Indian Journal of Chemistry
Vol. 61, July 2022, pp. 755-760

Synthetic investigations in epimerization reactions of β-lactams

Aarti Thakur[a,b], Suvidha Pandey[b] & Renu Thapar[a,*]

[a] University Institute of Engineering and Technology (U.I.E.T), Panjab University, Sector-25, Chandigarh-160 014, India

[b] Department of Chemistry & Centre of Advanced Studies in Chemistry, Panjab University, Sector-14, Chandigarh-160 014, India

*E-mail: renuarorachem_pu@yahoo.co.in

Received 10 December 2021; accepted (revised) 2 June 2022

A novel and facile synthesis of *cis*-3-phenylthio & *cis*-3-chloro-β-lactams using epimerization reaction has been studied. The optimized reaction conditions for this conversion using very mild base have been studied. All the new synthesized compounds have been characterized. The reported work gives easy conversion of *trans* isomers to *cis* without forming any side product.

Keywords: Antibiotics, β-lactams, Epimerization, Heterocycles, Carbanions

The history of β–lactam (2–azetidinone), arguably one of the most acclaimed heterocycles studied over last century, tells a tale rich in curiosity, serendipity, and gravity spanning the field of chemistry, biology, and medicine[1-7]. As such, methods for their construction with stereocontrol have been and still are highly important to continued development of the area[8]. The potential use of some β-lactams as therapeutic agent for lowering plasma cholesterol levels[9,10], as inhibitors of enzymes such as thrombin[11], HLE (Human leukocyte elastase)[12] and the protease, responsible for capsid assembly and viral maturation of HCMV (Human cyctomegalovirus)[13] has been reported as well. The reaction most widely used for construction of azetidinone ring is the (2+2) ketene – imine cycloaddition known as Staudinger synthesis[14]. Several variants of this reaction have been described, in which the ketene is formed in situ from precursors.

Over the years, structural diversity of β–lactam antibiotics has led to the development of various synthetic approaches with complete control of stereochemistry[15] at C-3 and C-4 of β–lactams. In particular, the control of the facial selectivity, in both the *cis* and *trans* series, has been solved in an efficient and elegant manner. However, regardless of the method used, the control of the *cis* – *trans* stereochemistry still relies on the intrinsic selectivity of the synthetic procedure used to prepare the 2-azetidinone ring. For example, with a few exceptions, the classical ketene-imine reaction leads mainly to 4-membered ring with *cis* stereochemistry. As most important biologically active β-lactams have a *trans*-2-azetidinone ring in their structure, the synthetic planning to obtain these compounds often has to include an epimerization step. Isomerization in presence of base by a deprotonation – reprotonation sequence at the C-3 position is the most frequently employed technique[16]. Other methods that have been described to achieve the ring isomerization are restricted to 2-azetidinones that have specific structural features. Although isomerization is a well-studied reaction but not all types of β-lactam substrates have been tested for this. In this communication, we report the first synthesis of *cis*-3-phenylthio & *cis*-3-chloro-β-lactams using the epimerization reaction and behavior of *cis*-3-hydroxy, *cis*-3-acetoxy towards epimerization conditions.

The literature survey shows a number of studies on the use of epimerization to invert stereochemistry. But majority of the work reported so far use this reaction to convert a sterically hindered *cis* isomer to *trans* one[17,18]. There are very few which also studied the conversion of sterically stable *trans* to *cis*[19]. Considering the importance of control of stereochemistry along with β-lactam modification, we decided to investigate the epimerization reaction further for other β-lactam substrates which have not been studied so far.

Experimental Details

Most of the chemicals such as aldehyde, amine, triethylamine, phosphorous oxychloride etc. were

