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FACILE SYNTHESIS OF BIOLOGICALLY ACTIVE HETEROCYCLES BY INDIUM-INDUCED REACTIONS OF AROMATIC NITRO COMPOUNDS IN AQUEOUS ETHANOL

Bimal K. Banik [‡,] *, Indrani Banik, Susanta Samajdar, and Mary Wilson [↑]

Department of Molecular Pathology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Box 89, Houston, Texas 77030, U.S.A.
bbanik@mail.mdanderson.org

Abstract - Indium/ammonium chloride-induced reduction of aromatic nitro compounds to aromatic amines in aqueous ethanol was developed. Useful chemo-selectivity was observed in the reduction reaction. This method was extended to reductive cyclization and rearrangement toward the synthesis of various biologically active heterocycles, including quinoline, oxazines, quinalonones, and phenanthridine in excellent yield. The oxophilicity of indium metal influenced the reaction in aqueous ethanol. Metals like zinc and tin were not effective in promoting this kind of reactions under the present environmentally friendly conditions.

Introduction

Our ongoing studies of metal-mediated chemical transformations have demonstrated various samarium- and indium-induced reactions including reduction of aromatic nitro compounds and imines to the amino derivatives.[1] Specifically, we demonstrated that a number of these aromatic amine derivatives possess anticancer activity.[2] As a result of these findings, we became interested in developing an easy access to several heteroaromatic compounds for a structure-activity study.

Increasing attention is being paid to the use of a wide variety of reactions using direct reaction of metals because of several positive factors. For example, the direct approach avoids the use of sensitive, expensive organometallics. The chemistry of indium metal is the subject of current investigation, especially because reactions induced by indium can be performed in an aqueous solution.[3, 4] Recently, indium metal has been used as a reducing agent in several organic transformation. The success of the reduction reaction has been related to its very low ionization potential (5.8 eV). Notably indium is inert toward water and mild acid solutions, and therefore, it becomes an attractive metal in organic chemistry

on the ground of environmentally benign synthesis. In this report, we describe facile reduction of aromatic nitro compounds by indium/ammonium chloride in aqueous ethanol and application of this method to the synthesis of several biologically significant polycyclic heterocyclic N- and O-containing compounds. Although, the chemistry of indium has been very successful in accomplishing Barbier-type of reactions and reduction chemistry, the use of this metal in the construction of multicyclic ring structure has not been explored.

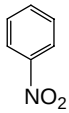
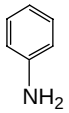
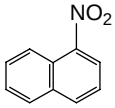
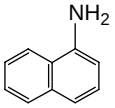
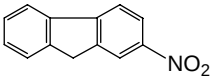
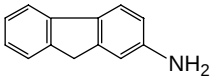
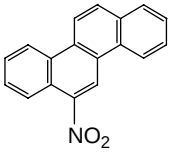
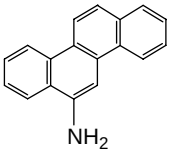
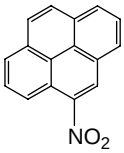
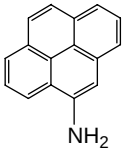
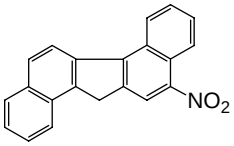
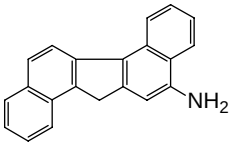
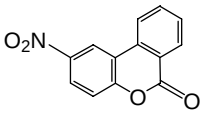
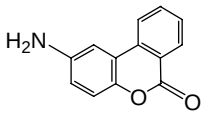
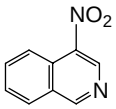
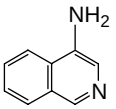
Results and Discussion

Reduction of the Aromatic Nitro Group. The reduction of aromatic nitro compounds to aromatic amines can be achieved using a number of methods that have been described in the literature.[1b, 4b-c] Although some of these methods are widely used, they still have limitations based on safety and handling considerations. For example, catalytic hydrogenation[5] of nitro or azido compounds in the presence of metals such as palladium carbon and Raney nickel requires taking stringent precautions because of their flammable nature when exposed to air. In addition, these methods require the use of compressed hydrogen gas and a vacuum pump to create high pressure within the reaction flask. To overcome these difficulties, several new methodologies[6] such as decaborane, electrochemically generated Raney nickel, dimethyl hydrazine/ferric chloride, hydrazine hydrate/ferric oxide-magnesium oxide, diethyl chlorophosphite and sodium borohydride-sodium methoxide in methanol have been reported in the recent literature. In general, the main drawbacks of these methods are long reaction times, conditions that are not environmentally friendly, and nonchemoselectivity. While our method of samarium-induced reduction of aromatic nitro compounds works well with a polycarbocyclic series, similar reactions with several heteroaromatic nitro compounds under identical conditions results in a mixture of products. Moreover, samarium-induced reduction of the nitro compounds requires anhydrous and inert reaction conditions. Therefore, we sought an alternative procedure.

