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MICROWAVE-ASSISTED SYNTHESIS OF OXAZINES *VIA* INDIUM-MEDIATED REDUCTIVE REARRANGEMENT OF NITROPHENYL-*B*-LACTAMS

Devalina Ray,*[1] Sakshi Oli,[1] Ritika Rawat[1] and Bimal Krishna Banik*[2]

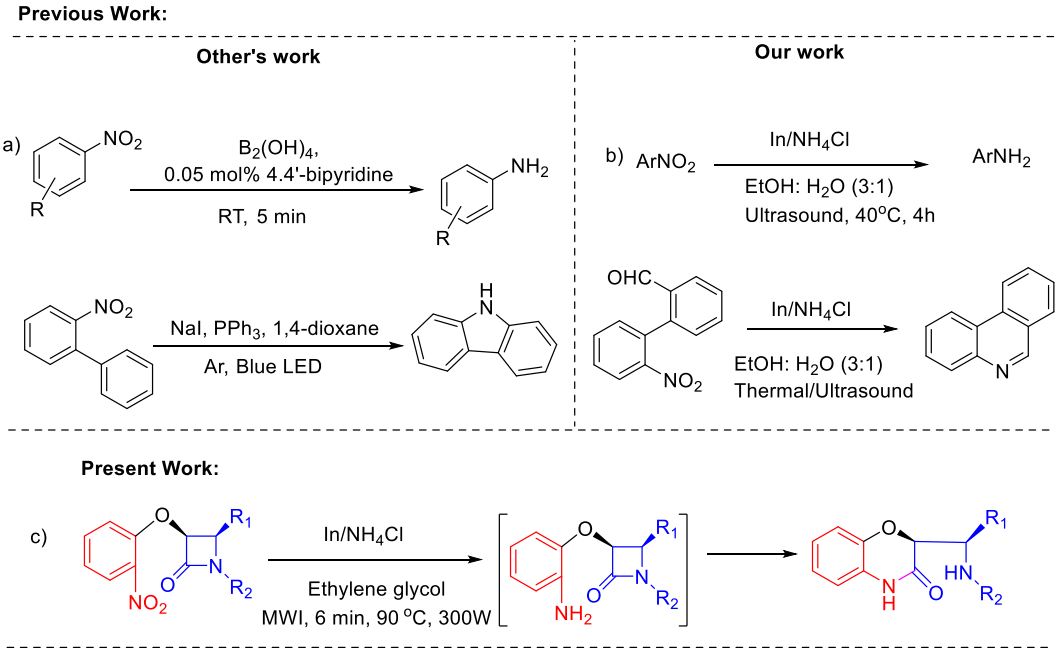
[1]Amity Institute of Biotechnology, Amity University, Sec 125, Noida, Uttar Pradesh, India 201313; [2]Department of Mathematics and Natural Sciences, College of Sciences and Human Studies, Prince Mohammad Bin Fahd University, Al Khobar 31952, Kingdom of Saudi Arabia; Email: devalinaray@gmail.com; bimalbanik10@gmail.com

Abstract:
Indium-promoted reduction of nitro group in *β*-lactams followed by intramolecular cyclization and ring opening has been executed to synthesize benzo [1,4]-oxazines in ethylene glycol as environmentally benign solvent using microwave irradiation, through a molecular rearrangement. The aromatic amines primarily generated from nitroarenes substitution in *β*-lactams are capable to undergo intramolecular attack to the amide carbonyl groups of the *β*-lactams through a nucleophilic pathway. Thereafter, cyclic amide formation *via* rupture of the N-C(O) bond in *β*-lactams generate oxazines in good yields.