commercially available (Merck, Himedia). All solvents used were of LR grade. Where necessary, the solvents were distilled & dried before use, when this seemed necessary by standard methods. Compounds **3(a-j)** were synthesized according to previous report.[1] All the reactions were conducted in oven dried round bottom flask (50 – 250 mL) & condenser. thin layer chromatography (TLC) was performed using TLC grade silica gel 'G' (Acme Synthetic Chemicals). The spots were made visible by exposing plates to iodine vapors or using the UV Chamber (250 nm). Column chromatography was performed with silica gel (Acme Synthetic Chemicals, 60-120 mesh) & eluted with ethylacetate: hexane mixtures. ^{1}H & ^{13}C spectra were recorded at 500 MHz & 100 MHz, respectively in $CDCl_3$ solution using BRUKER AVANCE II NMR spectrometer. Chemical shift is given in ppm relative to trimethylsilane (TMS) as an internal standard $\delta = 0$ ppm for $^{1}H°NMR$ & $\delta = 77.0$ ppm for $^{13}C°NMR$. The coupling constant *(J)* values are given in Hz. Resonance patterns are reported with the notation s (singlet), d (doublet), m (multiplet). IR spectra were taken on an FTIR spectrophotometer & are reported in cm^{-1}. High resolution mass spectra (HRMS) were measured on Agilent 2795 ESI/TOF MS Instrument.

General procedure for epimerization

Epimerization reaction was done by using 3-phenylthio / 3-chloro-β-lactams **3 (a-j).** Dissolved K_2CO_3(0.2 mmol) in minimum amount of H_2O in round bottom flask. To this well stirred solution of K_2CO_3, β-lactam **3a** (0.1 mmol) dissolved in CH_3CN (8 mL) was added. The reaction was monitored by TLC (10% EtOAc/hexane). After 7 h refluxing, the reaction was worked up. CH_2Cl_2 (3 x 15 mL) was added to the reaction mixture, organic layer was washed with brine. The Organic layer was dried over anhydrous Na_2SO_4. The crude reaction mixture was purified by column chromatography using 10% EtOAc/ hexane. The mixture was separated by column chromatography & isomers of β-lactam were crystallized from DCM/hexane.

Characterization data

***cis*-1-Phenyl-3-phenylthio-4-phenylazetidin-2-one, 4a:** White solid; Yield: 27%; m. p. 135-140°C; R_f = 0.41; IR (C=O; cm^{-1}): 1635. $^{1}H°NMR$ (500 MHz, $CDCl_3$, δ, ppm): 7.37-7.07 (m, Ar, 15H), 5.39 (d, *J* = 5.5 Hz, 1H), 4.93 (d, *J*= 5.5 Hz, 1H).$^{13}C°NMR$ (100 MHz, $CDCl_3$) δ: 164.0, 137.2, 133.9, 133.5, 131.2, 129.2, 129.1, 129.0, 128.9, 128.5, 127.6, 127.2, 124.3, 117.3, 117.2, 77.2, 77.0, 76.7, 59.9, 58.8.

***cis*-1-(4'-Methoxyphenyl)-3-phenylthio-4-phenylazetidin-2-one, 4b:** White solid; Yield: 20%; m. p. 138-142°C; R_f = 0.45; IR (C=O; cm^{-1}): 1634. $^{1}H°NMR$ (500 MHz, $CDCl_3$, δ, ppm):7.36-6.78 (m, Ar, 14H), 5.35 (d, *J* = 5.5 Hz, 1H), 4.92 (d, *J* = 5.5 Hz, 1H), 3.74 (s, $-OCH_3$, 3H).$^{13}C°NMR$ (100 MHz, $CDCl_3$) δ: 131.13, 128.90, 128.5, 127.7, 127.1, 118.6, 114.3, 77.2, 77.0, 76.7, 60.0, 58.8, 55.4. HRMS (ESI): Calculated for $C_{22}H_{19}NO_2S^+$ $[M+1]^+$ 362.113, found 362.1182.

***cis*-1-(4'-Bromophenyl)-3-phenylthio-4-phenylazetidin-2-one, 4c:** White solid; Yield: 28%; m. p. 115-120°C; R_f = 0.3; IR (C=O;cm^{-1}): 1635.$^{1}H°NMR$ (500 MHz, $CDCl_3$, δ, ppm): 7.52-7.04 (m, Ar, 14H), 5.37 (d, *J* = 5.6 Hz, 1H), 4.94 (d, *J* = 5.6 Hz, 1H).$^{13}C°NMR$ (100 MHz, $CDCl_3$) δ: 132.5, 132.1, 131.2, 128.9, 128.6, 127.6, 127.3, 118.9, 77.2, 77.0, 76.7, 60.0, 59.1, 29.7, 1.02.