At the beginning of our study, we examined reduction of a few aromatic nitro compounds with indium metal/ammonium chloride in the presence of aqueous ethanol and the amines were obtained in excellent yield (**Table 1**).[1b, 4b, 4c] This reduction method deserves special mention, as the use of polyaromatic (**Table 1**, Entries 4, 5 and 6) and heteroaromatic nitro compounds resulted in (**Table 1**, Entries 7 and 8) products in excellent yield. While we[2] and others[7] have demonstrated the anticancer activity of several derivatives of polyaromatic amino compounds, the supply of these expensive starting materials for a structure-activity relationship study is inadequate. However, the reduction method has been performed with 10 g of 6-nitrochrysene[8] and 1-nitropyrene and 2 g of 11-nitrodibenzofluorene derivatives, resulting in a very high product yield (**Table 1**). This method does not require purification *via* column chromatography as a single crystallization is enough to obtain pure compounds. As a result of this success, we are pursuing the structure-activity study using these amines in depth and already

demonstrated the importance of the multicyclic aromatic amines in the synthesis of anticancer agents.[2]

Table 1: Reduction of Aromatic Nitro Compounds by In/NH_4Cl/H_2O/C_2H_5OH

Entry	Nitro Compound	Amino Compound	Reduction Time (h)	Yield (%)	bp or mp (^oC)
1			5	90	bp 180-190 (lit.,[a] 184)
2			8	80	mp 48-50 (lit.,[a] 48-50)
3			8	90	mp 127-131 (lit.,[a] 128)
4			15	85	mp 208-210 (lit.,[a] 209-211)
5			14	85	mp 115-116 (lit.,[a] 115-117)
6			20	80[b]	
7			22	70	mp 190-193 (lit.,[a] 190-191)
8			20	70	mp 126-127 (lit.,[a] 125-128)

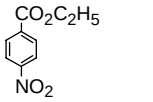
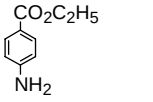
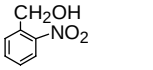
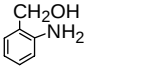
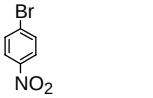
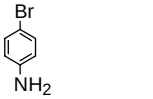
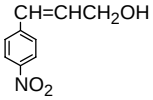
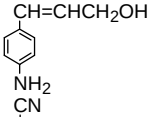
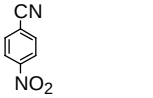
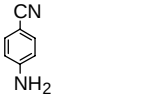
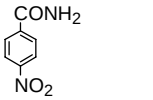
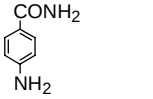
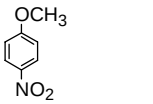
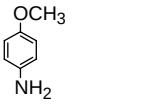
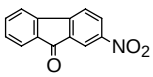
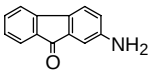
[a:] Aldrich Chemical Company; [b:] see reference 2b

We also achieved selective reduction of aromatic nitro groups using this reagent system (**Table 2**). Specifically, the reduction of ethyl-4-nitrobenzoate (Entry 1), 2-nitrobenzyl alcohol (Entry 2), 4-nitrobromobenzene (Entry 3), 4-nitrocinnamyl alcohol (Entry 4), 4-nitrocyanobenzene (Entry 5), 4-nitro-acetamide (Entry 6), 4-nitroanisole (Entry 7) and 2-nitrofluorenone (Entry 8) with indium metal in the presence of ammonium chloride using aqueous ethanol was performed. The corresponding amines were produced in good yield.

These results indicate useful chemo-selectivity in the aromatic nitro compound reduction procedure. For example, ester, nitrile, bromo, amide, benzylic ketone, benzylic alcohol, aromatic ether, and unsaturated bond remained unaffected during this transformation. In general, many of the previous methodologies produced a mixture of compounds. For instance, catalytic hydrogenation produced a compound mixture when nitrofluorenone (**Table 2**, Entry 8) and nitrocinnamyl alcohol (**Table 2**, Entry 4) was used. To test

the selectivity in other systems, reduction of methyl cinnamate was performed with indium-2% hydrochloric acid or indium/ammonium chloride in queous ethanol. Both reactions failed to produce 3-phenylmethyl propionate. Methyl cinnamate was recovered from the indium/ammonium chloride reaction, while cinnamic acid was recovered from the indium/hydrochloric acid reaction. No dimeric products due to a radical-radical coupling could be detected. This method had additional selectivity advantages. Many other metals, such as zinc, tin, and iron, usually require acid catalysts for the activation process with the resultant problems of waste disposal. Our present method avoids these problems and produces products in high yield.