Key words:
Nitrophenyl-*β*-Lactams, Oxazines, Indium, Microwave

Introduction:
β-Lactams exists either as core scaffold in various drug candidates or are used as key precursors in the synthesis of numerous pharmaceutically active analogues.[i-iii] Therefore the generation and transformations of *β*-lactams are meticulously explored in scientific community.[iv-vii] A wide range of synthetic strategies have been developed for various metal catalyzed reactions of *β*-lactams.[viii, ix] In this regard, the ultrasound mediated reduction of aromatic nitro group in *β*-lactams using metal catalyst have been successfully implemented by our group to initiate a series of C-C bond making and breaking processes.[x]
On the other hand, reduction of aromatic nitro compounds to the corresponding amines is the most basic and important transformation in the fine and bulk chemical industry. The development of metal catalysts with the first row transition metals e.g, Sc, Ti, V, Cr, Fe, Co, Ni, Cu and Zn has ended up in the enhanced synthetic protocols in last few years accelerating the application of general metal catalysts.[xi]The reduction of aromatic amines is very common in synthetic community. Numerous transition metal-free protocols have been developed by various groups recently including us for generation of amines with further cascade reactions (Scheme 1a & b).[xii-xiv]However, the cascade reactions in nitroarene-*β*-lactams involving reduction to amine followed by subsequent cyclization *via* nucleophilic attack to the carbonyl

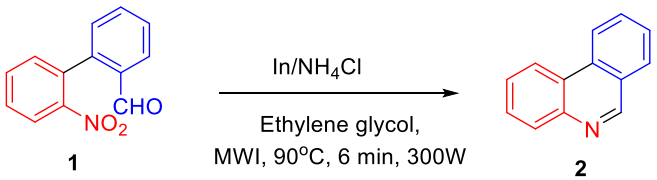
of *β*-lactam and ring rupture extends the procedural utility of the developed protocol.[xiv] The ring cleavage of -N-CO- bond in *β*-lactams through nucleophilic attack is more likely due to the higher ring strain of 4-membered cyclic system. Due to this property, numerous groups have established the ring opening/ring closing reactions. In this context, herein we have established a microwave assisted reduction of nitro to amine with indium/ NH_4Cl which was found to be effective which finally produced benzo [1,4]-oxazines through intramolecular nucleophilic attack on amide carbonyl of *β*-lactam and ring cleavage rearrangement. It was noteworthy to mention that, NH_4Br or NH_4I could not work as effectively as NH_4Cl under the reaction condition (Scheme 1c).



Scheme 1: Previous and present work on nitro reduction and rearrangement reaction

Results:

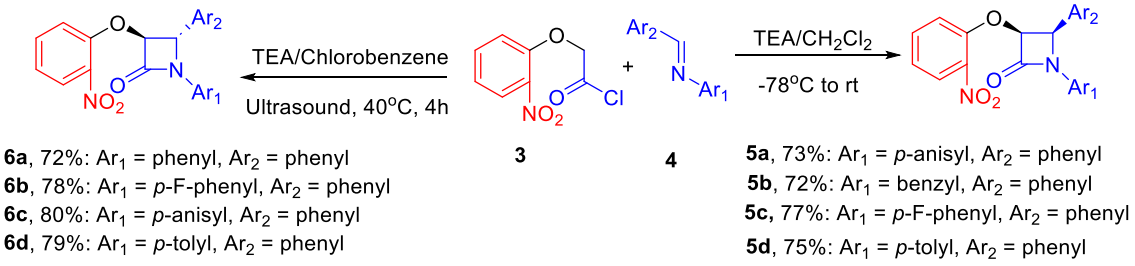
The annulation strategy for this microwave assisted and metal-mediated reduction was further explored for the synthesis of various heterocycles. Acridine (**2**) could be easily accessed from corresponding biphenyl nitroaldehyde (**1**) through this approach (Scheme 2). The reduction and subsequent cyclization process with this nitroarene substrate proved the reduction of nitro to amine followed by intramolecular imine formation to afford the cyclized product.