***cis*-1-(4'-Methoxyphenyl)-3-phenylthio-4-(4'-methoxyphenyl) azetidin-2-one (4d)**

White solid; Yield: 29%; m. p. 117-121°C; R_f = 0.41; IR (C=O; cm^{-1}) 1636.$^{1}H°NMR$ (500 MHz, $CDCl_3$, δ, ppm): 7.28-6.78 (m, Ar, 13H), 5.32 (d, *J* = 5.4 Hz, 1H), 4.89 (d, *J* = 5.4 Hz, 1H), 3.81 (s, $-OCH_3$, 3H), 3.74 (s, $-OCH_3$, 3H).$^{13}C°NMR$ (100 MHz, $CDCl_3$) δ: 130.9, 128.9, 128.8, 127.0, 125.5, 118.7, 114.3, 113.9, 77.2, 77.0, 76.7, 59.6, 58.9, 55.2.

***cis*-1-(4'-Chlorophenyl)-3-phenylthio-4-phenylazetidin-2-one, 4e:** White solid; Yield: 19%; m. p. 117-122°C; R_f = 0.35; IR(C=O; cm^{-1}) 1635.$^{1}H°NMR$ (500 MHz, $CDCl_3$, δ, ppm): 7.31-6.95 (m, Ar, 14H), 5.30 (d, *J* = 5.6 Hz, 1H), 4.79 (d, *J* = 5.6 Hz, 1H). $^{13}C°NMR$ (100 MHz, $CDCl_3$) δ: 137.5, 137.2, 131.9, 129.6, 129.1, 128.5, 127.7, 124.3, 117.3, 114.9, 77.3, 77.0, 76.7, 60.0.

***cis*-1-Phenyl-3-chloro-4-phenylazetidin-2-one, 4f:** White solid; Yield: 31%; m. p. 156-162°C; R_f = 0.25; IR(C=O; cm^{-1}) 1636.$^{1}H°NMR$ (500 MHz, $CDCl_3$, δ, ppm): 7.41-7.10 (m, Ar, 10H), 5.41 (d, *J* = 5.3 Hz, 1H), 5.27 (d, *J* = 5.3 Hz,

1H).^{13}C°NMR (100 MHz, $CDCl_3$) δ: 136.7, 132.6, 129.3, 129.2, 128.7, 127.8, 124.9, 117.5, 77.2, 77.0, 76.7, 60.8, 60.4.

***cis*-1-(4'-Methoxyphenyl)-3-chloro-4-phenylazetidin-2-one, 4g:** White solid; Yield: 32%; m. p. 135-14°C; R_f = 0.21; IR (C=O; cm^{-1}) 1635.^{1}H°NMR (500 MHz, $CDCl_3$, δ, ppm): 7.46-6.79 (m, Ar, 9H), 5.37 (d, *J* = 5.2 Hz, 1H), 5.26 (d, *J* = 5.2 Hz, 1H), 3.75 (s, -OCH_3, 3H).^{13}C°NMR (100 MHz, $CDCl_3$) δ: 160.6, 156.7, 132.7, 130.2, 129.1, 128.6, 127.8, 118.8, 114.4, 77.2, 77.0, 76.7, 60.8, 60.5, 55.4. HRMS (ESI): Calculated for $C_{16}H_{14}NO_2Cl^+$ $[M+1]^+$ 288.0708, found 288.0770.

***cis*-1-(4'-Bromophenyl)-3-chloro-4-phenylazetidin-2-one, 4h:** White solid; Yield: 21%; m. p. 158-162°C; R_f = 0.21; IR(C=O; cm^{-1}) 1636.^{1}H°NMR (500 MHz, $CDCl_3$, δ, ppm): 7.42-7.19 (m, Ar, 9H), 5.39 (d, *J* = 5.3 Hz, 1H), 5.28 (d, *J* = 5.3 Hz, 1H) ppm; ^{13}C°NMR (100 MHz, $CDCl_3$) δ: 136.5,132.3, 129.3, 128.8, 127.7, 119.0, 77.2, 77.0, 76.7.

