AN UNUSUAL LEWIS ACID PROMOTED ISOMERIZATION OF
\textit{trans}-3-HALO-3-PHENYLTHIO-\(\beta\)-LACTAMS

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Abstract - A method for C-3 epimerization of 3-halo-3-phenylthio-\(\beta\)-lactams, mediated by Lewis acids, is described. TiCl\(_4\) promotes isomerization of \textit{trans}-3-chloro-3-phenylthioazetidin-2-ones (2) to \textit{cis}-3-chloro-3-phenylthioazetidin-2-ones (3). TiBr\(_4\) promotes isomerization as well as substitution of chlorine with bromine affording isomeric \textit{cis}- and \textit{trans}-3-bromo-3-phenylthioazetidin-2-ones (5) and (6) respectively, while TiI\(_4\) is ineffective.

A variety of Lewis acid promoted reactions in organic chemistry are becoming valuable synthetic processes. Moreover, the processes which convert readily available chemical entities to their less readily accessible isomers are of a synthetic value besides being useful in mechanistic studies in organic synthesis.\(^1\) Over the years, structural diversity of \(\beta\)-lactam antibiotics has led to the development of various synthetic approaches with complete control of stereochemistry\(^2\) at C-3 and C-4 of \(\beta\)-lactams. However, with the discovery of new biologically active monocyclic \(\beta\)-lactams, the minimum requirement for biological activity of these heterocycles has been reduced to just suitably configured and substituted monocyclic \(\beta\)-lactam ring.\(^3\)-\(^6\)

In the most often employed methods\(^7\)-\(^{11}\) for \(\beta\)-lactam synthesis, the formation of kinetically controlled \textit{cis}-\(\beta\)-lactam\(^12\) is highly favoured. Leaving aside thermally induced isomerization\(^13\), all the reported procedures for isomerization\(^14\) of \textit{cis}-\(\beta\)-lactams to more stable \textit{trans}-\(\beta\)-lactams require the presence of an acid or base sensitive functionality at the site of epimerization.
In continuation to our studies\textsuperscript{15} with cationic β-lactam equivalents (Figure 1), we wish to report here a new isomerization methodology for 3-halo-3-phenylthio-β-lactams. It is now possible to isomerize azetidin-2-ones of type (2) at C-3 by a Lewis acid such as TiCl\textsubscript{4} or SnCl\textsubscript{4}. Thus, trans-3-chloro-3-phenylthioazetidin-2-ones (2) on treatment with TiCl\textsubscript{4} were transformed to cis-3-chloro-3-phenylthioazetidin-2-ones (3) (Scheme 1). Also, cis-3-bromo- and trans-3-bromo-3-phenylthioazetidin-2-ones (5) and (6) respectively, were obtained from 2 by \textit{in situ} substitution of C-3 chlorine with bromine using TiBr\textsubscript{4}. This may be helpful in devising new methodology for the synthesis of therapeutically important trisubstituted β-lactams. Besides it may find application in halogen exchange as well as halogen labelling studies using labelled titanium tetrahalide. To the best of our knowledge no such Lewis acid promoted isomerization of azetidin-2-ones has been reported so far.

We have reported\textsuperscript{16} earlier that 3α-chloro-3-phenylthio-β-lactam substrates of type (2) undergo a substitution at C-3 with active aromatic nucleophiles in the presence of a Lewis acid presumably \textit{via in situ} formation of cationic β-lactam synthons. Thus, trans-3-chloro-3-phenylthioazetidin-2-one (2a) (mp 166-168°C) with a confirmed stereochemistry\textsuperscript{17} at C-3, easily accessible from trans-3-phenylthioazetidin-2-one (1a), by stereospecific SO\textsubscript{2}Cl\textsubscript{2} chlorination underwent a facile alkylation with a number of active aromatic nucleophiles such as anisole in the presence of Lewis acids such as SnCl\textsubscript{4} or TiCl\textsubscript{4} in CH\textsubscript{2}Cl\textsubscript{2} at 0°C under nitrogen atmosphere (Scheme 1). This reaction, in effect, is equivalent to Friedel-Crafts reaction with a very active halide. Surprisingly, this reaction failed with benzene or toluene even under varied reaction conditions, to provide any anticipated substituted product. However, two other products could be isolated from this reaction when carried out in the presence of TiCl\textsubscript{4}. The minor one (7 % yield) was identified as 3,3-bis(phenylthio)-1-(4′-methoxyphenyl)-4-phenylazetidin-2-one (4a) through its spectroscopic data. The major component (78 % yield) with R\textsubscript{f} very close to the starting material and having lower mp (144-146°C) than the substrate was clearly indicated to be a different product formed during the Lewis acid treatment of 2a.
The $^1$H-NMR spectral analysis of the major product showed C-4 proton resonance upfield at $\delta$ 5.18 as compared to substrate (2a), which exhibits C-4 proton resonance at $\delta$ 5.38. There were also small changes in the positions of the remaining proton resonances in the spectrum, compared to the resonances of substrate (2a). The $^{13}$C-NMR spectrum also showed a similar upward shift in resonance of C-4 carbon appearing at $\delta$ 68.83 in comparison to substrate (2a) showing it at $\delta$ 71.88. However, C-3 carbon resonated at $\delta$ 80.1 for both isomers. The IR spectrum confirmed the presence of $\beta$-lactam carbonyl (1754 cm$^{-1}$, >C=O) in it.

