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REGULAR ARTICLE

Studies towards synthesis and Lewis acid catalysed functionalization of 3-(4′-substitutedphenylthio)-azetidin-2-ones

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Abstract. Medicinal chemistry of heterocycles especially β-lactams have been an important discovery in today's mankind. β-Lactam nucleus is structural feature and core of the biological activity of one of most successful classes of therapeutics to date characterized by a broad spectrum of activity and low toxicity. It constitutes classes of drugs that includes the antibiotics like penicillins, cephalosporins, clavulanic acid, monobactams and also shows wide range of important biological activities such as anti-cancer, anti-inflammatory and anti-malarial. The monocyclic β-lactams and their hetero-substituted conjugates are also applied for the synthesis of many classes of compounds which include taxol derivatives, alkaloids and amino acids. Antimicrobial resistance is one of the major and growing concerns in hospital and community acquired infections and new anti-microbial agents are therefore urgently required. So now, the organic chemists have focussed on the modification of existing molecules for the synthesis of new compounds having diverse pharmacological activities with broad spectrum activity. Monocyclic β-lactams are stable to hydrolysis by β-lactamases in comparison to other β-lactams and thus are attractive platform for searching anti-bacterial agents. The discovery of differently substituted 3-alkyl/aryl β-lactams having significant anti-microbial activities have given insight that substitution at C-3 and C-4 of β-lactam ring affects the biological activity of the ring. So, keeping this in mind and synthetic utility of β-lactams here we have made an attempt towards the feasibility and efficiency of 3-(*p*-substituted-phenylthio)-β-lactams towards Lewis acid functionalization reactions. In our previous works, we have explored the synthetic utility of *cis*-3-chloro-3-phenyl/benzyl/methylthio-β-lactams as suitable substrate for the Lewis acid catalysed nucleophilic substitution. The current work is designed to explore the effect of electronic changes at phenylthio group at C-3 on the products profile in the Lewis acid catalysed nucleophilic substitution reactions.

Keywords. β-Lactam; azetidin-2-one; C-3 substitution; Lewis acid; 3-(4′-substitutedphenylthio)-azetidin-2-ones.

1. Introduction

Heterocycles have always drawn the attention of chemists over the years because of their indispensable profile of biological properties. Among them, the four-membered heterocyclic compound azetidin-2-one (β-lactam) is endowed with a unique ring system and great biological potential.[1] The azetidin-2-one scaffold constitutes numerous biologically active molecules and natural products.[2] Their biological properties include antibacterial, antifungal, anti-HIV, anticancer and antimalarial activities.[3] Besides their importance as the key structural component of β-lactam antibiotics, these molecules have been attracting considerable interest in organic synthesis as versatile synthetic intermediates,[4] LHR antagonists[5] and cholesterol absorption inhibitors.[6]

In recent years, there has been regular and widespread use of β-lactam derived drugs to fight the ever-

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increasing bacterial infections over the course of time. This increased use of these drugs has led to the emergence of drug-resistant pathogens which have decreased the effectiveness of β-lactam antibiotics.[7] This has maintained the interest of organic chemists world over in the synthesis of new and effective β-lactam analogues with an improved broad spectrum of biological activity.[8] The researchers have focussed on the synthesis and modification of β-lactam ring to prepare compounds with diverse pharmacological activities. The discovery of biological activity of differently substituted 3-alkyl/aryl β-lactams[6] has led to the development of convenient approaches for the synthesis of β-lactams bearing a variety of appendages at C-3 & C-4.

In connection with our current research interest in the preparation[9–14] and synthetic utility of β-lactams, here we examine the feasibility and efficiency of 3-(*p*-substituted-phenylthio) β-lactams towards Lewis acid functionalization reactions.

2. Experimental

2.1 *General information*

^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively, in $CDCl_3$ solution using BRUKER AVANCE II NMR spectrometer. Chemical shifts are given in parts per million relative to tetramethylsilane as an internal standard ($\delta = 0$ ppm) for ^{1}H NMR and ($\delta = 77.0$ ppm) for ^{13}C NMR. The coupling constant J values are given in Hertz (Hz). While citing ^{1}H NMR data, following abbreviations have been used: s-singlet; br s-broad singlet; d-doublet; t-triplet; q-quartet and m-multiplet. IR spectra were taken on an FTIR spectrophotometer and are reported in cm^{-1}. 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 vapours. Column chromatography was performed with silica gel (Acme Synthetic Chemicals, 60–120 mesh) and eluted with ethyl acetate: hexanes mixtures unless otherwise stated. All commercially available compounds or reagents were used without further purification. All solvents used were of LR grade. Where necessary, the solvents were distilled and dried before use, when this seemed necessary by standard methods.

2.2 *General procedure for the synthesis of 3-(4′-methyl/chlorophenylthio) β-lactams (**4&5**)*

These compounds were prepared by the described procedure in the cited reference[16] for the synthesis of 3-phenyl/benzylthio/methylthio-β-lactams using 2-(4′-methyl/chlorophenylthio)ethanoic acid **1, 2** and appropriate schiff base **3a-c**. To a well-stirred solution of appropriate schiff base (5.5 mmol) and 4′-substituted phenylthio acid (8.2 mmol) in dry toluene (80 mL) added triethyl amine (22 mmol) under a nitrogen atmosphere and the reaction was subjected to refluxing. It was followed by dropwise addition of phosphorous oxychloride (8.2 mmol) using pressure equalizer over 30 min under refluxing conditions. After 5 h of refluxing, allowed the reaction to stir overnight at room temperature for overnight. The completion of the reaction was checked by TLC (10% EtOAc/hexane). Then evaporated the solvent (toluene) from the reaction mixture and dissolved the residue in dichloromethane, washed the organic layer with 1N HCl, followed by 5% $NaHCO_3$ and brine. Dried the organic layer over anhydrous Na_2SO_4. The crude product was purified by silica gel chromatography (10% EtOAc/hexane). The solid β-lactams were crystallized from DCM/hexane.

2.2a *Compound **4a**: trans-1-(4′-methoxyphenyl)-3-(4′-methylphenylthio)-4-phenylazetidin-2-one*: Colourless crystalline solid; yield: 55% (1.13 g); M.p. 116-117 °C; R_f: 0.46; $C_{23}H_{21}NO_2S$: Anal. Found: C, 73.52; H, 5.59; N, 3.79% Calc.: C, 73.57; H, 5.63; N, 3.72%. IR (cm^{-1}): $\nu_{(C=O)}$, 1720; ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.36-7.21 (m, 5H, Ph), 7.19-7.00 (m, 6H, Ph), 6.66-6.64 (m, 2H, Ph), 4.67 (d, ^3J = 2.3, 1H, C-3), 4.10 (d, ^3J = 2.3, 1H, C-4), 3.63 (s, 3H, OCH_3), 2.21 (s, 3H, CH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 162.9, 156.2, 138.4, 136.4, 133.0, 130.7, 130.0, 129.2, 128.8, 128.2, 126.0, 118.6, 114.2, 77.3, 77.2, 77.0, 76.7, 63.0, 61.9, 55.4, 21.1.

