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Facile Synthesis of Novel C-3 Monosubstituted 3-phenylthio-β-lactams

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Abstract

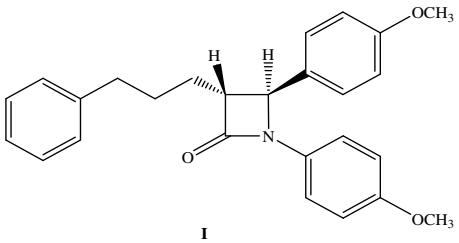
An efficient and operationally simple strategy for the synthesis of C-3 monosubstituted monocyclic β-lactams is described. Treatment of ethyl 2-phenylthioethanoate (1) with SO_2Cl_2 in dry methylene chloride at 0^oC yields ethyl 2-chloro-2-phenylthioethanoate(2). Lewis acid ($TiCl_4$, $SnCl_4$ and $ZnCl_2$) mediated functionalization of (2) using various aliphatic and aromatic compounds (nucleophiles) gives monosubstituted phenythioethanoates (3a-e). These esters on basic hydrolysis and subsequent acidification gave monosubstituted phenythioethanoic acids (4a-e). Reaction of these phenythioethanoic acids and appropriate imines in the Staudinger reaction using $POCl_3$ as condensing agent led to the synthesis of novel C-3 monosubstituted 3-phenylthio-β-lactams.

Keywords: 3-phenylthio- β-Lactam, Lewis acid, nucleophiles, *cis*- and *trans*-3-monosubstituted-3-phenylthio-β-lactams.

Introduction

The β-lactam heterocycle is the key structural unit of the most widely used β-lactam antibiotics[1-3]. The discovery of new biologically active β-lactams such as I as cholesterol acyl transferase inhibitors[4], II as thrombin inhibitors[5], antitumor active β-lactams[6] have motivated growing interest in the synthesis of new β-lactam systems. β-Lactams containing Pyrazoline ring have also been reported to have antimicrobial properties[7]. Biologically active derivatives of 1,3-diketones have been recently synthesized using aromatic amines/diazonium salts and N-benzy-N-phenylhydrazine[8] and with aromatic aldehydes and N-benzyl-N-phenyl hydrazine[9]. They show biological activity against gram-positive Cocci and Bacilli, and gram-negative Bacilli. Abdoulaye *et al.*[10] have synthesized 4-Acyl isochroman-1,3-Diones and demonstrated their anti-oxidant properties.

The biological activity of the azetidin-2-one ring is greatly influenced by the type of substitution attached to the ring. Therefore, functionalization of the azetidin-2-one framework, bearing a varied array of appendages at C-3 and C-4, is pivotal for the development of new β-lactam antibiotics. In our earlier studies towards C-3 functionalization of azetidin-2-ones[11-18], the synthetic potential of cationic β-lactam equivalent of type **III** has been explored for the synthesis of C-3 substituted azetidin-2-ones.



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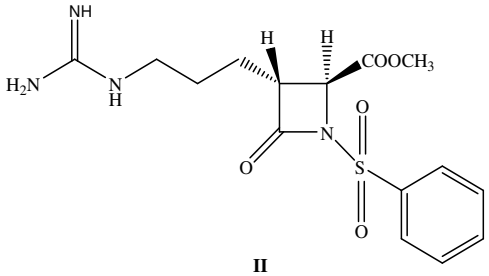
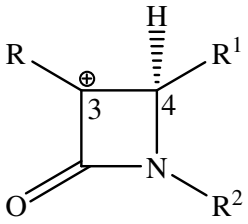


II

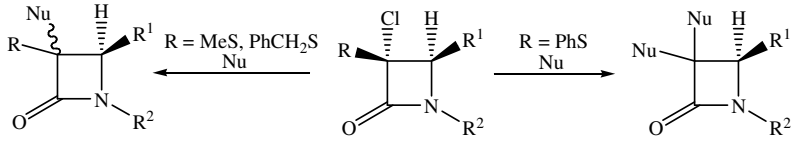
Figure-1
Biologically active monocyclic β-lactams



III

Figure-2
Cationic β-lactam equivalent

These studies revealed that *cis*-3-chloro-3-phenyl/benzyl/methylthio-β-lactams are capable of functioning as β-lactam carbocation equivalents in the presence of a Lewis acid ($TiCl_4$ or $SnCl_4$) and react with a number of active aromatic, heterocyclic and aliphatic compounds (nucleophiles) to afford substitution at C-3 of β-lactam ring. 3-Benzylthio and 3-methylthio-β-lactams favoured monosubstitution at C-3 of β-lactams whereas *cis*-3-chlorophenylthio-β-lactams preferentially undergo C-3 disubstitution and produced mainly *cis*-3-disubstituted β-lactams (scheme-1).



Scheme-1
Lewis acid mediated functionalization of cis-3-chloro-3-phenyl/benzyl/methylthio-β-lactams

Thus, in order to prepare C-3 monosubstituted phenylthio-β-lactams it was envisaged to synthesize various α-substituted 2-phenylthioethanoates and corresponding 2-phenylthioethanoic acids by using an efficient and operationally simple strategy. These α-substituted 2-phenylthioethanoic acids may serve as suitable synthons for synthesis of desired C-3 monosubstituted phenylthio-β-lactams via the Staudinger Reaction.

In this regards, we present here the synthesis and characterization of variety of structurally diverse substituted phenylthioethanoates and phenylthioethanoic acids and C-3 monosubstituted phenylthio-β-lactams.