Keeping in view all the spectroscopic information given above, it seemed that an epimerization at C-3 of $\beta$-lactam had taken place resulting in isomerization of $\beta$-lactam (2a). Intrigued by this transformation, this reaction was conducted in the presence of a Lewis acid alone to evaluate the feasibility of this transformation. The reaction indeed, proceeded equally well in the absence of anisole giving the same product profile. To the best of our knowledge, this is the first example of epimerization of $\beta$-lactams at C-3 effectively and efficiently by a Lewis acid. All the available spectral information was suggestive of only structure (3a) for this product, which could be tentatively assigned to it. However, the final unequivocal
confirmation of this structure was achieved through X-Ray crystal analysis\textsuperscript{18} as shown in ORTEP diagram (Figure 2).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure2.png}
\caption{ORTEP representation of 3a}
\end{figure}

Since this kind of isomerization is unprecedented, the feasibility and generality of this reaction in terms of various substrates and Lewis acids was evaluated. The reaction was carried out successfully with a number of substrates (2a-f) employing TiCl\textsubscript{4} or SnCl\textsubscript{4} and the results are summarized in Table 1.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Entry & \textit{trans}-3-chloro & Temp. (°C) & Lewis Acid & \textit{cis}-3-chloro (\%) & 3,3-bis(phenylthio) (\%) \\
& \textit{2} & & & 3 & 4 \\
\hline
1 & 2a & -78 & SnCl\textsubscript{4} & 55 & 15 \\
2 & 2a & 0 & TiCl\textsubscript{4} & 78 & 7 \\
3 & 2b & -78 & TiCl\textsubscript{4} & 58 & 17 \\
4 & 2c & 0 & SnCl\textsubscript{4} & 72 & 6 \\
5 & 2c & 0 & TiCl\textsubscript{4} & 67 & 0 \\
6 & 2d & 0 & TiCl\textsubscript{4} & 62 & 0 \\
7 & 2e & 0 & TiCl\textsubscript{4} & 81 & 0 \\
8 & 2f & 0 & TiCl\textsubscript{4} & 82 & 5 \\
\hline
\end{tabular}
\caption{Reaction of \textit{trans}-3-chloro-β-lactams (2a-f) with Lewis acids in CH\textsubscript{2}Cl\textsubscript{2}}
\end{table}

a. All new compounds have been characterized by IR, NMR spectral and CHN analysis.
b. Isolated yields after purification by chromatography on silica gel.
At this stage, it was considered important to investigate the source of halogen in the isomerized product, which in principle can either come from the starting substrate itself or from the Lewis acid during the course of the reaction. This information is critical in understanding the possible mechanism of this transformation as it can suggest the role of the Lewis acid in assisting the epimerization process. This aspect can easily be probed unequivocally, if the halogen in the substrate is different from that in the Lewis acid. Thus, in the reaction of trans-3-chloro-3-phenylthioazetidin-2-one (2c) with TiBr₄ at 0°C, both epimerization and substitution of chlorine with bromine at C-3 occurred producing cis-3-bromo-3-phenylthioazetidin-2-one (5c) as a major product. Here it is interesting to note that a mere substitution product trans-3-bromo-3-phenylthioazetidin-2-one (6c) was also formed as a minor product without undergoing epimerization. However, surprisingly no 3,3-bis(phenylthio)azetidin-2-one (4c) was formed in this reaction (Scheme 1). The structures of cis-3-bromo- and trans-3-bromoazetidin-2-ones, (5c) and (6c) respectively, were deduced from their spectroscopic data. The cis-isomer (5c) exhibited C-4 proton resonance up field at δ 5.20 compared to C-4 proton resonance at δ 5.62 of trans-isomer (6c). The ¹³C-NMR spectrum of cis-isomer showed upward shift in resonances of both C-3 and C-4 carbons appearing at δ 67.3 and 71.9 in comparison to substrate (2a) showing it at δ 80.14 and 69.12. However, the final confirmation of epimerization with substitution at C-3 was obtained from X-Ray crystal analysis¹⁹ of cis-isomer (5c).

