Heterocyclic Letters
Vol. 14| No.2|267-272|Feb-April|2024
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

INDIUM-MEDIATED REDUCTION OF AROMATIC NITRO GROUPS IN B-LACTAMS TO OXAZINES

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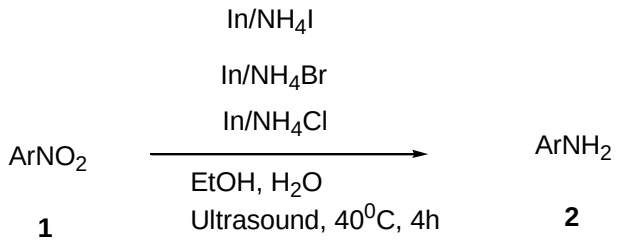
Abstract:
Metal-mediated reduction of nitro-substituted β-lactams has been performed to synthesize oxazines in aqueous ethanol using ultrasound at 40°C through a molecular rearrangement. The initially formed aromatic amines are capable of attacking the carbonyl groups in the β-lactams through a nucleophilic pathway and this can rupture the N-C-4 bond to form oxazines.

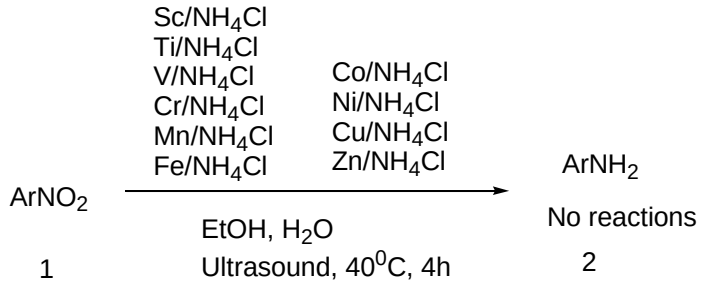
Key words:
β-Lactams, Oxazines, Indium, Ultrasound

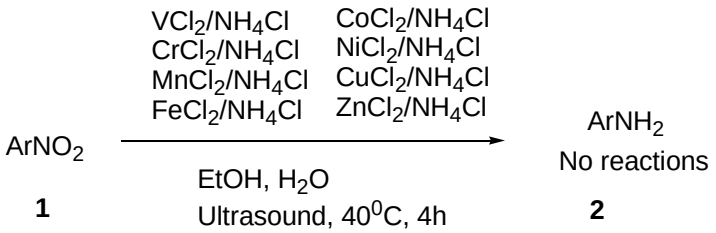
Introduction:

β-Lactams are used for the preparation of several biologically active heterocyclic compounds.[1]We reported metal-mediated reduction method of aromatic nitro group (**1**) to aromatic amino group (**2**) (**Scheme 1**)[2]. The reduction of nitro compounds to the corresponding amines is one of the most utilized catalytic processes in the fine and bulk chemical industry. The latest development of catalysts with cheap metals like Sc, Ti, V, Cr, Me, Fe, Co, Ni, Cu and Zn has led to their tremendous achievements over the last years prompting their greater application as "standard" catalysts. We also performed reduction reactions using indium metal using ultrasound with NH_4Cl, NH_4Br, and NH_4Cl and found that NH_4Cl is the best for the reduction reaction. We have attempted Sc, Ti, V, Cr, Me, Fe, Co, Ni, Cu and Zn metals as well as their corresponding chlorides and there were no reactions. This paper reports a reduction of the aromatic nitro group and a rearrangement of the β-lactams using In/NH_4Cl.

Scheme 1:



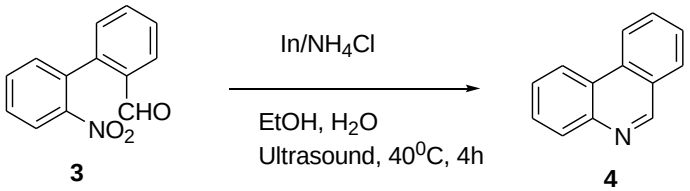




Results:

This metal-mediated reduction was extended for a cyclization route towards the synthesis of several heterocycles. For example, acridine **4** was synthesized from **3** in good yield by following this method (**Scheme 2**).[3]

Scheme 2:



Our interest in β-lactams[1] and metal-induced[2] reactions prompted us to explore the indium-mediated reaction toward the preparation of biologically active molecules.