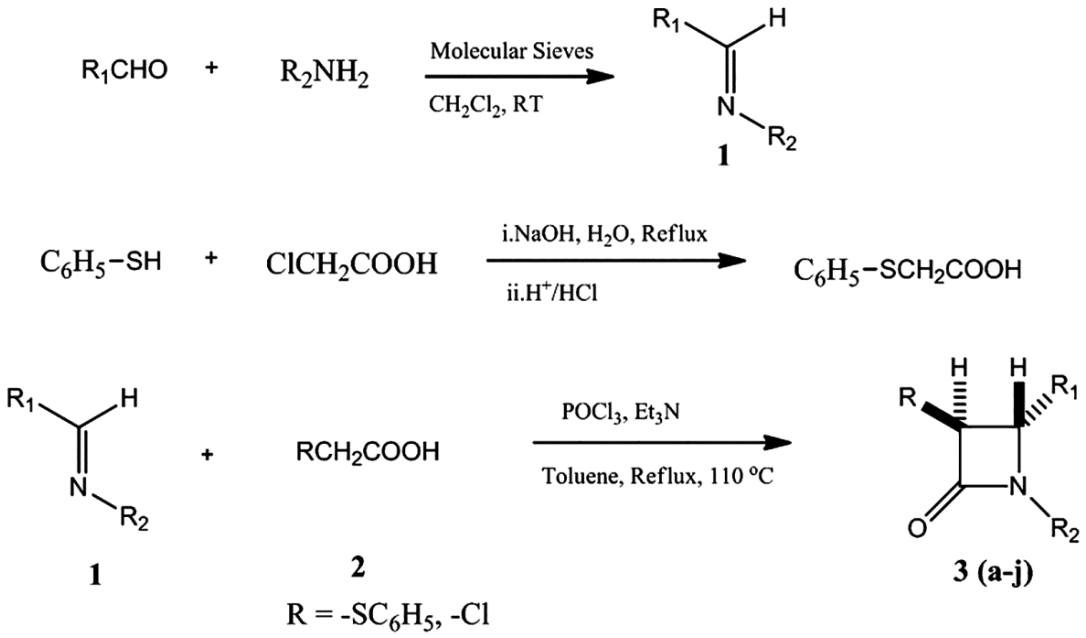
***cis*-1-(4'-Methoxyphenyl)-3-chloro-4-(4'-methoxyphenyl) azetidin-2-one, 4i:** White solid; Yield: 37%; m. p. 138-142°C; R_f = 0.28; IR(C=O; cm^{-1}) 1635.^{1}H°NMR (500 MHz, $CDCl_3$, δ, ppm): 7.27-6.79 (m, Ar, 8H), 5.32 (d, *J* = 5.2 Hz, 1H), 5.23 (d, *J* = 5.2 Hz, 1H), 3.81 (s, -OCH_3, 3H), 3.75 (s, -OCH_3, 3H).^{13}CNMR (100 MHz, $CDCl_3$) δ: 160.7, 160.3, 129.1, 124.5, 118.8, 114.4, 114.1, 77.2, 77.0, 76.7, 60.8, 60.6, 55.4, 55.2.

***cis*-1-(4'-Chlorophenyl)-3-chloro-4-phenylazetidin-2-one, 4j:** White solid; Yield: 28%; m. p. 158-162°C; R_f = 0.20; IR(C=O; cm^{-1}) 1638.^{1}H°NMR (500 MHz, $CDCl_3$, δ, ppm): 7.27-6.79 (m, Ar, 9H), 5.32 (d, *J* = 5.2 Hz, 1H), 5.23 (d, *J* = 5.2 Hz, 1H).^{13}C°NMR (100 MHz, $CDCl_3$) δ: 160.7, 160.3, 129.1, 124.5, 118.8, 114.4, 114.1, 77.2, 77.0, 76.7, 60.8, 60.6, 55.4, 55.2.

Results and Discussion

The cycloaddition reaction of phenylthioethanoic acid / chloroethanoic acid & Schiff base in the presence of $POCl_3$ & NEt_3 is known to give stereospecifically *trans*-3-phenylthio/chloro-β-lactams (Scheme 1, Table 1)[20]. Although, with some of the specific electron withdrawing groups like $–NO_2$ at carbon of Schiff base, some research work has been reported showing synthesis of *cis* β-lactams as well, but otherwise as such this reaction does not give even trace of *cis* isomer[21]. So, these compounds cannot be synthesized by this method.