The feasibility of this conversion was studied by reacting a number of substrates (2a-e) with TiBr₄ and the results are summarized in Table 2. It is quite clear from the results that trans-3-chloro-3-phenylthio-β-lactams can be effectively converted to their cis-3-bromo analogs by epimerization accompanied by simultaneous substitution of chlorine at C-3 with bromine. In all cases, there is also the formation of a minor substitution product, the trans-isomer that formed without undergoing epimerization. The ratio of the two bromo isomeric products was ascertained from ¹H-NMR. It seems that low temperature (-78°C) favours the substitution with retention of stereochemistry at C-3. Interestingly, with relatively bulky TiI₄ no reaction occurred.
Table 2: Reaction of \textit{trans}-3-chloro-3-phenylthioazetidin-2-ones (2a-e) with TiBr$_4$

<table>
<thead>
<tr>
<th>Entry</th>
<th>\textit{trans}-3-chloro-substrate</th>
<th>Temp.(°C)</th>
<th>Lewis acid (equiv.)</th>
<th>Ratio of products$^{a,b}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td>cis-3-bromo isomer 5</td>
</tr>
<tr>
<td>1</td>
<td>2a</td>
<td>0</td>
<td>1.0</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>rt</td>
<td>1.0</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>-78</td>
<td>1.0</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>2b</td>
<td>0</td>
<td>1.0</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>2c</td>
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</tr>
<tr>
<td>7</td>
<td>2e</td>
<td>0</td>
<td>1.5</td>
<td>78</td>
</tr>
</tbody>
</table>

$^a$ All new compounds have been characterized by IR, NMR spectral and CHN analysis.
$^b$ Isolated yields reported in experimental after purification by chromatography.

Considering all the above noted observations, a transition state (7) in which C-3 halogen of azetidin-2-one coordinates to the central titanium atom, can be put forward. In addition, a sulfur atom in the SPh group could also coordinate to the central metal atom giving an octahedral or most likely a distorted octahedral (almost like a square bipyramidal) arrangement. In such a transitory arrangement (Figure 3), the S and X from the \(\beta\)-lactam ring may occupy the equatorial positions still maintaining the tetrahedral nature of C-3 carbon atom. Thus, two halogen atoms of Lewis acid marked P and Q being equatorial, either of the other two axial halogens becomes the preferred candidate for the exchange possibly \textit{via} \textit{S}_\text{N}2 type reaction giving epimerization at C-3. The two different halogen exchange processes \(A\) and \(B\) can result in products with opposite stereochemistry at C-3.

The formation of an intermediate (8) may be ruled out since the subsequent approach of the nucleophile to the C-3 carbon from the less hindered face (\(R^1 = H\)) would lead to the opposite selectivity contrary to the observed facts in this epimerization reaction. However, further studies are required to confirm the intermediacy of 7 or 8 in this reaction.
In summary, we have reported a Lewis acid catalyzed epimerization reaction. This is potentially useful for C-3 epimerization of trans-3-halo-3-phenylthio-β-lactams as well as for preparing trans- and cis-3-bromo-3-phenylthio-β-lactams. Further studies using alkylthio-β-lactams and chiral Lewis acids for asymmetric version of this isomerization are in progress in our laboratory.

**EXPERIMENTAL**

General experimental procedures for the starting β-lactams have previously been reported.\(^{20}\) \(^1\)H-NMR spectra were recorded in CDCl\(_3\) using BRUKER or JEOL 300 MHz NMR spectrometers. Chemical shifts are given in ppm relative to TMS as an internal standard (\(\delta = 0\) ppm) for \(^1\)H-NMR and CDCl\(_3\) (\(\delta = 77.0\) ppm) for \(^{13}\)C-NMR spectra. IR spectra were taken on a FTIR spectrophotometer and are reported in cm\(^{-1}\). All commercially available compounds / reagents were used without further purification. Dichloromethane distilled over P\(_2\)O\(_5\) was redistilled over CaH\(_2\) before use.

