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FACILE ONE-POT SYNTHESIS OF 3-HYDROXY-β-LACTAMS BY GRINDING

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ABSTRACT:

A convenient and environmentally benign one-pot method for the synthesis of 3-hydroxy-*cis*-β-lactams has been developed using a solvent-free grinding approach. The process begins with the in-situ formation of imines by grinding various aldehydes with aromatic amines using a mortar and pestle. Subsequently, acid chlorides and triethylamine (TEA) are added directly to the reaction mixture, and grinding is continued to facilitate Staudinger cycloaddition reaction followed by aqueous sodium hydroxide and further grinding promotes to yield 3-hydroxy-*cis*-β-lactams in excellent yields. This mechanochemical method offers a rapid, efficient, one-pot and sustainable alternative to conventional multi-step synthetic approaches.

KEYWORDS:

Grinding, Imines, β-Lactams, One-pot, Cycloaddition, Staudinger reaction

INTRODUCTION:

The β-lactam framework, particularly hydroxy-substituted β-lactams, has gathered significant attention in recent years due to its role in the development of both natural and synthetic bioactive molecules[i]. The unique combination of a highly strained four-membered lactam ring and a strategically positioned hydroxyl group renders these compounds valuable synthetic intermediates and pharmacophores[ii]. The β-lactam moiety contributes pronounced electrophilic character, facilitating diverse chemical transformations, while the hydroxyl functionality enhances solubility, hydrogen bonding potential, and stereochemical interactions attributes crucial for biological activity[iii].

These compounds have attracted increasing attention due to their wide range of bioactivities, notably as antibiotics[iv], antibacterial[v], antifungal[vi], antiviral[vii], and anticancer[viii] agents. Of particular importance is their role in overcoming bacterial resistance, as hydroxyl-β-lactams have shown potential to inhibit β-lactamases and other resistance-conferring enzymes[ix].Additionally, their utility as intermediates in the synthesis of complex natural products and advanced pharmaceuticals further highlights their synthetic and pharmacological relevance[x].

A wide range of methods have been developed for the synthesis of structurally diverse 3-hydroxy-β-lactams due to their biological relevance. These include the Staudinger [2+2] cycloaddition between ketenes and imines[xi,xii], Kinugasa-type reactions involving alkynes and nitrones, and enolate–iminium ion cyclization for stereoselective ring construction[xiii]. A light-driven strategy has been established for the synthesis of 3-phenyl-3-hydroxy-β-lactams, where exposure of aryl-β-ketoformamides to UV light results in efficient formation of the target β-lactams[xiv].A practical and efficient route to β-lactams involves the cabalt-carbonyl-catalyzed carbonylation of diazo compounds to generate reactive ketenes, which subsequently undergo [2 + 2] cycloaddition with imines. However, a notable drawback is the use of cobalt carbonyl, which is toxic and air-sensitive[xv]. A Rh(I)-catalyzed method enables direct ketene generation from terminal alkynes using 4-picoline N-oxide, offering a selective route to trans-β-lactams via the Staudinger reaction under mild conditions. However, the use of expensive rhodium catalysts and the requirement for specific oxidants limit its scalability and practicality[xvi].

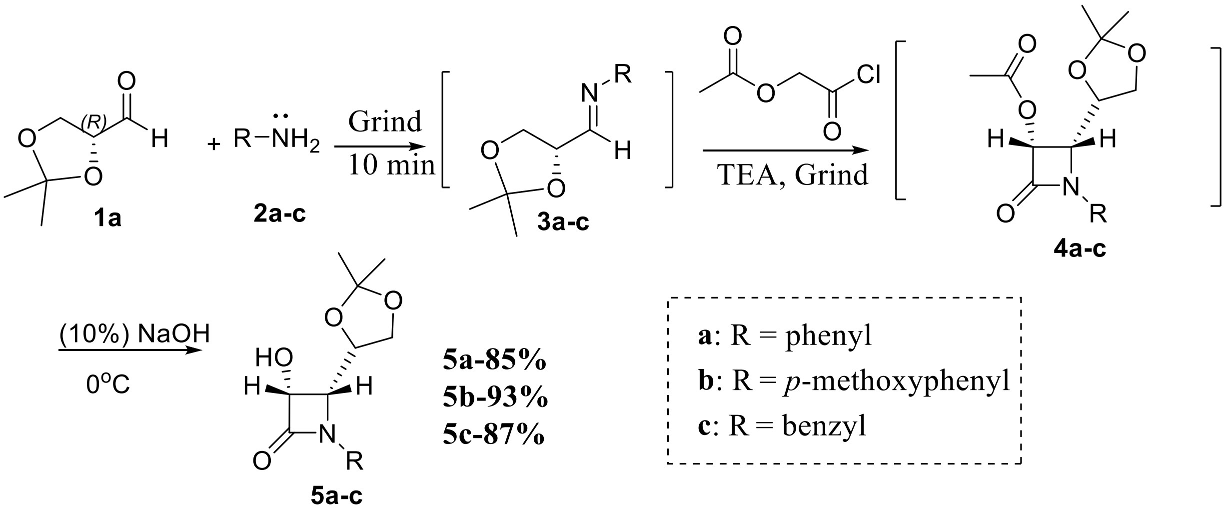
Despite the effectiveness of these methods, many rely on toxic solvents, long reaction times, expensive catalysts, or harsh conditions that limit their sustainability and scalability. In contrast, grinding-based (mechanochemical) methods have gained attention for being solvent-free, energy-efficient, and environmentally benign[xvii]. These methods enable chemical transformations through simple mechanical agitation (such as ball milling), which enhances reaction rates, minimizes waste, and often eliminates the need for external heating[xviii]. Moreover, grinding offers better atom economy, facilitates cleaner work-up procedures, and aligns with the principles of green chemistry, making it an attractive alternative for the sustainable synthesis of 3-hydroxy-β-lactams. Our ongoing research into hydroxy β-lactams focuses on the development of efficient, stereoselective, and environmentally friendly synthetic routes. This paper describes a simple one-pot grinding method for the preparation of 3-hydroxy-β-lactams.