Table 2. Selective Reduction of Aromatic Nitro Compounds by Indium Metal in the Presence of $NH_4Cl/H_2O/C_2H_5OH$

Entry	Nitro compounds	Products	Reduction time (h)	Yield (%)	mp ^oC
1			2½	94	88 (lit.,[a] 88-90)
2			2	68.5	84 (lit.,[a] 83-85)
3			1½	80	59 (lit.,[a] 60-64)
4			1	oil	oil
5			2	75	85 (lit.,[a] 83-85)
6			1¾	71	182 (lit.,[a] 181-183)
7			5	90	58-60 (lit.,[a] 57-60)
8			8	80	157-160 (lit.,[a] 160)

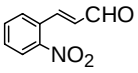
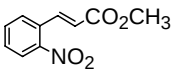
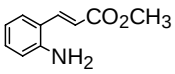
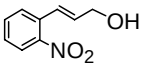
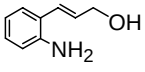
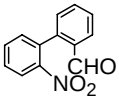
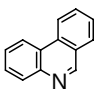
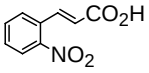
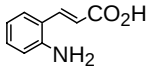
[a]: Aldrich Chemical Company

To gain insight into the mechanistic course of indium-mediated reduction, a few experiments were carried out with 1-nitropyrene and 6-nitrochrysene. Reaction of these substrates with indium trichloride in the presence of ammonium chloride using ethanol under identical conditions failed to produce the amino compounds. Indium trichloride alone also failed to yield the amines. This indicates the critical role of ammonium chloride in the reaction, as indium metal in refluxing aqueous ethanol did not yield the amines. Interestingly, the same reaction mixture yielded amines when ammonium chloride was added to it and refluxing was continued for several more hours. These experiments ruled out the possibility of formation of trivalent or low-valent indium species in the reaction before addition of ammonium chloride. However, the role of ammonium chloride is not known at this time. We are aware that the reactivity of

metal-induced processes can be altered drastically with the use of suitable additives.[9] Our research also established the critical role of additive in some reactions.[1c, 1f, 1g]

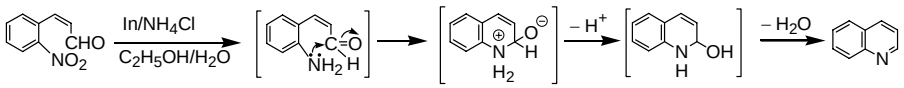
Reductive Cyclization. Construction of ring systems in organic chemistry is an attractive objective. After having an excellent route of reduction, our goal was to extend this method to intramolecular reductive cyclization chemistry toward several biologically active natural and synthetic compounds. Because of our interest in nucleophilic and Michael reactions[10] we envisioned that it could be possible to perform a useful study by reacting the aromatic amino functionality with a suitable partner. One of the most common reactive groups with which an amino group can react very easily is an aldehyde group. Therefore, at the inception of this study, synthesis of quinoline was undertaken using reductive cyclization of 2-nitrocinnamaldehyde by indium/ammonium chloride in ethanol. As expected, quinoline was formed at a yield of about 20%. The same reaction with water-ethanol (1:1) or water-ethanol (9:1) produced quinoline in 90% yield (**Table 3**, 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 the solvent composition in reductive cyclization reactions mediated by indium. In addition, we prepared phenanthridine (**Table 3**, Entry 4) *via* reduction of nitro aldehyde. Synthesis of these types of compounds using zinc and other reduction methods in organic solvents in the presence of acids has been reported.[11, 12] Some of the methods used for the preparation of phenanthridines[13] have a limited scope.

Table 3: Reductive Cyclization by In/NH_4Cl/C_2H_5OH/H_2O

Entry	Nitro Compounds	Products	Yield (%)
1			90
2			85
3			85
4			90
5			68

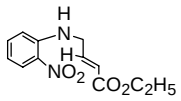
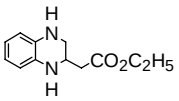
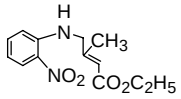
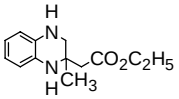
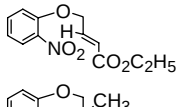
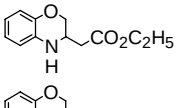
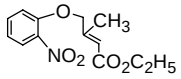
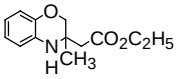
Reduction of the nitro group to the amino group, nucleophilic attack to the aldehyde and subsequent aromatization are believed to be involved in the cyclization reactions (**Scheme 1**). This was further supported by the fact that methyl 2-nitrocinnamate, 2-nitrocinnamyl alcohol, and 2-nitrocinnamic acid produced methyl 2-aminocinnamate, 2-aminocinnamyl alcohol, and 2-aminocinnamic acid, respectively (Entries 2, 3, and 5). Cyclization of the amino group to the unsaturated moiety or carboxyl and alcohol groups were not detected.