**General procedure for synthesis of trans-3-chloro-3-phenylthio-β-lactams:** trans-1-(4’-Methoxyphenyl)-3-chloro-3-phenylthio-4-phenylazetidin-2-one (2a): To a well stirred solution of trans-1-(4’-methoxyphenyl)-3-phenylthio-4-phenylazetidin-2-one (1a) (360 mg, 1 mmol) in dry CH\(_2\)Cl\(_2\) (5 mL) was added sulfuryl chloride (SO\(_2\)Cl\(_2\)) (130 mg, 1 mmol, 0.08 mL) under nitrogen atmosphere via a syringe. The contents were stirred for additional 30 min at rt. Progress of the reaction was monitored by TLC. After completion of the reaction, it was quenched with water, extracted with dichloromethane (3 x 10 mL), washed with 5% NaHCO\(_3\) solution, dried over anhydrous Na\(_2\)SO\(_4\) and filtered. The residue after solvent evaporation was purified by column chromatography using silica gel eluting with ethyl acetate-hexanes (10%). Solvent evaporation yielded trans-3-chloro-3-phenylthio-β-lactam (2a) (370 mg, 95%) which showed following spectral data: mp 166-168°C; IR(KBr): 1754 cm\(^{-1}\); \(^1\)H-NMR(CDCl\(_3\))\(\delta\): 3.75(s, 3H, OCH\(_3\)), 5.45(s, 1H), 6.8-7.55(m, 14H, aromatic protons); \(^{13}\)C-NMR (CDCl\(_3\))\(\delta\): 55.55, 71.97, 80.14, 114.59, 119.31, 126.62, 128.33, 128.71, 129.11, 129.40, 129.81, 131.76, 137.26.
trans-1-(4’-Methoxyphenyl)-3-chloro-3-phenylthio-4-(4’-methoxyphenyl)azetidin-2-one (2b):
mp 75-76°C; IR(KBr): 1764 cm\(^{-1}\); \(^1\)H-NMR(CDCl\(_3\)): 3.7(s, 3H, OCH\(_3\)), 3.8(s, 3H, OCH\(_3\)), 5.39(s, 1H), 6.81-7.5(m, 13H, aromatic protons); \(^1^3\)C-NMR(CDCl\(_3\)): 55.37, 55.48, 71.51, 80.32, 114.03, 114.48, 119.28, 123.42, 128.48, 128.7, 129.30, 129.63, 129.82, 135.35, 156.74, 160.28, 160.68; Anal. Calcd for C\(_{22}\)H\(_{18}\)NO\(_2\)ClS: C, 66.74; H, 4.59; N, 3.54; found: C, 66.63; H, 4.51; N, 3.51.

trans-1-Benzyl-3-chloro-3-phenylthio-4-phenylazetidin-2-one (2c):
mp 90-92°C; IR(KBr): 1776 cm\(^{-1}\); \(^1\)H-NMR(CDCl\(_3\)): 3.9(d, 1H, J = 15.1 Hz), 4.82(s,1H), 5.05(d, 1H, J = 15.0 Hz), 7.15-7.45(m, 15H, aromatic protons); \(^1^3\)C-NMR(CDCl\(_3\)): 44.68, 71.14, 80.90, 128.20, 128.38, 128.53, 128.65, 129.02, 129.18, 129.76, 131.81, 134.12, 135.14, 163.92; Anal. Calcd for C\(_{22}\)H\(_{18}\)NOClS: C, 69.55; H, 4.78; N, 3.68; found: C, 69.47; H, 4.71; N, 3.63.

trans-1-(4’-Methylphenyl)-3-chloro-3-phenylthio-4-(4’-chlorophenyl)azetidin-2-one (2d):
mp 135-137°C; IR(KBr): 1760 cm\(^{-1}\); \(^1\)H-NMR(CDCl\(_3\)): 2.29(s, 3H, CH\(_3\)), 5.35(s, 1H), 7.03-7.52(m, 13H, aromatic protons); \(^1^3\)C-NMR(CDCl\(_3\)): 21.16, 71.06, 79.93, 117.80, 128.40, 128.77, 129.36, 129.55, 129.89, 130.52, 134.13, 134.49, 135.55, 135.87, 159.7; Anal. Calcd for C\(_{22}\)H\(_{17}\)NOCl\(_2\): C, 63.77; H, 4.13; N, 3.38; found: C, 63.71; H, 4.74; N, 3.60.

trans-1-(4’-Bromophenyl)-3-chloro-3-phenylthio-4-phenylazetidin-2-one (2e):
mp 138-140°C; IR(CHCl\(_3\)): 1762.5 cm\(^{-1}\); \(^1\)H-NMR(CDCl\(_3\)): 5.44(s, 1H), 7.15-7.48(m, 14H, aromatic protons); \(^1^3\)C-NMR(CDCl\(_3\)): 72.0, 117.9, 119.51, 126.37, 127.53, 128.23, 128.81, 129.59, 129.89, 130.01, 131.20, 132.39, 135.62, 160.64; Anal. Calcd for C\(_{21}\)H\(_{15}\)NOBrClS: C, 56.71; H, 3.39; N, 3.15; found: C, 56.59; H, 3.27; N, 3.08.

