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Sandeep Goyal, Anang Pal, Mangilal Chouhan, Mukesh Gangar, Sharad Sarak, Vipin A. Nair

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Graphical Abstract

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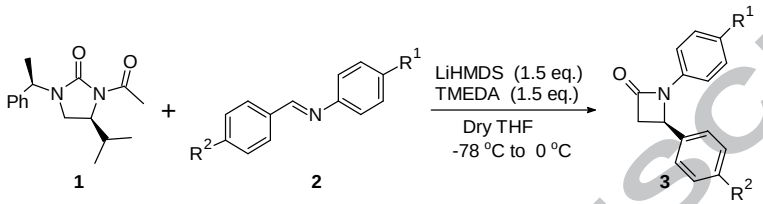
Sandeep Goyal[a], Anang Pal[a], Mangilal Chouhan[b], Mukesh Gangar[a], Sharad Sarak[a], Vipin A. Nair[a,]*



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A highly efficient stereoselective synthesis of β-lactams

Sandeep Goyal[a], Anang Pal[a], Mangilal Chouhan[b], Mukesh Gangar[a], Sharad Sarak[a], Vipin A. Nair[a,]*

[a] Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Sector 67, Mohali, Punjab 160062, India.
[b]Department of Pharmaceutical Sciences, Mohanlal Sukhadia University, Udaipur, Rajasthan, 313001, India.

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ABSTRACT

An efficient strategy for a one-pot, single step synthesis of β-lactams employing an imidazolidinone based chiral auxiliary with various aldimines *via* asymmetric Mannich-type reaction has been described.

Introduction

The azetidin-2-one scaffold, also known as β-lactam, constitutes numerous biologically important drug molecules and natural products.[1] Besides β-lactam antibiotics, stereoselective construction of the β-lactam core generates considerable research interest as versatile building blocks for the synthesis of numerous organic molecules.[2] Examination of the literature offers various approaches[3] for the construction of the β-lactam core such as Staudinger reaction,[4] enolate-imine condensation,[5] carbene insertion reaction,[6] Kinugasa reaction[7] and asymmetric catalysis.[3b]

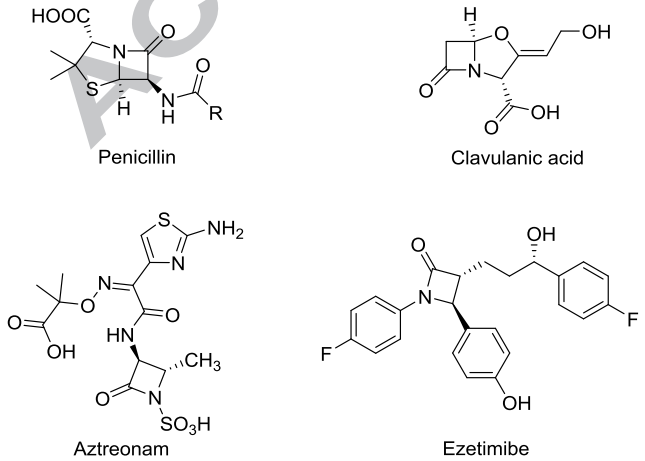
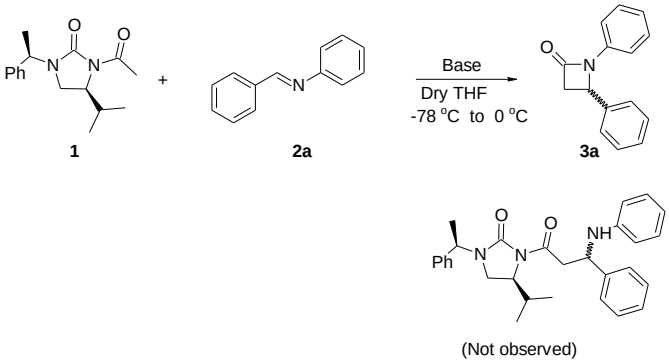


Figure 1. A few biologically active molecules containing a β-lactam ring

Most of these approaches are associated with drawbacks such as poor yields, multiple steps and low regio- and stereoselectivity.[8] Considering these drawbacks and based on our keen interest[9] in the asymmetric synthesis of bioactive molecules, we decided to synthesize β-lactams using a chiral auxiliary mediated approach. The present research discloses an efficient auxiliary mediated strategy for the stereoselective synthesis of these molecules in a single step. The chiral auxiliary employed in this study was synthesized by a procedure developed in our laboratory (Scheme 1).[9b] To standardize the reaction conditions, a model reaction was studied in which kinetic deprotonation of *N*-acetyl auxiliary **1** (1.0 equiv.) was performed using LiHMDS (1.0 equiv.) in dry THF at -78 °C (Scheme 1) followed by addition of imine electrophile **2a** (1.05 equiv.) at the same temperature. The reaction failed to afford the alkylated product. Very slow progress of the reaction was witnessed when the reaction temperature was increased to 0 °C.