Scheme 1



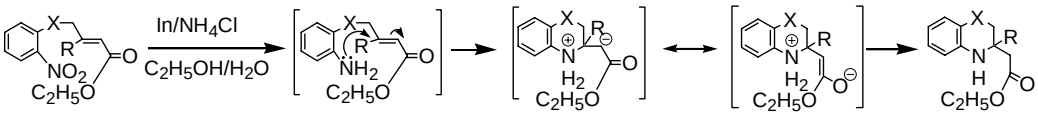
Next, a few more bicyclic compounds of different structures were synthesized using this indium-mediated method (**Table 4**). Tetrahydroquinoxalines are important structural fragments in a number of biologically active compounds.[14] Tandem cyclization *via* reductive amination and reduction-lactam formation for the synthesis of these types of compounds was reported previously.[15] Recently, iron powder in refluxing acetic acid was shown to be effective for this type of transformation.[16] The starting nitroarene was prepared by following a method described in the literature.[11] Reduction of the nitroarenes using indium metal and ammonium chloride in an ethanolic aqueous solution afforded the quinoxalines in 95% yield (**Table 4**, Entries 1 and 2). Similarly, a tetrahydrobenzoxazine derivative was prepared in excellent yield *via* reduction of its precursor without any degradation of the side chain[17] (**Table 4**, Entries 3 and 4). Initial reduction of the nitro group to the amino group and then favorable 6-*exo*-*trig* cyclization are believed to be involved in this process.

Table 4: Reductive Cyclization by In/NH_4Cl/C_2H_5OH/H_2O

Entry	Nitro Compounds	Products	Yield (%)
1			61
2			60
3			79
4			80

Given the results described above, we hypothesize that a Michael-type reaction between amino and the activated ester group and, as a result, cyclization to the β-carbon of the unsaturated moiety is possible (**Scheme 2**). The failure of nitrocinnamyl alcohol to cyclize was obvious with this mechanism. Furthermore, the failure of nitro cinnamates to cyclize was clearly due to an unfavorable cyclization path (**Table 3**).

Scheme 2



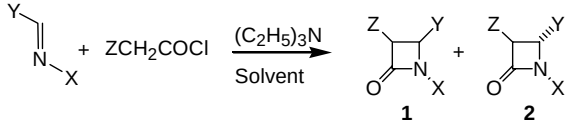
X = NH, O; R = H, CH_3

Rearrangement of the β-Lactam Rings. In continuation of our indium-induced chemical transformation, we discovered that oxazines and quinolinones can be easily prepared by an indium-induced reaction on substituted nitro β-lactams in aqueous ethanol.

β-Lactams have been used as synthons in the preparation of various heterocyclic compounds of biological significance.[18] For example, suitably substituted β-lactams have been used in the semi synthesis of paclitaxel (Taxol), docetaxel (Taxotere), carbohydrate derivatives, amino acids, peptides, and heterocycles through cleavage of the ring.[19] Continuing our research on β-lactams,[20] we envisioned the use of substituted nitro β-lactams in exploring the possibility of ring expansion/rearrangement reactions toward oxazines and quinolinones using our indium-induced reaction method in aqueous ethanol.

Therefore, synthesis of nitro-substituted β-lactams is our initial goal. Of the known methods of construction of β-lactam rings, the Staudinger reaction, which features variation at C3 and C4, is the most suitable.[21] This reaction involves the cycloaddition of imines to acid chloride (or an equivalent) in the presence of a tertiary base. The stereochemistry of the resulting β-lactam can be *cis* (**1**), *trans* (**2**), or a mixture of the two (**Scheme 3**). Many authors have attempted to establish the basis for formation of the *cis*- and *trans*-β-lactams by considering a number of factors. For example, the substituents present in the imines and acid chloride, conditions of the reaction, nature of the base and solvent, order of the addition of reagents, and temperature of the reactions have been implicated in the formation of the β-lactam ring.[22] To explain the stereoselectivity, some computer-assisted theoretical calculations have been reported.[23]

Scheme 3

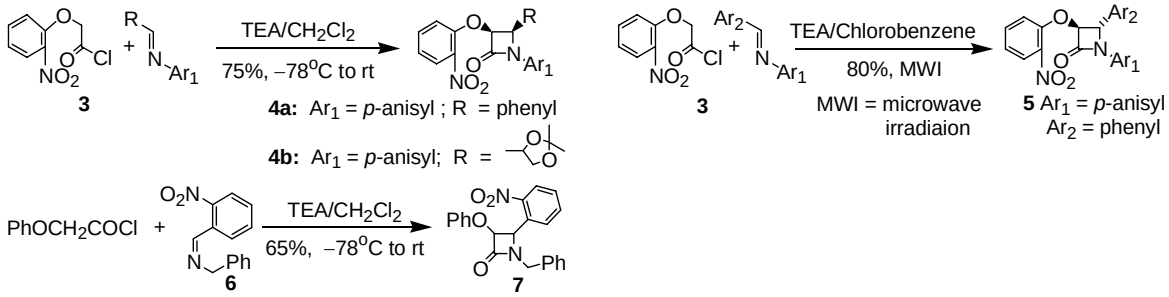


Annulation of nitro acid chloride (**3**) with imines having various structures produced *cis*- (**4**) and *trans* β-lactam (**5**) (**Scheme 4**) depending on the conditions of the experiments.[22] Slow addition of **3** to the imine solution containing triethylamine at −78 ^{o}C to room temperature afforded **4** as the only product in good yield (80%). However, irradiation of the same reactants in chlorobenzene solution using microwave irradiation[24] produced **5** in 70% yields.[25] The *trans*-β-lactam (**5**) were also prepared using a method described by Endo *et al*.[26] A similar cycloaddition reaction (−78 ^{o}C to room temperature) with diarylimine (**6**) having an aromatic nitro group in one of their components produced *cis*-β-lactam (**7**) in excellent yield. Although imines derived from nitro aniline produced *trans*-β-lactams as the predominant isomers, apparently, imines derived from nitro aldehyde follow the standard stereochemical distribution. In addition, nitro acid chloride produced products according to the standard prediction rules. These experiments supported earlier results.[22, 23]