2.2b *Compound **4b**: trans-1-(4′-methoxyphenyl)-3-(4′-chlorophenylthio)-4-phenylazetidin-2-one*: Colourless crystalline solid; yield 50% (1.08 g); M.p. 132-134 °C; R_f: 0.33; $C_{22}H_{18}NO_2SCl$: Anal. Found: C, 66.71; H, 4.60; N, 3.51% Calc.: C, 66.74; H, 4.58; N, 3.53%. IR (cm^{-1}): $\nu_{(C=O)}$, 1722; ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.46-7.36 (m, 4H, Ph), 7.31-7.14 (m, 7H, Ph), 6.76-6.73 (m, 2H, Ph), 4.75 (d, ^3J = 2.2, 1H, C-3), 4.21 (d, ^3J = 2.2, 1H, C-4), 3.71 (s, 3H, OCH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 162.47, 156.42, 136.18, 134.27, 133.54, 133.54, 130.83, 130.55, 129.38, 129.33, 129.08, 126.05, 118.66, 114.37, 77.38, 77.27, 77.06, 76.75, 62.96, 61.33, 55.42.

2.2c *Compound **4c**: trans-1-phenyl-3-(4′-methylphenylthio)-4-phenylazetidin-2-one*: White solid; yield 39.2% (0.74 g); M.p. 112-113 °C; R_f: 0.50; $C_{22}H_{19}NOS$: Anal. Found: C, 76.52; H, 5.51; N, 4.01% Calc.: C, 76.49; H, 5.54; N, 4.05%. IR (cm^{-1}): $\nu_{(C=O)}$, 1730; ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.36-7.34 (m, 2H, Ph), 7.26-7.19 (m, 6H, Ph), 7.12-7.11 (m, 3H, Ph), 7.01-6.93 (m, 3H, Ph), 4.70 (d, ^3J = 2.4, 1H, C-3), 4.11 (d, ^3J = 2.4, 1H, C-4); 2.20 (s, 3H, CH_3); ^{13}C NMR (δ, ppm in

$CDCl_3$, 100 MHz): 163.59, 138.52, 137.19, 136.37, 133.11, 130.05, 129.27, 129.08, 128.91, 128.09, 126.02, 124.28, 117.29, 77.42, 77.10, 76.78, 62.85, 61.92, 21.18.

2.2d *Compound **4d**: trans-1-phenyl-3-(4′-chlorophenylthio)-4-phenylazetidin-2-one*: White solid, yield 40.59% (0.82 g); M.p. 126-128 °C; R_f: 0.63; $C_{21}H_{16}NOSCl$: Anal. Found: C, 68.70; H, 4.42; N, 3.79% Calc.: C, 68.9; H, 4.40; N, 3.82%. IR (cm^{-1}): $\nu_{(C=O)}$, 1725; ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.49-7.46 (m, 2H, Ph), 7.42-7.33 (m, 5H, Ph), 7.30-7.06 (m, 7H, Ph), 4.81 (d, $^3J = 2.4$, 1H, C-3), 4.25 (d, $^3J = 2.4$, 1H, C-4); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 163.47, 138.92, 137.54, 135.45, 132.12, 130.96, 129.27, 128.91, 128.72, 128.24, 126.54, 124.52, 118.30, 77.50, 77.20, 76.90, 63.85, 61.85.

2.2e *Compound **4e**: trans-1-(4′-methoxyphenyl)-3-(4′-methylphenylthio)-4-(4′-methoxyphenyl)azetidin-2-one*: Yellow oil; yield 75% (1.67 g); R_f: 0.26; $C_{24}H_{23}NO_3S$: Anal. Found: C, 71.17; H, 5.74; N, 3.41% Calc.: C, 71.14; H, 5.72; N, 3.45%. IR (cm^{-1}): $\nu_{(C=O)}$, 1755; ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.41-7.38 (m, 2H, Ph), 7.23-7.05 (m, 6H, Ph), 6.87-6.69 (m, 4H, Ph), 4.71 (d, $^3J = 2.2$, 1H, C-3), 4.16 (d, $^3J = 2.2$, 1H, C-4), 3.75 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 163.01, 160.02, 156.24, 138.25,132.80, 130.75, 130.01, 128.45, 127.45, 118.71, 114.62, 114.27, 77.52, 77.20, 76.88, 62.83, 61.85, 55.40, 55.33.

2.2f *Compound **4f**: trans-1-(4′-methoxyphenyl)-3-(4′-chlorolphenylthio)-4-(4′-methoxyphenyl)azetidin-2-one*: Yellow oil; yield 79% (1.85 g); R_f: 0.13; $C_{23}H_{20}NO_3SCl$: Anal. Found: C, 64.89; H, 4.71; N, 3.25% Calc.: C, 64.89; H, 4.71; N, 3.25%. IR (cm^{-1}): $\nu_{(C=O)}$, 1750; ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.42-7.40 (m, 2H, Ph), 7.25-7.15 (m, 6H, Ph), 6.89-6.72 (m, 4H, Ph), 4.72 (d, $^3J = 2.2$, 1H, C-3), 4.21 (d, $^3J = 2.2$, 1H, C-4), 3.77 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 162.52, 160.16, 156.36, 134.09, 133.29, 131.11, 130.58, 129.35, 127.95, 127.45,118.70, 114.72, 114.39, 77.47, 77.15, 76.83, 62.80, 61.24, 55.41, 55.35.

2.2g *Compound **5c**: cis-1-phenyl-3-(4′-methylphenylthio)-4-phenylazetidin-2-one*: White solid; yield 12.69% (0.24 g); M.p. 176-177 °C; R_f: 0.43; $C_{22}H_{19}NOS$: Anal. Found: C, 76.54; H, 5.49; N, 4.02% Calc.: C, 76.49; H, 5.54; N, 4.05%. IR (cm^{-1}): $\nu_{(C=O)}$, 1725; ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.32-7.28 (m, 3H, Ph), 7.27-7.20 (m, 6H, Ph), 7.14-7.11 (m, 2H, Ph), 7.02-6.95 (m, 3H, Ph), 5.30 (d, $^3J = 5.6$, 1H, C-3), 4.80 (d, $^3J = 5.6$, 1H, C-4), 2.22 (s, 3H, CH_3). ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 137.57, 137.29, 131.93, 129.71, 129.14, 128.53, 127.73, 124.32, 128.53, 127.73, 124.32, 117.37, 114.92, 77.39, 77.03, 76.71, 60.02. EI-MS m/z (R.I %, [assignment]$^+$): 368 (22, $[M+23]^+$), 346 (100, $[M]^+$), 222 (64, $[C_{15}H_{12}NO]^+$), 182 (19, $[C_6H_5CH{=}NC_6H_5]^+$).