trans-1-(4’-Methoxylphenyl)-3-chloro-3-phenylthio-4-(1’-methyl-2’-phenylvinyl)azetidin-2-one (2f):
mp 176-178°C; IR(KBr): 1764 cm\(^{-1}\); \(^1\)H-NMR(CDCl\(_3\)): 2.4(s, 3H, CH\(_3\)), 3.73(s, 3H, OCH\(_3\)), 5.34(s, 1H), 6.74-7.52(m, 15H, aromatic protons); \(^1^3\)C-NMR(CDCl\(_3\)): 21.58, 55.21, 71.68, 80.15, 114.53, 119.17, 128.33, 128.66, 128.94, 129.10, 129.37, 130.29, 135.41, 139.43, 156.74, 159.78; Anal. Calcd for C\(_{25}\)H\(_{22}\)NO\(_2\): C, 68.87; H, 5.08; N, 3.21; found: C, 68.74; H, 5.01; N, 3.14.
General procedure for epimerization of trans-3-chloro-3-phenylthio-β-lactams: cis-1-(4’-Methoxyphenyl)-3-chloro-3-phenylthio-4-phenylazetidin-2-one (3a): trans-3-Chloro-3-phenylthio-azetidin-2-one (2a) (50 mg, 0.13 mmol) in dry CH$_2$Cl$_2$ (10 mL) was placed in a flame dried two necked round bottom flask (50 mL) equipped with a magnetic stirrer under nitrogen atmosphere. The contents were cooled to 0°C and stirred. To this TiCl$_4$ (28 mg, 0.15 mmol, 0.016 mL) was added rapidly via a syringe. The reaction mixture was stirred for one hour at the same temperature. The progress of the reaction was checked by TLC, which showed the appearance of two new spots. Then the reaction mixture was quenched by water, extracted with dichloromethane (3 x 10 mL), washed with 5% NaHCO$_3$ solution, dried over anhydrous Na$_2$SO$_4$ and filtered. The residue after solvent evaporation was purified by column chromatography using silica gel eluting with ethyl acetate-hexanes (8%). The major component was collected, crystallized from ethyl acetate / hexanes and identified as cis-3-chloro-3-phenylthio-β-lactam (3a) (39 mg, 78%) on the basis of its following spectral data; mp 144-146°C; IR(KBr):1754 cm$^{-1}$; $^1$H-NMR(CDCl$_3$)$\delta$: 3.72(s, 3H, OCH$_3$), 5.18(s, 1H), 6.78-7.77(m, 14H, aromatic protons); $^{13}$C-NMR(CDCl$_3$)$\delta$: 55.21, 68.83, 80.12, 114.48, 118.93, 127.83, 128.65, 129.16, 129.2, 129.28, 129.88, 130.1, 132.99, 135.45, 135.75, 156.77, 159.46; EIMS: m/z 397, 396, 395, 360, 246, 211, 196, 167, 121; Anal. Calcd for C$_{22}$H$_{18}$NO$_2$ClS: C, 66.74; H, 4.59; N, 3.54; found: C, 66.61; H, 4.52; N, 3.49.

The minor component (7%) was identified to be 1-(4’-methoxyphenyl)-3,3-bis(phenylthio)-4-phenylazetidin-2-one (4a) on the basis of its following spectral data; mp 118-120°C; IR(KBr):1741 cm$^{-1}$; $^1$H-NMR(CDCl$_3$)$\delta$: 3.73(s, 3H, OCH$_3$), 5.18(s, 1H, C$_4$-H), 6.73-7.68(m, 19H, aromatic protons); $^{13}$C-NMR(CDCl$_3$)$\delta$: 55.41, 55.53, 68.78, 72.52, 114.28, 118.90, 128.14, 128.35, 128.55, 130.13, 139.50, 132.54, 134.9, 135.75, 139.16, 139.62, 156.39, 162.79; EIMS: m/z 469(M+), 320, 223, 211, 196, 134, 121, 109; Anal. Calcd for C$_{28}$H$_{23}$NO$_2$S$_2$: C, 71.61; H, 4.95; N, 2.98; found: C, 71.61; H, 4.95; N, 2.94.

cis-1-(4’-Methoxyphenyl)-3-chloro-3-phenylthio-4-(4’-methoxyphenyl)azetidin-2-one (3b): The major component was crystallized from ethyl acetate/hexanes and identified as (3b) (35 mg, 58%) on the basis of its spectral data; mp 154-156°C; IR(KBr):1751 cm$^{-1}$; $^1$H-NMR(CDCl$_3$)$\delta$: 3.74(s, 3H, OCH$_3$), 3.78(s, 3H, OCH$_3$), 5.22(s, 1H, C$_4$-H), 6.85-7.78(m, 13H, aromatic protons); $^{13}$C-NMR(CDCl$_3$)$\delta$: 55.41, 55.53, 68.78, 80.35, 114.11, 114.35, 119.26, 123.38 128.46, 128.83 129.34, 129.69, 129.84, 135.39, 156.79, 159.81, 160.88; Anal. Calcd for C$_{23}$H$_{20}$NO$_3$ClS: C, 64.24; H, 4.73; N, 3.28; found: C, 64.50; H, 4.55; N, 3.15.