The nitro-substituted β-lactams are our starting materials for the synthesis of oxazines and quinolinone. As expected, and in conformity with our hypothesis, treatment of β-lactams (**4**) and (**5**) with indium/ammonium chloride in aqueous ethanol produced oxazines (**8**) and (**9**) in excellent yield.

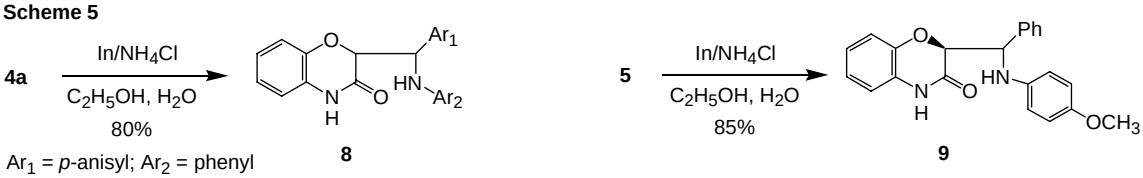
However, as stated previously, this reaction does not proceed in the absence of water. Thus, a mixture of

Scheme 4



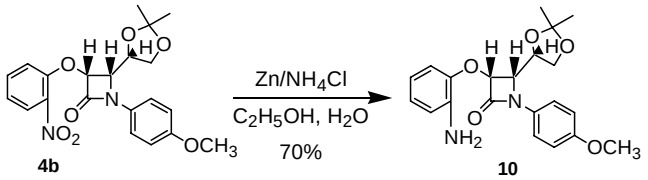
alcohol and water is necessary for the success of the rearrangement reaction (**Scheme 5**). Also, other metals, such as zinc and tin, did not promote the ring cleavage reaction effectively and oxazines in poor yields (10-15%) were obtained. The major product was the amine (**4b** to **10**, **Scheme 6**). This clearly showed the importance of indium in promoting the rearrangement.

Scheme 5

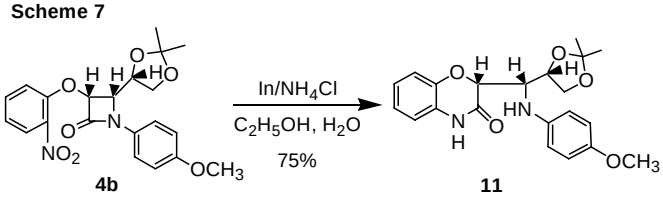


Application of this methodology to asymmetric synthesis of oxazines[27] was achieved with great success. Our method as described above can produce different types of optically active oxazines because chiral β-lactams with opposite stereostructures are very easily accessible (**4b** to **11**, **Scheme 7**).

Scheme 6



Scheme 7

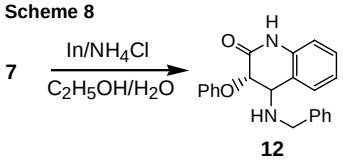


Quinolinones (**12**) were also prepared by following an identical sequence. The reaction proceeded exceedingly well at the reflux temperature, although, no reaction products were detected at room temperature for several days. In particular, the combination and proportion of indium/ammonium chloride was found to be crucial to the success of the reaction. A reaction was attempted using indium and concentrated hydrochloric acid to evaluate the role of ammonium chloride. However, it resulted in formation of a complex mixture containing the product (**Scheme 8**).

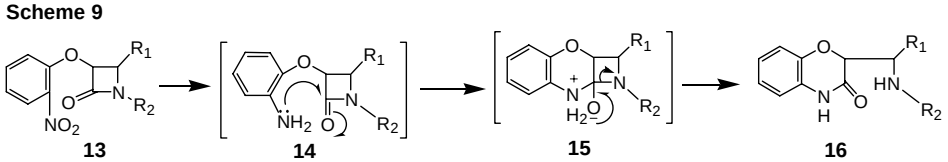
Reduction of the aromatic nitro group to the amino group and its nucleophilic attack to the β-lactam carbonyl presumably are the steps involved in the rearrangement toward oxazines (**13** to **16**, **Scheme 9**). Because of the oxophilic nature of indium[3] coordination to the β-lactam carbonyl is possible.

This may increase the vulnerability to a nucleophilic attack by the amino group.