Scheme 2: Reduction followed by intramolecular imine formation

Considering the successful implementation of cascade reaction in the indium mediated protocol, the reactions conditions were explored for various *β*-lactam substrates. The nitroarene substituted *β*-lactams were accessed *via* the classical Staudinger reaction which appeared as most appropriate and general technique for diversely substituted *β*-lactam synthesis. It necessitates the cycloaddition of an imine and acid chloride in presence of a tertiary base. The *β*-lactams generated possess either *trans* or a *cis* stereochemistry.

However, the formation of major *β*-lactam isomer was dictated mostly by the groups present in the imine and acid chloride along with the reaction conditions and temperature. The substrate needed for the reaction mandates the presence of nitroarene group in *β*-lactam.
Therefore, *rac* (+/-) *trans* and *rac* (+/-) *cis* *β*-lactams were created when nitroaryl acid chloride (**3**) reacted with an imine (**4**). A slow addition of acid chloride to the imine at ambient temperature resulted in 73-77% yield of *rac* (+/-) *cis* *β*-lactam (**5**) whereas an ultrasound-induced reaction yielded *rac* (+/-) *trans* *β*-lactam (**6**) in 72-80%.
The desired benzo [1,4]-oxazines were generated in good yields *via* the reaction of *β*-lactams with indium/ammonium chloride in ethylene glycol utilizing microwave irradiation. The reaction mixture was heated in microwave till a total of 6 mins in an interval of 1 min instead of continuous heating for 6 mins to control the temperature to 90^{o}C and avoid overheating.

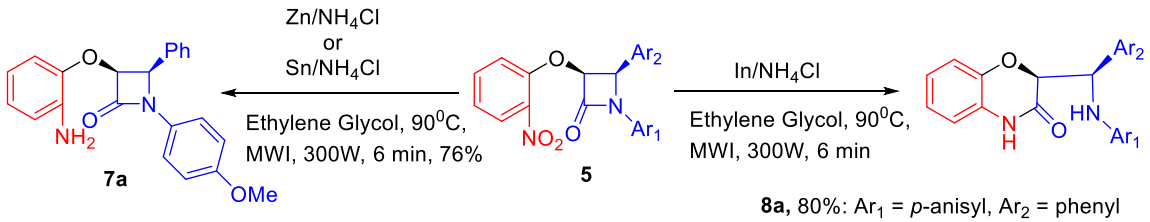


6a, 72%: Ar_1 = phenyl, Ar_2 = phenyl
6b, 78%: Ar_1 = *p*-F-phenyl, Ar_2 = phenyl
6c, 80%: Ar_1 = *p*-anisyl, Ar_2 = phenyl
6d, 79%: Ar_1 = *p*-tolyl, Ar_2 = phenyl

5a, 73%: Ar_1 = *p*-anisyl, Ar_2 = phenyl
5b, 72%: Ar_1 = benzyl, Ar_2 = phenyl
5c, 77%: Ar_1 = *p*-F-phenyl, Ar_2 = phenyl
5d, 75%: Ar_1 = *p*-tolyl, Ar_2 = phenyl

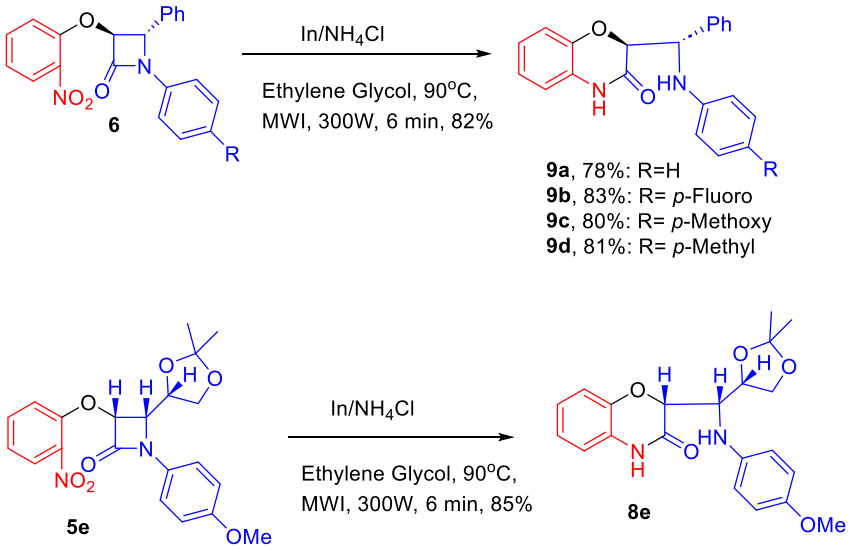
Scheme 3: Synthesis of of *β*-lactams via Staudinger reaction