The other component (12 mg, 17%) was identified to be 1-(4’-methoxyphenyl)-3,3-bis(phenylthio)- 4-(4’-methoxyphenyl)azetidin-2-one (4b) on the basis of its following spectral data; mp 123-124°C; IR(KBr):1747 cm$^{-1}$; $^1$H-NMR(CDCl$_3$)$\delta$: 3.72(s, 3H, OCH$_3$), 3.78(s, 3H, OCH$_3$), 5.12(s, 1H, C$_4$-H), 6.71-7.78(m, 18H, aromatic protons).
cis-1-Benzyl-3-chloro-3-phenylthio-4-phenylazetidin-2-one (3c):
mp 140-142°C; ¹H-NMR(CDCl₃)δ: 3.9(d, 1H, J = 14.95 Hz), 4.67(s, 1H), 4.9(d, 1H, J = 15.1 Hz), 7.01-7.72(m, 15H, aromatic protons); ¹³C-NMR(CDCl₃)δ: 44.38, 70.94, 80.63, 128.31, 128.49, 128.57, 128.69, 129.14, 129.30, 129.77, 131.87, 134.61, 135.28, 164.45; Anal. Calcd for C₂₂H₁₈NOClS: C, 69.55; H, 4.78; N, 3.68; found: C, 69.44; H, 4.69; N, 3.61.

cis-1-(4’-Methylphenyl)-3-chloro-3-phenylthio-4-(4’-chlorophenyl)azetidin-2-one (3d):
mp 120-121°C; IR(KBr): 1766cm⁻¹; ¹H-NMR(CDCl₃)δ: 2.28(s, 3H, CH₃), 5.17(s, 1H), 6.9-7.75(m, 13H, aromatic protons); ¹³C-NMR(CDCl₃)δ: 21.18, 68.20, 80.2, 117.60, 129.06, 129.14, 129.27, 129.86, 130.0, 131.64, 134.20, 134.46, 135.36, 135.42, 135.9, 159.41; Anal. Calcd for C₂₂H₁₇NOCl₂S: C, 63.77; H, 4.13; N, 3.38; found: C, 63.63; H, 4.04; N, 3.26.

cis-1-(4’-Bromophenyl)-3-chloro-3-phenylthio-4-phenylazetidin-2-one (3e):
yellow oil; ¹H-NMR(CDCl₃)δ: 5.26(s, 1H), 6.68-8.0(m, 14H, aromatic protons); ¹³C-NMR(CDCl₃)δ: 68.84, 79.64, 117.42, 119.21, 127.54, 128.31, 128.76, 129.21, 129.45, 129.97, 130.11, 131.84, 132.40, 132.46, 135.31, 135.82, 135.94, 159.91.

cis-1-(4’-Methoxyphenyl)-3-chloro-3-phenylthio-4-(1’-methyl-2’-phenylvinyl)azetidin-2-one (3f):
mp 165-169°C; IR(KBr): 1764cm⁻¹; ¹H-NMR(CDCl₃)δ: 2.35(s, 3H, CH₃), 3.72(s, 3H, OCH₃), 5.12(s, 1H), 6.71-7.73(m, 15H, aromatic protons); ¹³C-NMR(CDCl₃)δ: 21.33, 55.5, 69.02, 80.24, 114.46, 119.11, 127.74, 129.27, 129.36, 130.0, 135.7, 139.27, 150, 156.8; Anal. Calcd for C₂₅H₂₂NO₂ClS: C, 68.87; H, 5.08; N, 3.21; found: C, 68.76; H, 5.01; N, 3.09.

General procedure for synthesis of trans-3-bromo- and cis-3-bromo-3-phenylthio-β-lactams:
cis-1-Benzyl-3-bromo-3-phenylthio-4-phenylazetidin-2-one (5c) and trans-1-benzyl-3-bromo-3-phenylthio-4-phenylazetidin-2-one (6c): TiBr₄ (60 mg, 0.15 mmol) was transferred to a clean round bottom flask (25 mL) using a nitrogen dry box. Dichloromethane (5 mL) was added to it and cooled to 0°C. trans-3-Chloro-3-phenylthioazetidin-2-one (2c) (50 mg, 0.14 mmol) in dry methylene chloride (5mL) was added dropwise to this stirred solution, under nitrogen atmosphere. The reaction mixture was allowed to stir for one hour at the same temperature and the progress of reaction was monitored by TLC, which showed the formation of two new compounds. The reaction was quenched with water and extracted with methylene dichloride (3 x 10 mL). The combined organic extract was washed with brine, dried over anhydrous sodium sulfate and filtered. The residue after solvent evaporation was purified by column chromatography using silica gel, eluting with ethyl acetate-hexanes (12%). Fast moving
component (R_f 0.6) was separated and identified as trans-1-benzyl-3-bromo-3-phenylthio-4-phenylazetidin-2-one (6c) as an oil (18 mg, 33%) on the basis of following spectral data; IR(Nujol): 1771 cm⁻¹; ¹H-NMR(CDCl₃): 3.95(d, 1H, J=14.9 Hz), 4.96(d, 1H, J=15 Hz), 4.98 (s, 1H), 7.02-7.45, (m, 15H, aromatic protons); Anal. Calcd for C₂₂H₁₈NOBrS: C, 62.26; H, 4.28; N, 3.29; found: C, 62.38; H, 4.33; N, 3.37.

