

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.

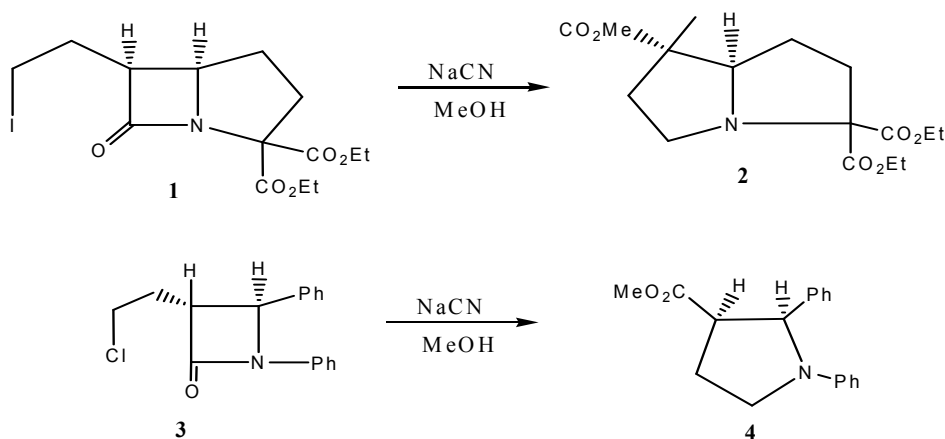
Introduction:

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 Taxol^R and Taxotere^R 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:

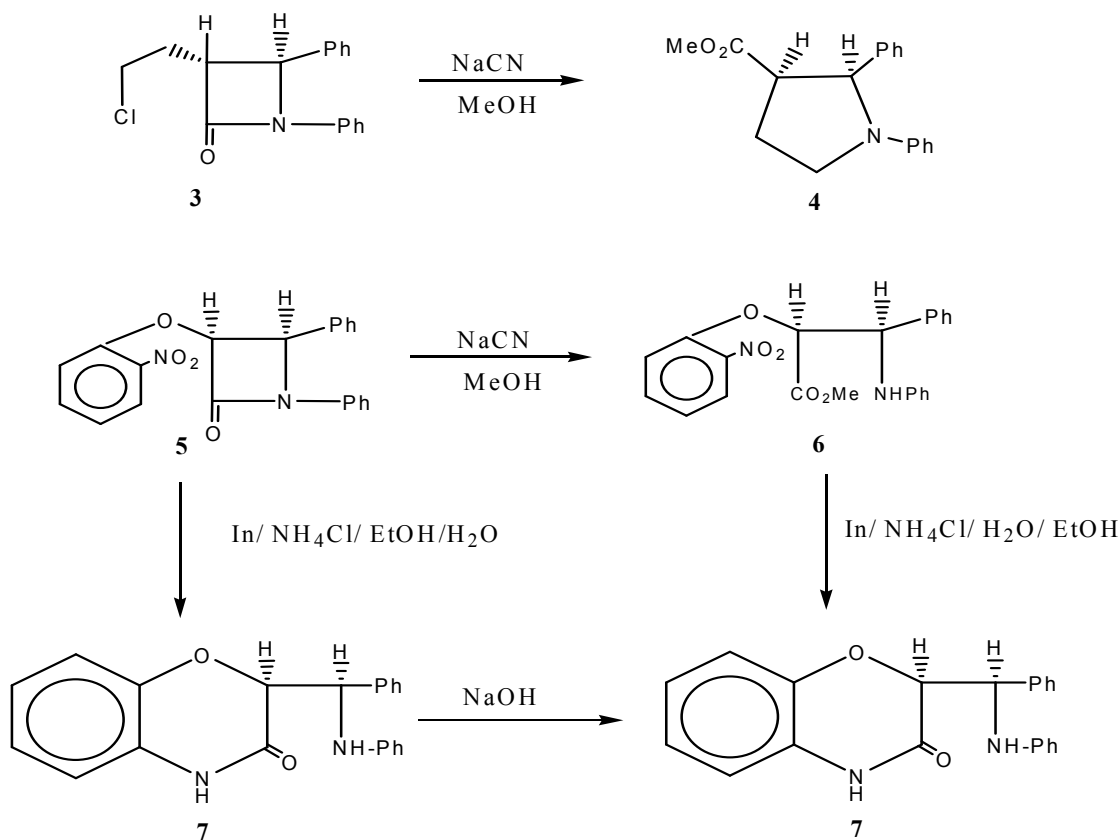
A β -lactam rearrangement to important heterocycles was reported by Hoechst scientists for the first time.⁵ They observed that the rearrangement of a suitably substituted bicyclic β -lactam (**1**) with cyanide as the nucleophile led to pyrrolizidine (**2**). The stereochemistry at C-5 and C-6 remained 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 β -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:

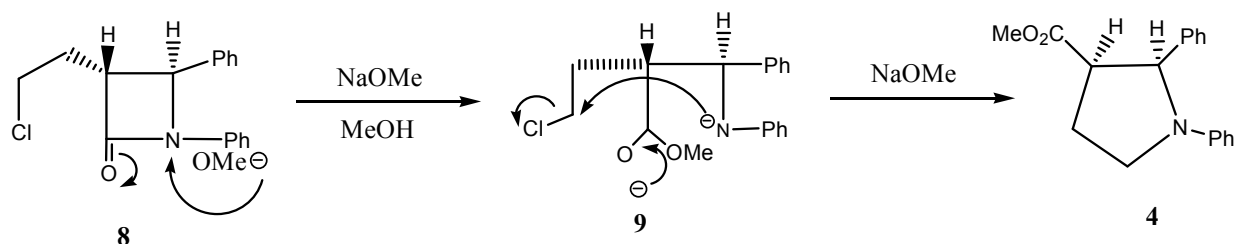


During the course of our investigation with indium-induced reactions, we observed a similar rearrangement of a β -lactam (**5**) to oxazine (**7**).⁷ A similar reaction with sodium cyanide, however, produced an amino ester (**6**). The amino ester (**6**) was cyclized to oxazine (**7**). The stereochemistry 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 β -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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