RESULTS AND DISCUSSIONS:

Diverse aldehydes **1a-d** (D-glyceraldehyde acetonide, L-glyceraldehyde, benzaldehyde, 4-methoxy benzaldehyde) in reaction with diverse aromatic amines **2a-c** (aniline, *p*-anisidine and benzylamine) produced the corresponding imines **3a-c** in quantitative yield. The reactants are taken in a grinder and mixed thoroughly with a mortar-pestle. To these imines was added acetoxyacetyl chloride and triethyl amine. Grinding was continued for another few minutes and an aqueous solution of sodium hydroxide was added to the mortar pestle and grinding was performed for about 10 min. Interestingly this reaction produced only *cis*-3-hydroxy-β-lactams in excellent yield (**Scheme 1, 2, 3,** and **4**).

Thus optically active hydroxy-β-lactams in both enantiomeric forms **5a-c** and **8a-c** are prepared efficiently by this method. Diverse racemic β-lactams **11a-c** and **14a-c** were also synthesized by this method. Earlier all these three steps were performed through step-wise process (imine synthesis, acetoxy-β-lactam synthesis, and hydroxy-β-lactam synthesis). Appropriate solvents were used to perform these reactions successfully. Moreover, the reactions in presence of solvents were slow.

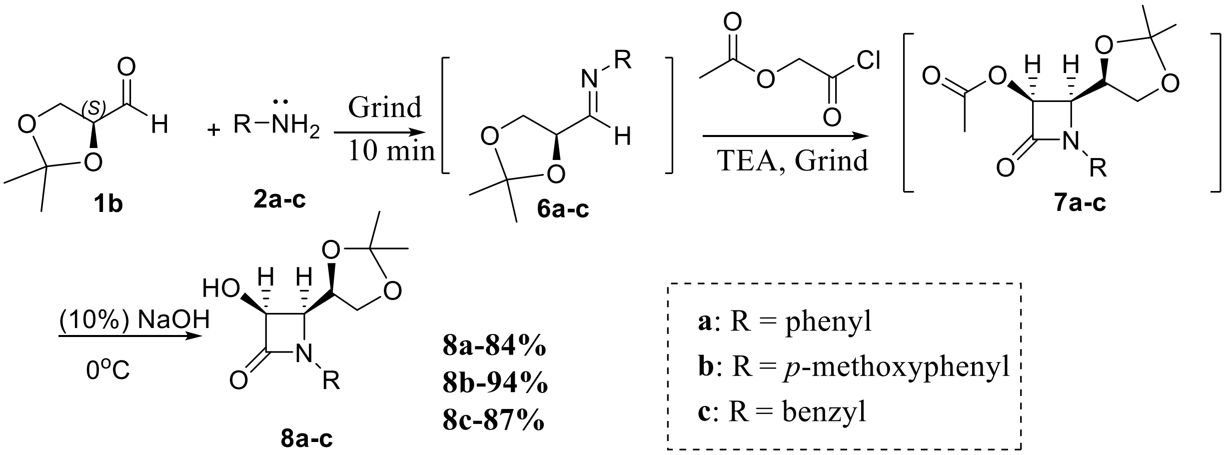
Scheme 1:



