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INDIUM-MEDIATED REDUCTIVE CYCLIZATIONS IN AQUEOUS ETHANOL: HIGHLY EFFICIENT SYNTHESIS OF HETEROCYCLIC COMPOUNDS OF BIOLOGICAL INTERESTS[↑]

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[↑]Dedicated to Professor J. P. Kutney on the occasion of his 70th birthday.

Abstract - Indium/ammonium chloride in the presence of aqueous ethanol was found to be very effective in reductive cyclization reactions leading to the development of several heterocyclic compounds of biological significance.

The chemistry of indium metal is the subject of current investigation, especially since the reactions induced by indium can be performed in aqueous solution.[1] Previously, our ongoing studies of metal-mediated chemical transformations demonstrated samarium-induced reduction of aromatic nitro compounds and imines to the amino derivatives.[2] We have demonstrated that a number of these aromatic amines posses anticancer activity.[3] As a result of these findings, we became interested in developing an easy access to several heteroaromatic compounds as the key compounds in a structure-activity study. While our samarium-induced reduction of aromatic nitro compounds works well for the polycarbocyclic series, similar reaction with several heteroaromatic nitro compounds produced a mixture of products under identical conditions. For this reason, our interests have focussed on other metal-catalyzed reduction reactions. Towards this goal, we recently described a reduction method of aromatic and heteroaromatic nitro compounds to the corresponding amines by indium in the presence of ammonium chloride in aqueous ethanol[4] (Scheme 1).

$$ArNO_2 \xrightarrow[EtOH/H_2O]{In/NH_4Cl} ArNH_2$$

Scheme 1

The use of water as solvent for organic reactions in the indium-induced reaction is of special interest from anenvironmental point of view.[1] Many metals like zinc, tin, magnesium, and iron usually require acid-catalysts for the activation process, with the resultant problems of waste disposal.

We postulated that the indium-induced reduction of the nitro compound and simultaneous cyclization with suitably located functional groups can yield a facile synthesis of heterocyclic compounds. This paper describes the application of such a concept with the development of several polycyclic heterocyclic N- and O-containing compounds of biological significance without using any promoter or acid media.

At the inception of this project, synthesis of quinoline was undertaken by the reductive cyclization of 2-nitrocinnamaldehyde by indium/ammonium chloride in ethanol and quinoline was formed at about 20% yield. The same reaction with water-ethanol (1:1) or water-ethanol (9:1) produced quinoline in 90% yield (Table 1, Entry 1). However, use of water as the only solvent afforded the product in 50% yield and the reaction proceeded much more slowly. These experiments indicated the importance of solvent composition in the reductive cyclizations reactions mediated by indium.

As an extension of this method, we prepared phenanthridine by the reduction of nitro aldehyde (Entry 2). The reduction of the nitro group to the amino group and a nucleophilic attack to the formyl group are believed to be involved in the cyclization reactions (Entries 1 and 2). Synthesis of these types of compounds was previously reported by zinc and other reduction methods in organic solvents in the presence of acids.[5,6] Some of these methods for the preparation of phenanthridines[7] have limited scope.

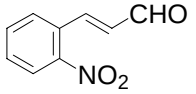
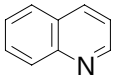
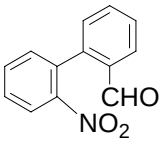
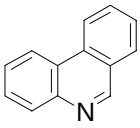
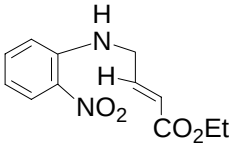
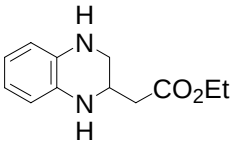
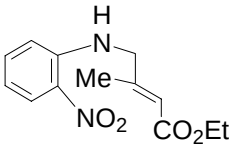
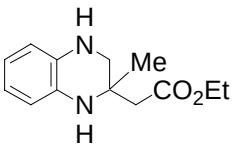
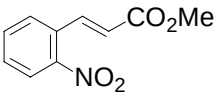
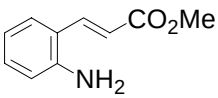
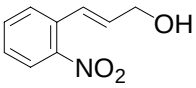
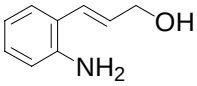
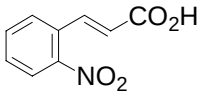
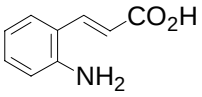
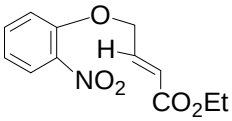
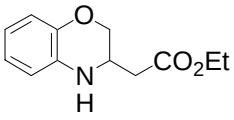
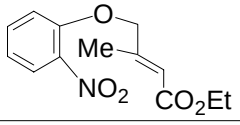
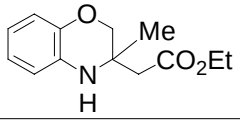
Next, bicyclic and tricyclic compounds were synthesized by using this indium-mediated method. Tetrahydroquinoxalines are important structural fragments in a number of biologically active compounds.[8] Tandem cyclization *via* reductive amination and reduction-lactam formation methods were reported previously for the synthesis of these types of compounds.[9] Recently, iron powder in refluxing acetic acid was shown to be effective for this kind of transformation.[10]

We believed that our indium-induced reductive cyclization method may be used for the synthesis of these types of ring systems. The starting nitroarene was prepared by following the literature method.[10] Reduction of the nitroarenes by using indium metal and ammonium chloride in ethanolic aqueous solution afforded the quinoxalines in 60-61% yield (Entries 3 and 4). An initial reduction of the nitro group to the amino group and then a favorable 6-*exo*-*trig* cyclization is believed to be involved in this process. This has been further supported by the fact that 2-nitromethylcinnamate, 2-nitrocinnamyl alcohol and 2-nitrocinnamic acid produced the 2-aminomethylcinnamate, 2-aminocinnamyl alcohol and 2-aminocinnamic acid respectively (Entries 5, 6 and 7). No cyclization of the amino group to the unsaturated moiety, ester or carboxyl group was detected, possibly because of an unfavorable cyclization path. By following this method, tetrahydrobenzoxazine derivatives were prepared in excellent yield by the reduction of its precursor without any degradation of the side chains[11] (Entries 8 and 9).

The notable characteristic of this method includes an environmentally friendly simple reaction condition in aqueous ethanol without any acid or activation of the reagent. We believe this method is a practical alternative of many of the existing methodologies and should prove useful for the preparation of a large

quantitity of polycyclic heterocyclic compounds with widely different skeletons in high yield. [12]

Table 1: Reductive Cyclization Mediated by Indium in the Presence of Ammonium Chloride in Aqueous Ethanol

Entry	Starting Material	Product	Yield (%)
1			90
2			90
3			61
4			60
5			85
6			85
7			68
8			79
9			80

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12. A representative experimental procedure: To a solution of the nitro compound (1 mmol) in ethanol (1 mL) was added water (9 mL), ammonium chloride (214 mg, 4 mmol) and indium powder (344 mg, 3 mmol). The mixture was refluxed with vigorous stirring and the progress of the reaction was followed by TLC. After the completion of the reaction (4-12 h), it was filtered, extracted with dichloromethane (20 mL), washed with brine and evaporated. The pure product was isolated after column chromatography over silica gel (ethyl acetate-hexanes, 10: 90).