Slow moving component (R_f = 0.53) was isolated and crystallized from ethyl acetate-hexanes and identified as cis-1-benzyl-3-bromo-3-phenylthio-4-phenylazetidin-2-one (5c) (36 mg, 64%) on the basis of following spectral data; mp 128-130°C; IR(KBr): 1775 cm⁻¹; ¹H-NMR(CDCl₃): δ: 3.85(d, 1H, J=15.1 Hz), 4.63 (s, 1H), 4.9(d, 1H, J=14.9 Hz), 6.97-7.69(m, 15H, aromatic protons); ¹³C-NMR(CDCl₃): δ: 45.04, 67.40, 72.58, 127.91, 128.05, 128.38, 128.52, 128.91, 129.30, 130.03, 133.84, 135.59, 163.72. Anal. Calcd for C₂₂H₁₈NOBrS: C, 62.26; H, 4.28; N, 3.29; found: C, 62.38; H, 4.23; N, 3.25.

trans-1-(4’-Methoxyphenyl)-3-bromo-3-phenylthio-4-phenylazetidin-2-one (6a):
yellow oil; ¹H-NMR(CDCl₃): 3.73(s, 3H, OCH₃), 5.62(s, 1H), 6.82-7.48(m, 14H, aromatic protons); ¹³C-NMR(CDCl₃): 55.58, 68.21, 72.54, 114.15, 118.85, 127.36, 128.58, 129.31, 129.85, 130.20, 133.91, 135.64, 156.92, 160.11.

cis-1-(4’-Methoxyphenyl)-3-bromo-3-phenylthio-4-phenylazetidin-2-one (5a):
mp 118-120°C; ¹H-NMR(CDCl₃): 3.75(s, 3H, OCH₃), 5.20(s, 1H), 6.77-7.78(m, 14H, aromatic protons); ¹³C-NMR(CDCl₃): 55.53, 68.28, 72.27, 114.55, 119.08, 127.66, 128.61, 129.32, 129.90, 130.19, 133.96, 135.63, 156.90, 160.09; EIMS: m/z 441, 439, 292, 290, 211, 149; Anal. Calcd for C₂₂H₁₈NO₂BrS: C, 66.01; H, 4.12; N, 3.18; found: C, 59.88; H, 4.08; N, 3.13.

trans-1-(4’-Methoxyphenyl)-3-bromo-3-phenylthio-4-(4’-methoxyphenyl)azetidin-2-one (6b):
yellow oil; ¹H-NMR(CDCl₃): 3.79(s, 3H, OCH₃), 3.82(s, 3H, OCH₃), 5.58(s, 1H), 6.78-7.46(m, 13H, aromatic protons); ¹³C-NMR(CDCl₃): 55.46, 55.54, 70.19, 72.87, 113.91, 114.39, 119.04, 125.68, 128.98, 129.11, 129.30, 134.95, 135.46, 156.81, 159.95.

cis-1-(4’-Methoxyphenyl)-3-bromo-3-phenylthio-4-(4’-methoxyphenyl)azetidin-2-one (5b):
mp 124-126°C; IR(KBr): 1760 cm⁻¹; ¹H-NMR(CDCl₃): 3.74(s, 3H, OCH₃), 3.78(s, 3H, OCH₃), 5.16(s, 1H), 6.76-7.77(m, 13H, aromatic protons); ¹³C-NMR(CDCl₃): 55.32, 55.53, 68.14, 72.92, 114.01, 114.50, 119.11, 125.78, 129.07, 129.15, 129.31, 130.09, 134.99, 135.47, 156.83, 160.33; Anal. Calcd for C₂₃H₂₀NO₃BrS: C, 58.72; H, 4.29; N, 2.97; found: C, 58.61; H, 4.23; N, 2.93.
trans-1-(4’-Methylphenyl)-3-bromo-3-phenylthio-4-(4’-chlorophenyl)azetidin-2-one (6d):
mp 120-121°C; IR(KBr): 1766 cm\(^{-1}\); \(^1\)H-NMR(CDCl\(_3\))\(\delta\): 2.23(s, 3H, CH\(_3\)), 5.48(s, 1H), 6.9-7.67(m, 13H, aromatic protons); \(^{13}\)C-NMR(CDCl\(_3\))\(\delta\): 21.16, 70.14, 72.13, 117.74, 128.76, 128.96, 129.36, 129.41, 129.82, 129.89, 130.16, 130.64, 132.63, 133.98, 134.02, 134.6, 135.29, 135.83, 156.68; Anal. Calcd for C\(_{22}\)H\(_{17}\)NOBrClS: C, 57.59; H, 3.73; N, 3.05; found: C, 57.47; H, 3.63; N, 3.01.