Scheme 8

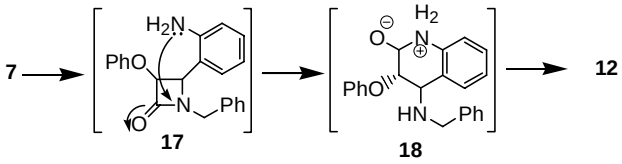


Scheme 9



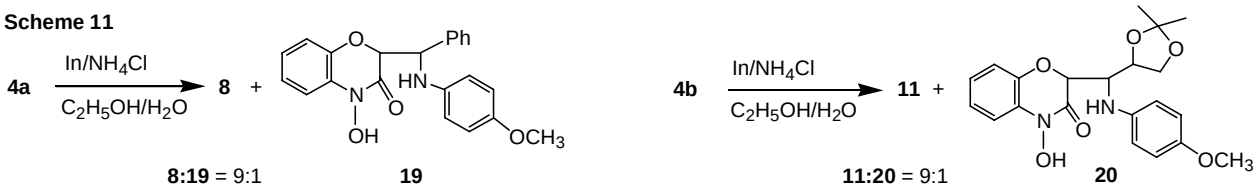
A similar mechanism is believed to be involved in the formation of quinolinone (**12**). The generated amino group is suitably located to attack the β-lactam carbonyl. As a result of the strain of the amide bond in the β-lactam, cleavage of the bond clearly takes place, producing the quinolinone (**Scheme 10**, **7** to **12**).

Scheme 10



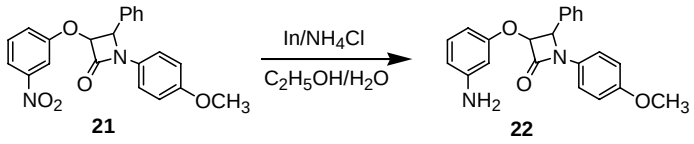
However, a small amount of *N*-hydroxy oxazine derivatives (**19** and **20**) arising through a cyclization of intermediate hydroxylamine was isolated in some experiments. This clearly indicated that hydroxyl amine is an intermediate in the reduction of the aromatic nitro group under this reaction condition. However, it has been demonstrated that *N*-hydroxy derivative can also be reduced under the reaction conditions.[4a]

Scheme 11



A proper location of the aromatic nitro group is clearly necessary for the success of this rearrangement reaction. For example, 3-nitro substituted β-lactam (**21**) on treatment with indium/ammonium chloride did not afford oxazine: instead the product was an amine (**22**) (**Scheme 12**).

Scheme 12



Conclusion

The notable part of this method is the unique role of indium as a reducing agent and its oxophilicity in environmentally benign conditions. In principle, reduction of an aromatic nitro group to the amines could have been achieved using earlier methods. However, indium proved to be an effective metal in promoting the subsequent cyclization and rearrangement toward biologically active products under environmentally friendly conditions. Facile preparation of chiral and achiral heterocycles using eco-friendly approaches as described herein should find application in organic and medicinal chemistry. We are exploring such possibilities.

EXPERIMENTAL

Melting points were determined with a mel-temp. instrument and were uncorrected. IR spectra were recorded on a Perkin Elmer instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300

spectrometer using TMS as an internal standard and $CDCl_3$ as the solvent. TLC was performed with Aldrich plate, and the spots were detected in a UV viewing and iodine chambers. Dichloromethane was dried over P_2O_5. All of the extracts were dried over anhydrous Na_2SO_4. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, New York.

Reduction of the aromatic nitro groups: A representative procedure was given for ethyl 4-aminobenzoate. To a suspension of the nitro compound, ethyl 4-nitrobenzoate (**Table 1**, Entry 1) (1 g, 5.12 mmol) in ethanol (30 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer, were added 50% solution of ammonium chloride (2.74 g, 51.2 mmol) and indium powder (2.35 g, 20.5 mmol). The mixture was refluxed for 2 h, supplemented with 50 mL of water and filtered under vacuum. The filtrate was extracted with dichloromethane (90 mL), and extract was washed with brine (60 mL) and dried with anhydrous sodium sulfate. After evaporation of the solvent under reduced pressure, NMR spectrum was recorded. Analysis of the crude product using NMR spectrum indicated greater than 97% conversion of the starting nitro compound to the amino compound. The crude amino product was purified by column chromatography (hexane/ethyl acetate 70/30) or by crystallization from dichloromethane-hexanes to afford a pure product (82%).

Reductive cyclization: A representative experimental procedure was performed for phenanthridine. Water (9 mL), ammonium chloride (214 mg, 4 mmol), and indium powder (344.4 mg, 3 mmol) were added to a solution of the nitro compound (**Table 3**, Entry 4) (227 mg, 1 mmol) in ethanol (1 mL). The mixture was refluxed with vigorous stirring, and the progress of the reaction was followed by TLC. After completion of the reaction, it was filtered, extracted with dichloromethane (20 mL), and washed with brine. The pure product was isolated after column chromatography over silica gel (ethyl acetate-hexanes, 10:90).

