MICROWAVE-INDUCED SODIUM-METHOXIDE-MEDIATED MOLECULAR REARRANGEMENTS OF β-LACTAMS TO 3-SUBSTITUTED PYRROLIDINES

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Abstract: Microwave-induced reaction of suitably substituted β-lactam has produced pyrrolidine via treatment with sodium methoxide in methanol.

Introduction:
The discovery of β-lactam antibiotics led to extreme extensive synthetic efforts for the preparation of α-amino-β-lactam derivatives of various types.1 In recent years α-hydroxy-β-lactams have received increasing attention as starting materials for diverse types of heterocycles as well as natural products such as amino sugars, alkaloids, amino acids and antibiotics.2 Interest by chemists3 in α-hydroxy-β-lactams has been generated by the discovery that these compounds are intermediates for the semi-synthesis of important antitumor drugs TaxolR and TaxotereR and their analogs. We present here a facile preparation of pyrrolidine from appropriately substituted β-lactam via sodium methoxide-mediated reaction using microwave-induced organic reaction enhancement chemistry.4

Results and Discussion:
A β-lactam rearrangement to important heterocycles was reported by Hoechst scientists for the first time.5 They observed that the rearrangement of a suitably substituted bicyclic β-lactam (1) with cyanide as the nucleophile led to pyrrolizidine (2). The stereochemistry at C-5 and C-6 remained unaffected under the conditions and no racemization was observed. Due to the rearrangement which involves rotation of bonds, the geometry becomes trans instead of cis (Scheme 1).

Scheme 1:
A ring expansion proceeded to pyrrolidine derivative (4) when the starting material (3) was a monocyclic \(\beta\)-lactam with a suitable side chain at C-3 (Scheme 1). These reactions were performed in presence of sodium cyanide and refluxing methanol.\(^6\)

**Scheme 2:**

During the course of our investigation with indium-induced reactions, we observed a similar rearrangement of a \(\beta\)-lactam (5) to oxazine (7).\(^7\) A similar reaction with sodium cyanide, however, produced an amino ester (6). The amino ester (6) was cyclized to oxazine (7). The stereochemistry and structure of compound (7) remained unaltered when it was treated with dilute sodium hydroxide (5\%). The failure of (5) to produce (7) with sodium cyanide/methanol rather than (6) suggests that alternative reagent could be used to expand a 4-membered ring to a 5-membered ring (Scheme 2).

Domestic microwave-induced reaction of an appropriately substituted \(\beta\)-lactam (3) in the presence of sodium methoxide in methanol produced pyrrolidine (4) in comparable yield within a few minutes. To maintain the temperature of the reaction mixture, a beaker of water (200 mL) was placed next to the reactants. The on-off cycle present in the microwave was used to maintain the temperature of the reaction below the boiling point of methanol. A funnel was placed at the top of the reaction flask to prevent vaporization of methanol.
The mechanism of the reaction has not been investigated. We believe a nucleophilic attack by the methoxide ion to the amide bond takes place (8 to 9) and this attack opens up the 4-membered cyclic structure. The resulting intermediate (9) then undergoes an intramolecular rearrangement reaction displacing the chlorine and forms the pyrrolidine (4) (Scheme 3). Compound (5) cannot undergo rearrangement reaction in the presence of sodium cyanide/methanol because of the absence of a leaving group in it and therefore, compound (6) was formed. But the nitro group present in compound (5) can be easily reduced to an amino group in the presence of indium. A nucleophilic attack by the amino group is highly possible and this can produce (7) through a rearrangement reaction. The important advantages of this method are: simplicity of the procedure, environmentally benign reaction conditions and rapid method without any by-products. In contrast, sodium cyanide method is time-consuming and the toxicity of this reagent is extremely high.

**Scheme 3**

**Conclusion:** Microwave-induced rapid synthesis of pyrrolidine has been realized from β-lactam using sodium methoxide-mediated simple method.

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**References:**