Material and Methods

^{1}H and ^{13}C NMR spectra were recorded at 300/400 and 75/100 MHz, respectively, in $CDCl_3$ solution using JEOL 300 and BRUCKER AVANCE II 400 MHz NMR spectrometers. Chemical shifts are given in parts per million relative to tetramethylsilane as an internal standard (δ=0 ppm) for ^{1}H NMR and $CDCl_3$ (δ=77.0 ppm) for ^{13}C NMR. IR spectra were taken on an FTIR spectrophotometer and are reported in cm^{-1}. The elemental analysis (C, H, N) was carried out in microanalytical section of Sophisticated Analytical Instrumentation Facility (SAIF), Panjab University, Chandigarh using a PERKIN-ELMER 2400 elemental analyzer. Column chromatography was performed using Merck Silica Gel (60-120 mesh) using ethyl acetate/hexanes (8:92) as an eluent system. Thin-layer chromatography (TLC) was performed using Merck Silica Gel G using ethyl acetate/hexanes (10:90) as an eluent system. For visualization, TLC plates were stained with iodine vapours. Melting points are uncorrected. All commercially available compounds/reagents were used without further purification. Dichloromethane and Chloroform distilled over P_2O_5 was redistilled over CaH_2 before use. Toluene was distilled over sodium-benzophenone immediately before use. Crystallographic data (excluding structure factors) of compound **6h**[19] in CIF format have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21 EZ, UK [Fax: (internet) +44 1223/336033; e-mail: deposit@ccdc.cam.ac.uk]. All other relevant information regarding the data and supplementary publication CCDC number is presented in respective reference.

Compounds ethyl 2-phenylthioethanoate **1** and ethyl 2-chloro-2-phenylthioethanoate **2** were prepared by the procedures[11] and characterized as described in the cited reference (scheme 2).

Synthesis of ethyl α-substituted-2-phenylthioethanoate 3(a-e): Compounds **3(a-e)** were prepared by using the same method as reported for C-3 substituted β-lactams[12] in the cited reference, starting from chloro-β-lactams.

Ethyl 2-(2',5'-dimethoxyphenyl)-2-phenylthioethanoate (3a): To a well stirred solution of **2** (1 mmol) in 10 mL dry methylene chloride was added 1,4-dimethoxybenzene (1.1 mmol) followed by stannic chloride (1.2 mmol) via a syringe, under inert atmosphere, at 0 °C. The reaction mixture was stirred for 1h at the same temperature. The progress of the reaction was checked by TLC. The work-up was done as usual to give the product as a colourless oil. Yield: 65%. I.R. (cm^{-1}, $CHCl_3$): 1737 (C=O). ^{1}H NMR (δ ppm): 7.29-6.61 (8H, m, Ar-*H*), 5.24 (1H, s, C*H*), 4.00 (2H, q, J = 7.2 Hz, OCH_2), 3.62 (3H, s, OCH_3), 3.60 (3H, S, OCH_3), 1.07 (3H, t, J = 7.2 Hz, CH_3). ^{13}C NMR (δ ppm): 170.3, 153.6, 150.7, 134.3, 132.6, 128.7, 127.6, 125.2, 114.7, 114.6, 111.9, 61.3, 56.2, 55.5, 48.6, 14.1. Analysis calculated for $C_{18}H_{20}SO_4$: C, 65.04; H, 6.06; S, 9.65. Found: C, 64.42; H, 6.04; S, 9.60%.

Ethyl 2-(2'-methoxynaphthyl)-2-phenylthioethanoate (3b): colourless oil. Yield: 55%. I.R. (cm^{-1}, $CHCl_3$): 1735 (C=O). ^{1}H NMR (δ ppm): 7.98-6.98 (11H, m, Ar-*H*), 5.46 (1H, s, C*H*), 4.04 (2H, q, J = 7.2 Hz, OCH_2), 3.89 (3H, s, OCH_3), 1.04 (3H, t, J = 7.2 Hz, CH_3). ^{13}C NMR (δ ppm): 170.3, 158.2, 134.6, 132.9, 132.7, 130.4, 130.0, 129.5, 128.9, 128.0, 127.8, 127.5, 123.0, 118.6, 61.6, 54.3, 29.8, 14.2. Analysis calculated for $C_{21}H_{20}SO_3$: C, 71.56; H, 5.72; S, 9.10. Found: C, 70.76; H, 5.68; S, 9.06%.

Ethyl 2-(allyl)-2-phenylthioethanoate (3c): yellow oil. Yield: 75%. I.R. (cm^{-1}, $CHCl_3$): 1732 (C=O), 1641 (C=C). ^{1}H NMR (δ ppm): 7.39-7.18 (5H, m, Ar-*H*), 5.79-5.66 (1H, m, CH_2CH=CH_2), 5.08-5.00 (2H, m, CH_2CH=CH_2), 4.01 (2H, q, J = 7.2 Hz, OCH_2), 3.62-3.57 (1H, m, C*H*), 2.60-2.38 (2H, m, CH_2CH=CH_2), 1.10 (3H, t, J = 7.2 Hz, CH_3). ^{13}C NMR (δ ppm): 171.4, 133.8, 133.2, 133.1, 128.8, 127.9, 117.9, 60.9, 50.2, 35.8, 14.0. Analysis calculated for $C_{13}H_{16}SO_2$: C, 66.07; H, 6.82; S, 13.57. Found: C, 66.02; H, 6.43; S, 13.76%.

Ethyl 2-(prop-2-enyloxy)-2-phenylthioethanoate (3d): colourless oil. Yield: 60%. I.R. (cm^{-1}, $CHCl_3$): 1737 (C=O), 1562 (C=C). ^{1}H NMR (δ ppm): 7.41-7.19 (5H, m, Ar-*H*), 5.88-5.75 (1H, m, OCH_2CH=CH_2), 5.24-5.10 (3H, m, OCH_2CH=CH_2 and C*H*), 4.35-4.09 (2H, m, OCH_2CH=CH_2), 4.01 (2H, q, J = 7.2 Hz, OCH_2), 1.13 (3H, t, J = 7.2 Hz, CH_3). ^{13}C NMR (δ

ppm): 166.4, 133.1, 131.8, 130.2, 127.8, 127.6, 118.2, 82.7, 67.9, 60.6, 13.1. Analysis calculated for $C_{13}H_{16}SO_3$: C, 61.88; H, 6.39; S, 12.71. Found: C, 6O.58; H, 6.31; S, 12.62%.