2.2h *Compound **5d**: cis-1-phenyl-3-(4′-chlorophenylthio)-4-phenylazetidin-2-one*: White solid; yield 13.4% (0.27 g); M.p. 186-187 °C; R_f: 0.56; $C_{21}H_{16}NOSCl$: Anal. Found: C, 68.30; H, 4.35; N, 3.85% Calc.: C, 68.9; H, 4.40; N 3.82%. IR (cm^{-1}): $\nu_{(C=O)}$, 1730; ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.38-7.35 (m, 3H, Ph), 7.33-7.22 (m, 8H, Ph), 7.19-7.06 (m, 3H, Ph), 5.39 (d, $^3J = 5.6$, 1H, C-3), 4.87 (d, $^3J = 5.6$, 1H, C-4); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 138.56, 137.90, 132.85, 129.70, 129.05, 128.72, 126.52, 125.83, 118.90, 114.50, 77.50, 77.42, 76.05, 60.50.

2.3 *General procedure for the synthesis of cis-3-chloro-3-(4′-methyl/chlorophenylthio)-β-lactams (**6**)*

These compounds were prepared by the procedure as described for *cis*-3-chloro-3-phenylthio-β-lactams.[16] To a solution of *trans*-β-lactam **4a-d** (1.2 mmol) in dry dichloromethane (30 mL) was added SO_2Cl_2 (1.4 mmol) rapidly under nitrogen atmosphere at 0 °C. The reaction was monitored using TLC (10% EtOAc/hexane). Confirming the complete disappearance of reactant, the reaction was quenched with water, extracted with dichloromethane. Then washed the organic layer with brine and dried it over anhydrous Na_2SO_4. The crude product was purified with silica gel chromatography (10% EtOAc/hexane) and recrystallized from DCM/hexane.

2.3a *Compound **6a**: cis-1-(4′-methoxyphenyl)-3-chloro-3-(4′-methylphenylthio)-4-phenyl azetidin-2-one*: White solid; yield 90% (0.44 g); M.p. 154-156 °C; R_f: 0.50; $C_{23}H_{20}NO_2SCl$: Anal. Found: C, 67.42; H, 4.87; N, 3.46% Calc.: C, 67.39; H, 4.91; N, 3.41%. IR (cm^{-1}): $\nu_{(C=O)}$, 1752; ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.35-7.27 (m, 7H, Ph), 7.18-7.01 (m, 4H, Ph), 6.75-6.72 (m, 2H, Ph), 5.36 (s, 1H, C-4), 3.68 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 137.90, 136.5, 132.40, 129.8, 129.5, 128.8, 127.6, 127.2, 126.52, 125.9, 118.8, 77.8, 77.2, 76.5, 71.5, 54.7, 21.55.

2.3b *Compound **6b**: cis-1-(4′-methoxyphenyl)-3-chloro-3-(4′-chlorophenylthio)-4-phenyl azetidin-2-one*: White solid; yield 92% (0.47 g); M.p. 135-136 °C; R_f: 0.36; $C_{22}H_{17}NO_2SCl_2$: Anal. Found: C, 61.38; H, 3.92; N, 3.30% Calc.: C, 61.40; H, 3.98; N, 3.25%. IR (cm^{-1}): $\nu_{(C=O)}$, 1735; ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.44-7.37 (m, 7H, Ph), 7.27-7.22 (m, 4H, Ph), 6.83-6.80 (m, 2H, Ph), 5.44 (s, 1H, C-4), 3.76 (s, 3H, OCH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 159.96, 156.87, 136.78, 136.01, 131.50, 129.85, 129.70, 128.93, 128.70, 128.19, 126.64, 119.23, 114.52, 79.71, 77.34, 77.02, 76.70, 71.71, 55.47.

2.3c *Compound **6c**: cis-1-phenyl-3-chloro-3-(4′-methylphenylthio)-4-phenylazetidin-2-one*: White solid; yield 92% (0.42 g); M.p. 150-152 °C; R_f: 0.53; $C_{22}H_{18}NOSCl$: Anal. Found: C, 69.59; H, 4.73; N, 3.72%. Calc: C, 69.55; H, 4.77; N, 3.68%. IR (cm^{-1}): $\nu_{(C=O)}$, 1760; ^1H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.42-7.40 (m, 5H, Ph), 7.38-7.28 (m, 6H, Ph), 7.11-7.09 (m, 3H, Ph), 5.47 (s, 1H, C-4), 2.3 (s, 3H, CH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 160.79, 139.96; 136.57, 135.98, 131.62, 129.73, 129.55, 128.65, 128.19, 124.91, 124.28, 117.88, 77.34, 77.22, 77.02, 76.70, 71.72, 21.33.

2.3d *Compound **6d**: cis-1-phenyl-3-chloro-3-(4′-chlorophenylthio)-4-phenylazetidin-2-one*: White solid; yield 90% (0.42 g); M.p. 150-151 °C; R_f: 0.66; $C_{21}H_{15}NOSCl_2$: Anal. Found: C, 63.03; H, 3.72; N, 3.53% Calc.: C, 63.00; H, 3.77; N, 3.49%. IR (cm^{-1}): $\nu_{(C=O)}$, 1765; ^1H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.45-7.39 (m, 7H, Ph), 7.30-7.12 (m, 7H, Ph), 5.48 (s, 1H, C-4); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 136.87, 136.40, 131.39, 129.89, 129.30, 128.97, 128.74, 128.13, 126.52, 125.09, 117.90, 77.34, 77.22, 77.02, 76.70, 71.63.

2.4 *General procedure for the synthesis of C-3 substituted β-lactams (**7**, **8**, **9** & **10**)*

These compounds were prepared by the procedure as described for nucleophilic substitutions of *cis*-3-chloro-3-phenyl/benzyl/methylthioβ-lactams.[9–12] To a solution of *cis*-3-chloro-β-lactam **6a-d** (0.24 mmol) and nucleophile (0.36 mmol) in dry DCM (15 mL) was added Lewis acid $TiCl_4$ (0.36 mmol) rapidly under nitrogen atmosphere at 0 °C. The reaction was monitored by TLC. When reaction profile changes no further, the reaction was quenched with water, extracted with DCM, washed the organic layer with 5% $NaHCO_3$ and dried it over anhydrous Na_2SO_4. The crude reaction mixture was purified with silica gel chromatography (10% EtOAc/hexane) and solid products were recrystallized from DCM/hexane.

2.4a *Compound **7aa/ba**: 1-(4′-methoxyphenyl)-3,3-bis(4′methoxyphenyl)-4-phenylazetidin-2-one*: Colourless oil; yield 63.6% (0.07 g); R_f: 0.13; $C_{30}H_{27}NO_4$: Anal. Found: C, 77.43; H, 5.81; N, 3.04% Calc.: C, 77.40; H, 5.84; N, 3.00%. IR (cm^{-1}): $\nu_{(C=O)}$, 1745; ^1H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.54-7.31 (m, 4H, Ph), 7.14-6.99 (m, 7H, Ph), 6.91-6.76 (m, 4H, Ph), 6.55-6.53 (m, 2H, Ph), 5.67 (s, 1H, C-4), 3.77 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 167.25, 159.25, 158.75, 137.25, 135.74, 133.20, 129.75, 129.25, 129.05, 128.72, 128.25, 127.95, 127.45, 124.05, 117.75, 114.75, 113.63, 77.42, 77.29, 77.05, 76.75, 72.74, 68.49, 55.95, 55.25, 55.05.

