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STEREOSELECTIVE SYNTHESIS OF *TRANS* ACETOXY β-LACTAMS UNDER SONICATION

Ram Naresh Yadav,[1] Aarif Latif Shaikh[2] and Bimal Krishna Banik [3*]

[1]Department of Chemistry, Faculty of Engineering & Technology, Veer Bahadur Singh Purvanchal University, Jaunpur Uttar Pradesh; [2]Laxai Life Sciences, Research & Development Centre, Building No.900, MN Park, Synergy Square I, Genome Valley, Shameerpet, Hyderabad-500078, Telangana, India; [3]Department of Mathematics and Natural Sciences, College of Sciences and Human Studies, Deanship of Research Development, Prince Mohammad Bin Fahd University, Al Khobar 31952, Kingdom of Saudi Arabia; Email: bimalbanik10@gmail.com

Abstract:
An efficient ultrasound-assisted racemic and asymmetric synthesis of *trans* acetoxy β-lactams is demonstrated. A nucleophilic substitution reaction of *cis* 3-mesyl β-lactams with sodium acetate produces *trans* 3-acetoxy β-lactams following sonication is rapid and high yielding.

Key Words: Ultrasound, β-Lactam, Stereoselective, Inversion of Configuration.

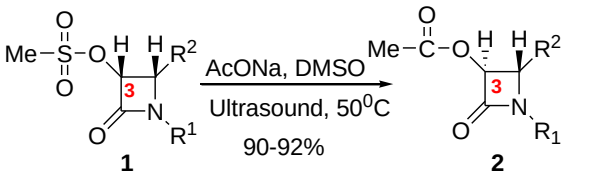
Introduction:

Stereoselective synthesis of β-lactams have maintained the interest of chemists for decades [I]. Several methods are reported to prepare *cis* β-lactams. However, synthesis of *trans* β-lactams as a pure isomer remains a challenge [II]. It was known that *cis* β-lactams demonstrates clinical activity [III]. However, discovery of clinically active *trans* β-lactams prompted many to prepare this type of molecules [IV]. An efficient method for the synthesis of racemic as well as chiral *trans* 3-acetoxy β-lactams through ultrasound assisted reaction of *cis* 3-mesyl β-lactams with sodium acetate is reported herein [V, VI].

Results and Discussions:

Racemic acetoxy and hydroxyl compounds were used to synthesize racemic *cis* 3-mesyl acetoxy β-lactam **1.** Reaction of **1** with sodium acetate in DMSO under ultrasound method for 2 minutes at 50^0C produced *trans* 3-acetoxy β-lactam **2** in excellent yields **(Scheme 1 and Table 1).**

SCHEME 1: Ultrasound induced synthesis of *trans* -monocyclic β-lactam



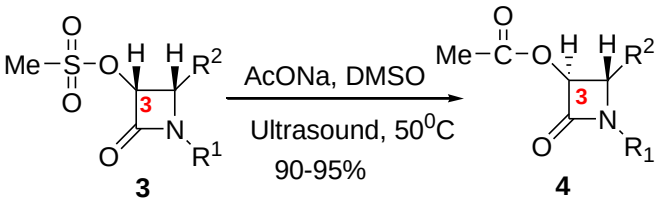
1 *rac*-(+/-)-*cis*-β-lactam

2 *rac*-(+/-)-*trans*-β-lactam

Table 1

Entry	**1** R^1	R^2	T (^{0}C)	Time (min)	Yield (%)
1	**Ph**	**Ph**	50	2	90
2	**Ph**	**PMP**	50	2	92
3	**Ph**	**p-methyl**	50	4	90
4	**Ph**	**p-flurophenyl**	50	5	91

SCHEME 2: Ultrasound induced synthesis *trans* -monocyclic chiral β-lactam (+)-enatiommers



3 *(+)-cis*-β-lactam

4 *(+)- trans*-β-lactam

Table 2

Entry	**1** R^1	R^2	T (^{0}C)	Time (min)	Yield (%)
1	**Ph**	**Ph**	50	2	90
2	**Ph**	**PMP**	50	2	91
3	**Ph**	**p-methyl**	50	4	95
4	**Ph**	**cinnamyl**	50	4	92

SCHEME 3: Ultrasound induced synthesis ,
-monocyclic chiral β-lactam of (-)- enatiomers

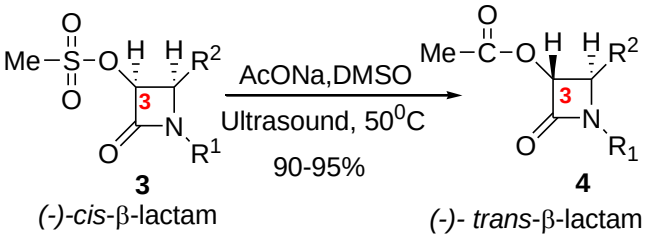


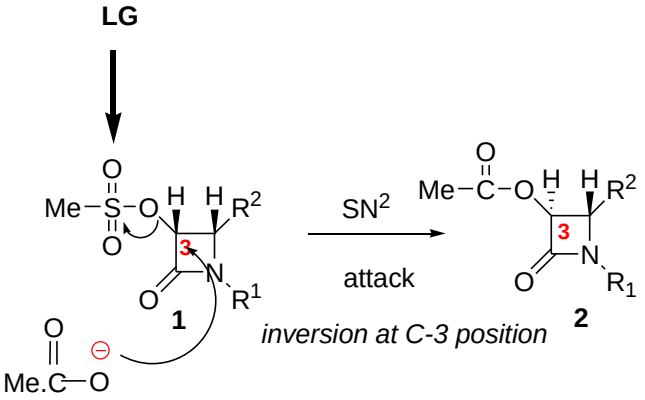
Table 3

Entry	1 R^1	1 R^2	T (^{0}C)	Time (min)	Yield (%)
1	**Ph**	**Ph**	50	2	90
2	**Ph**	**PMP**	50	2	95

Following a similar method *cis* 3-mesyl 3*R*, 4*S* (**3**) (derived from D-glycerladehyde acetonide) and *cis* 3-mesyl 3*S*, 4*R* (**4**) (derived from L-glycerladehyde acetonide) were subjected to react with sodium acetate under ultrasound irradiation condition. The product obtained from this route is *trans*-3-acetoxy β-lactams. The mechanism of this reaction follows $S_N2$pathways that requires the attack of nucleophile from the back side of the carbon atom. So there is inversion of configuration at the C-3 center (**Scheme-2** and **Scheme-3**).

The enantiomeric β-lactams **3** were also isomerized at C-3 position successful. Ultrasound irradiation supplied the necessary energy for the departure of the mesylate group (**Scheme 4**).

SCHEME 4: Plausible mechanism of concomitant demesylation



LG **: Leaving Group**

Experimental:

A representative procedure is given below. In a 125 mL Erlenmeyer Flask, DMSO (2 mL) was added to a the β-lactam **1** (1 mmol). To the reaction mixture sodium acetate (3 mmol) were then added and the reaction mixture was irradiated in an ultrasound for 2-5 min. To the reaction mixture dichloromethane (20 mL) was added and it was shaken. The reaction mixture was washed with brine (2 mL). The organic extracts were then evaporated and passed through a short column of silica gel (5 g) using ethylacetate and *n*-hexanes (20: 80) as the solvent to afford the pure product **2**.

Conclusions:

In summary, we have demonstrated efficient, rapid, and highly stereoselective synthesis of *trans* 3-acetoxy β-lactams in racemic and optically active forms using sonochemical method. Synthesis of enantiomerically pure *trans*-β-lactams with defined stereochemistry is a challenging objective.

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