cis-1-(4’-Methylphenyl)-3-bromo-3-phenylthio-4-(4’-chlorophenyl)azetidin-2-one (5d):
yellow oil; IR(KBr): 1765.8 cm\(^{-1}\); \(^1\)H-NMR(CDCl\(_3\))\(\delta\): 2.21(s, 3H, CH\(_3\)), 5.07(s, 1H), 6.87-7.67(m, 13H, aromatic protons); \(^{13}\)C-NMR(CDCl\(_3\))\(\delta\): 21.16, 67.35, 72.18, 117.52, 128.75, 128.95, 129.25, 129.57, 129.80, 130.06, 132.8, 134.17, 134.37, 134.94, 135.34, 135.67, 159.40.

trans-1-(4’-Bromophenyl)-3-bromo-3-phenylthio-4-phenylazetidin-2-one (6e):
mp 120-122°C; IR(KBr): 1768 cm\(^{-1}\); \(^1\)H-NMR(CDCl\(_3\))\(\delta\): 5.51(s, 1H), 6.94-7.67 (m, 14H, aromatic protons); \(^{13}\)C-NMR(CDCl\(_3\))\(\delta\): 70.5, 71.95, 117.88, 119.11, 119.35, 127.61, 128.28, 128.79, 128.84, 129.27, 129.39, 129.52, 129.91, 129.94, 130.14, 131.75, 132.36, 132.43, 135.26, 135.76, 135.87, 159.87; Anal. Calcd for C\(_{21}\)H\(_{15}\)NOBr\(_2\)S: C, 51.55; H, 3.09; N, 2.86; found: C, 51.45; H, 3.00; N, 2.72.

cis-1-(4’-Bromophenyl)-3-bromo-3-phenylthio-4-phenylazetidin-2-one (5e):
mp 176-178°C; IR(KBr): 1767 cm\(^{-1}\); \(^1\)H-NMR(CDCl\(_3\))\(\delta\): 5.04(s, 1H), 6.96-7.68 (m, 14H, aromatic protons); \(^{13}\)C-NMR(CDCl\(_3\))\(\delta\): 68, 71.93, 117.84, 119.08, 119.10, 127.62, 128.75, 128.8, 128.84, 129.24, 129.27, 129.44, 129.46, 130.0, 130.13, 132.34, 132.44, 133.72, 135.27, 135.74, 135.77, 135.81, 159.33; Anal. Calcd for C\(_{21}\)H\(_{15}\)NOBr\(_2\)S: C, 51.55; H, 3.09; N, 2.86; found: C, 51.40; H, 3.00; N, 2.68.

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REFERENCES AND NOTES
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17. Structure was confirmed by X-Ray crystal analysis. Crystal data for 2a: monoclinic, P2$_1$/c, $a = 11.950(1)$, $b = 15.192(1)$, $c = 11.062 (1)$ Å, $\beta = 103.07(1)^\circ$, $V = 1956.2 (3)$ Å$^3$, $Z = 4$, $\rho$ calc = 1.344 Mg/m$^3$, $\mu$(Mo-K$\alpha$) = 0.319 mm$^{-1}$, full matrix least – square on $F^2$, $R_f = 0.0373$, $wR_2 = 0.0932$ for 2549 reflections [$I$>2$\sigma$(I)].

18. Crystal data for 3a: monoclinic, P2$_1$/c, $a = 16.738(2)$, $b = 5.867(1)$, $c = 21.256 (2)$ Å, $\beta = 108.96(1)^\circ$, $V = 1974.1 (5)$ Å$^3$, $Z = 4$, $\rho$ calc = 1.332 Mg/m$^3$, $\mu$(Mo-K$\alpha$) = 0.316 mm$^{-1}$, full matrix least – square on $F^2$, $R_f = 0.0386$, $wR_2 = 0.0921$ for 2428 reflections [$I$>2$\sigma$(I)].

19. Structure was confirmed by X-Ray crystal analysis. Crystal data for 5c: monoclinic, P2$_1$/n, $a = 10.214(2)$, $b = 9.745(1)$, $c = 20.264 (2)$ Å, $\beta = 100.03(1)^\circ$, $V = 1986.2 (5)$ Å$^3$, $Z = 4$, $\rho$ calc = 1.419 Mg/m$^3$, $\mu$(Mo-K$\alpha$) = 2.185 mm$^{-1}$, full matrix least – square on $F^2$, $R_f = 0.0369$, $wR_2 = 0.0812$ for 2459 reflections [$I$>2$\sigma$(I)].