2.4b *Compound **7ca/da**: 1-phenyl-3,3-bis(4′methoxyphenyl)-4-phenylazetidin-2-one*: Colourless oil; yield 45% (0.042 g); R_f: 0.16; $C_{29}H_{25}NO_3$: Anal. Found: C, 79.92; H, 5.81; N, 3.19% Calc.: C, 79.98; H, 5.78; N, 3.21%. IR (cm^{-1}): $\nu_{(C=O)}$, 1752; ^1H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.55-7.38 (m, 4H, Ph), 7.25-6.91 (m, 9H, Ph), 6.89-5.72 (m, 5H, Ph), 5.72 (s, 1H, C-4), 3.77 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 167.68, 158.80, 158.15, 137.58, 135.04, 133.19, 129.61, 129.53, 129.05, 128.45, 128.41, 128.13, 127.58, 124.08, 117.50, 114.15, 113.25, 77.40, 77.29, 77.08, 76.77, 71.20, 67.42, 55.35, 55.09.

2.4c *Compound **8ab**: trans-1-(4′-methoxyphenyl)-3-(2′,5′-dimethoxyphenyl)-3-(4′-methylphenyl thio)-4-phenylazetidin-2-one*: White crystalline solid; yield 45% (0.045 g); M.p. 146-147 °C; R_f: 0.33; $C_{31}H_{29}NO_4S$: Anal. Found: C, 72.72; H, 5.75; N, 2.76% Calc.: C, 72.77; H, 5.71; N, 2.73%. IR (cm^{-1}): $\nu_{(C=O)}$, 1735; ^1H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.40-7.32 (m, 3H, Ph), 7.09-6.98 (m, 9H, Ph), 6.69-6.34 (m, 4H, Ph), 5.11 (s, 1H, C-4), 3.69 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 2.25 (s,3H, CH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 164.67, 156.00, 152.78; 150.24, 139.58, 136.89, 135.27, 130.62, 129.22, 128.10, 127.43, 126.88, 122.77, 118.84, 115.05, 114.82, 114.03, 111.32, 77.36, 77.24, 77.04, 76.72, 69.13, 68.13, 55.83, 55.38, 54.87, 21.26. EI-MS m/z (R.I %, [assignment]$^+$): 534 (12, $[M+23]^+$), 513 (18, $[M+1]^+$), 512 (35, $[M]^+$), 390 (69, $[C_{24}H_{23}NO_4]^+$), 389 (100, $[C_{24}H_{22}NO_4]^+$), 360 (69, $[C_{23}H_{22}NO_4]^+$).

2.4d *Compound **9ab**: cis-1-(4′-methoxyphenyl)-3-(2′,5′-dimethoxyphenyl)-3-(4′-methylphenyl thio)-4-phenylazetidin-2-one*: White crystalline solid; yield 40% (0.040 g); M.p. 158-160 °C; R_f: 0.40; $C_{31}H_{29}NO_4S$: Anal. Found: C, 72.80; H, 5.68; N, 2.75% Calc.: C, 72.77; H, 5.71; N, 2.73%. IR (cm^{-1}): $\nu_{(C=O)}$, 1732; ^1H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.62-7.22 (m, 7H, Ph), 6.96-6.71 (m, 9H, Ph), 5.52 (s, 1H, C-4), 3.80 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 2.22 (s, 3H, CH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 166.52, 156.02, 152.71, 150.65, 138.80, 137.21, 134.00, 130.79, 129.35, 128.84, 128.71, 128.00, 126.67, 126.30, 118.81, 115.37, 114.24, 114.19, 112.12, 77.39, 77.28, 77.07, 76.75, 67.15, 66.45, 55.64, 55.51, 55.42, 21.17.

2.4e *Compound **9ac**: cis-1-(4′-methoxyphenyl)-3-allyl-3-(4′-methylphenylthio)-4-phenylazetidin-2-one*: White solid; yield 89% (0.1 g); M.p. 126-129 °C; R_f: 0.50; $C_{26}H_{25}NO_2S$: Anal. Found: C, 75.19; H, 6.09; N, 3.31% Calc.: C, 75.15; H, 6.06; N, 3.36%. IR (cm^{-1}): $\nu_{(C=O)}$, 1740; ^1H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.44-7.23 (m, 9H, Ph), 7.07-6.78 (m, 4H, Ph), 5.98 (m, 1H, H_2C=C<u>H</u>), 5.25 (m, 2H, <u>H_2</u>C=CH), 5.10 (s, 1H, C-4), 3.54 (s, 3H, OCH_3), 2.6 (m, 2H, CH_2), 2.30 (s, 3H, CH_3); ^{13}C

NMR (δ, ppm in $CDCl_3$, 100 MHz): 166.61, 156.23, 138.81, 135.80, 133.59, 132.68, 130.80, 129.60, 128.77, 128.36, 128.02, 126.37, 119.73, 118.84, 118.77, 114.40, 77.41, 77.30, 77.10, 76.78, 65.99, 63.57, 55.52, 37.93, 21.28.

2.4f *Compound **9bb**: cis-1-(4′-methoxyphenyl)-3-(4′-chlorophenylthio)-3-(2′,5′-dimethoxy phenyl)-4-phenylazetidin-2-one*: Colourless crystals; yield (0.059 g); M.p. 152-154 °C; R_f: 0.26; $C_{30}H_{26}NO_4SCl$: Anal. Found: C, 67.76; H, 4.88; N, 2.69% Calc.: C, 67.72; H, 4.92; N, 2.63%. IR (cm^{-1}): $\nu_{(C=O)}$, 1730; ^1H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.60-7.41 (m, 5H, Ph), 7.25-6.95 (m, 7H, Ph), 6.81-6.73 (m, 4H, Ph), 5.50 (s, 1H, C-4), 3.79 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 165.09, 156.15, 152.88, 150.59, 138.26, 135.17, 133.80, 130.64, 129.29, 128.95, 128.92, 128.04, 125.93, 118.84, 115.43, 114.36, 114.27, 112.22, 77.34, 77.23, 77.02, 76.71, 67.31, 66.53, 55.73, 55.41.

2.4g *Compound **9bc**: cis-1-(4′-methoxyphenyl)-3-allyl-3-(4′-chlorophenylthio)-4-phenylazetidin-2-one*: White solid; yield 90% (0.092 g); M.p. 100-103 °C; R_f: 0.36; $C_{25}H_{22}NOSCl$: Anal. Found: C, 68.81; H, 5.02; N, 3.25% Calc.: C, 68.87; H, 5.08 N, 3.21%. IR (cm^{-1}): $\nu_{(C=O)}$, 1720; ^1H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.51-7.33 (m, 5H, Ph), 7.29-7.20 (m, 6H, Ph), 6,83-6.79 (m, 2H, Ph), 5.95 (m, 1H, H_2C=C<u>H</u>), 5.50 (m, 2H, <u>H_2</u>C=CH), 5.11 (s, 1H, C-4), 3.75 (s, 3H, OCH_3), 2.65 (m, 2H, CH_2); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 167.52, 158.23, 137.75, 135.25, 134.60, 132.25 131.75, 130.50, 128.50, 128.25, 127.50, 126.73, 120.50, 119.75, 118.30, 116.20, 77.25, 77.05, 76.90, 76.75, 65.25, 63.25, 55.75, 39.52.