Scheme 1. Synthesis of β-lactam **3a** using different bases

* Corresponding author. Tel.: +91-172-229-2045; fax: +91-172-221-4692; e-mail: vn74nr@yahoo.com

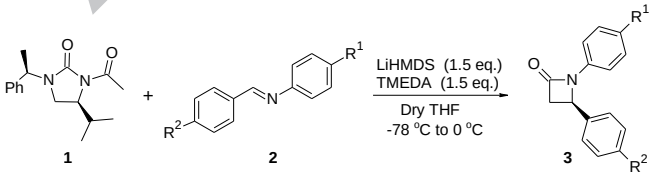
Quite surprisingly the reaction resulted in the formation of a *β*-lactam in low yield (Table 1) instead of the expected alkylated adduct. Increase in temperature above 0 °C led to degradation of the desired product. A study to optimize the stoichiometry of LiHMDS indicated 1.5 equivalents to be the best, as the yields did not improve at increased loadings. A similar result was obtained when the reaction was attempted with LDA (Table 1; entry 4). Contrary to this, other bases such as *n*-BuLi, NaHMDS and KHMDS gave very sluggish reactions and did not afford the desired product (Table 1; entries 5-7). The available literature reports[10] and our previous experience[9c] strongly support the utility of the additive TMEDA as a cation chelator. Thus the hexamethyldisilylamide anion would be sufficiently basic for proton abstraction. Further attempts were made to enhance the yield of the desired *β*-lactam by using TMEDA as an additive. In a separate reaction, addition of equimolar amounts (1.5 equiv.) of LiHMDS and TMEDA to a solution of the acetylated auxiliary **1** in THF at -78 °C followed by introduction of the imine electrophile **2a** resulted in improvement of the yield from 40% to 65% (Table 1; entry 8). On the contrary a similar reaction with equimolar amounts (1.5 equiv.) of LDA and TMEDA afforded only 40% yield of the desired *β*-lactam (Table 1; entry 9).

Table 1. Optimization of reaction conditions[a]

Entry	Reagent	Equivalent	Solvent	Yield (%)
1	LiHMDS	1.0	THF	35
2	LiHMDS	1.5	THF	40
3	LiHMDS	2.0	THF	30
4	LDA	1.5	THF	30
5	NaHMDS	1.5	THF	nd
6	KHMDS	1.5	THF	nd
7	*n*-BuLi	1.5	THF	nd
8	LiHMDS, TMEDA	1.5	THF	65
9	LDA, TMEDA	1.5	THF	40

[a] **1** (1.0 equiv.), **2a** (1.05 equiv.), Temp. -78 °C to 0 °C.

The developed protocol was further extended to different aromatic imines bearing electron donating and withdrawing groups to generalise the scope of the reaction (Scheme 2). The reactions afforded the *β*-lactam derivatives with ease and good yield, providing excellent stereoselectivity (Table 2). Contrary to this, the imines derived from aliphatic aldehydes and/or aliphatic amines (Scheme 3) did not afford the desired product[11] (Table 3).



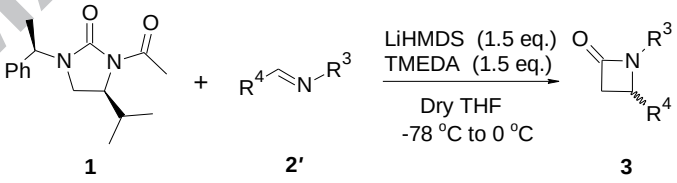
Scheme 2. Synthesis of aryl substituted *β*-lactams