As our studies have proved that *trans*-3-phenylthio-β-lactams serve as important synthons for C-3 functionalized-β-lactams, so, the *cis* isomer of these compounds can lead to the synthesis of other biologically important isomers[20]. Also, the *cis* isomer of biologically active chloro-β-lactam[22] can be



Scheme 1 — Synthesis of *trans*-3-phenylthio-β-lactams &*trans*-3-chloro-β-lactams

important for activity studies. This curiosity led us to study epimerization reaction for synthesis of *cis* β-lactams. The starting substrates were synthesized according to Scheme 1.

The initial studies were done using *trans*-3-phenylthio-β-lactams. In our test reaction, substrate **3a** was treated with K_2CO_3 in acetone at room temperature. The progress of reaction was monitored with TLC, which showed the formation of one new spot having R_f value (0.41) lower than that of substrate. However, even after overnight stirring, the spot did not grow further. So, it was put to refluxing. The lower spot kept growing till 7 h, but after that even 24 h reflux didn't show any further change in TLC & hence the reaction was worked up. The new spot after purification was found to be the desired *cis*-3-phenylthio-β-lactam on the basis of analysis by ^{1}H°NMR which showed a change in *J* value of C-3 & C-4 protons from 2.3Hz to 5.7 Hz. The *trans* - *cis* ratio in the product was found to be 60:14% indicating 14% conversion to *cis* product. The results indicated the feasibility of this isomer conversion. So, the reaction was studied further for optimization. The investigations were done by using bases like NEt_3, K_2CO_3, Na_2CO_3 & DBN. Among these, K_2CO_3 showed the maximum conversion of *trans* to *cis* isomer. After selecting the base, the optimizations for solvent and reaction temperature were done. The reaction was found to be highly efficient in CH_3CN at refluxing. The attempts to promote epimerization beyond 35% could not be achieved. (Scheme 2, Table 2).

After the reaction optimization, studies were done to check the substrate suitability for this conversion. The reaction showed promising results for a number of substrates **3 (a-e)** (Table 3). Encouraged by these results, the studies were extended further to other *trans* β-lactams. The *trans*-3-chloro-β-lactams showed same reactivity pattern for this reaction as observed for *trans*-3-phenylthio-β-lactams. The

Table 1— Synthesis of *trans*-β-lactams

Entry	R	R_1	R_2	Yield: (%) **(3)**
1	C_6H_5S	C_6H_5	C_6H_5	**3a** (60)
2	C_6H_5S	C_6H_5	$C_6H_4.OCH_3(4)$	**3b** (62)
3	C_6H_5S	C_6H_5	$C_6H_4.Br(4)$	**3c** (54)
4	C_6H_5S	$C_6H_4.OCH_3(4)$	$C_6H_4.OCH_3(4)$	**3d** (70)
5	C_6H_5S	C_6H_5	$C_6H_4.Cl(4)$	**3e** (52)
6	Cl	C_6H_5	C_6H_5	**3f** (51)
7	Cl	C_6H_5	$C_6H_4.OCH_3(4)$	**3g** (71)
8	Cl	C_6H_5	$C_6H_4.Br(4)$	**3h** (53)
9	Cl	$C_6H_4.OCH_3(4)$	$C_6H_4.OCH_3(4)$	**3i** (74)
10	Cl	C_6H_5	$C_6H_4.Cl(4)$	**3j** (50)

Reagents & conditions: 1 (9.4 mmol), 2 (14.5 mmol), NEt_3 (37 mmol), $POCl_3$ (16 mmol), toluene (70 mL), refluxing (110°C, 5 h)