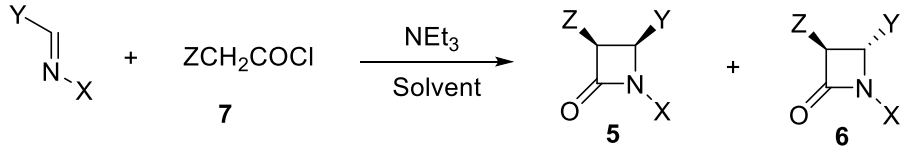
Synthesis of nitro-substituted β-lactams is our initial target. Of the known methods of construction of β-lactams rings, the Staudinger reaction is the most suitable.[4]It involves the cycloaddition of imine with acid chloride, in the presence of a tertiary base. The stereochemistry of the resulting β-lactam can be *cis* (**5**), *trans* (**6**) or a mixture of the two (**Scheme-3** and **Scheme 4**). Many authors have attempted to establish the mechanism for formation of the *cis* and *trans* β-lactams by considering a number of factors. The groups

present in the imine and acid chloride, condition of the reaction, nature of the base and solvent, order of the addition of the reagents, and temperature of the reactions have controlled the formation of the β-lactam ring.[5]

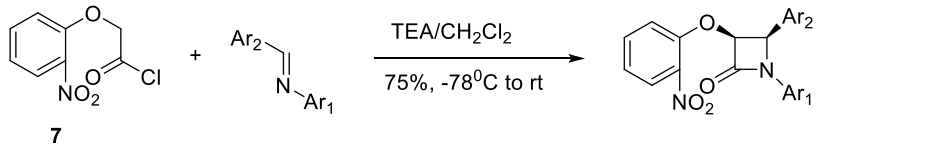
A reaction of nitro acid chloride **7** with imine produced *cis* **8** and *trans* β-lactams **9**. A slow addition of **7** to the imine at -78°C room temperature produced *cis* β-lactam **8** in excellent yield (75%). In contrast, reaction in chlorobenzene using ultrasound produced *trans* β-lactam **9** in 80% yields.

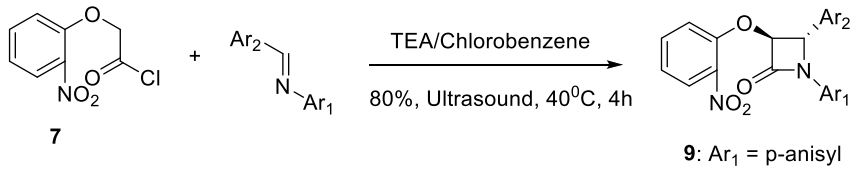
A reaction of the β-lactams **8** and **9** by indium/ammonium chloride in aqueous ethanol using ultrasound gave oxazines **10** and **11** in good yield. A mixture of alcohol and water was required for the rearrangement.

Scheme 3:

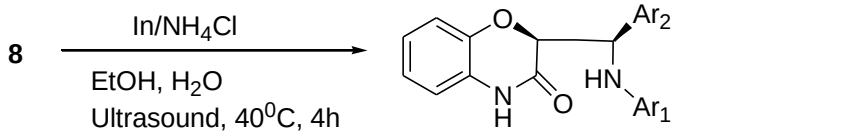


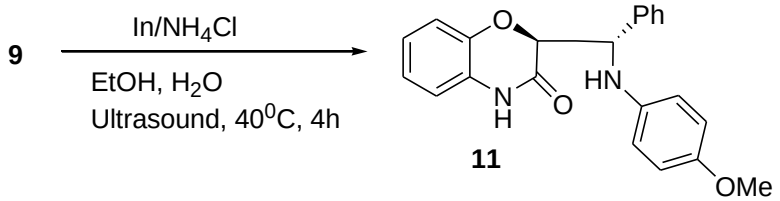
Scheme 4:





