

**Indium/Ammonium Chloride Mediated Selective Reduction of
Aromatic Nitro Compounds: Practical Synthesis of 6-
AminoChrysene**

Bimal K. Banik*, Michelle Suhendra, Indrani Banik, and Frederick F. Becker

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

Abstract: Reduction of aromatic and heteroaromatic nitro compounds to the corresponding amino compounds was achieved by indium/ammonium chloride induced reaction in aqueous ethanol. This method was extended for the preparation of large quantities of 6-aminochrysene in excellent yield.

The synthesis and biological evaluation of aromatic amines are active and important areas of research and their chemistry by derivative formation is widely studied.¹ There are many methods available in the literature for the

affecting these functionalities. Finally, after considerable experimentation, this method has been scaled up for a relatively simple, large scale preparation of 6-aminochrysene (entry 6).

While, we⁶ and others¹⁵ have demonstrated the anti-tumor effects of several of the derivatives containing the 6-amino chrysene functionality, the supply of this expensive starting material is often inadequate. The synthetic method¹⁶ reported in 1940 for its preparation requires large amounts of acids. Therefore, we are pleased to report our method of utilizing indium/ammonium chloride for the large scale reduction of relatively inexpensive 6-nitrochrysene. Reduction of 6-nitrochrysene in 5 gram scale with indium and ammonium chloride afforded 6-aminochrysene in more than 85% yield. This method does not require any purification by column chromatography¹⁷. Because of the non-flammable nature of the process and ready availability of indium and ammonium chloride, we believe this method is practical for the preparation of several polyaromatic amines. Further, this method which is performed in aqueous ethanol is extremely safe from the environmental view point and should prove useful in medicinal organic chemistry. Reduction of other groups by this reagent is in progress in our laboratory.

Experimental Section:

Some of the compounds described here are potential carcinogens. All reactions were carried out in well-ventilated hood. A representative procedure is as follows: To a suspension of 6-nitrochrysene (5g) in water (100mL) and ethanol (70mL) was added solid ammonium chloride (5.5g) and indium powder