Ethyl 2-(prop-2-ynyloxy)-2-phenylthioethanoate (3e): colourless oil. Yield: 58%. I.R. (cm^{-1}, $CHCl_3$): 2361 (C≡C), 1751 (C=O). ^{1}H NMR (δ ppm): 7.51-7.27 (5H, m, Ar-*H*), 5.49 (IH, s, C*H*), 4.66 (1H, dd, J = 2.4 Hz, J = 15.9 Hz, OCH_aH_b), 4.48 (1H, dd, J = 2.4 Hz, J = 15.9 Hz, OCH_aH_b), 4.11 (2H, q, J = 7.2 Hz, OCH_2), 2.48 (1H, t, J = 2.4 Hz, C≡CH), 1.10 (3H, t, J = 7.2 Hz, CH_3). ^{13}C NMR (δ ppm): 167.0, 134.3, 130.5, 128.9, 128.8, 82.6, 78.1, 76.2, 61.7, 54.9, 13.9. Analysis calculated for $C_{13}H_{14}SO_3$: C, 62.38; H, 5.64; S, 12.81. Found: C, 61.78; H, 5.58; S, 12.73%.

Synthesis of α-substituted-2-phenylthioethanoic acid 4(a-e): Compounds **4(a-e)** were prepared by using the same method as reported for phenylselenoalkanoic acids in the cited reference[14].

2-(2',5'-Dimethoxyphenyl)-2-phenylthioethanoic acid (4a): To a solution of potassium hydroxide (1.4 mmol) in methanol/water (3/1; 4 mL) at 0°C, ethyl 2-(2',5'-dimethoxyphenyl)-2-phenylthioethanoate **3a** (1 mmol) in methanol (60 mL) was added dropwise. The resultant mixture was stirred for 1h. Progress of the reaction was monitored by TLC. The precipitates obtained were further dissolved in a minimum amount of water and acidified with conc. hydrochloric acid. The completion of the reaction was monitored by change of pH, which was checked at regular intervals. The work-up was done as usual to give the product **4a**. Yield: 83%. I.R. (cm^{-1}, $CHCl_3$): 3380 (O-H), 1708 (C=O). ^{1}H NMR (δ ppm): 10.33 (1H, bs, O-*H*), 7.28-6.60 (8H, m, Ar-*H*), 5.21 (1H, s, C*H*), 3.58 (3H, s, OCH_3), 3.56 (3H, S, OCH_3). ^{13}C NMR (δ ppm): 170.3, 153.6, 150.7, 134.3, 132.6, 128.7, 127.6, 125.2, 114.7, 114.6, 111.9, 56.2, 55.5, 48.6. Analysis calculated for $C_{16}H_{16}SO_4$: C, 63.14; H, 5.30; S, 10.54. Found: C, 63.10; H, 5.12; S, 10.42%.

2-(2'-Methoxynaphthyl)-2-phenylthioethanoic acid (4b): Yield: 80%. I.R. (cm^{-1}, $CHCl_3$): 3360 (O-H), 1710 (C=O). ^{1}H NMR (δ ppm): 10.25 (1H, bs, O-*H*), 7.98-6.98 (11H, m, Ar-*H*), 5.46 (1H, s, C*H*), 3.89 (3H, s, OCH_3). ^{13}C NMR (δ ppm): 170.3, 158.2, 134.6, 132.9, 132.7, 130.4, 130.0, 129.5, 128.9, 128.0, 127.8, 127.5, 123.0, 118.6, 61.6, 54.3, 29.8, 14.2. Analysis calculated for $C_{19}H_{16}SO_3$: C, 71.56; H, 5.72; S, 9.10. Found: C, 70.76; H, 5.68; S, 9.06%.

2-(Allyl)-2-phenylthioethanoic acid (4c): Yield: 85%. I.R. (cm^{-1}, $CHCl_3$): 3380 (O-H), 1708 (C=O), 1583 (C=C). ^{1}H NMR (δ ppm): 10.54(1H, bs, O-*H*), 7.40-7.06 (5H, m, Ar-*H*), 5.79-5.68 (1H, m, CH_2CH=CH_2), 5.10-5.02 (2H, m, CH_2CH=CH_2), 3.58-3.53 (1H, m, C*H*), 2.59-2.40 (2H, m, CH_2CH=CH_2). ^{13}C NMR (δ ppm): 171.4, 133.8, 133.2, 133.1, 128.8, 127.9, 117.9, 50.2, 35.8. Analysis calculated for $C_{11}H_{12}SO_2$: C, 63.43; H, 5.81; S, 15.40. Found: C, 63.32; H, 5.68; S, 14.56%.

2-(Prop-2-enyloxy)-2-phenylthioethanoic acid (4d): Yield: 82%. I.R. (cm^{-1}, $CHCl_3$): 3358 (O-H), 1710 (C=O), 1556 (C=C). ^{1}H NMR (δ ppm): 8.96 (1H, bs, O-*H*), 7.41-7.22 (5H, m, Ar-*H*), 5.81-5.79 (1H, m, OCH_2CH=CH_2), 5.24-5.10 (3H, m, OCH_2CH=CH_2 and C*H*), 4.35-4.14 (2H, m, OCH_2CH=CH_2). ^{13}C NMR (δ ppm): 166.4, 133.1, 131.8, 130.2, 127.8, 127.6, 118.2, 82.7, 67.9. Analysis calculated for $C_{11}H_{12}SO_3$: C, 58.90; H, 5.39; S, 14.30. Found: C, 58.86; H, 5.31; S, 13.69%.

2-(Prop-2-ynyloxy)-2-phenylthioethanoic acid (4e): Yield: 85%. I.R. (cm^{-1}, $CHCl_3$): 3360 (O-H), 2361 (C≡C), 1708 (C=O). ^{1}H NMR (δ ppm): 8.94 (1H, bs, O-H), 7.51-7.27 (5H, m, Ar-*H*), 5.49 (IH, s, C*H*), 4.66 (1H, dd, J = 2.4 Hz, J = 15.9 Hz, OCH_aH_b), 4.48 (1H, dd, J = 2.4 Hz, J = 15.9 Hz, OCH_aH_b), 2.48 (1H, t, J = 2.4 Hz, C≡CH). ^{13}C NMR (δ ppm): 167.0, 134.3, 130.5, 128.9, 128.8, 82.6, 78.1, 76.2, 54.9. Analysis calculated for $C_{11}H_{10}SO_3$: C, 59.44; H, 4.54; S, 14.43. Found: C, 59.38; H, 4.52; S, 13.88%.

