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ULTRASOUND-INDUCED SYNTHESIS OF OXAZINES FROM NITRO-B-LACTAMS: SCOPE OF THE REDUCING AGENTS

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β-Lactams, Oxazines, Nitro-reduction, Cyclization, Ultrasound, Staudinger

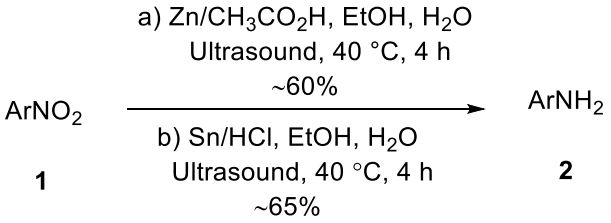
Abstract:
The ultrasound assisted facile synthesis of oxazines from nitro-β-lactams was attempted using different reducing agents. Aqueous ethanol was used as solvent and the reactions were carried out at 40-50 °C for 4 h under ultrasonic condition. Only indium metal in the presence of ammonium chloride was successful for the preparation of oxazines. A reduction of the aromatic nitro group to the amine, followed by a nucleophilic attack to the carbonyl and rearrangement was responsible for the synthesis of oxazines.

Introduction:
β-Lactams which possess key azetidin-2-one skeleton, are very potent species utilized for exploring various newer heterocyclic derivatives and their biological significance.[1] There are many ways to synthesize amines from its nitro-precursors. In fact, the nitro-to-amine conversion has been one of the most important processes in fine chemical industry. The bulk size production needed constant process optimization using cost effective metal catalyst. In this direction, over the years many metals (Sc, Ti, V, Cr, Me, Fe, Co, Ni, Cu, In, Pd and Zn) and catalysts derived from them have been used as reducing agents.
We demonstrated indium metal/NH_4Cl-induced reduction of aromatic nitro groups in β-lactams and a subsequent rearrangement under MW-assisted or ultrasonic condition.[3] Our interest in β-lactams[1] and metal-induced[4] reactions prompted us to explore Zn, Sn, Ni, Pd, ammonium formate for these oxazine derivatives under ultrasonic conditions.

Results and Discussion:
The reduction of an aromatic nitro group (**1**) to an aromatic amino group (**2**) was conducted with In/NH_4Cl, Sn, Zn, Ni/NH_2NH_2, Pd/C/H_2, Pd/C/HCO_2NH_4, under ultrasonic condition and

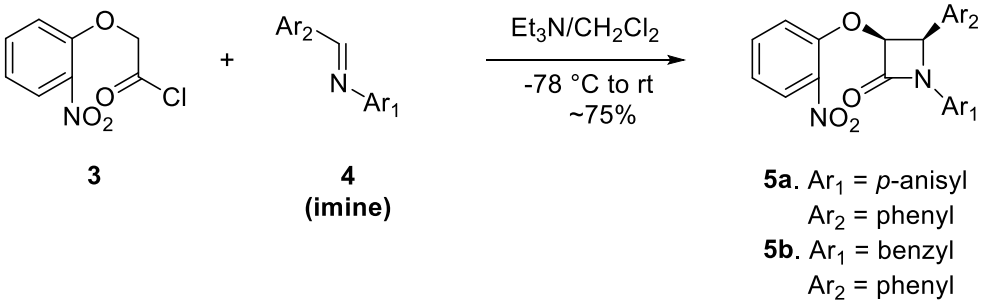
using EtOH as the solvent. These reagents produced aromatic amines in good yield **(Scheme-1).**

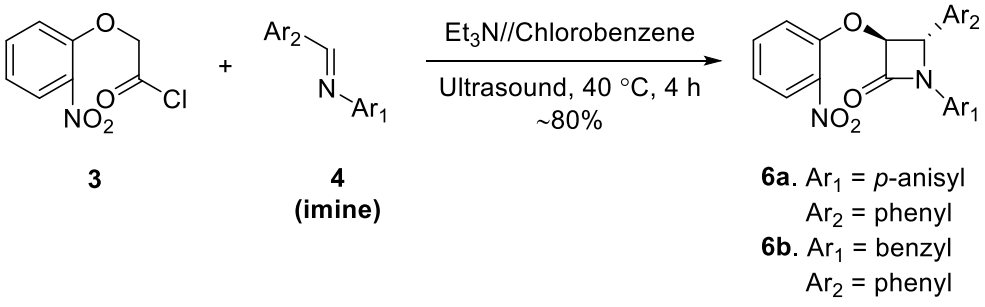
Scheme 1: Reduction of aromatic nitro compounds to aromatic amines