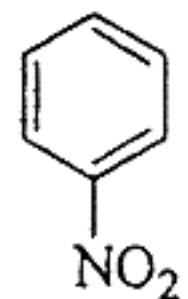
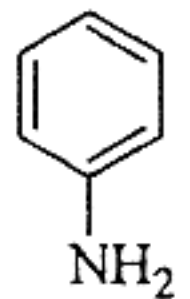
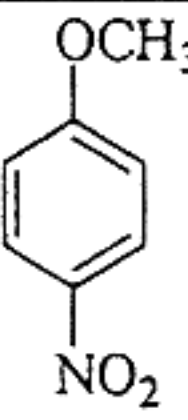
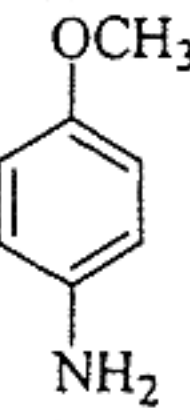
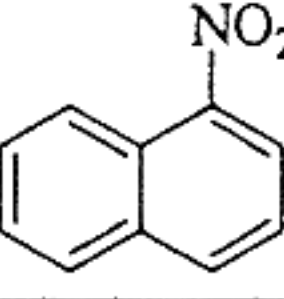
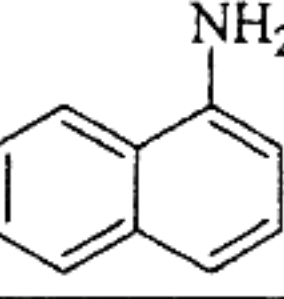
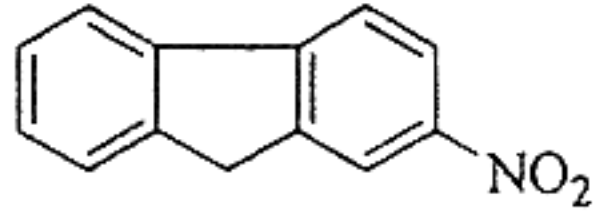
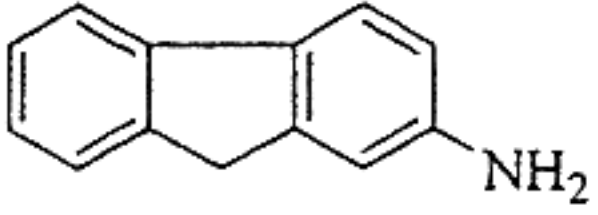
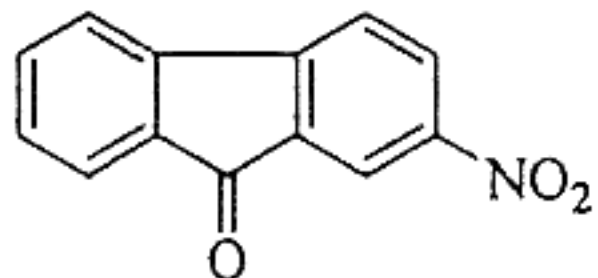
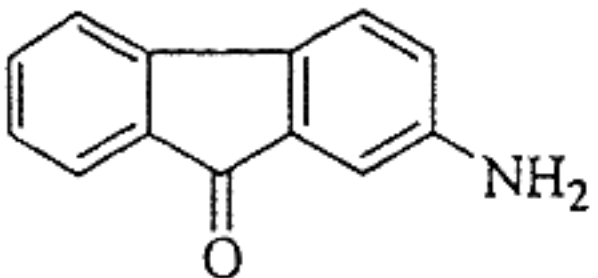
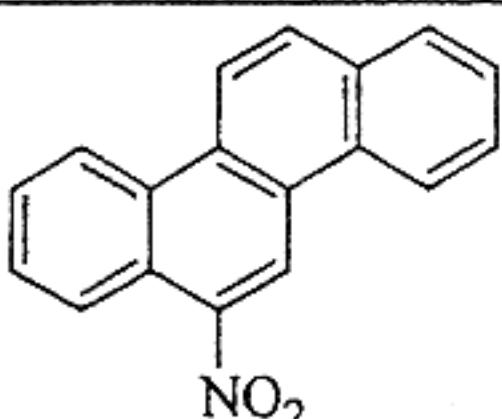
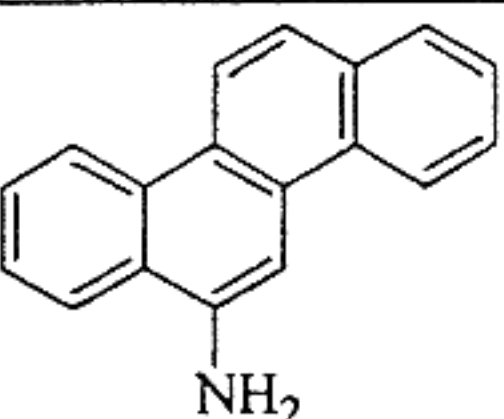
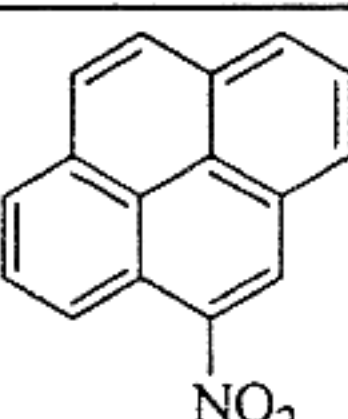
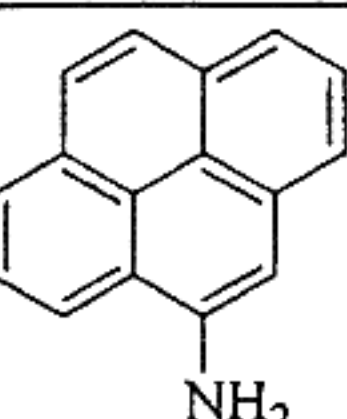
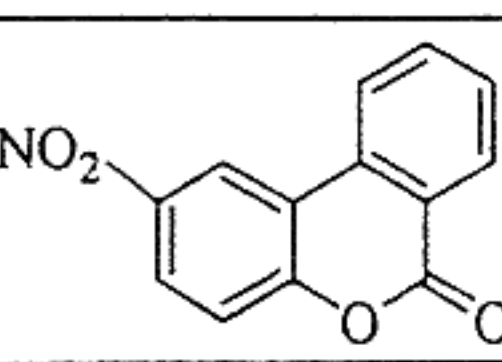
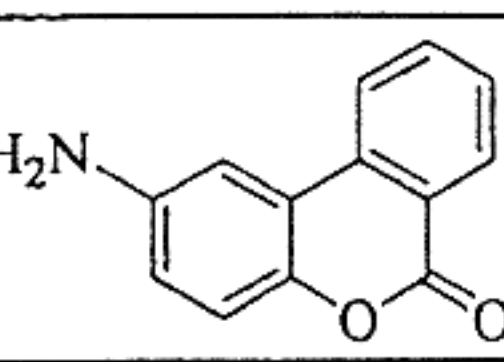
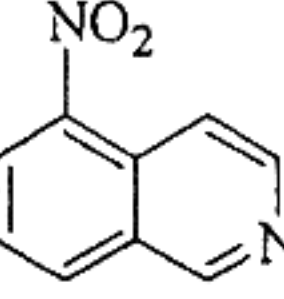
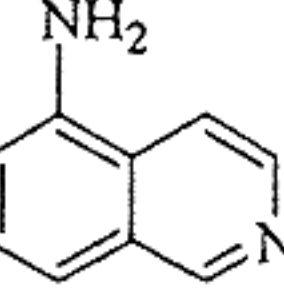
(5.72g). The mixture was refluxed for 16h, filtered and extracted with dichloromethane, washed with water, dried with sodium sulfate and evaporated. The pure product (85%) was isolated after crystallization from dichloromethane-hexanes.