Synthesis of *cis*-and *trans*-C-3 monosubstituted phenylthio-β-lactams 6(a-j) and 7(a-j): Compounds **6(a-j)** and **7(a-j)** were prepared by using the same method as for C-3 substituted phenylthio-β-lactams[11,12] in the cited reference, starting from the appropriate Schiff's base and α-substituted phenylthioethanoic acids **4(a-e).** The spectroscopic data of compounds **6c**[12], **7e**[18] have been reported in the cited reference.

***cis*-1-(4'-Methoxyphenyl)-3-(2',5'-dimethoxyphenyl)-3-phenythio-4-phenylazetidin-2-one (6a):** To a solution of 2-(2',5'-Dimethoxyphenyl)-2-phenylthioethanoic acid **4a** (1.5 mmol), N-(4'-methoxyphenyl)benzylidine **5a** (1 mmol) and triethylamine (3 mmol) in 25 mL dry methylene chloride was added dropwise, under nitrogen atmosphere at 0 °C, a solution of phosphorus oxychloride ($POCl_3$) (1.5 mmol) in 10 mL dry methylene chloride with constant stirring. The reactants were stirred at room temperature and the progress of the reaction was followed by TLC. The work-up was done as usual to give the compound **6a** as a white solid. Yield: 45%. mp 122-125 ^{o}C. I.R. (cm^{-1}, $CHCl_3$): 1740 (C=O). ^{1}H NMR (δ ppm): 7.23-6.23 (17H, m, Ar-*H*), 5.02 (1H, s, C4-*H*), 3.62 (3H, s, OCH_3), 3.59 (3H, s, OCH_3), 3.20 (3H, s, OCH_3). ^{13}C NMR (δ ppm): 164.2, 156.1, 152.8, 135.9, 134.2, 129.2, 128.3, 128.1, 127.4, 118.8, 115.2, 114.7, 114.1, 68.1, 67.6, 55.7, 55.2, 54.5. Analysis calculated for $C_{30}H_{27}NO_4S$: C, 72.41; H, 5.47; N, 2.81; S, 6.44. Found: C, 71.29; H, 5.30; N, 2.78; S, 6.22%.

***trans*-1-(4'-Methoxyphenyl)-3-(2',5'-dimethoxyphenyl)-3-phenythio-4-phenylazetidin-2-one (7a):** White semisolid. Yield: 20%. I.R. (cm^{-1}, $CHCl_3$): 1749 (C=O). ^{1}H NMR (δ ppm): 7.32-6.48 (17H, m, Ar-*H*), 5.41 (1H, s, C4-*H*), 3.71 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.41 (3H, s, OCH_3).

***cis*-1-(4'-Methoxyphenyl)-3-(2',5'-dimethoxyphenyl)-3-phenythio-4-(4'-methoxyphenyl)-azetidin-2-one (6b):** white solid. mp 130-135 ^{o}C. Yield: 30 %. I.R. (cm^{-1}, $CHCl_3$): 1741 (C=O). ^{1}H NMR (δ ppm): 7.44-6.27 (16H, m, Ar-*H*), 4.98 (1H,

s, C4-*H*), 3.60 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.24 (3H, s, OCH_3). ^{13}C NMR (δ ppm): 164.0, 156.0, 153.5, 151.2, 150.1, 137.2, 133.8, 131.2, 129.2, 128.6, 128.1, 127.8, 127.6, 126.7, 118.7, 114.7, 114.4, 114.2, 113.2, 66.9, 65.2, 56.0, 55.8, 55.5, 55.0. Analysis calculated for $C_{31}H_{29}NO_5S$: C, 70.57; H, 5.54; N, 2.65; S, 6.08. Found: C, 70.42; H, 5.45; N, 2.55; S, 6.00%.

***trans*-1-(4'-Methoxyphenyl)-3-(2',5'-dimethoxyphenyl)-3-phenythio-4-(4'-methoxyphenyl)-azetidin-2-one (7b):** yellow oil. Yield: 30 %. I.R. (cm^{-1}, $CHCl_3$): 1741 (C=O). ^{1}H NMR (δ ppm): 7.53-6.60 (16H, m, Ar-*H*), 5.39 (1H, s, C4-*H*), 3.78 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.42 (3H, s, OCH_3).

***cis*-1-(4'-Methoxyphenyl)-3-(2'-methxynaphthyl)-3-phenythio-4-(4'-methoxyphenyl)-azetidin-2-one (6d):** yellow oil. Yield: 35 %. I.R. (cm^{-1}, $CHCl_3$): 1730 (C=O). ^{1}H NMR (δ ppm): 8.40-6.20 (19H, m, Ar-*H*), 5.20 (1H, s, C4-*H*), 3.70 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.60 (3H, s, OCH_3) (for one isomer) and 8.50-6.60 (19H, m, Ar-*H*), 5.30 (1H, s, C4-*H*), 3.75 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.64 (3H, s, OCH_3) (for other isomer). The ^{1}H NMR spectrum showed it to be a mixture of two rotamers as evident from the appearance of two signals for C4-H and a downfield appearance of an aromatic proton. Analysis calculated for $C_{34}H_{29}NO_4S$: C, 74.56; H, 5.34; N, 2.56; S, 5.85. Found: C, 74.43; H, 5.28; N, 2.38; S, 5.67%.