2.4h *Compound **9cb**: cis-1-phenyl-3-(2′,5′-dimethoxyphenyl)-3-(4′-methylphenylthio)-4-phenylazetidin-2-one*: White crystalline solid; yield 42.85 (0.06 g); M.p. 106-108 °C; R_f: 0.40; $C_{30}H_{27}NO_3S$: Anal. Found: C, 74.85; H, 5.71; N, 2.85% Calc.: C, 74.82; H, 5.65; N, 2.90%. IR (cm^{-1}): $\nu_{(C=O)}$, 1770; ^1H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.64-7.41 (m, 5H, Ph), 7.30-7.15 (m, 4H, Ph), 7.03-6.93 (m, 4H, Ph), 6.87-6.71 (m, 4H, Ph), 5.55 (s, 1H, C-4), 3.81 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 2.22 (s, 3H, CH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 166.14, 152.72, 150.69, 138.87, 137.27, 137.22, 133.91, 129.30, 129.22, 129.01, 128.89, 128.81, 128.74, 128.04, 126.60, 126.13, 124.00, 117.55, 115.42, 114.20, 112.27, 77.40, 77.29, 77.08, 76.76, 67.08, 66.40, 55.64, 55.55, 21.18.

2.4i *Compound **9cc**: cis-1-phenyl-3-allyl-3-(4′-methylphenylthio)-4-phenylazetidin-2-one*: Light yellow semisolid; yield 90% (0.083 g); R_f: 0.53; $C_{25}H_{23}NOS$: Anal. Found: C, 77.82; H, 6.05; N, 3.66% Calc.: C, 77.88; H, 6.01; N, 3.63%. IR (cm^{-1}): $\nu_{(C=O)}$, 1770; ^1H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.48-7.45 (m, 2H, Ph), 7.39-7.25 (m, 9H, Ph), 7.11-7.07 (m, 3H, Ph), 6.00 (m, 1H, H_2C=C<u>H</u>), 5.27 (m, 2H, <u>H_2</u>C=CH), 5.17 (s, 1H, C-4), 2.66 (m, 2H, CH_2), 2.33 (s, 3H, CH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 167.29, 138.99, 137.42, 135.96, 133.56, 132.68, 129.74, 129.28, 128.91, 128.80, 128.75, 128.49, 128.09, 126.40, 124.30, 119.94, 117.72, 117.68, 117.62, 77.56, 77.45, 77.25, 76.93, 66.05, 63.62, 37.99, 21.41.

2.4j *Compound **9db**: cis-1-phenyl-3-(4′-chlorophenylthio)-3-(2′,5′-dimethoxyphenyl)-4-phenylazetidin-2-one*: Yellow oil; yield 69% (0.1 g); R_f: 0.43; $C_{29}H_{24}NO_3SCl$: Anal. Found: C, 69.42; H, 4.86; N, 2.73% Calc.: C, 69.38; H, 4.81; N, 2.78%. IR (cm^{-1}): $\nu_{(C=O)}$, 1754; ^1H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.61-7.42 (m, 5H, Ph), 7.30-7.18 (m, 4H, Ph), 7.03-6.96 (m, 6H, Ph), 6.81-6.74 (m, 2H, Ph), 5.54 (s, 1H, C-4), 3.79 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 165.75, 152.87, 150.63, 138.82, 137.14, 135.27, 133.70, 129.27, 129.07, 128.86, 128.12, 125.73, 124.19, 117.59, 115.48, 114.36, 112.27, 77.44, 77.12, 76.81, 67.25, 66.47, 55.75, 55.47.

2.4k *Compound **9dc**: cis-1-phenyl-3-allyl-3-(4′-chlorophenylthio)-4-phenylazetidin-2-one*: Light yellow semi solid; yield 94% (0.091cg); R_f: 0.66; $C_{24}H_{20}NOSCl$: Anal. Found: C, 71.05; H, 4.92 N, 3.46% Calc.: C, 71.01; H, 4.96; N, 3.44%. IR (cm^{-1}): $\nu_{(C=O)}$, 1760; ^1H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.40-7.39 (m, 2H, Ph), 7.30-7.12 (m, 10H, Ph), 7.01-6.97 (m, 2H, Ph), 5.87 (m, 1H, H_2C=C<u>H</u>), 5.17 (m, 2H, <u>H_2</u>C=CH), 5.07 (s, 1H, C-4), 2.75 (m, 2H, CH_2); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 166.76, 137.12, 137.02, 136.66, 134.96, 133.17, 132.06, 129.46, 129.31, 129.19, 128.97, 128.89, 128.80, 128.68, 128.42, 127.88, 124.36, 120.11, 117.73, 117.51, 77.40, 77.29, 77.09, 76.72, 66.00, 63.55, 37.91.

2.4l *Compound **10aa/ab**: 1-(4′-methoxyphenyl)-3,3-bis(4′-methylphenylthio)-4-phenylazetidin-2-one*: Colourless crystals; yield 36.3% (0.04 g); M.p. 108-110 °C; R_f: 0.53; $C_{30}H_{27}NO_2S$: Anal. Found: C, 72.36; H, 5.49; N, 2.85% Calc.: C, 72.40; H, 5.46; N, 2.81%. IR (cm^{-1}): $\nu_{(C=O)}$, 1730; ^1H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.55-7.53 (m, 2H, Ph), 7.38-7.25 (m, 5H, Ph), 7.13-7.05 (m, 8H, Ph), 6.74-6.72 (m, 2H, Ph), 5.12 (s, 1H, C-4), 3.72 (s, 3H, OCH_3), 2.31 (s, 6H, CH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 163.07, 156.53, 139.84, 138.80, 135.84, 135.36, 132.80, 130.30, 129.89, 129.33, 128.92, 128.27, 128.16, 127.01, 126.27, 118.91, 114.24, 77.36, 77.25, 77.04, 76.72, 72.53, 66.92, 55.43, 21.30.

2.4m *Compound **10ba/bb**: 1-(4′-methoxyphenyl)-3,3-bis(4′-chlorophenylthio)-4-phenylazetidin-2-one*: White solid; yield 54.1% (0.065 g); M.p.

118-120 °C; R_f: 0.40; $C_{28}H_{21}NO_2S_2Cl_2$: Anal. Found: C, 62.36; H, 3.89; N, 2.64% Calc.: C, 62.40; H, 3.93; N, 2.60%. IR (cm^{-1}): $\nu_{(C=O)}$, 1735; ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.59-7.56 (m, 2H, Ph), 7.36-7.28 (m, 7H, Ph), 7.20-7.10 (m, 6H, Ph), 6.77-6.74 (m, 2H, Ph), 5.13 (s, 1H, C-4), 3.72 (s, 3H, OCH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 164.05, 157.75; 138.85, 138.25, 135.20, 134.89, 132.90, 130.75, 129.90, 129.25, 128.95, 128.20, 127.95, 127.05, 126.75, 118.95,114.50, 77.75, 77.25, 77.02, 76.75, 72.25, 67.85, 55.50.

