) and heterocyclic amine (entry 2) were used with equal success. Mixing the ketone with the amines in toluene and refluxing the solution with Dean-Stark water system for 20 h produced the imines in good yield (Table 1).

The reduction was effectively accomplished by stirring a solution of the imine in methanol with metallic samarium and catalytic amounts of iodine. After the method described below, and purification, monoamines were obtained in good yield. No trace of diamines could be detected in the crude reaction mixtures.

Encouraged by these results, we attempted to combine the two steps synthetic sequence into a one-pot operation.[7] For example, imines were prepared as described above and this was added to a preformed solution of Sm-iodine in methanol. The product obtained from this reaction was found to be identical with the compound prepared by the two-step method.

Experiments with CD_3OD produced the D-labeled compound indicating the trapping of the dianion by the solvent (entry **8**). The dianion **B** is probably formed by the single electron transfer to the C–N bond to generate the ion-radical and then further electron transfer to the ion radical **A**. Radical-radical coupling product (dimeric product **C**) could not be formed because of the considerable steric crowding at the radical centre due to the bulkier adamantane system. In contrast to this, it has been reported that the reduction of some structurally dissimilar imines with samarium diiodide solution under various conditions produced diamines[8] in excellent yield (Scheme 2).



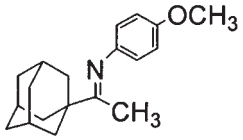
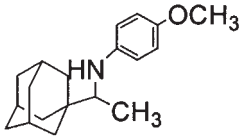
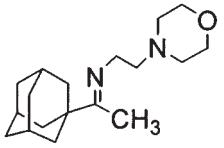
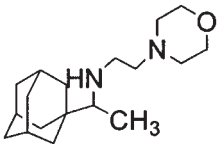
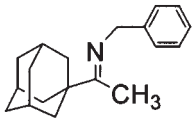
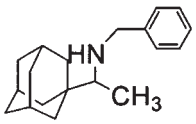
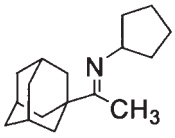
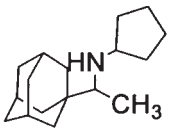
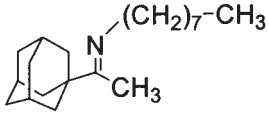
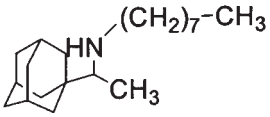
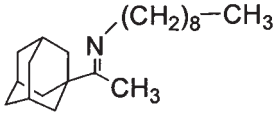
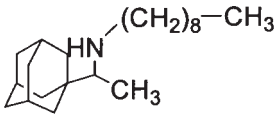
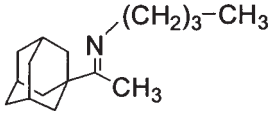
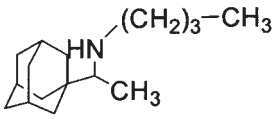
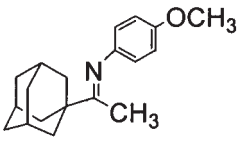
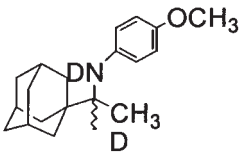
Scheme 2

In conclusion, a simple reduction of adamantyl imines to the corresponding adamantyl amines by samarium-induced iodine-catalyzed reaction was demonstrated. We believe that the overall simplicity and the mild reaction conditions should get wide application in synthetic organic chemistry.

* To receive any correspondence. E-mail: banik@solace.mdacc.tmc.edu

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Sm/I_2-induced reduction of adamantyl imines

Entry	Starting material	Product	Yield (%)
1.		 **1**	50
2.		 **2**	28
3.		 **3**	51
4.		 **4**	47
5.		 **5**	54
6.		 **6**	51
7.		 **7**	48
8.		 **8**	45

A representative procedure is as follows: To the solution of adamantyl methyl ketone (80 mg, 0.45 mmol) in toluene (10 ml), amine (0.67 mmol) and molecular sieves (4Å) were added. The mixture was heated under reflux for 20h and then it was cooled. The toluene solution of the imine was added to methanol (1 ml) containing samarium metal (168 mg, 1.12 mmol) and iodine (28 mg, 0.22 mmol). After being stirred for 3h at room temperature under argon atmosphere, the reaction was quenched by the addition of water (2 ml). Dichloromethane (10 ml) was added and the mixture was filtered through Celite, the organic layer was separated and dried over sodium sulfate. The product was then purified by column chromatography over silica gel using ethyl acetate-hexanes (1:5) as the eluent.