***cis*-1-(4'-Methoxyphenyl)-3-allyl-3-phenythio-4-phenyl-azetidin-2-one (6e):** yellow oil. Yield: 19 %. I.R. (cm^{-1}, $CHCl_3$): 1741 (C=O). ^{1}H NMR (δ ppm): 7.51-6.60 (14H, m, Ar-*H*), 5.98-5.76 (1H, m, CH_2C*H*=CH_2), 5.00-4.65 (3H, m, CH_2CH=CH_aH_b, CH_2CH=CH_aH_b and C4-H), 3.70 (3H, s, OCH_3), 2.60 (2H, m, CH_2CH=CH_2). ^{13}C NMR (δ ppm): 164.1, 155.6, 135.2, 133.7, 132.8, 131.0, 130.7, 129.3, 128.2, 128.1, 126.3, 119.4, 118.5, 114.4, 65.9, 63.6, 55.1, 38.0. Analysis calculated for $C_{25}H_{23}NO_2S$: C, 74.78; H, 5.77; N, 3.49; S, 7.99. Found: C, 74.40; H, 5.48; N, 3.23; S, 7.77%.

***cis*-1-(4'-Methoxyphenyl)-3-allyl-3-phenythio-4-(4'-methoxyphenyl)-azetidin-2-one (6f):** colourless oil. Yield: 20 %. I.R. (cm^{-1}, $CHCl_3$): 1740 (C=O). ^{1}H NMR (δ ppm): 7.41-6.20 (13H, m, Ar-*H*), 5.80-5.72 (1H, m, CH_2C*H*=CH_2), 5.10-4.78 (3H, m, CH_2CH=CH_aH_b, CH_2CH=CH_aH_b and C4-*H*), 3.70 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 2.48 (2H, m, CH_2CH=CH_2). ^{13}C NMR (δ ppm): 162.1, 157.4, 156.3, 136.4, 135.1, 134.2, 132.1, 129.1, 129.3, 128.8, 127.8, 126.4, 119.4, 117.8, 113.7, 68.9, 62.5, 55.5, 55.3, 38.0.

***trans*-1-(4'-Methoxyphenyl)-3-allyl-3-phenythio-4-(4'-methoxyphenyl)-azetidin-2-one (7f):** semisolid. Yield: 45 %. I.R. (cm^{-1}, $CHCl_3$): 1741 (C=O). ^{1}H NMR (δ ppm): 7.51-6.40 (13H, m, Ar-*H*), 5.88-5.64 (1H, m, CH_2C*H*=CH_2), 5.17 (1H, bs, CH_2CH=CH_aH_b), 5.12 (1H, m, CH_2CH=CH_aH_b), 4.95 (1H, s , C4-*H*), 3.76 (3H, s, OCH_3), 3.63 (3H, s, OCH_3), 2.56 (2H, d, J = 7.2 Hz, CH_2CH=CH_2). ^{13}C NMR (δ ppm): 163.1, 158.1, 156.4, 135.2, 132.7, 131.8, 130.0, 129.7, 129.3, 128.2, 128.0, 126.6, 119.4, 118.8, 114.4, 65.9, 63.6, 55.9, 55.1, 43.0. Analysis calculated for $C_{26}H_{25}NO_3S$: C, 72.36; H, 5.84; N, 3.25; S, 7.43. Found: C, 72.18; H, 5.32; N, 3.17; S, 7.37%.

***cis*-1-(4'-Methoxyphenyl)-3-(prop-2-enyloxy)-3-phenythio-4-phenyl-azetidin-2-one (6g):** yellow oil. Yield: 35 %. I.R. (cm^{-1}, $CHCl_3$): 1740 (C=O). ^{1}H NMR (δ ppm): 7.48-6.65 (14H, m, Ar-*H*), 5.58-5.47 (1H, m, OCH_2C*H*=CH_2), 4.99-4.78 (3H, m, CH_2CH=CH_aH_b, CH_2CH=CH_aH_b and C4-*H*), 4.36-4.30 (1H, m, OC*H*aH_bCH=CH_2), 4.15-4.09 (1H, m, OCHaH_bCH=CH_2), 3.60 (3H, s, OCH_3). ^{13}C NMR (δ ppm): 162.0, 155.6, 136.3, 133.2, 131.8, 130.6, 130.2, 129.8, 129.1, 128.6, 128.2, 126.4, 124.9, 118.6, 116.7, 114.2, 113.8, 102.1, 68.9, 68.0, 55.9. Analysis calculated for $C_{25}H_{23}NO_3S$: C, 71.92; H, 5.55; N, 3.35; S, 7.68. Found: C, 71.56; H, 5.42; N, 3.27; S, 7.65%.

***trans*-1-(4'-Methoxyphenyl)-3-(prop-2-enyloxy)-3-phenythio-4-phenyl-azetidin-2-one (7g):** colourless oil. Yield: 33 %. I.R. (cm^{-1}, $CHCl_3$): 1750 (C=O). ^{1}H NMR (δ ppm): 7.50-6.68 (14H, m, Ar-*H*), 5.99-5.90 (1H, m, OCH_2C*H*=CH_2), 5.24-5.14 (1H, m, CH_2CH=CH_aH_b), 5.12-5.07 (1H, m, CH_2CH=CH_aH_b), 5.07 (1H, s, C4-H), 4.49-4.43 (1H, m, OC*H*aH_bCH=CH_2), 4.24-4.18 (1H, m, OCHaH_bCH=CH_2), 3.87 (3H, s, OCH_3), 3.73 (3H, s, OCH_3). ^{13}C NMR (δ ppm): 162.4, 156.4, 154.4, 135.3, 133.3, 133.0, 130.3, 128.9, 128.6, 128.3, 127.8, 126.3, 119.0, 117.8, 114.4, 97.3, 68.2, 68.1, 55.6, 55.3.