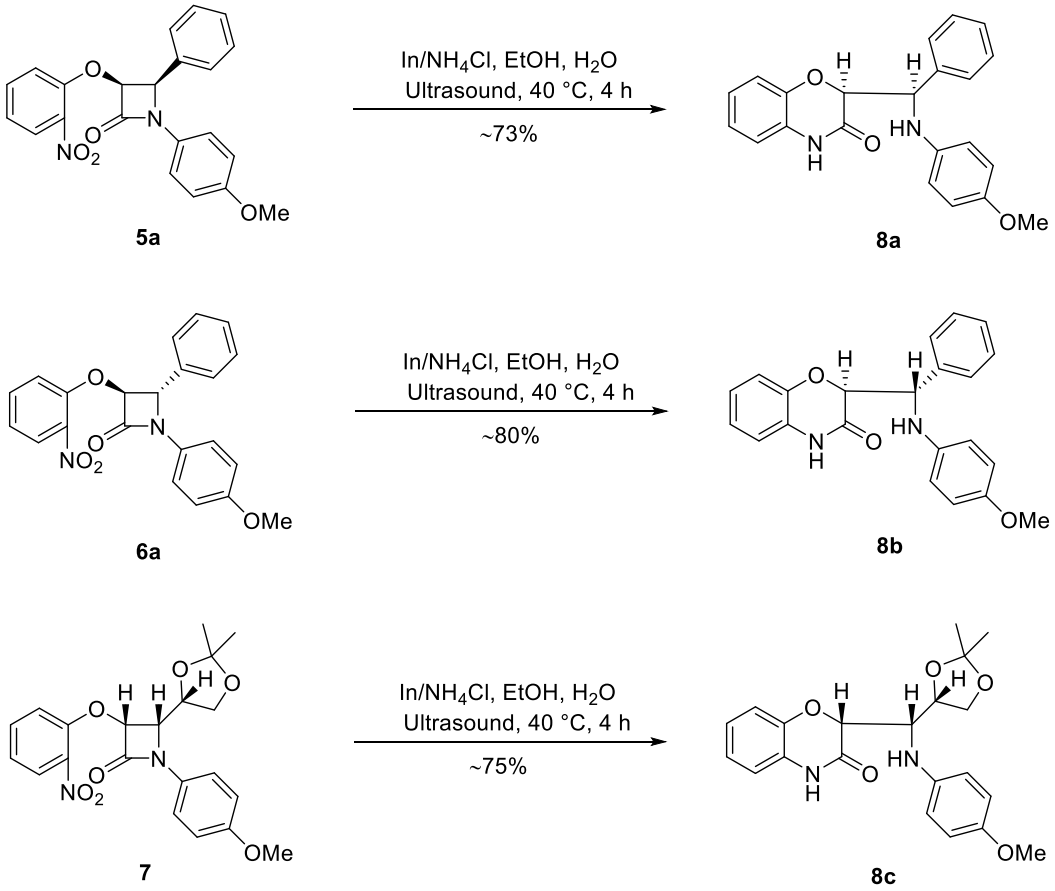
The reduction of nitro-β-lactams by these reducing agents was our next target. Nitro acid chloride **3** on reaction with the imine **4** following cycloaddition reaction produced cis- and trans-β-lactams **5 (a,b)** and **6 (a, b)**. Under two different reaction conditions, two isomers were formed (**Scheme-2**)

Scheme 2:





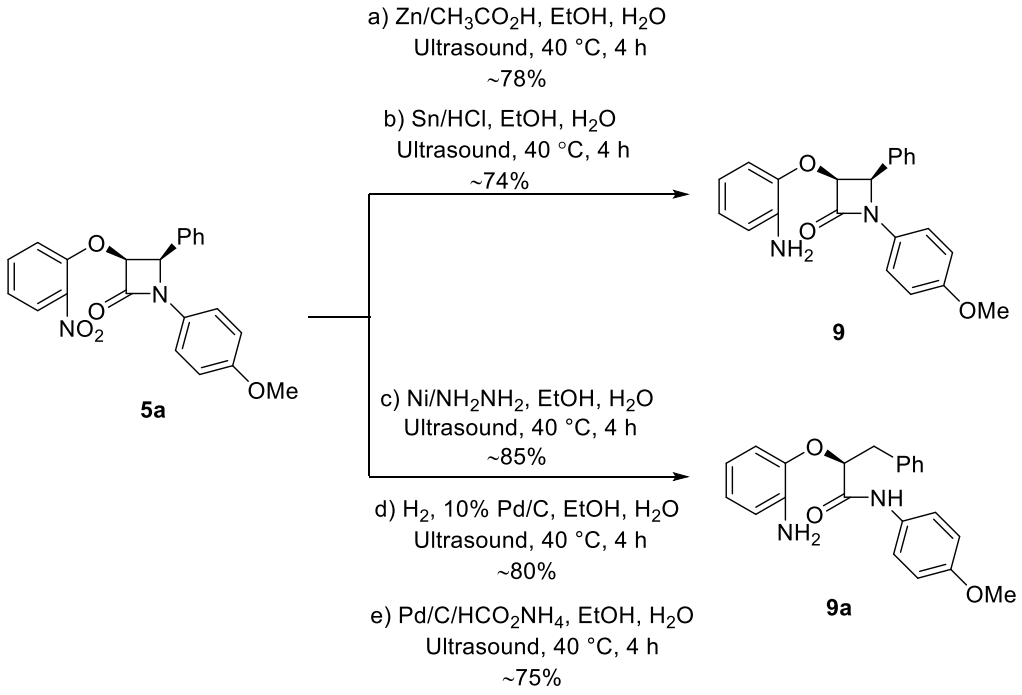
Scheme 3.