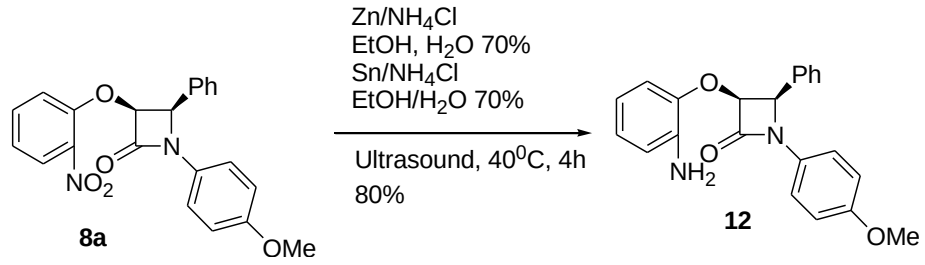
Scheme 5:





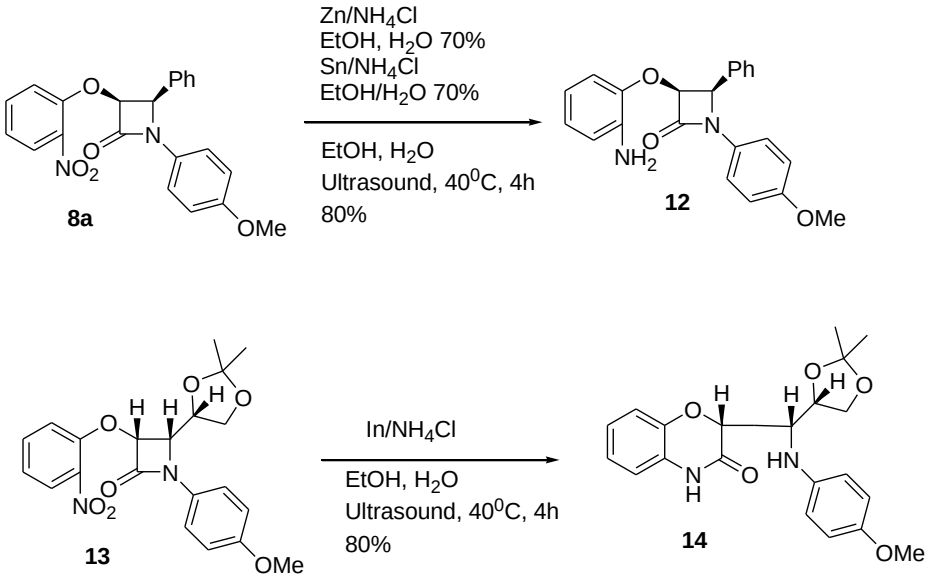
Zinc and tin did not cleave the ring effectively and therefore, oxazines were obtained in poor yield (10-15%). The main product from this reaction was the amine (**8a** to **12**, **Scheme 6**).

Scheme 6:



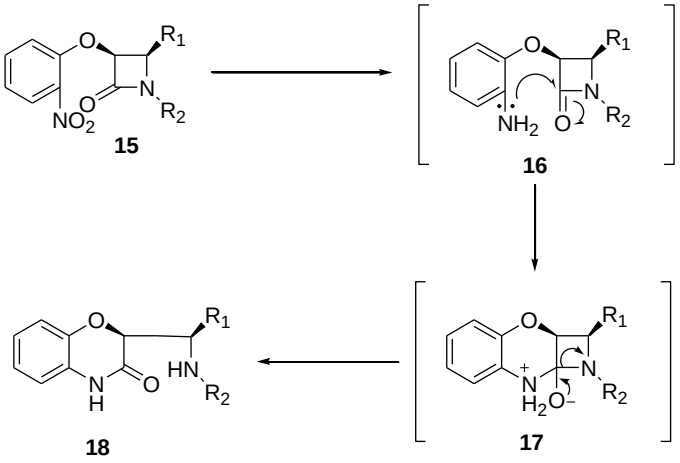
This method with indium produced optically active oxazines with chiral β-lactam (**13** to **14**, **Scheme-7**).

