Asian Pub. Corp.

www.asianpubs.org

ARTICLE

Studies Towards C-3 Functionalization of *cis*-3-Methoxy-3-phenylthio-β-lactams

Aman Bhalla[1,✉], Kiran Sharma[1], Shamsher S. Bari[1] and Bimal K. Banik[2]

Asian Journal of Organic & Medicinal Chemistry

Volume: 2 Year: 2017
Issue: 3 Month: July–September
pp: 102–106
DOI: https://doi.org/10.14233/ajomc.2017.AJOMC-P39

Received: 15 December 2016
Accepted: 12 March 2017
Published: 30 September 2017

ABSTRACT

Synthetic investigations of monosubstituted and disubstituted β-lactams *via* C-3 functionalization of *cis*-3-methoxy-3-phenylthio-β-lactams are described. β-Lactam carbocation equivalents of type **1** on treatment with methanol and zinc chloride-silica rendered *cis*-3-methoxy-3-phenylthio-β-lactams **2**, which on further treatment with active aliphatic/aromatic nucleophiles in the presence of a Lewis acid promote a facile and stereoselective C-3 substitution to provide monosubstituted β-lactams **3** and symmetrically disubstituted β-lactams **4, 5** and **6**. The stereochemistry of monosubstituted product **3** was established by performing desulfurization with Raney-Ni, which led to the formation of *cis*-β-lactam **7**. The structural and stereochemical establishment of novel β-lactams was made by using FT-IR, NMR (^{1}H and ^{13}C) and elemental analysis (CHNS). The *cis* or *trans* configuration of hydrogen/PhS/OMe/nucleophile at C-3 was assigned with respect to C4-H.

KEYWORDS

β-Lactams, Lewis acid, Nucleophiles, Monosubstituted, Disubstituted, Desulfurization.

INTRODUCTION

With the beginning of "antibiotic era", new observations were bountiful, each being welcomed and dealt with warmth and vivacity. These miracle drugs can be seen as the 'Fairy Godmother' who played a major role in increasing the human life expectancy. Any new antibiotic is expected to possess some features of superiority over all the impressive finery of available β-lactam antibiotic [1]. Over the years, researchers have made umpteen structural modifications in naturally occurring β-lactam antibiotics to scavenge for necessaries with a promise of better therapeutic properties [1]. The β-lactam antibacterials block the final step in the biosynthesis of the bacterial cell wall and thus ultimately causing the death of the organism by lysing the cell wall [2]. In an activated β-lactam antibiotic, the specific spatial arrangement of its substituents and the rings decisively affect the potency, biological spectrum, pharmacokinetics and toxicity [3].

The possible use of *cis*-3-alkoxy-β-lactams in the synthesis of C-13 side chain of Taxol has been catalogued [4]. A class of 3-methoxy-β-lactam **A** (Fig. 1) has been found to have apoptotic activity against human leukaemia, breast, prostate and head-

Author affiliations:

[1]Department of Chemistry and Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh-160 014, India
[2]Community Health Systems of South Texas; 3135 South Sugar Road, Edinburg, Texas, 8539, USA

✉To whom correspondence to be addressed:

Fax: +91 172 254 5074
Tel: +91 172 253 4417
E-mail: amanbhalla@pu.ac.in

Available online at: http://ajomc.asianpubs.org

neck cancer cells, thus exhibiting antitumour activity [5]. In addition to this, 3-methoxy spiro-β-lactam **B** (Fig. 1) has also been found to be an inhibitor of both poliovirus and human rhinovirus 3C-proteinases [6]. Disubstituted β-lactams **C** (Fig. 1) have been shown to exhibit antibacterial and antifungal activities [7] whereas monosubstituted β-lactams **D** (Fig. 1) act as cholesterol transferase inhibitors [8].