Both *rac* (+/-) *cis* (**5a-e**) and *rac* (+/-) *trans* *β*-lactams (**6a-d**) afforded expected oxazine products (**8a-e** & **9a-d**) in good yields ranging from 78-86% (Scheme 4 & 5). It was noteworthy to mention that the ring cleavage of *β*-lactam was supressed by zinc and tin resulting in the reduction of nitro for complete generation of amine product (**7a,** Scheme 4). The progress of the reaction till amine could be justified as thereafter further imine formation and *β*-lactam ring rupture didn't occur owing to the weaker coordination of Zn with the oxygen of amide of *β*-lactam as compared to the indium-oxygen coordination.



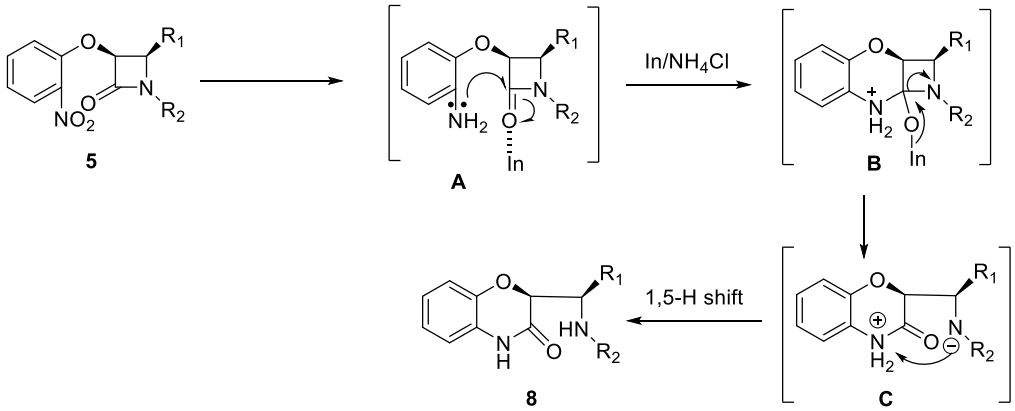
8a, 80%: Ar_1 = *p*-anisyl, Ar_2 = phenyl
8b, 84%: Ar_1 = benzyl, Ar_2 = phenyl
8c, 86%: Ar_1= *p*-F-phenyl, Ar_2 = phenyl
8d, 79%: Ar_1= *p*-tolyl, Ar_2 = phenyl

Scheme 4: Reduction of nitroaryl *β*-lactam with In/NH_4Cl and Zn or Sn/ NH_4Cl



Scheme 5: In/NH_4Cl mediated synthesis of oxazines

This plausible mechanism of the microwave mediated reaction was outlined based on the results obtained with various substrates. It was predicted that the process initially undergoes the usual In/NH_4Cl mediated reduction of aromatic nitro group in *β*-lactam to the amino intermediate **A**. Thereafter the oxophilic property of indium can strengthen the activation the of *β*-lactam oxygen toward nucleophilic attack through significant coordination. The intramolecular attack of amine to the indium bonded carbonyl group leads to the cyclized intermediate **B**. Further regeneration of carbonyl group followed by cleavage of N-C(O) bond from *β*-lactam afforded the intermediate **C** which on capture of proton from the amide nitrogen with in oxazine ring through 1,5-H shift resulted in the formation of chiral oxazine.