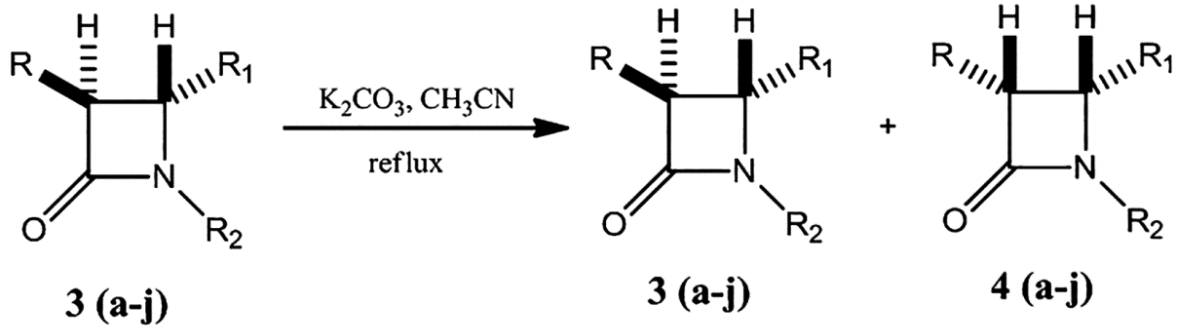
Table 2 — Optimization of solvent

Entry	Substrate	Solvent	Yield: (*trans*-*cis*%)
1	**3a**	THF	70:6
2	**3a**	Acetone	60:14
3	**3a**	**CH_3CN**	53:21
4	**3a**	Ethanol	-

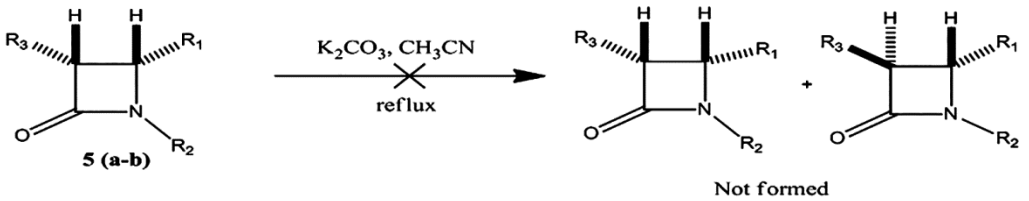
Base & conditions: 3a (0.1 mmol), K_2CO_3 (0.2 mmol), refluxing (56°C, 7 h)

Table 3 — Substrate scope of epimerization reaction

Entry	Substrate	**3** (Yield:,%)	**4** (Yield:,%)
1	**3a**	**3a** (53)	**4a** (21)
2	**3b**	**3b** (57)	**4b** (16)
3	**3c**	**3c** (51)	**4c** (21)
4	**3d**	**3d** (90)	**4d** (20)
5	**3e**	**3e** (50)	**4e** (19)
6	**3f**	**3f** (54)	**4f** (25)
7	**3g**	**3g** (52)	**4g** (28)
8	**3h**	**3h** (27)	**4h** (15)
9	**3i**	**3i** (77)	**4i** (35)
10	**3j**	**3j** (50)	**4j** (18)



Scheme 2 — Epimerization of 3-phenylthio & 3-chloro-β-lactams



5a, R_3 = OAc
R_1 / R_2 = C_6H_5 / $C_6H_4.OCH_3(4)$, C_6H_5 / C_6H_5, $C_6H_4.OCH_3(4)$ / $C_6H_4.OCH_3(4)$
5b, R_3 = OH
R_1 / R_2 = C_6H_5 / $C_6H_4.OCH_3(4)$, C_6H_5 / C_6H_5, $C_6H_4.OCH_3(4)$ / $C_6H_4.OCH_3(4)$