A general experimental procedure for the synthesis of *cis*-β-lactams (**4** and **7)**: A solution consisting of acid chloride (0.015 mol) in dry dichloromethane (50 mL) was added drop-wise to a stirred solution containing imines (0.013 mol) and distilled triethyl amine (3.03 g, 0.03 mol) in dry dichloromethane (100 mL) at 0-5 ^oC. The reaction mixture was stirred overnight at rt, washed with saturated sodium bicarbonate solution (40 mL), and brine (40 mL), dried, and evaporated to obtain the crude product. The pure product was obtained by column chromatography over silica gel using ethyl acetate and hexane as the eluent (20:80).

Microwave-assisted experimental procedure for the synthesis of *trans*-β-lactam (5): To a solution of the imine (10 mmol) in chlorobenzene (10 mL) in a 250-mL Erlenmeyer flask was added triethylamine (30 mmol) followed by acid chloride (12 mmol). The flask was capped with a glass funnel and placed in a microwave oven (G. E. model, 1450 W). A 250-mL beaker containing 100 mL of water was placed in the oven next to the reaction flask to serve as a heat sink as described previously. The mixture was

irradiated for 5 min. After usual work up, the *trans*-β-lactam (**5**) was isolated in 60% yield.

A general experimental procedure for the synthesis of oxazines (8, 9 and **11)** and **quinoline (12)**: Indium powder (114.8 mg, 1 mmol) and solid ammonium chloride (8-10 equivalents) were added to a suspension of β-lactam (1 mmol) in ethanol (2 mL) and water (2 mL). The mixture was refluxed for 10 h and then filtered through a Celite pad. The filtrate was then extracted with ethyl acetate (50 mL), and extract was washed with brine (10 mL), dried with sodium sulfate and the solvent was evaporated. The crude mass on column chromatography, afforded the product (80-85% yield).

4a: oil; IR (CH_2Cl_2) 1750, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.75 (3 H, s), 5.38 (1 H, d, *J* = 5.1 Hz), 5.59 (1 H, d, *J* = 5.1 Hz), 6.80-6.83 (2 H, m), 7.02-7.05 (1 H, m), 7.29-7.52 (9 H, m), 7.88 (1 H, dd, *J* = 1.5 and 8.1 Hz); Anal. Calcd for $C_{22}H_{18}N_2O_5$: C, 67.74; H, 4.64; N, 7.18. Found: C, 67.50; H, 4.54; N, 7.01.

4b: mp 150-152 ^oC (crystallization solvent: ethyl acetate/hexane); IR (CH_2Cl_2) 1750, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (3 H, s), 1.58 (3 H, s), 3.80 (3 H, s), 3.88 (1 H, dd, *J* = 5.1 and 9.6 Hz), 4.39-4.46 (2 H, m) 4.61-4.72 (1 H, m), 5.45 (1 H, d, *J* = 5.7 Hz), 6.86-6.91 (2 H, m), 7.13-7.19 (1 H, m), 7.54-7.74 (4 H, m), 7.89 (1 H, d, *J* = 1.5 and 8.1 Hz); Anal. Calcd for $C_{21}H_{22}N_2O_7$: C, 60.92; H, 5.35; N, 6.76. Found: C, 60.84; H, 5.42; N, 6.66.

5: mp 138 ^oC (crystallization solvent: ethyl acetate/hexane); IR (CH_2Cl_2) 1750, 1605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.74 (3H, s), 5.12 (1 H, d, *J* = 1.5 Hz), 5.20 (1 H, d, *J* = 1.5 Hz), 6.79-6.82 (2 H, m), 7.10-7.15 (1 H, m), 7.23-7.27 (2 H, m), 7.37-7.42 (6 H, m), 7.49-7.55 (1 H, m), 7.86 (1 H, dd, *J* = 1.8 and 8.1 Hz); Anal. Calcd for $C_{22}H_{18}N_2O_5$: C, 67.74; H, 4.64; N, 7.18. Found: C, 67.48; H, 4.64; N, 7.08.

7: IR (CH_2Cl_2) 1745, 1610, 1500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10 (d, *J* = 15 Hz, 1 H), 4.97 (d, *J* = 15 Hz, 1 H), 5.45 (d, *J* = 6 H, 1 H), 5.57 (d, *J* = 6 Hz, 1 H), 6.81-6.91 (m, 2 H), 7.13-7.33 (m, 9 H), 7.60-7.88 (m, 2 H), 8.07-8.10 (m, 1 H); Anal. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.64; H, 4.85; N, 7.49. Found: C, 70.75; H, 5.10; N, 7.26.

8: oil; IR (CH_2Cl_2) 3200, 1680, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.67 (3 H, s), 4.67 (1 H, br), 4.94 (1 H, dd, *J* = 3.0 and 6.0 Hz), 5.21 (1 H, br), 6.55-6.59 (2 H, m), 6.65-6.69 (2 H, m), 6.90-6.96 (3 H, m), 7.22-7.32 (4 H, m), 7.37-7.50 (2 H, m); MS: m/z (ES+) 361; Anal. Calcd for $C_{22}H_{20}N_2O_3$: C, 73.39; H, 5.60; N, 7.78. Found: C, 73.61; H, 5.71; N, 7.94.