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Table 1

Entry	Nitro Compound	Amino compound	Reduction Time (h)	Yield (%)	bp or mp
1			5	90	bp 180-190° (lit 184°)
2			5	90	mp 58-60° (lit 57-60°)
3			8	80	mp 48-50° (lit 48-50°)
4			8	90	mp 127-131° (lit 128°)
5			8	80	mp 157-160° (lit 160°)
6			15	85	mp 208-210° (lit 209-211°)
7			14	85	mp 115-116° (lit 115-117°)
8			22	70	mp 190-193° (lit 190-191°)
9			20	70	mp 126-127° (lit 125-128°)

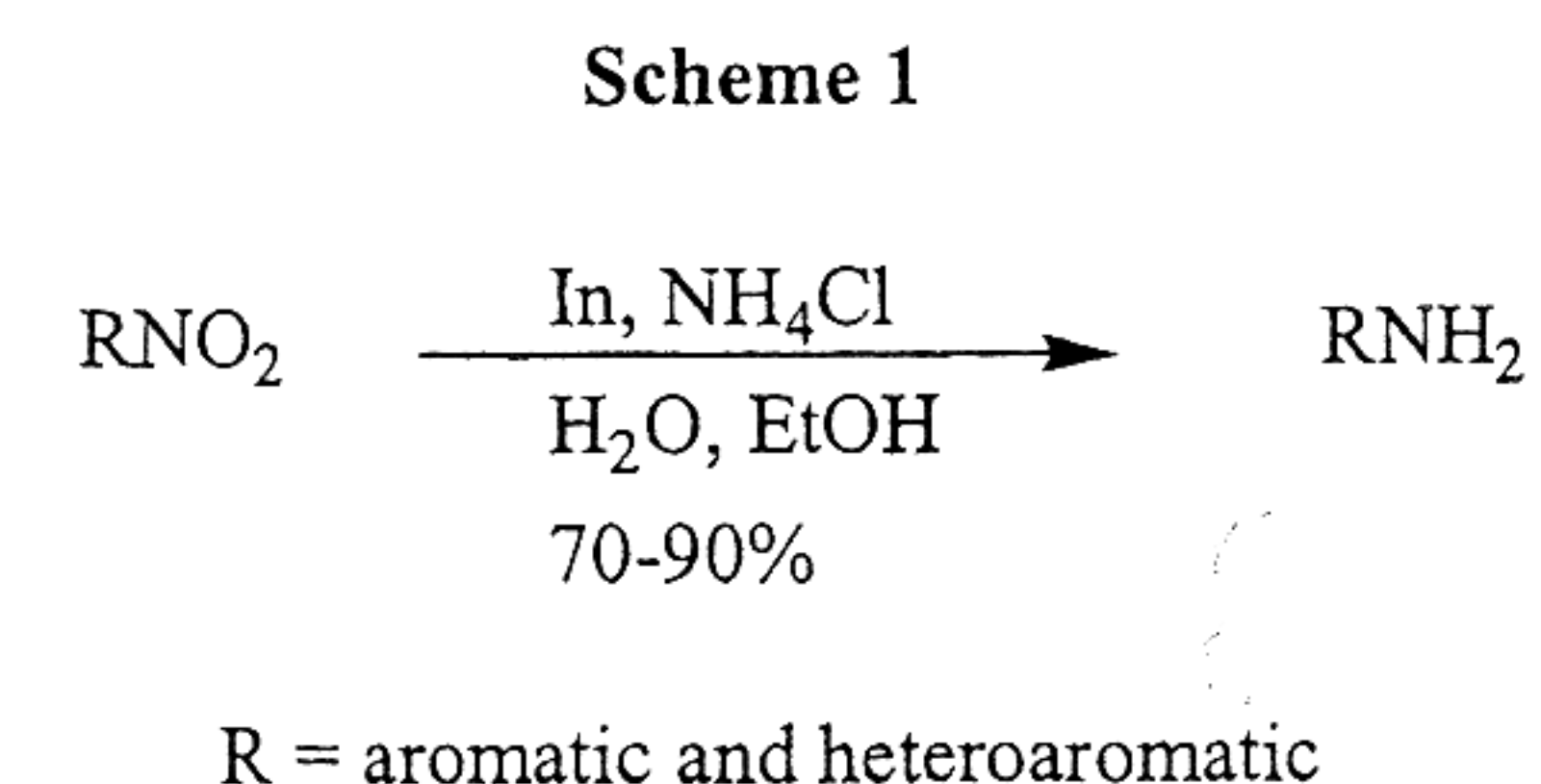
produce any amino compound. Also, indium trichloride alone in aqueous ethanol under identical conditions failed. Therefore, the presence of ammonium chloride is essential for the success of the reaction, since indium metal in refluxing ethanol or aqueous ethanol did not yield any trace of the product even after 10h. In the presence of ammonium chloride, however, the reaction mixture revealed the gradual formation of the amino compound as evident from thin layer chromatography by a direct comparison with authentic sample.