2.4n *Compound* ***10ca/cb****: 1-phenyl-3,3-bis(4′-methylphenylthio)-4-phenylazetidin-2-one*: White solid; yield 54% (0.051 g); M.p. 90-93 °C; R_f: 0.56; $C_{29}H_{25}NOS_2$: Anal. Found: C, 74.51; H, 5.32; N, 2.95% Calc.: C, 74.48; H, 5.38; N, 2.99%. IR (cm^{-1}): $\nu_{(C=O)}$, 1750; ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.55-7.53 (m, 2H, Ph), 7.39-7.25 (m, 5H, Ph), 7.21-7.11 (m, 6H, Ph), 7.07-7.01 (m, 5H, Ph), 5.17 (s, 1H, C-4), 2.30 (s, 3H, CH_3), 2.31 (s, 3H, CH_3); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 163.31, 139.96, 138.91, 136.89, 135.88, 135.43, 132.65, 129.95, 129.39, 129.01, 128.98, 128.33, 128.09, 126.88, 126.22, 124.34, 117.55, 77.41, 77.30, 77.09, 76.77, 72.51, 66.82, 21.34.

2.4o *Compound* ***10da/db****: 1-phenyl-3,3-bis(4′-chlorophenylthio)-4-phenylazetidin-2-one*: White solid; yield 42.2% (0.052 g); M.p. 101-102 °C; R_f: 0.7; $C_{27}H_{19}NOS_2Cl_2$: Anal. Found: C, 63.72; H, 3.79; N, 2.72% Calc.: C, 63.77; H, 3.76; N, 2.75%. IR (cm^{-1}): $\nu_{(C=O)}$, 1740; ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.70-7.67 (m, 2H, Ph), 7.59-7.45 (m, 5H, Ph), 7.31-7.25 (m, 6H, Ph), 7.11-7.05 (m, 5H, Ph), 5.17 (s, 1H, C-4); ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 162.76, 132.02, 136.68, 136.56, 136.14, 135.13, 132.39, 132.12, 129.96, 129.39, 129.32, 129.18, 128.78, 128.69, 128.52, 128.25, 128.05, 127.69, 125.12, 124.16, 117.71, 117.55, 77.36, 77.25, 77.05, 76.73, 72.35, 68.71, 67.23.

3. Results and Discussion

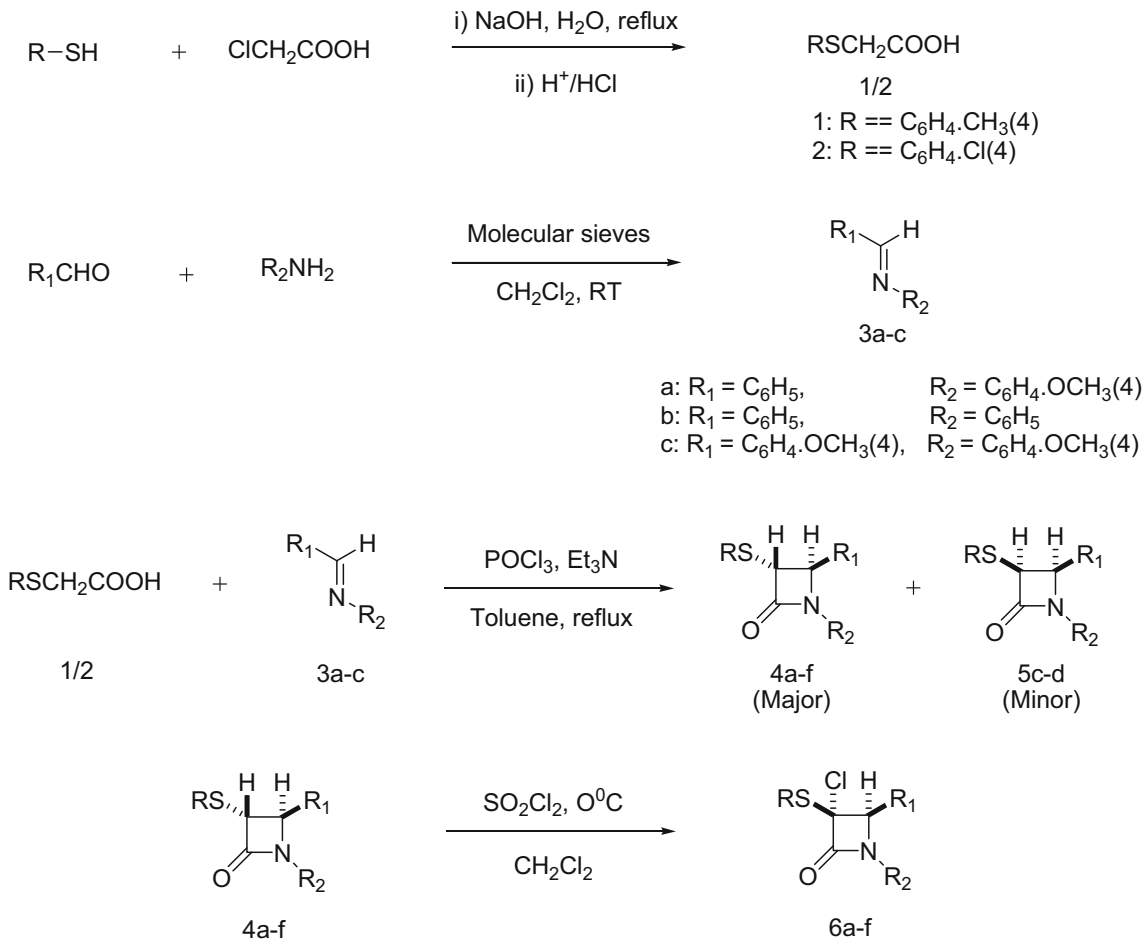
Our previous studies have shown that *cis*-3-chloro-3-phenyl/benzyl/methylthioβ-lactams[9–12] are suitable substrates for C-3 nucleophilic substitution in the presence of Lewis acid ($TiCl_4$/$SnCl_4$). However, the reaction results in the formation of a mixture of products which included monosubstituted, disubstituted as well as 3,3–bisphenylthio-β-lactams as the side product. So, the present studies were aimed to find if the substitution of phenylthio group at C-3 by some electron releasing or electron-withdrawing group will change the product profile. Further, it was envisaged to study whether this substitution on the phenyl ring will have any effect on the stereochemistry of the product formed.