9: mp 164-166 ^oC (crystallization solvent: ethyl acetate/hexane); IR (CH_2Cl_2) 1680, 1605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.65 (3 H, s), 4.88 (1 H, d, *J* = 5.4 Hz), 4.99 (1 H, d, *J* = 5.4 Hz), 6.53-6.56 (2 H, m), 6.64-6.67 (3 H, m), 6.86-6.96 (3 H, m), 7.16-7.23 (3 H, m), 7.33-7.36 (2 H, m); MS: m/z (ES+) 361; Anal. Calcd for $C_{22}H_{20}N_2O_3$: C, 73.39; H, 5.60; N, 7.78. Found: C, 73.50; H, 5.55; N, 7.97.

10: oil; IR (CH_2Cl_2) 1750, 1605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (3 H, s), 1.53 (3 H, s), 3.79 (3 H, s), 3.86 (1 H, dd, *J* = 6 and 9.0 Hz), 4.26 (1 H, dd, *J* = 6.9 and 9.0 Hz), 4.38 (1 H, dd, *J* = 5.4 and 9.0

Hz), 4.53-4.60 (1 H, m), 5.31 (1 H, d, *J* = 5.4 Hz), 6.71-6.74 (2 H, m), 6.83-6.92 (3 H, m), 7.06-7.09 (1 H, m), 7.63-7.68 (2 H, m); MS m/z (ES+): 385; Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.67; H, 6.30; N, 7.29. Found: C, 65.46; H, 6.45; N, 7.11.

11: mp 148-150 ^{o}C (crystallization solvent: ethyl acetate/hexane); IR (CH_2Cl_2) 1670, 1605 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (3 H, s), 1.39 (3 H, s), 3.69 (3 H, s), 3.92 (1 H, m), 4.03 (1 H, dd, *J* = 6.6 and 8.1 Hz), 4.17 (1 H, brt), 4.44 (1 H, m), 4.83 (1 H, d, *J* = 3.3 Hz), 6.54 (2 H, m), 6.67 (3 H, d, *J* = 9 Hz), 6.90-6.96 (3 H, m), 8.72 (1 H, s); ^{13}C NMR (75 MHz) δ 25.72 (CH_3), 26.80 (CH_3), 56.07 (CH_3), 56.90 (CH), 66.80 (CH_2), 76.19 (CH), 110.00, 115.12 (CH), 115.68 (CH), 116.14 (CH), 116.86 (CH), 122.91 (CH), 124.56 (CH), 125.94, 141.51, 143.44, 152.93, 166.92; MS: (ES+) 385; Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.67; H, 6.30; N, 7.29. Found: C, 65.53; H, 6.43; N, 7.17.

12: mp 204-206 ^{o}C (crystallization solvent: ethyl acetate/hexane); IR (CH_2Cl_2) 3190, 3085, 1683, 1596, 1489, 1396, 1315, 1238 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (q, *J* = 12 Hz, 2 Hz), 4.30 (d, *J* = 7.2 Hz, 1 H), 4.80 (d, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 10 Hz, 1 H), 6.96-7.28 (m, 12 H), 7.33 (d, *J* = 10 Hz, 1 H), 8.05 (s, 1 H); Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.69; H, 5.81; N, 8.13. Found: C, 76.51; H, 5.73; N, 8.00.

20: oil; IR (CH_2Cl_2) 1750, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (3 H, s), 1.38 (3 H, s), 3.70 (3 H, s), 3.86 (1 H, dd, *J* = 7.2 and 8.1 Hz), 3.98 (1 H, dd, *J* = 6.6 and 8.1 Hz), 4.06 (1 H, br), 4.38 (1H, dt, *J* = 3.6 and 10.2 Hz), 4.97 (1 H, d, *J* = 3.3 Hz), 6.49 (2 H, m), 6.64 (2 H, m), 6.86 (1 H, m), 7.02 (2 H, m), 7.24 (1 H, m); ^{13}C NMR (75 MHz) δ 25.46 (CH_3), 26.72 (CH_3), 56.07 (CH_3), 57.19 (CH), 66.66 (CH_2), 75.86 (CH), 78.20 (CH), 110.00, 113.57 (CH), 115.14 (CH), 115.96 (CH), 116.48 (CH), 123.03 (CH), 125.16 (CH), 125.94, 141.51, 143.44, 152.93, 166.92; MS: (ES+) 399.94.

21: oil; IR (CH_2Cl_2) 1740, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (1 H, d, *J* = 14.4 Hz), 4.84 (1 H, d, *J* = 4.5 Hz), 4.91 (1 H, d, *J* = 14.4 Hz), 5.46 (1 H, d, *J* = 4.5 Hz), 7.09 (1 H, m), 7.17 (2 H, m), 7.23-7.38 (9 H, m), 7.51 (1 H, t, *J* = 2.1 Hz), 7.72 (1 H, m).

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↑ Undergraduate research participant

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