The stereoselectivity of the developed protocol was established by comparing the specific rotation of the synthesized *β*-lactam **3n** with the reported[5b] value [observed $[\alpha]_D^{25}$ = -89.5 (c 0.11, $CHCl_3$), reported for the antipode $[\alpha]_D$ = +87.8 (c 0.115, $CHCl_3$)] and was found to be in good agreement. The enantiomeric excess of all the synthesized compounds were evaluated by chiral HPLC

Table 2. Synthesis of aryl substituted *β*-lactams[a]

Entry	R^1	R^2	Product	Yield (%)[b]	ee[c]
1	H	H	**3a**	65	90:10
2	H	F	**3b**	62	>99
3	H	Cl	**3c**	63	100
4	H	Br	**3d**	64	100
5	F	H	**3e**	63	85:15
6	OCH_3	H	**3f**	60	100
7	H	OCH_3	**3g**	61	100
8	CH_3	H	**3h**	62	93:07
9	CH_3	OCH_3	**3i**	61	100
10	OCH_3	OCH_3	**3j**	60	100
11	CH_3	CH_3	**3k**	63	88:12
12	CH_3	Br	**3l**	62	78:22
13	F	OBn	**3m**	63	100
14	F	CH_3	**3n**	64	78:22

[a] **1** (1.0 equiv.), LiHMDS (1.5 equiv.), TMEDA (1.5 equiv.), **2** (1.05 equiv.), THF, Temp. -78 °C to 0 °C, [b]Isolated yield, [c]determined by chiral HPLC using Chiralcel OD-H column; *n*-Hex / *i*-PrOH = 95:5, 1.0 mL/min, 254 nm.



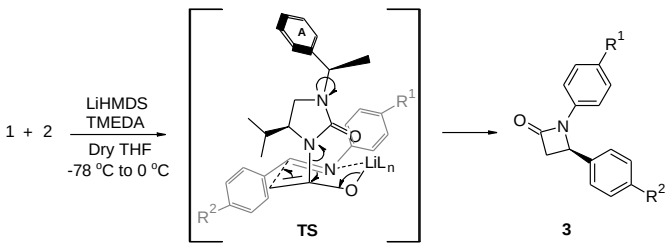
Scheme 3. Synthesis of alkyl substituted *β*-lactams

Table 3. Synthesis of alkyl substituted *β*-lactams

Entry	R^3	R^4	Product	Yield
1	Pr	Ph	**3o**	Nil
2	Ph	Pr	**3p**	Nil
3	C_6H_{11}	Pr	**3q**	Nil

[a] **1** (1.0 equiv.), LiHMDS (1.5 equiv.), TMEDA (1.5 equiv.), **2′** (1.05 equiv.), THF, Temp. -78 °C to 0 °C.

analysis (Table 2). The observed stereoselectivity in acetate alkylation reaction may be envisaged by the proposed transition state model (TS). Deprotonation of the *N*-acetyl auxiliary at -78 °C using LiHMDS/TMEDA affords the *Z*-enolate which upon reaction with an imine electrophile would lead to a six-membered chelated transition state (Scheme 4).



Scheme 4. Proposed transition state for the stereoselective synthesis of *β*-lactams

This would give rise to *β*-lactam **3** as the major product. Further the stoichiometric use of TMEDA increases the basicity of the generated enolate and assists in the *in situ* formation of *β*-lactam in good yield and stereoselectivity.

Conclusion

The present work describes a chiral auxiliary mediated highly efficient, single step synthesis of *β*-lactams stereoselectively. The developed protocol afforded the desired products with good yield and high selectivity.

Acknowledgments

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Supplementary data

Supplementary material which includes experimental procedures and compound data can be found in the online version.

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Sandeep Goyal[a], Anang Pal[a], Mangilal Chouhan[b], Mukesh Gangar[a], Sharad Sarak[a],

Vipin A. Nair[a,] *

[a]Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Sector-67, Mohali, Punjab 160062, India.
[b]Department of Pharmaceutical Sciences, Mohanlal Sukhadia University, Udaipur, Rajasthan, 313001, India.

Highlights

- Chiral auxiliary mediated asymmetric Mannich-type reactions with aldimines.
- One-pot, single step synthesis of *β*-lactams.
- Transition state model for the formation of *β*-lactams.
- Good overall yield and high enantioselectivity.

* Corresponding author. Tel.: +91-172-229-2045; fax: +91-172-221-4692; e-mail: vn74nr@yahoo.com