For these studies, *p*-methyl and *p*-chlorothiophenol were taken as the starting substrates which on reaction with chloroacetic acid gave 2-(4′-methyl/chlorophenylthio)ethanoic acid **1** & **2** respectively.[15] Further reaction of compound **1** & **2** with Schiff base **3** in the presence of triethylamine and phosphorus oxychloride resulted in the formation of *trans*-3-(4′-methyl/chlorophenylthio) β-lactams **4** as the major product. However, with Schiff base **3b**, the reaction also gave *cis*-3-(4′-methyl/chlorophenylthio) β-lactam **5b** as the minor product. The stereochemistry of these β-lactams was assigned based on the coupling constant values of C3-H and C4-H ($J = 2.36$ Hz for *trans* & $J = 5.6$ Hz for *cis* isomer) (Scheme 1). The preferential formation of *trans*-β-lactams in this reaction can be rationalized on the basis of cyclization of isomerized zwitterionic intermediate.[16,17] However, the formation of minor *cis* β-lactams **5c** & **5d** indicates direct ring closure of zwitterionic intermediate substituted with sterically less hindered substituent at C-4.[16, 17]

The formation of *cis* β-lactams with phenyl/benzyl/methylthio substituents at C-3 has not been reported so far. So, to the best of our knowledge, this is the first example where *cis* β-lactams of type **5** have been synthesised. However, as the *cis* isomer was a minor product so it could not be used for further studies. The results are summarized in Table 1.

Only *trans*-3-(4′-methyl/chlorophenylthio) β-lactams **4** was subjected to chlorination reaction with sulfuryl chloride in dichloromethane at 0 °C. The reaction furnished *cis*-3-chloro-3-(4′-methyl/chlorophenylthio)-β-lactams **6** in good yields (Table 2). The structures of compounds **6** were confirmed on the basis of FTIR, ^{1}H NMR and ^{13}C NMR spectroscopic analysis. The stereochemistry of β-lactams was assigned on the basis of correlation of spectral data of **6** with that of *cis*-3-chloro-3-phenylthio-β-lactams whose stereochemistry has already been established by X-ray crystallographic analysis.[16] These compounds were then used as a substrate for Lewis acid promoted C-3 functionalization.

Initial studies were carried out using **6a** and treating it with anisole as the nucleophile in the presence of $TiCl_4$ in dichloromethane under nitrogen atmosphere at 0 °C. The reaction was done using optimised conditions from our previous work. The product profile showed the formation of two compounds which after chromatographic purification were found to be 1-(4′-methoxyphenyl)-3,3-bis(4′-methoxyphenyl)-4-phenylazetidin-2-one **7aa** and 1-(4′-methoxyphenyl)-3,3-bis(4′-methylphenylthio)-4-phenylazetidin-2-one **10aa** based on their spectroscopic characterization. These results were similar as reported earlier for *cis*-3-



Scheme 1. Synthesis of *trans* and *cis*-3-(4′-methyl/chlorophenylthio) β-lactams.

Table 1. Synthesis of *trans* and *cis*-3-(4′-methyl/chlorophenylthio) β-lactams (**4a-f** & **5c-d**) from 2-(4′-methyl/chlorophenylthio)ethanoic acid (**1/2**) and Schiff base (**3a-c**) using $POCl_3$ and Et_3N.

Entry	R	R_1	R_2	Total yield (%)	*Trans* (%) (**4**)	*Cis* (%) (**5**)
1	$C_6H_4.CH_3(4)$	C_6H_5	$C_6H_4.OCH_3(4)$	55	**4a** (55)	-
2	$C_6H_4.Cl(4)$	C_6H_5	$C_6H_4.OCH_3(4)$	50	**4b** (50)	-
3	$C_6H_4.CH_3(4)$	C_6H_5	C_6H_5	52	**4c** (39.3)	**5c** (12.7)
4	$C_6H_4.Cl(4)$	C_6H_5	C_6H_5	54	**4d** (40.6)	**5d** (13.4)
5	$C_6H_4.CH_3(4)$	$C_6H_4.OCH_3(4)$	$C_6H_4.OCH_3(4)$	75	**4e** (75)	-
6	$C_6H_4.Cl(4)$	$C_6H_4.OCH_3(4)$	$C_6H_4.OCH_3(4)$	79	**4f** (79)	-

chloro-3-phenylthio β-lactams[9,11] indicating that substrate **6a** has the same reactivity.

Next, for these reactions, 1,4-dimethoxybenzene was used as the nucleophile. The treatment of compound **6a** with this nucleophile resulted in the formation of three new spots. After chromatographic purification, the upper spot was found to be that of 1-(4′-methoxyphenyl)-3,3-bis(4′-methylphenylthio)-4-phenylazetidin-2-one **10ab** and both the lower two spots showed the data for the monosubstituted product. The main difference was in the position of C-4 proton which resonated at $\delta = 5.52$ & 5.12 ppm. The same reaction with *cis*-3-chloro-3-phenylthio β-lactam had been reported to give disubstituted product while 3-benzylthio gave *trans* monosubstituted product ($\delta = 5.19$) whose stereochemistry had been established on the basis of their stereospecific desulfurization studies.[11] The 3-methylthio-β-lactams had a

Table 2. Synthesis of *cis*-3-chloro-3-(4′-methyl/chlorophenylthio)-β-lactams (**6a-d**) from *trans*-3-(4′-methyl/chlorophenylthio) β-lactams (**4a-d**) using SO_2Cl_2.

Entry	Substrate	Product yield (%)
1	**4a**	**6a** (90)
2	**4b**	**6b** (92)
3	**4c**	**6c** (91)
4	**4d**	**6d** (89)

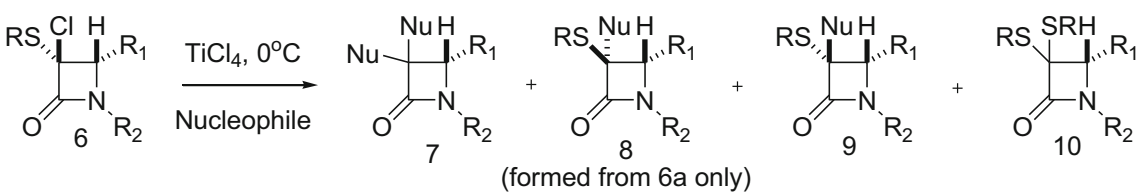
preference for *cis* monosubstituted products ($\delta = 5.21$) over *trans* isomer ($\delta = 4.97$), whose stereochemistry was assigned on the basis of single-crystal X-ray structure analysis.[12] Based on these correlation studies that *trans* isomer resonates at lower value and other spectroscopic data, the upper compound was identified to be *cis*-1-(4′-methoxyphenyl)-3-(2′,5′-dimethoxyphenyl)-3-(4′-methylphenylthio)-4-phenylazetidin-2-one **9ab** ($\delta = 5.52$) and lower as *trans*-1-(4′-methoxyphenyl)-3-(2′,5′-dimethoxyphenyl)-3-(4′-methylphenylthio)-4-phenylazetidin-2-one **8ab** ($\delta = 5.12$).

The other substrate tried for these studies was **6b** having electron-withdrawing chloro group at phenylthio substituent at C-3. It was envisaged that this different substitution may have a different effect on reaction results. However, here also the reaction showed the same reactivity profile as seen in the case of **6a**. With 1,4-dimethoxy benzene as the nucleophile, for these compounds again *cis* monosubstituted product was obtained preferably (Table 3). Further to study the effect of the stoichiometry of nucleophile and temperature on product distribution, the studies were done and the results are summarized in Table 3.