Scheme 7:



The mechanism of this process was not investigated. A reduction of the aromatic nitro group to the amino was believed to be the first step of this method. A nucleophilic attack by the amino group to the β-lactam carbonyl was involved in the rearrangement for the preparation of oxazines (**15** to **18**, **Scheme-8**). Due to the oxophilic nature of indium, a coordination to the β-lactam carbonyl can take place and this may enhance the power of a nucleophilic attack by the amino group present in the system.

Scheme 8:



Conclusions:

The facile preparation of chiral and achiral oxazines[6] using eco-friendly approaches as described herein should find application in organic and medicinal chemistry. We are also exploring these possibilities.

Acknowledgments:

Bimal Krishna Banik is grateful to NIH, NCI, and Kleberg Foundation.

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6. General experimental procedure: To a suspension of *β*-lactams (1 mmol) in ethanol (2 mL) and water (2 mL) was added indium powder (1 mmol) and solid ammonium chloride (8–10 equiv.). The reaction mixture was sonicated at 40°C for 4h in and then it was filtered through a Celite pad. The filtrate was extracted with ethyl acetate (50 mL), washed with brine (10 mL), dried with sodium sulphate and solvent was evaporated. After column chromatography, the crude mass afforded the product (80–85% yield).

   Compound **8a**: ^{1}H NMR: δ 3.75 (3H, s), 5.38 (1H, d, J =5.1 Hz), 5.59 (1H, d, J =5.1 Hz), 6.80–6.83 (2H, m), 7.02–7.05 (1H, m), 7.29–7.52 (9H, m), 7.88 (1H, dd, J =1.5 and 8.1 Hz).

   Compound **10a**: ^{1}H NMR: δ 3.67 (3H, s), 4.67 (1H, br),4.94 (1H, dd, J =3.0 and 6.0 Hz), 5.21 (1H, br), 6.55–6.59 (2H, m), 6.65–6.69 (2H, m), 6.90–6.96 (3H, m), 7.22–7.32 (4H, m), 7.37–7.50 (2H, m); MS: m/z (ES+) 361.

   Compound **9**: ^{1}H NMR: δ 3.74 (3H, s), 5.12 (1H, d, J =1.5 Hz), 5.20 (1H, d, J =1.5 Hz), 6.79–6.82 (2H, m), 7.10–7.15 (1H, m), 7.23–7.27 (2H, m), 7.37–7.42 (6H, m), 7.49–7.55 (1H, m), 7.86 (1H, dd, J =1.8 and 8.1 Hz).

   Compound **11**: ^{1}H NMR: δ 3.65 (3H, s), 4.88 (1H, d, J =5.4 Hz), 4.99 (1H, d, J =5.4 Hz), 6.53–6.56 (2H, m), 6.64–6.67 (3H, m), 6.86–6.96 (3H, m), 7.16–7.23 (3H, m), 7.33–7.36 (2H, m); MS: m/z (ES+) 361.

   Compound **14**: ^{1}H NMR: δ 1.34 (3H, s), 1.39 (3H, s), 3.69 (3H, s), 3.92 (1H, m), 4.03 (1H, dd, J =6.6 and 8.1 Hz), 4.17 (1H, brt), 4.44 (1H, m), 4.83 (1H, d, J =3.3 Hz), 6.54 (2H, m), 6.67 (3H, d, J =9 Hz), 6.90–6.96 (3H,m), 8.72 (1H, s); ^{13}C NMR: 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.

Received on February 27, 2024.