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INDIUM-INDUCED REFORMATSKY REACTION FOR THE SYNTHESIS OF β-LACTAMS

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Abstract: Synthesis of a few 3,4-disubstitued *β*-lactams has been achieved following Reformatsky reaction of imines with bromo esters in the presence of indium metal.

Keywords: *β*-lactams, Reformatsky reaction, Indium, Stereochemistry

Introduction: The use *β*-lactams as medicinally important compounds is well-known.[1] Therefore, research on *β*-lactams as a synthetic target is one of the most attractive areas of study.[2] The versatility of our research in this area has been confirmed by the synthesis of *β*-lactams[3,4,5] and biological testing as anticancer agents.[6,7,8] We describe indium metal-induced synthesis of a few 3-unsubstituted and 3,4-disubstituted *β*-lactams using imines and bromo ester following Reformatsky-type of reaction.[9]

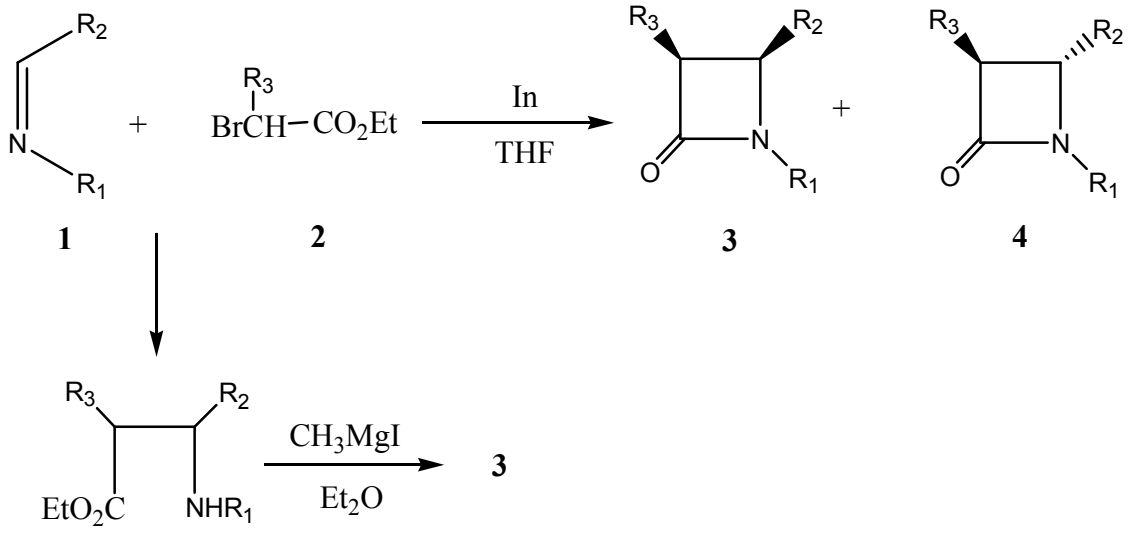
Results and Discussion: Reformatsky reaction has not been investigated systematically for the preparation of *β*-lactams. Activation of metal is necessary for the success of this reaction. Zinc was used for this type of reaction.[9c] But, the success of this reaction is limited. Appropriate activation of zinc metal is a tedious operation. In contrast, indium metal can be used as an alternative without any activation. Indium metal is not sensitive in the presence of moisture and oxygen.

Reaction of imine **1d** with ethyl bromoacetate **2d** was performed in dry THF at reflux temperature and a 3-unsubstituted *β*-lactam **3d** was obtained in 70% yield. But, a similar reaction of **1a**, **1b**, **1c**, **1e**, **1f**, **1g** and **1h** produced mixture of products. In some cases isomeric *β*-lactams **3** and **4** were obtained along with uncyclized product **5**. The presence of an aromatic group directly linked to the nitrogen of the imine produced 3-unsubstituted β-lactam and/or the isomeric *β*-lactam (**3** and **4**) along with **5**. A benzyl group at the nitrogen was helpful to obtain *β*-lactam (3-unsusbstituted or 3,4-disubstituted) (**Scheme 1**). The product **5** could be cyclized to **3** using a Grignard reagent. This reaction is interesting since it produces only *cis*-*β*-lactam **3**.

The synthesis 3-alkyl-substituted *β*-lactams is an important objective because a number of antibiotics have this type of group. Direct cycloaddition of saturated alkyl acid chloride via Staudinger reaction is difficult to achieve for the preparation of these types of *β*-lactams.

Synthesis of 3-unsusbtituted *β*-lactams is also important since alkyl, aryl and a hydroxyethyl side chain can be added to them via aldol condensation reaction.

Scheme 1:



a: R_1 = R_2 = phenyl, R_3 = H
b: R_1 = R_2 = *p*-methoxyphenyl, R_3 = H
c: R_1 = *p*-methoxyphenyl, R_2 = phenyl, R_3= H
d: R_1 = benzyl, R_2= phenyl, R_3 = H
e: R_1 = R_2 = phenyl, R_3 = CH_3
f: R_1 = R_2 = *p*- methoxyphenyl, R_3 = CH_3
g: R_1= R_2 = phenyl, R_3 = C_2H_5
h: R_1= R_2 = *p*- methoxyphenyl, R_3 = C_2H_5
i: R_1 = benzyl, R_2= phenyl, R_3 = CH_3
j: R_1 = benzyl, R_2 = phenyl, R_3 = C_2H_5

Conclusion: Reformatsky reaction of imines with bromoesters in the presence of indium metal offers opportunities to prepare *β*-lactams in good yield.

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