5a-85%
5b-93%
5c-87%

a: R = phenyl
b: R = *p*-methoxyphenyl
c: R = benzyl

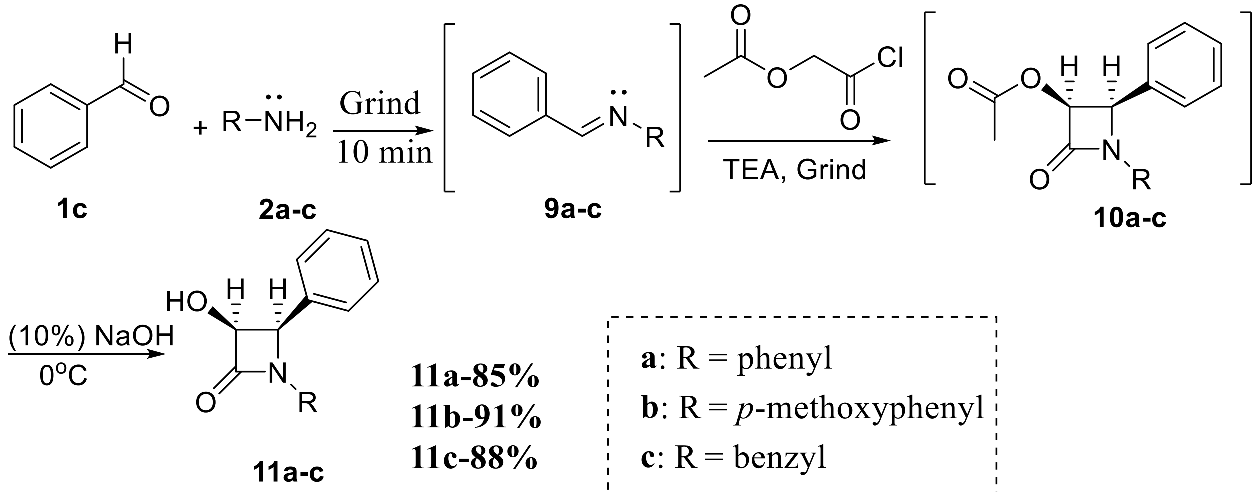
Scheme 2:



8a-84%
8b-94%
8c-87%

a: R = phenyl
b: R = *p*-methoxyphenyl
c: R = benzyl

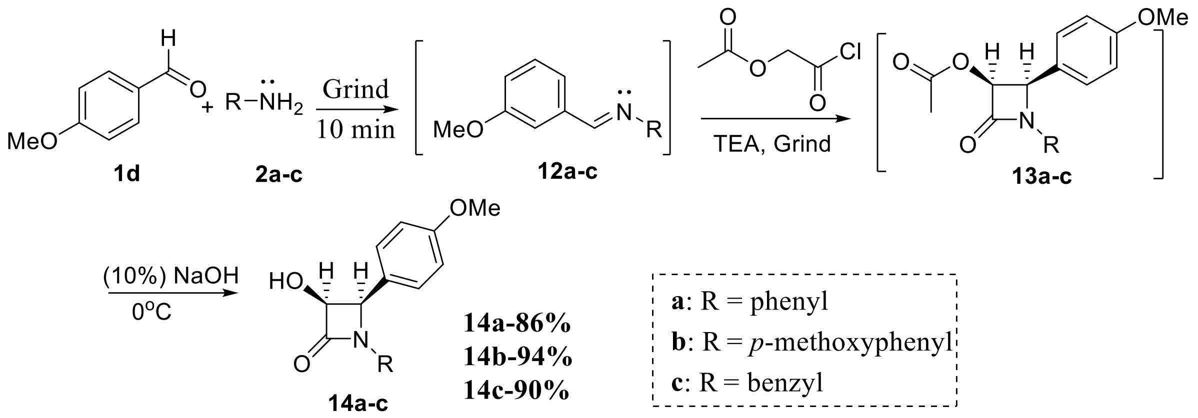
Scheme 3:



11a-85%
11b-91%
11c-88%

a: R = phenyl
b: R = *p*-methoxyphenyl
c: R = benzyl

Scheme 4:



a: R = phenyl
b: R = *p*-methoxyphenyl
c: R = benzyl

EXPERIMENTAL:

Synthesis of 4-Substituted-3-Hydroxy-*cis*-β-Lactams (5a-c, 8a-c, 11a-c and 14a-c):

A neat reaction of aldehydes (1 mmol) with diverse aromatic amines (1 mmol) in mortar-pestle was conducted for 20 minutes. The reaction mixture was grinded well. The in situ formed imines were reacted with acetoxyacetyl chloride (1 mmol) and triethyl amine (3 mmol) in the same grinder and mixed thoroughly about with a mortar-pestle. This grinding was continued for another 20 minutes and then an aqueous solution of sodium hydroxide (10%, 2 mL) was added to the mortar pestle and grinding was performed for about 10 min. Water (5 mL) and dichloromethane (10 mL) was added to the reaction mixture, the organic part was collected and then it was evaporated to isolate product 3-hydroxy-*cis*-β-lactams **5a-c, 8a-c, 11a-c** and **14a-c** in excellent yield. All these 3-hydroxy-*cis*-β-lactams were confirmed by 1H NMR analysis and matched with authentic data of earlier reports[iii,xix].

CONCLUSION:

A convenient and eco-friendly one-pot grinding technique has been successfully employed for the synthesis of 3-hydroxy-*cis*-β-lactams. This method involves the sequential insitu formation of imines, followed by Staudinger cycloaddition and ester hydrolysis reaction all under solvent-free conditions. The use of mechanical grinding not only simplifies the procedure but also enhances the overall yield of the desired products. This approach represents a sustainable and efficient alternative to traditional methods, with potential applications in the synthesis of biologically relevant β-lactam derivatives.

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