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A facile synthesis of oxazines by indium-induced reduction-rearrangement of the nitro β-lactams

Bimal K. Banik,* Susanta Samajdar and Indrani Banik

The University of Texas, M. D. Anderson Cancer Center, Department of Molecular Pathology, Box 89,
1515 Holcombe Boulevard, Houston, TX 77030, USA

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Abstract—An indium-induced reduction-rearrangement reaction of nitro-substituted β-lactams has been used for facile synthesis of oxazines in aqueous ethanol. © 2003 Elsevier Science Ltd. All rights reserved.

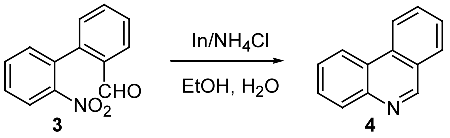
β-Lactams have been used extensively for the synthesis of several biologically active heterocyclic compounds through molecular rearrangement.[1] In continuation of our research on metal-induced[2] chemical transformation; we have discovered that oxazines can be easily prepared by an indium-induced reaction on substituted nitro β-lactams in aqueous ethanol, the results of which are represented here.

We have demonstrated a facile reduction of aromatic nitro compound **1** to the aromatic amine **2** by indium-induced reaction in aqueous ethanol (Scheme 1).[3]

During this course of our study, we have reported an indium-induced reductive cyclization route toward several heterocycles. For example, acridine **4** was prepared from **3** in good yield by following this method (Scheme 2).[4]

$$\underset{\mathbf{1}}{\mathrm{ArNO_2}} \xrightarrow[\mathrm{EtOH,\ H_2O}]{\mathrm{In/NH_4Cl}} \underset{\mathbf{2}}{\mathrm{ArNH_2}}$$

Scheme 1.



Scheme 2.

Our continued interest in β-lactams[5] and metal-mediated[2] reactions prompted us to explore the indium-induced reaction further toward the synthesis of other biologically active compounds. We envisioned the use of substituted nitro β-lactams for exploring the possibility of their ring expansion/rearrangement reaction toward oxazines through our indium-induced reaction. Therefore, synthesis of nitro-substituted β-lactams is our initial target. Of the known methods of construction of β-lactam rings, the Staudinger reaction is the most suitable.[6] It involves the cycloaddition of imines to 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). Many authors have attempted to establish the mechanism 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 β-lactam ring.[7] To explain the stereoselectivity, some computer-assisted theoretical calculations have been reported.[8]

Annulation of nitro acid chloride **7** with imines of various structures produced *cis* **8** and *trans* β-lactams **9** (Scheme 4) depending on the conditions of the experiments.[9] A slow addition of **7** to the imine solution containing triethylamine at −78°C–room temperature afforded **8** as the only product with excellent yield (80%). However, irradiation of the same reactants in chlorobenzene solution using microwave irradiation produced **9** in 70% yields. These experiments supported the earlier results.[7–9]

Keywords: β-lactams; oxazines; indium.

* Corresponding author. E-mail: bbanik@mail.mdanderson.org

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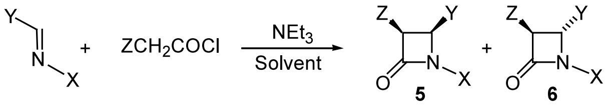
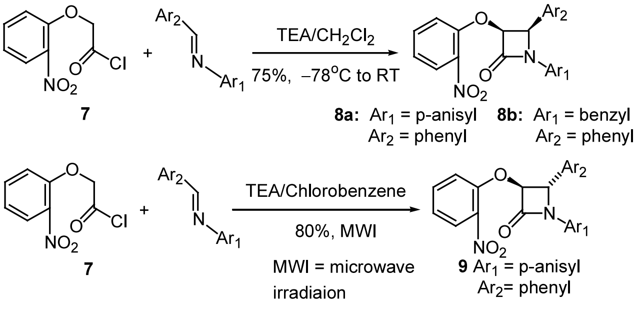


Scheme 3.

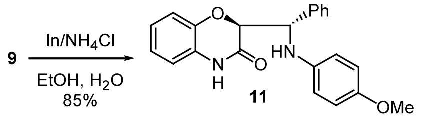


Scheme 4.

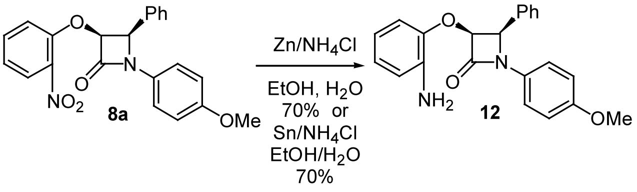
The nitro-substituted β-lactams are our starting materials for the synthesis of oxazines. As expected, and in conformity with our hypothesis, treatment of the β-lactams **8** and **9** by indium/ammonium chloride in aqueous ethanol under reflux produced oxazines **10** and **11** with an excellent yield. However, the reaction does not proceed in the absence of water. A mixture of 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: oxazines in poor yields (10–15%) were obtained. The major product was the amine (**8a** to **12**, Scheme 6). This clearly showed the importance of indium in promoting the rearrangement.

Application of this methodology to the asymmetric synthesis of oxazines[10] was also achieved with great success. Our method as described above can produce different types of optically active oxazines since chiral β-lactams of opposite stereostructure are accessible very easily (**13** to **14**, Scheme 7).

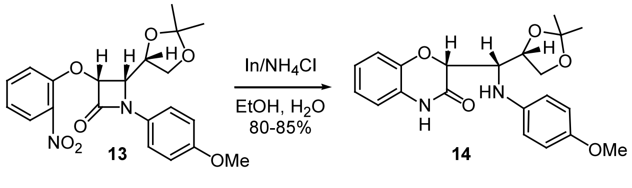
The reduction of the aromatic nitro group to the amino group and its nucleophilic attack to the β-lactam carbonyl presumably are the steps involved in the rearrangement toward oxazines (**15** to **18**, Scheme 8). Because of the oxophilic nature of indium,[11] coordination to the β-lactam carbonyl is possible and this may increase the vulnerability of a nucleophilic attack by the amino group.



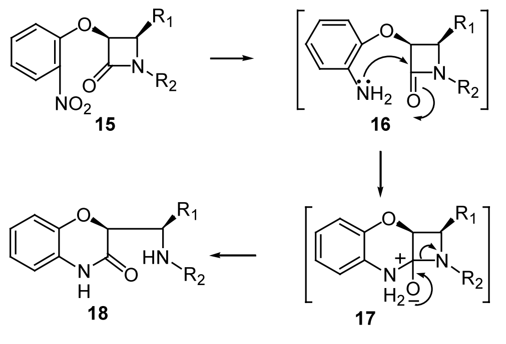
Scheme 5.



Scheme 6.



Scheme 7.



Scheme 8.

The facile preparation of chiral and achiral oxazines[12] using eco-friendly approaches as described herein should find application in organic and medicinal chemistry. We are also exploring these possibilities.

Acknowledgements

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12. *General experimental procedure*: To a suspension of β-lactam (1 mmol) in ethanol (2 mL) and water (2 mL) was added indium powder (1 mmol) and solid ammonium chloride (8–10 equiv.). The mixture was refluxed for 10 h 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 sulfate and solvent was evaporated. After column chromatography, the crude mass afforded the product (80–85% yield). Selected NMR data:

    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: 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.