Impressively, no other intermediates, such as nitroso or hydroxyl amine could be detected in the reaction mixture. In order to test the selectivity, reduction of methyl cinnamate was attempted with indium-2% hydrochloric acid or indium-ammonium chloride in aqueous ethanol. However, both the reactions failed to produce the saturated 3-phenylmethylpropionate. Methyl cinnamate was recovered from the indium-ammonium chloride reaction while the product from the indium-hydrochloric acid was found to be cinnamic acid. No dimeric product due to the radical-radical coupling could be detected. Therefore, the present method can give selective reduction of the aromatic nitro group in the presence of olefinic group. For example, 4-nitrocinnamyl alcohol was reduced to the 4-aminocinnamyl alcohol in good yield by the reagent system. Therefore, because of its effectiveness and non-toxic nature we used indium-ammonium chloride for the subsequent study.

From a series of experiments, it was discovered that high temperature (approximately 80°C) is required for the completion of the reaction.

Based on these results, we attempted to reduce the nitro group in polyheteroaromatic systems by this procedure. In contrast to the samarium-induced reaction⁷, the method of indium-ammonium chloride resulted in high yields of amino compounds (entries 8 and 9). Samarium-induced iodine-catalyzed reaction of 5-nitroisoquinoline (entry 9) gave a complex mixture of products probably because of partial reduction of the heterocyclic unit along with the reduction of the nitro group. Table 1 shows that the reduction of the nitro group can be performed in the presence of lactone (entry 8) without

synthesis of these compounds. Though some of these are widely used, still they have limitations based on safety or handling considerations. For example, catalytic hydrogenation² of the nitro or azido compounds in the presence of metals such as palladium carbon or Raney nickel require stringent precautions because of their flammable nature in the presence of air. In addition, these methods require compressed hydrogen gas and vacuum pump to create high pressure within the reaction flask. To overcome these difficulties, several new methodologies have been reported in the recent literature.³ We⁴ have also described a new method for the reduction of the aromatic nitro compounds and imines to the aromatic amines by a novel samarium-induced iodine catalyzed reduction reaction.⁵ We have utilized the resultant aromatic amines for the synthesis of several new anticancer agents.⁶ In our ongoing program to use organometallics in these reactions,⁷ we became interested in developing an easy access to several polyaromatic amino compounds, for structure-activity study. While our samarium-induced reduction of aromatic nitro compounds works well in the polycarbocyclic series, similar reaction with several heteroaromatic nitro compounds results in a mixture of products under identical conditions.⁸ Moreover, samarium-induced reduction of the nitro compounds requires anhydrous reaction conditions. The present study describes a selective reduction method of aromatic and heteroaromatic nitro compounds to the corresponding amines by indium in the presence of ammonium chloride in aqueous ethanol (Scheme 1). The method has been extended to the practical synthesis of 6-amino chrysene in large scale and excellent yield.



The use of indium metal in synthetic organic chemistry has been explored by several research groups.⁹⁻¹³ The reactions induced by indium can be performed in aqueous solution.¹¹

Using the method developed by Moody and Pitts¹⁴, we examined the effect on carbocyclic aromatic nitro compounds (Scheme 1) and the results of indium-induced reduction are represented in Table 1. Thus, reaction of nitrobenzene (entry 1), 4-nitro anisole (entry 2), 1-nitro naphthalene (entry 3), 2-nitrofluorene (entry 4), 2-nitro 9-keto fluorene (entry 5), 6-nitrochrysene (entry 6), 1-nitropyrene (entry 7) with indium metal in the presence of ammonium chloride using aqueous ethanol was performed and the corresponding amines were produced in good yield. The table 1 illustrates some important features. This method produced a single compound from the reduction of nitrofluorenone whereas catalytic hydrogenation produced a mixture of compounds (entry 5) even using stringently controlled conditions.

In order to gain an insight into the mechanistic course of the indium mediated reaction, several experiments were carried out with 1-nitropyrene (entry 7). For example, the reaction of 1-nitropyrene with indium trichloride in the presence of ammonium chloride using ethanol as the solvent failed to

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