1: ^{1}H NMR($CDCl_3$) δ: 1.05 (d, J=6.5 Hz, 3H), 1.55 (m, 3H), 1.71 (m, 9H), 2.02 (bs, 3H), 2.95 (q, *J*=6.5 Hz, 1H), 3.10 (bs, 1H exchangable with D_2O), 6.57 (d, *J*=8.8 Hz, 2H), 6.77 (d, *J*=8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 14.38, 27.93, 28.50, 36.46, 37.26, 38.83, 55.88, 58.98, 114.41, 114.91, 143.11, 151.45; *m/e* 286.17 $(M+H)^+$.

2: ^{1}H NMR($CDCl_3$) δ: 0.95 (d, *J*=6.5 Hz, 3H), 1.72–1.47 (m, 13H), 2.01 (m, 4H), 2.47 (m, 7H), 2.83 (m, 1H), 3.71 (m, 4H); ^{13}C NMR

($CDCl_3$) δ: 13.66, 28.56, 36.04, 37.32, 38.71, 45.45, 53.50, 57.90, 63.57, 67.14; *m/e* 291.50 $(M+H)^+$.

3: ^1H NMR($CDCl_3$) δ: 0.98 (d, *J*=6.5 Hz, 3H), 1.47 (m, 3H), 1.66 (m, 10H), 1.96 (bs, 3H), 2.11 (q, *J*=6.5 Hz, 1H), 3.78 (dd, *J*=13.2 Hz, 2H), 7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 13.69, 28.78, 36.58, 37.58, 39.09, 53.09, 61.82, 127.10, 128.60, 128.65, 141.71; *m/e* 270 $(M+H)^+$.

4: ^1H NMR($CDCl_3$) δ: 0.93 (d, *J*=6.5 Hz), 1.22 (m, 2H), 1.43–1.74 (m, 18H), 1.84, (m, 1H), 1.95 (m, 4H), 2.071 (q, *J*=6.5 Hz, 1H), 3.09 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.29, 16.87, 24.10, 24.28, 28.72, 29.01, 33.11, 34.54, 36.21, 37.65, 37.79, 38.11, 58.45, 60.95; *m/e* 248 $(M+H)^+$.

5: ^1H NMR($CDCl_3$) δ: 0.88 (m, 3H), 0.93 (d, *J*=6.5 Hz, 3H), 1.27 (bs, 10H), 1.43–1.72 (m, 15H), 1.96 (bs, 3H), 2.03 (q, *J*=6.5 Hz, 1H), 2.40 (m, 1H), 2.69 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 13.86, 14.52, 23.07, 27.87, 28.97, 29.71, 29.96, 30.60, 32.26, 36.32, 37.75, 39.10, 49.41, 62.95; *m/e* 290 $(M+H)^+$.

6: ^1H NMR($CDCl_3$) δ: 0.88 (m, 3H), 0.93 (d, *J*=6.5 Hz, 3H), 1.27 (bs, 12H), 1.43–1.72 (m, 14H), 1.97 (bs, 3H), 2.04 (q, *J*=6.5 Hz, 1H), 2.40 (m, 1H), 2.70 (m, 1H); ^{13}C NMR($CDCl_3$) δ: 13.57, 14.11, 22.68, 27.45, 28.59, 29.29, 29.60, 30.34, 31.88, 35.97, 37.37, 38.72, 49.14, 62.58; *m/e* 306 $(M+H)^+$.

7: ^1H NMR($CDCl_3$) δ: 0.92 (m, 6H), 1.25–1.72 (m, 18H), 1.97 (bs, 3H), 2.05 (q, *J*=6.5 Hz, 1H), 2.41 (m, 1H), 2.72 (m, 1H); ^{13}C NMR($CDCl_3$) δ: 13.53, 14.09, 20.61, 28.59, 32.40, 35.97, 37.40, 38.71, 48.76, 62.63; m/e 236 $(M+H)^+$.

8: ^1H NMR($CDCl_3$) δ: 1.64 (m, 12H), 1.97 (bs, 3H), 3.71 (s, 3H), 6.53 (d, *J*=8.8 Hz, 2H), 6.73 (d, *J*=8l8 Hz, 2H); ^{13}C NMR($CDCl_3$) δ: 28.47, 36.32, 37.23, 38.77, 55.85, 114.37, 114.89, 143.07, 151.42; *m/e* 288 $(M+H)^+$.

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