It was concluded from the studies that the 1: 1.5 (substrate: nucleophile) at 0 °C was the best reaction conditions (Entry 3 and 10, Table 3). It has also been observed that higher temperature gave an unidentified mixture and higher nucleophile concentration has no significant effect on product ratio.

Table 3. Study of the effect of stoichiometry and temperature on Lewis acid-catalyzed reactions of *cis*-3-(4′-methyl/chlorophenylthio) β-lactams.

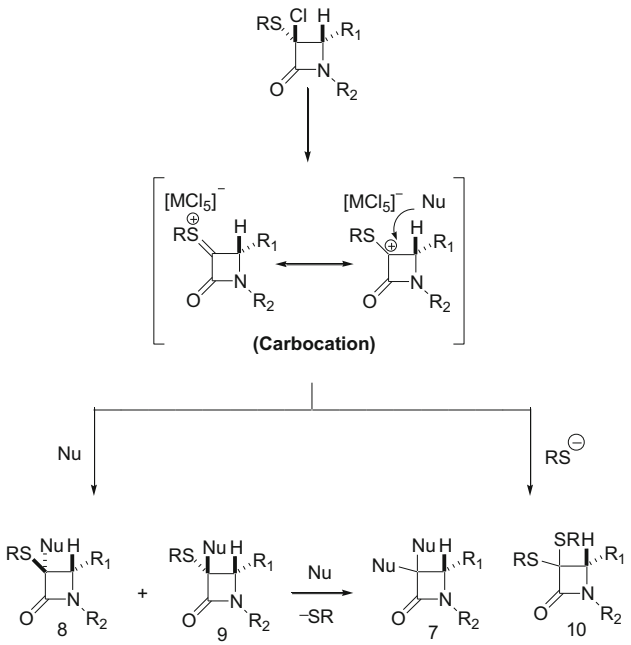
Entry	Substrate	Nucleophile (equivalents)	Temp. (°C)	**7** (%)	**8** (%)	**9** (%)	**10** (%)	Unreacted reactant (%)
1	**6a**	Anisole (1.0)	0	57.4	-	-	24.6	18
2	**6a**	Anisole (1.0)	25	50.4	-	-	21.6	16
3	**6a**	Anisole (1.5)	0	63.6	-	-	36.3	-
4	**6a**	Anisole (2.0)	0	63	-	-	37	-
5	**6b**	Anisole (1.0)	0	36.8	-	-	43.2	20
6	**6b**	Anisole (1.0)	25	33.2	-	-	38.8	15
7	**6b**	Anisole (1.5)	0	45.8	-	-	54.1	-
8	**6b**	Anisole (2.0)	0	46.2	-	-	53.8	-
9	**6a**	1,4-Dimethoxybenzene (1.0)	0	-	41	37	12	10
10	**6a**	1,4-Dimethoxybenzene (1.5)	0	-	45	40	15	-
11	**6a**	1,4-Dimethoxybenzene (1.5)	25	-	42.2	36.8	13	-
12	**6a**	1,4-Dimethoxybenzene (2.0)	0	-	44.5	40.5	15	-
13	**6b**	1,4-Dimethoxybenzene (1.5)	0	-	-	48.7	51.3	-
14	**6b**	1,4-Dimethoxybenzene (2.0)	0	-	-	49	51	-
15	**6b**	1,4-Dimethoxybenzene (2.0)	25	-	-	43	48	-



Scheme 2. Lewis acid-catalyzed reactions *cis*-3-(4′-methyl/chlorophenylthio) β-lactams.

Table 4. Results of Lewis acid catalyzed reactions of *cis*-3-chloro-3-(4′-methyl/chlorophenylthio)-β-lactams (**6a-d)** with nucleophiles using $TiCl_4$ at 0 °C.

Entry	Substrate (**6**)	Nucleophile	**7** (% yield)	**8** (% yield)	**9** (% yield)	**10** (% yield)
1	**6a**	Anisole	**7aa** (63.6)	-	-	**10aa** (36.3)
2	**6a**	1,4-dimethoxy benzene	-	**8ab** (45)	**9ab** (40)	**10ab** (15)
3	**6a**	Allylsilane	-	-	**9ac** (89)	-
4	**6b**	Anisole	**7ba** (45.8)	-	-	**10ba** (54.1)
5	**6b**	1,4-dimethoxy benzene	-	-	**9bb** (48.7)	**10bb** (51.3)
6	**6b**	Allylsilane	-	-	**9bc** (90)	-
7	**6c**	Anisole	**7ca** (45)	-	-	**10ca** (54)
8	**6c**	1,4-dimethoxy benzene	-	-	**9cb** (42.8)	**10cb** (57)
9	**6c**	Allylsilane	-	-	**9 cc** (90)	-
10	**6d**	Anisole	**7da** (57.7)	-	-	**10da** (42.2)
11	**6d**	1,4-dimethoxy benzene	-	-	**9db** (69)	**10db** (31)
12	**6d**	Allylsilane	-	-	**9dc** (94)	-



Scheme 3. Mechanism showing C-3 substitution.

The similar reactions were tested with substrate **6c** and **6d** which stereospecifically gave *cis* monosubstituted product **9**. The reaction using allylsilane as nucleophile furnished the same product as obtained from earlier studies. It was characterized by spectroscopic data and based on that it can be inferred that for this product the stereochemistry is not altered by the type of substituent at C-3 of the starting substrate.[11,12] However, the substrate was found to be unreactive towards many nucleophiles like toluene, phenol, thiophene, pyrrole, bromobenzene which otherwise had been reported to give 3-substituted products.[9,11] The results of these studies are summarized in Scheme 2 and Table 4.

The structures of all new compounds **7-9** were confirmed by spectroscopic analysis such as FTIR, NMR and elemental analysis.

These results indicate the low reactivity of substrates of type **6a-d** towards these reactions. Also, the substantial formation of 3,3-bisthio β-lactams supports this fact. These substrates give stereoselective *cis*-monosubstituted products. All these facts support the intermediacy of stabilized carbocation which gives preferably *cis* product if it is monosubstituted. However, the overall outcome may be combined effect of stabilization by substituents at C-3 and steric hindrance posed by substituents at C-4 & N. The reaction also gives disubstituted and bisthio products due to the ambiphilic behavior of -SPh group. The possible mechanism for the reaction is given in Scheme 3.

4. Conclusions

To summarize, we have investigated the synthetic utility of 3-substituted phenylthio azetidine-2-ones towards C-3 functionalization. The substitution of phenylthio group at C-3 by either electron releasing or withdrawing does not have much effect on the product profile. However, in some cases, it results in the formation of starting *cis* β-lactams with phenyl substituent at C-4 and nitrogen which otherwise cannot be prepared using unsubstituted thio groups. Also, these substituted *cis*-3-chloro β-lactams gave stereoselective *cis*-3-monosubstituted products with some nucleophiles although these are not as reactive as 3-unsubstituted phenylthioβ-lactams and failed to give substitution with many nucleophiles.

Supplementary Information (SI)

All additional information about the characterization of compounds (**4-10**) using ^{1}H NMR, ^{13}C NMR and HR-MS technique (Figures S1-S56) are given in the supporting information. Supplementary Information is available at www.ias.ac.in/chemsci.

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