Scheme 3 — Epimerization studies of 3-Acetoxy / 3- Hydroxy-β-lactam

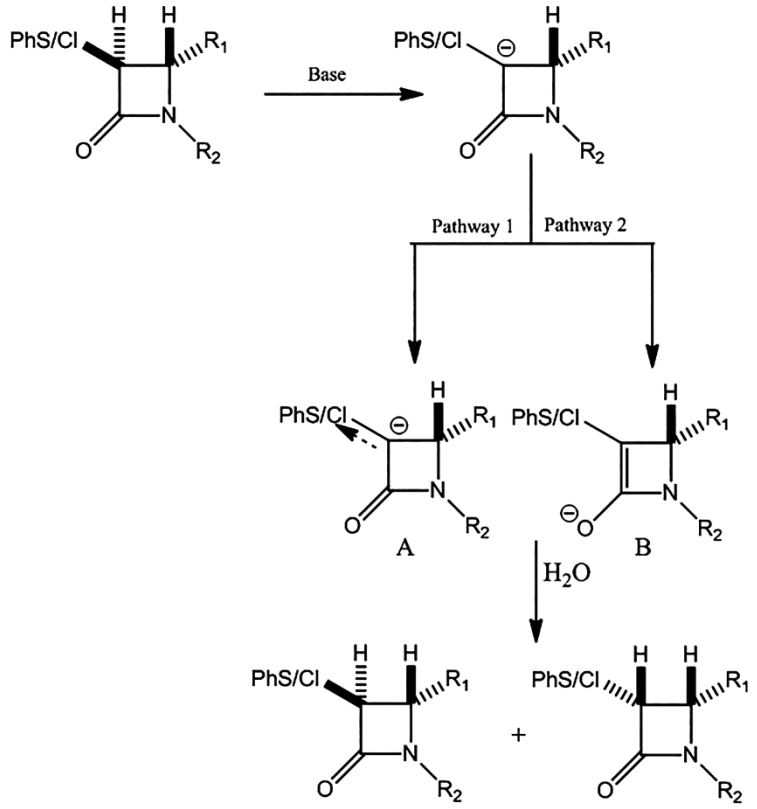


Fig. 1 — Plausible pathway for base catalyzed epimerization of *trans*-β-lactams

already optimized conditions (Table 2) were used to convert substrate **3(f-j)** to mixture of **3** & **4 (f-j)**. The outcomes are summarized in Scheme 2 and Table 3.

Further, some *cis*-β-lactams which have not been studied for epimerization behavior so far, were selected. In this *cis*-3-hydroxy / *cis*-3-acetoxy-β-lactams were subjected to epimerization conditions. As done with substrates **3(a-j)**, similar reaction conditions were given to compounds **5a** & **5b**. However, surprisingly none of these was found to be reactive under these conditions. The reactions were carried with substrates **5a** & **5b** having varying substituents at C-4 & N-1. All these gave negative results, so unreacted material was recovered back, thus indicating unsuitability of these substrates towards this reaction (Scheme 3).

These results however, proved helpful in emphasizing the importance of C-3 substituent toward stereochemistry inversion. Based on these outcomes, the plausible mechanism shown in Fig. 1 is proposed. The reaction can either follow the path **1** or **2**. The

first step is generation of carbanion by base which can be stabilized either by the substituent attached at C-3 (Intermediate A-stabilized by inductive effect) or by carbonyl group (Intermediate B - stabilized by resonance effect). Now if pathway **2** is followed, then all the substrates would have given the epimerized product. However, if pathway **1** is followed, then only those substrates having C-3 stabilizing substituent for carbanion will be reactive. This exactly matches our experimental findings. Out of acetoxy, hydroxyl, chloro & phenylthio at C-3, only chloro & phenylthio could stabilize carbanion inductively resulting in formation of equilibrium, which upon reprotonation by hydrolysis give two isomers. However, due to spatial resistance of large groups, the sterically more stable *trans* isomer is still formed more predominantly. Thus, the possibility of pathway **2** is completely ruled out.

Conclusion

In conclusion, we can say that *trans*-3-chloro & *trans*-3-phenylthio-β-lactams have been proved to be active substrate for epimerization thereby giving the *cis* isomer of these compounds which as such cannot be synthesized by usual cycloaddition reaction. The reaction although goes up to 35% conversion only but is efficient in Yield:ing the *cis* isomer. In contrast to this, *cis*-3-hydroxy & *cis*-3-acetoxy-β-lactams are completely unreactive under these conditions.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/58776.

Acknowledgement

The authors thank UIET, Panjab University, Chandigarh for the research facilities.