***cis*-1-(4'-Methoxyphenyl)-3-(prop-2-enyloxy)-3-phenythio-4-(4'-methoxyphenyl)-azetidin-2-one (6h):** white crystalline solid. mp: 128-132 °C. Yield: 42 %. I.R. (cm^{-1}, $CHCl_3$): 1750 (C=O). ^{1}H NMR (δ ppm): 7.41-6.63 (13H, m, Ar-*H*), 5.63-5.51 (1H, m, OCH_2C*H*=CH_2), 4.94-4.85 (3H, m, OCH_2CH=CH_aH_b, OCH_2CH=CH_aH_b and C4-*H*), 4.37-4.31 (1H, m, OC*H*aH_bCH=CH_2), 4.14-4.08 (1H, m, OCHaH_bCH=CH_2), 3.68 (3H, s, OCH_3), 3.63 (3H, s, OCH_3). ^{13}C NMR (δ ppm): 161.2, 159.9, 154.4, 133.3, 133.1, 132.8, 131.4, 130.5, 129.4, 128.9, 128.3, 128.1, 124.9, 118.9, 116.7, 114.3, 113.8, 96.2, 68.8, 66.9, 55.2, 55.0. Analysis calculated for $C_{26}H_{25}NO_4S$: C, 69.78; H, 5.63; N, 3.13; S, 7.16. Found: C, 69.66; H, 5.52; N, 3.10; S, 7.02%.

***trans*-1-(4'-Methoxyphenyl)-3-(prop-2-enyloxy)-3-phenythio-4-(4'-methoxyphenyl)-azetidin-2-one (7h):** colourless oil. Yield: 20 %. I.R. (cm^{-1}, $CHCl_3$): 1750 (C=O). ^{1}H NMR (δ ppm): 7.52-6.68 (13H, m, Ar-*H*), 5.85-5.72 (1H, m, OCH_2C*H*=CH_2), 5.24-5.18 (1H, m, CH_2CH=CH_aH_b), 5.12-5.08 (1H, m, CH_2CH=CH_aH_b), 5.07 (1H, s, C4-*H*), 4.49-4.43 (1H, m, OC*H*aH_bCH=CH_2), 4.24-4.18 (1H, m, OCHaH_bCH=CH_2), 3.87 (3H, s, OCH_3), 3.73 (3H, s, OCH_3). ^{13}C NMR (δ ppm): 162.4, 156.4, 154.4, 135.3, 133.3, 133.0, 130.3, 128.9, 128.6, 128.3, 127.8, 126.3, 119.0, 117.8, 114.4, 97.3, 68.2, 68.1, 55.6, 55.3.

***cis*-1-(4'-Methoxyphenyl)-3-(prop-2-ynyloxy)-3-phenythio-4-phenyl-azetidin-2-one (6i):** semi-solid. Yield: 35%. I.R. (cm^{-1}, $CHCl_3$): 1755 (C=O). ^{1}H NMR (δ ppm): 7.53-7.20 (14H, m, Ar-

H), 5.04 (IH, s, C4-*H*), 4.58 (1H, dd, J = 2.4 Hz, J = 15.9 Hz, OCH_aH$_b$), 4.40 (1H, dd, J = 2.4 Hz, J = 15.9 Hz, OCH$_a$$H_b$), 3.67 (3H, s, OC$H_3$), 2.27 (1H, t, J = 2.4 Hz, C≡CH). ^{13}C NMR (δ ppm): 161.1, 158.9, 133.3, 133.0, 132.8, 131.4, 130.9, 129.0, 128.9, 128.3, 128.1, 125.9, 118.0, 115.7, 114.3, 112.8, 98.2, 78.7, 76.8, 68.7, 55.9, 55.0. Analysis calculated for $C_{25}H_{21}NO_3S$: C, 72.27; H, 5.09; N, 3.37; S, 7.72. Found: C, 71.10; H, 5.00; N, 3.28; S, 7.67%.

***trans*-1-(4'-Methoxyphenyl)-3-(prop-2-ynyloxy)-3-phenythio-4-phenyl-azetidin-2-one (7i):** oil. Yield: 20%. I.R. (cm^{-1}, $CHCl_3$): 1755 (C=O). ^{1}H NMR (δ ppm): 7.53-7.30 (14H, m, Ar-*H*), 5.24 (IH, s, C4-*H*), 4. 88 (1H, dd, J = 2.4 Hz, J = 15.9 Hz, OCH_aH$_b$), 4.67 (1H, dd, J = 2.4 Hz, J = 15.9 Hz, OCH$_a$$H_b$), 3.76 (3H, s, OC$H_3$), 2.54 (1H, t, J = 2.4 Hz, C≡CH).

***cis*-1-(4'-Methoxyphenyl)-3-(prop-2-ynyloxy)-3-phenythio-4-(4'-methoxyphenyl)-azetidin-2-one (6j):** semi-solid. Yield: 27 %. I.R. (cm^{-1}, $CHCl_3$): 1755 (C=O). ^{1}H NMR (δ ppm): 7.41-7.20 (13H, m, Ar-*H*), 4.93 (IH, s, C4-*H*), 4.46 (1H, dd, J = 2.4 Hz, J = 15.9 Hz, OCH_aH$_b$), 4.34 (1H, dd, J = 2.4 Hz, J = 15.9 Hz, OCH$_a$$H_b$), 3.59 (3H, s, OC$H_3$), 3.48 (3H, s, OC$H_3$), 2.21 (1H, t, J = 2.4 Hz, C≡CH). ^{13}C NMR (δ ppm): 160.1, 158.9, 154.7, 133.3, 133.0, 132.8, 131.4, 130.9, 129.0, 128.9, 128.3, 128.1, 125.9, 118.0, 115.7, 114.3, 112.8, 96.2, 78.7, 76.0, 68.7, 55.9, 55.2, 55.0. Analysis calculated for $C_{26}H_{23}NO_4S$: C, 70.09; H, 5.20; N, 3.14; S, 7.20. Found: C, 70.00; H, 5.10; N, 3.08; S, 7.17%.