The nitro β-lactams (**5a, 6a,** and **7**) on reaction with indium metal in the presence of ammonium chloride under ultrasonic exposure afforded oxazines **8a-c (Scheme-3).**

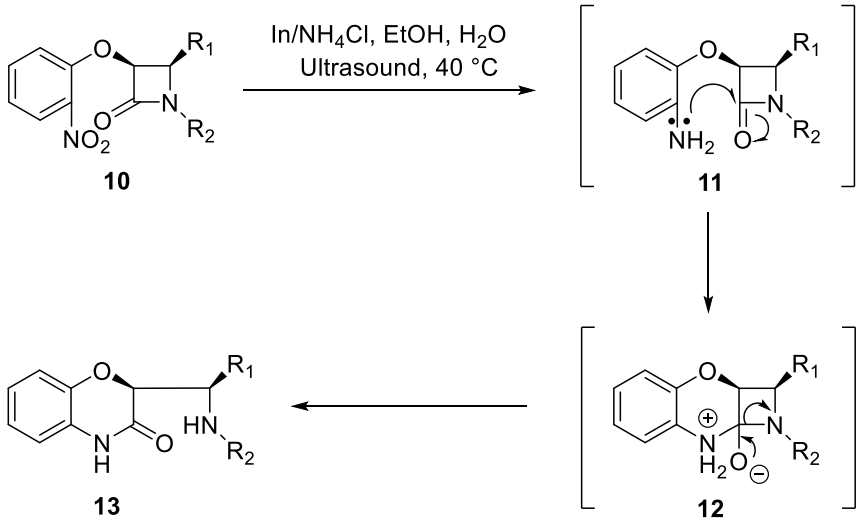
The other metals (Zn, Sn, Ni, Pd) produced amines **9 or 9a** without giving rearrangement (**Scheme 4**). Moreover, catalytic hydrogenation with Pd or transfer hydrogenation with ammonium formate was able to cleave the –N-C-4 bond to give **9a,** and therefore, this method was not suitable for oxazine synthesis.

Scheme 4: Reduction of the Aromatic nitro group



These reactions support a special feature role of indium in this reaction. It appears, indium due to its high oxophilic nature can coordinate with the carbonyl group and therefore, a nucleophilic attack by the amino group is possible. This reaction was responsible for oxazine production (**10-13**, **Scheme 5**).

Scheme 5: Nucleophilic reaction of the aromatic amino group



Experimental Section:

NMR spectra were recorded on a Bruker spectrometer and TMS used as a standard. Chemical ionization mass spectra were recorded on a Biospect instrument using CH4. Ultrasonic bath (Model 6.5l200 H, Dakshin, India, 4.5 L capacity) with the internal dimensions of 300 mm × 150 mm × 150 mm and four transducers placed at the bottom was used as a source of ultrasonic irradiations. All reactions performed in an ultrasound apparatus which was placed in a hood and the reaction vessel with large size used for the reactions. Desired temperature was maintained 40 °C for performing reactions. The catalyst was quickly introduced under inert

nitrogen atmosphere and quickly covered with the solvent. Ultrasound irradiation was carried out for predetermined period of 4 h. The catalyst Pd/C (10 wt. % loading, with matrix activated carbon support) and ammonium formate was procured from Sigma Aldrich, India. All other chemicals and solvents used for reactions and analysis were of high purity, and used as received.

Compound **5a**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (1H, dd, *J* =1.5 and 8.1 Hz), 7.02–7.05 (1H, m), 6.80–6.83 (2H, m), 5.59 (1H, d, *J* =5.1 Hz), 5.38 (1H, d, *J* =5.1 Hz), 3.75 (3H, s).

Compound **6a**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 (1H, dd, *J* =1.8 and 8.1 Hz), 7.37–7.42 (6H, m), 7.23–7.27 (2H, m), 7.10–7.15 (1H, m), 6.79–6.82 (2H, m), 5.20 (1H, d, *J* =1.5 Hz), 5.12 (1H, d, *J* =1.5 Hz), 3.74 (3H, s).

Compound **8c**: ^{1}H NMR ($CDCl_3$, 400 MHz): 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: 166.92, `143.44, 141.51, 125.94, 124.56 (CH), 122.91 (CH), 116.86 (CH), 116.14 (CH), 115.68 (CH), 115.12 (CH), 110.00, 76.19 (CH), 66.80 (CH_2), 56.90 (CH), 56.07 (CH_3), 26.80 (CH_3), 25.72 (CH_3); MS: (ES+) 385.

Conclusions:

We believe that the simple and convenient and eco-friendly approach as described herein for the synthesis of oxazines should help the organic and medicinal chemistry researchers worldwide. In addition to that as the ultrasound technique is safe, rapid and efficient. Many reduce metals are unable to produce oxazines.

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