References

1 Pitts C R & Lectka T, *Chem Rev*, 114 (2014) 7930.
2 Wong G, Brinkman A, Benefield R J, Carlier M, De Waele J J, Helali N E1, Frey O, Harbarth S, Huttner A, McWhinney B, Misset B, Pea F, Preisenberger J, Roberts M S, Robertson T A, Roehr A, Sime F B, Taccone F S, Ungerer J P J, Lipman J & Roberts J A *J Antimicrob Chemother*, 69 (2014) 1416.
3 Tang S S, Apisarnthanarak A & Hsu L Y, *Adv Drug Deliv Rev*,78 (2014) 3.
4 Huttner A, Harbarth S, Hope W W, Lipman J & Roberts J A, *J Antimicrob Chemother*, 70 (2015) 3178.
5 Gudiol C, Royo-Cebrecos C, Tebe C, Abdala E, Akova M, Alvarez R, Maestro-dela Calle G, Cano A, Cervera C, Clemente W T, Martin-Davila P, Freifeld A, Gomez L, Gottlieb T, Gurgui M, Herrera F, Manzur A, Maschmeyer G, Meije Y, Montejo M, Peghin M, Rodriguez-Bano J, Ruiz-Camps I, Sukiennik T C, Carratala J & Group B S, *BMJ Open,* 7 (2017) e013268.
6 Cohen K A, E1-Hay T, Wyres K L, Weissbrod O, Munsamy V, Yanover C, Aharonov R, Shaham O, Conway T C, Goldschmidt Y, Bishai W R & Pym A S, *EBioMedicine*, 9 (2016) 170.
7 Grupper M, Kuti J L & Nicolau D P, *Clin Microbiol Rev*, 29 (2016) 759.
8 (a) Ojima I & Delaloge F, *Chem Soc Rev*, 26 (1997) 377; (b) Fujieda H, Kanai M, Kamabara T, Iida A & Tomioka K A*, J Am Chem Soc*, 119 (1997) 2060; (c) Miura M, Enna M, Okuro K & Nomura M, *J Org Chem*, 60 (1995) 4999.
9 Clader J W, Burnett D A, Caplen M A, Domalski M S, Dugar S, Vaccaro W, Sher R, Browne M E, Zhao H, Burrier R E, Salisbury B & Davis H R, *J Med Chem*, 39 (1996) 3684.
10 Burnett D A, Caplen M A, Davis H R, Burrier R E & Clader J W, *J Med Chem*, 37 (1994) 1733.
11 Annunziata R, Benaglia M, Cinquini M, Cozzi F, Maggioni F & Pugliesi A, *J Org Chem*, 68 (2003) 2952.
12 Konaklieva M I, *Med Chem Rev*, 1 (2002) 133.
13 Deziel R & Malenfant E, *Bioorg Med Chem Lett*, 8 (1998) 1437.
14 Alcaide B, Almendros P & Aragoncillo C, *Chem Rev*, 107 (2007) 4437.
15 Southgate R, *Contemp Org Synth*, 1 (1994) 417.
16 Alcazar R, Ramirez P, Vicente R, Mancheno M J, Sierra M A & Gallego M G, *Heterocycles*, 55 (2001) 511.
17 Bose A K, Narayana C S & Manhas M S , *J Chem Soc D, Chem Commun*, (1970) 975.
18 Kawabatta T, Itoh K & Hiyama T, *Tetrahedron Lett*, 30 (1989) 4837.
19 Firestone R A, Maciejewioz N S, Ratcliffe R W & Christensen B G , *J Org Chem*, 39 (1974) 437.
20 (a) Pandey S, Thakur A, Reshma, Bari S S & Thapar R, *ChemistrySelect*, 4 (2019) 13912; (b) Pandey S, Thakur A, Reshma, Bari S S & Thapar R, *J Chem Sci*, 132 (2020) 1; (c) Reshma, Thapar R, Hundal G, Bhalla R & Bari S S, *J Chem Sci*, 127 (2015) 1957; (d) Thapar R, Reshma & Bari S S, *J Chem Sci*, 128 (2016) 1745.
21 (a) Jiao L, Liang Y & Xu J, *J Am Chem Soc*, 128 (2006) 6060; (b) Nelson D A, *J Org Chem*, 37 (1972) 1447 .
22 Chimento A, Sala M, Gomez- Monterrey I M, Musella S, Bertamino A, Caruso A, Sinicropi M S, Sirianni R, Puoci F, Parisi O I, Campana C, Martire E, Novellino E, Saturnino C, Campiglia P & Pezzi V, *Bioorg Med Chem Lett*, 23 (2013) 6401.