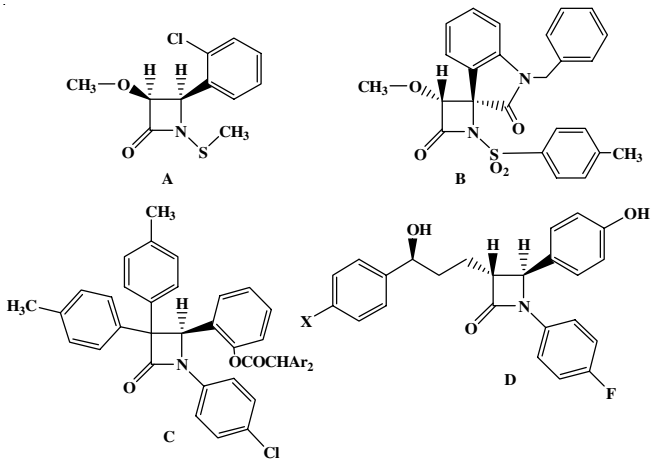


Fig. 1. Biologically active β-lactams

Our research group has been actively engaged in the designing, synthesis, characterization and biological evaluation of novel β-lactam heterocycles [9]. We pursued the synthesis of monocyclic, bicyclic, spirocyclic β-lactams including *cis*- and *trans*-alkoxy β-lactams and successfully performed the C-3 functionalization of these 3-thio/seleno-β-lactams [3,9]. In continuation to the previous work, we here envisaged the studies towards the C-3 functionalization of *cis*-3-methoxy-3-phenylthio-β-lactams with active aliphatic/aromatic nucleophiles.

EXPERIMENTAL

^{1}H NMR was recorded using BRUKER or JEOL 400 MHz and 300 MHz NMR spectrometers respectively. The chemical shifts are expressed in δ values (ppm) using tetramethylsilane as an internal standard. Infrared spectra were recorded using Perkin-Elmer Model 1430 spectrophotometer with potassium bromide (KBr) plates or Nujol with NaCl optic plates and are reported in cm^{-1}. The elemental analysis (C, H, N) was carried out using a Perkin-Elmer 2400 elemental analyzer. Column chromatography was performed using Merck Silica Gel (60-120 mesh) and eluted with ethyl acetate: hexanes mixtures. Thin-layer chromatography (TLC) was performed using Merck Silica Gel G. For visualization, TLC plates were stained with iodine vapours. All the melting points are uncorrected were determined with a Thomas-Hoover capillary melting point apparatus. The synthesis of β-lactams was carried out under dry and deoxygenated nitrogen atmosphere. Phosphorus oxychloride (Merck), triethylamine (Qualigen), ethyl acetate (Merck) and all other commercially available compounds/reagents/solvents were of reagent grade quality and used without any further purification. Dichloromethane and acetone were dried and distilled over anhydrous P_4O_{10}. Toluene was distilled under N_2 from sodium-benzophenone immediately before use.

C-3 monosubstituted/disubstituted β-lactams: To a well stirred solution of *cis*-3-methoxy-3-phenylthio-β-lactam **2** (1 eq.) and nucleophile (1 eq.) in dry methylene chloride at 0 °C was added Lewis acid (1 eq.) rapidly under nitrogen atmosphere. The resulting solution was stirred for 2 h at the same temperature. The progress of the reaction was checked by TLC, which showed the appearance of new spots having R_f value different with respect to the starting compound. The reaction was quenched with water, extracted with methylene chloride (4 × 10 mL), washed with 5 % $NaHCO_3$ solution (2 × 5 mL) and then dried over anhydrous Na_2SO_4. After evaporation of the solvent under vacuum, the residue was purified by silica gel column chromatography using 8 % ethyl acetate: hexane as eluent and products were identified using spectroscopic studies.