Scheme 6: Plausible mechanism for the formation of benzo [1,4]-oxazines

General experimental procedure:

To a suspension of *β*-lactam (2 mmol) in ethylene glycol (4 mL) was added indium powder (1 mmol) and solid ammonium chloride (8–10 equiv.). The reaction mixture was heated in microwave (Kitchen microwave, 300W) subsequently for 6 mins in an interval of 1 min at a stretch to control the temperature to 90°C at maximum. Thereafter the reaction mixture was cooled and brine (100 mL) was added to it. The mother liquor was extracted with ethyl acetate (50 mL) twice, washed with brine (30 mL) for 3 times, dried with sodium sulphate

and solvent was evaporated. After column chromatography, the crude mass afforded the product (80–86% yield). The characterization data of selected compounds are given here.

Compound **5a**: ^{1}H NMR: δ 3.74 (3H, s), 5.39 (1H, d, *J* =5.1 Hz), 5.58 (1H, d, *J* =5.1 Hz), 6.78, 6.82 (2H, m), 7.03–7.05 (1H, m), 7.27–7.51 (9H, m), 7.86 (1H, dd, *J* =1.5 and 8.1 Hz).

Compound **8a**: ^{1}H NMR: δ 3.64 (3H, s), 4.66 (1H, br),4.9 (1H, dd, *J* =3.0 and 6.0 Hz), 5.23 (1H, br), 6.54–6.58 (2H, m), 6.63–6.67 (2H, m), 6.92–6.96 (3H, m), 7.23–7.33 (4H, m), 7.35–7.48 (2H, m); MS: m/z (ES+) 361.11.

Compound **6c**: ^{1}H NMR: δ 3.75 (3H, s), 5.14 (1H, d, *J* =1.5 Hz), 5.23 (1H, d, *J* =1.5 Hz), 6.78–6.81 (2H, m), 7.09–7.14 (1H, m), 7.25–7.28 (2H, m), 7.36–7.43 (6H, m), 7.48–7.53 (1H, m), 7.87 (1H, dd, *J* =1.8 and 8.1 Hz).

Compound **9c**: ^{1}H NMR: δ 3.67 (3H, s), 4.87 (1H, d, *J* =5.4 Hz), 4.95 (1H, d, *J* =5.4 Hz), 6.51–6.55 (2H, m), 6.60–6.65 (3H, m), 6.84–6.93 (3H, m), 7.13–7.21 (3H, m), 7.32–7.35 (2H, m); MS: m/z (ES+) 361.21.

Compound **8e**: ^{1}H NMR: δ 1.32 (3H, s), 1.37 (3H, s), 3.67 (3H, s), 3.89 (1H, m), 4.01 (1H, dd, *J* =6.6 and 8.1 Hz), 4.14 (1H, brt), 4.41 (1H, m), 4.82 (1H, d, *J* =3.3 Hz), 6.52 (2H, m), 6.64 (3H, d, *J* =9 Hz), 6.88–6.95 (3H,m), 8.71 (1H, s); ^{13}C NMR: 25.76 (CH_3), 26.82 (CH_3), 56.05 (CH_3), 56.91 (CH), 66.82 (CH_2), 76.16 (CH), 110.00, 115.11 (CH), 115.66 (CH), 116.12 (CH), 116.84 (CH), 122.90 (CH), 124.53 (CH), 125.92, 141.48, 143.41, 152.92, 166.90; MS: (ES+) 385.1.

Conclusions:

An environmentally benign protocol for the synthesis of achiral and chiral oxazines was introduced with In/NH_4Cl mediated reaction in ethylene glycol under microwave-assisted reaction conditions. The reaction proceeds with the formation of amines followed by intramolecular cyclization resulting in oxazine ring formation with further *β*-lactam ringrupture. Both the *cis* and *trans* products were obtained in high yields. The method demonstrated here can have extensive applications in medicinal and organic chemistry.

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