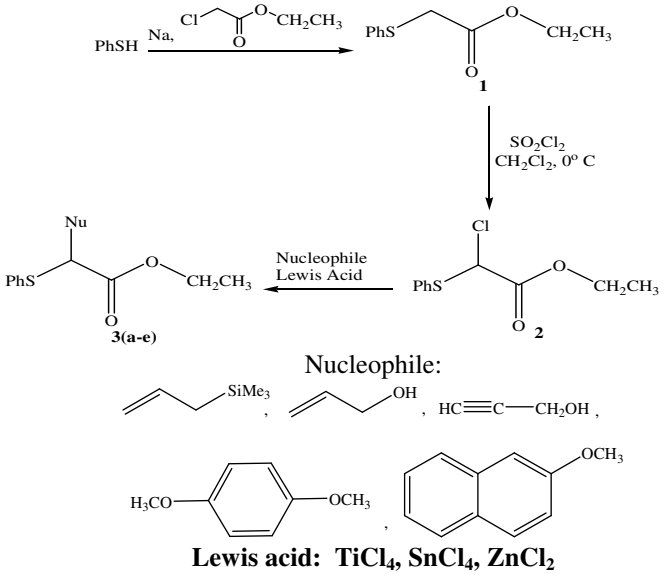
***trans*-1-(4'-Methoxyphenyl)-3-(prop-2-ynyloxy)-3-phenythio-4-(4'-methoxyphenyl)-azetidin-2-one (7j):** semi-solid. Yield: 25 %. I.R. (cm^{-1}, $CHCl_3$): 1755 (C=O). ^{1}H NMR (δ ppm): 7.51-7.27 (13H, m, Ar-*H*), 5.17 (IH, s, C4-*H*), 4. 72 (1H, dd, J = 2.4 Hz, J = 15.9 Hz, OCH_aH$_b$), 4.51 (1H, dd, J = 2.4 Hz, J = 15.9 Hz, OCH$_a$$H_b$), 3.73 (3H, s, OC$H_3$), 3.60 (3H, s, OC$H_3$), 2.44 (1H, t, J = 2.4 Hz, C≡CH). ^{13}C NMR (δ ppm): 161.9, 156.3, 155.4, 135.2, 133.2, 130.2, 129.6, 129.0, 128.8, 128.3, 128.1, 127.9, 125.7, 119.0, 114.4, 97.6, 79.2, 75.7, 67.7, 55.9, 55.3, 53.1.

Results and Discussion

Preparation of α-organylsulfanyl carbocations requires the use of sulfoxides(Pummerer Reaction),[20] α-chloro-α-organylsulfanylalkanes[21] and bis (organylsufanyl)alkanes (S,S-acetals)[22,23] as precursors. Yoshimatsu *et. al.*[24] have used α-fluoro-α-organylsulfanylalkanes as precursors for the carbocations and have used $Sc(OTf)_3$ as the Lewis acid because α-chloro-α-organylsulfanylalkanes are difficult to prepare. N-chlorosuccinimide is the most popular reagent for the chlorination of the organylsulfanylalkanes. Marzorati *et.al.*[25] have synthesized various α-phenylsulfanylarylacetates by the monosulfanylation of carboxylic esters.

In our earlier studies[11-18], various nucleophile substituted phenylthioethanoates have been prepared. However, the nuclephiles attached were limited to only few alkoxy groups. Therefore, it was considered to extend this synthetic approach for the preparation of various aliphatic and aromatic substituted esters and acids.

The reaction of ethyl chloroacetate with thiophenol in the presence of sodium in toluene at refluxing temperature gave a quantitative yield of ethyl 2-phenylthioethanoate **1,** which was further treated with 1 equiv. of SO_2Cl_2 in dry methylene chloride at 0^{o}C, to yield ethyl 2-chloro-2-phenylthioethanoate **2.** This α-chlorophenylthioacetate was treated with various aliphatic and aromatic nuclephiles in the presence of a Lewis acid to afford **3** in excellent yield (scheme 2).



Lewis acid: $TiCl_4$, $SnCl_4$, $ZnCl_2$

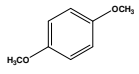
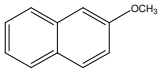
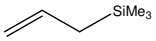
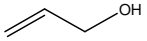
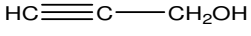
Scheme-2

Synthesis of C-3 nucleophile substituted phenylthioethanoate

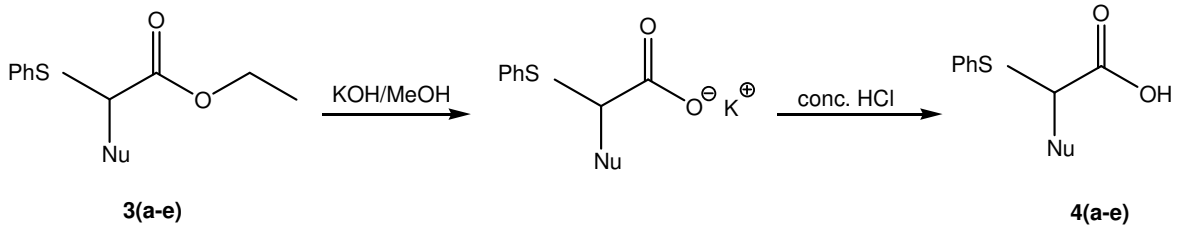
The potential of these α-chlorosulfides as reactive intermediates has already been explored. These have been found to be useful and reactive electrophiles for many of sulphur-mediated alkylation reactions of aromatic substrates[26], alkenes[27] and trimethylsilylenol ethers[28] etc.

The various α-substituted esters **3(a-e)** were further hydrolysed with KOH in methanol to afford potassium phenylthioethanoates which on acidification with conc. HCl gave phenylthioethanoic acids in high yields.

Table-1
Synthesis of Nuclephile substituted phenylthioesters 3(a-e) from ethyl 2-chloro-2-phenylthioethanoate 2

Entry	Nuclepohile	Lewis Acid	Compound 3	Yield (%)[a]
1		$SnCl_4$	**a**	65
2		$SnCl_4$	**b**	55
3		$TiCl_4$	**c**	75[29]
4		$ZnCl_2$	**d**	60
5		$ZnCl_2$	**e**	58

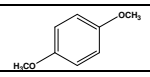
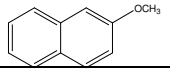
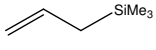
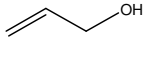
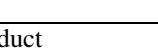
[a]Yields quoted are for the isolated products.



3(a-e) **4(a-e)**

Scheme-3
Synthesis of C-3 nucleophile substituted phenylthioethanoic acids

Table-2
Synthesis of Nuclephile substituted Phenylthioethanoic acids 4(a-e) from 3(a-e)

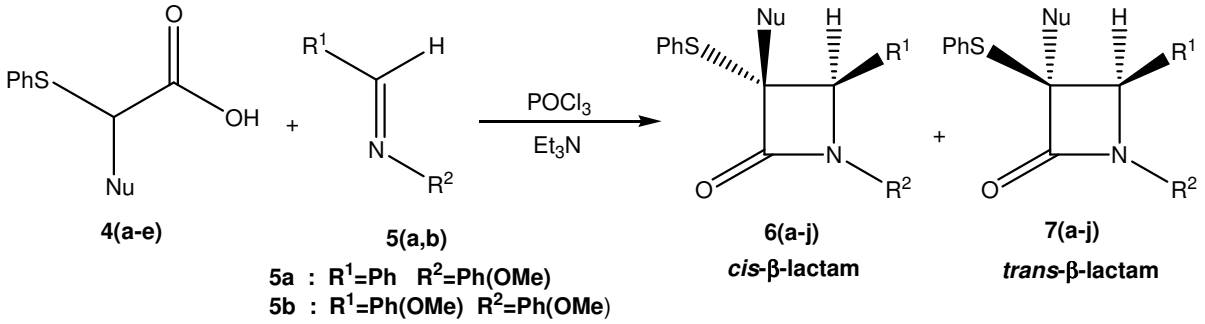
Entry	Nucleophile	Compound 4	Yield (%)[a]
1		**a**	83
2		**b**	80
3		**c**	85
4		**d**	82
5		**e**	85

[a]Yields quoted are for the isolated product

Initial studies for synthesis of C-3 monosubstituted β-lactams were carried out by treating **4a** with Schiff's base **5a** in the presence of $POCl_3$ as a condensing agent and triethylamine as a base in dichloromethane at 0^oC. After usual work-up and purification the product was found to be a mixture of *cis*- and *trans*-β-lactams **6a** and **7a** (C-4 H being *cis*- or *trans*- to C-3 PhS respectively). These were separated by column chromatography on Silica gel (60-120 mesh) using ethyl actate/hexanes (8:92) as an eluent system.

The reaction conditions were optimised by varying the solvent and reaction temperature. As indicated in table 3, high reaction temperature did not favour the increase in selectivity. However, dichloromethane at 0^oC was considered as most suitable reaction conditions for the reaction.

Employing these optimum reaction conditions, a variety of *cis*- and *trans*- C-3 monosubstituted phenylthio-β-lactams, **6(a-j)** and **7(a-j)**, were prepared in good yields (Scheme 5). It is clearly evident from Table-4 that in some cases (entries 3, 4, 7 and 8) formation of only *cis*-β-lactams was favoured.



Scheme-4
Synthesis of cis- and trans-C-3-monosubstituted phenylthio-β-lactams

Table-3
Synthesis of 3-(1,4-Dimethoxybenzene)-3-phenylthio-β-lactams in different solvent and temperature conditions

Entry	Solvent	Temperature (^oC)	Ratio 6a:7a (cis : trans)
1	Dichloromethane	0	70:30
2	Dichloromethane	40(reflux)	73:27
3	Toluene	110(reflux)	63:37

Table-4
Synthesis of C-3 monosubstituted phenythio-β-lactams

Entry	4(Substrate)	Schiff's base 5	Product of type(% Yield) 6 (cis-β-lactam)	7 (trans-β-lactam)
1	4a	5a	**6a(45)**	**7a(20)**
2	4a	5b	**6b(30)**	**7b(30)**
3	4b	5a	**6c (40)**	**7c(-)**
4	4b	5b	**6d(35)**	**7d(-)**
5	4c	5a	**6e(19)**	**7e(51)**
6	4c	5b	**6f(20)**	**7f(45)**
7	4d	5a	**6g(35)**	**7g(-)**
8	4d	5b	**6h(42)**	**7h(-)**
9	4e	5a	**6i(35)**	**7i(20)**
10	4e	5b	**6j(27)**	**7j(25)**

The structures of these β-lactams **6(a-j)** and **7(a-j)** were established by spectroscopic studies such as FTIR, ^{1}H NMR and ^{13}C NMR and elemental analysis. The stereochemical assignment of the substituent at C-3 of β-lactam **6h** with respect to C4-H was established as *cis*- through single crystal X-ray structure analysis as shown in ORTEP diagram (figure 3).

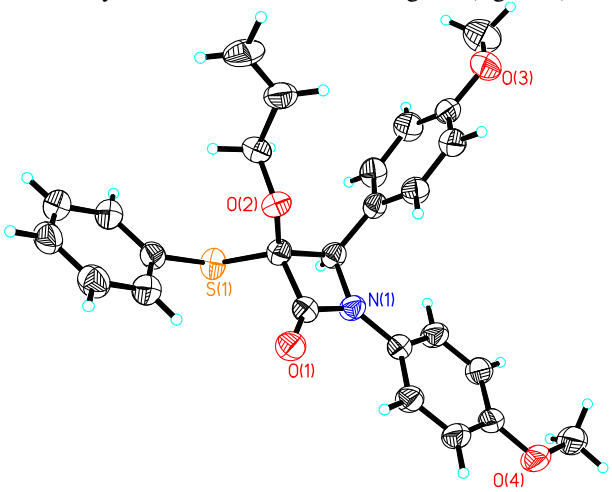


Figure-3
ORTEP diagram of 6h

Conclusion

In conclusion, we have developed a novel synthetic route to *cis*- and *trans*-C-3 monosubstituted phenylthio-β-lactams. Methodology for novel α-monosustituted phenythioethanoates and phenythioethanoic acids has also been developed. The X-ray crystallographic analysis of compound 6h allowed establishment of stereochemistry at C-3 of cis-1-(4'-Methoxyphenyl)-3-(prop-2-enyloxy)-3-phenythio-4-(4'-methoxyphenyl)-azetidin-2-one.

Acknowledgement

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