Desulfurization: To a suspension of Raney-nickel (10 eq., 100 % activated) in absolute ethanol was added **3c** (1 eq.). The suspension was refluxed for 1 h. Progress of the reaction was checked by TLC. After disappearance of spot corresponding to starting β-lactam and appearance of new spot, the suspension was filtered and ethanol was evaporated under vacuum, extracted with methylene chloride (3 × 20 mL) and then dried over anhydrous Na_2SO_4. After evaporation of the solvent under vacuum, the residue was purified by silica gel column chromatography using 8 % ethyl acetate: hexane as eluent to furnish the reduced product (69 %) as oil.

Data for the synthesized compounds is given below:

Spectroscopic data for synthesized compounds **3b, 4a**-**c**, **4e**, **5a**-**b** has already been reported in earlier publications [3,10].

***trans*-1-Benzyl-3-(2′,5′-dimethoxyphenyl)-3-phenylthio-4-phenylazetidin-2-one (3a):** IR ($CHCl_3$): 1741 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29-6.12 (m, 16H, ArH), 5.36 (s, 1H, C4-H), 4.55 (d, *J* = 15.0 Hz, 1H, CH_2Ph), 3.79 (d, *J* = 15.0 Hz, 1H, CH_2Ph), 3.72 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ: 174.2, 153.3, 150.4, 137.8, 136.5, 136.4, 128.9, 128.2, 127.8, 127.0, 125.8, 124.6, 120.5, 116.3, 113.9, 67.4, 65.7, 57.8, 54.6, 47.7.

***cis*-1-Benzyl-3-allyl-3-phenylthio-4-phenylazetidin-2-one (3c):** IR ($CHCl_3$): 1746 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62-6.73 (m, 15H, ArH), 5.81-5.75 (m, 1H, CH_2CH=CH_2), 5.23 (br s, 1H, CH_2CH=CH_2), 5.22-5.19 (m, 1H, CH_2CH=CH_2), 5.05 (s, 1H, C4-H), 4.60 (d, *J* = 15.1 Hz, 1H, CH_2Ph), 3.80 (d, *J* = 15.0 Hz, 1H, CH_2Ph), 2.81 (d, *J* = 7.3 Hz, 2H, CH_2CH=CH_2). ^{13}C NMR ($CDCl_3$) δ: 179.2, 138.4, 136.8, 136.7, 134.7, 129.5, 128.9, 128.7, 128.4, 128.1, 127.6, 127.1, 126.5, 123.2, 114.5, 66.2, 63.4, 47.1, 41.2.

1-Benzyl-3,3-*bis*(2',5'-dimethoxyphenyl)-4-phenylazetidin-2-one (4d): IR ($CHCl_3$): 1741 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29-6.12 (m, 16H, ArH), 5.36 (s, 1H, C4-H), 4.55 (d, *J* = 15.0 Hz, 1H, CH_2Ph), 3.79 (d, *J* = 15.0 Hz, 1H, CH_2Ph), 3.72 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 2.80 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ: 170.1, 155.6, 151.7, 137.4, 136.3, 135.8, 128.9, 128.2, 125.7, 116.6, 114.0, 111.1, 67.5, 55.8, 55.2, 54.9, 47.2.

1-Benzyl-3,3-*bis*(2',4'-dimethoxyphenyl)-4-phenylazetidin-2-one (4f): IR ($CHCl_3$): 1749 (C=O) cm^{-1}; ^{1}H NMR

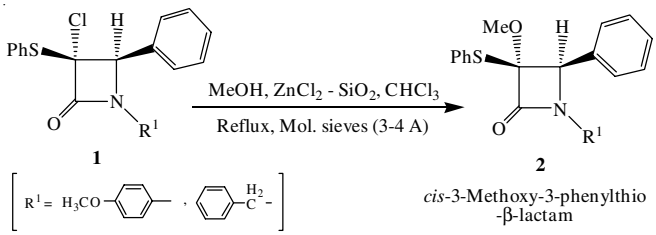
(400 MHz, $CDCl_3$) δ: 7.72-5.92 (m, 16H, ArH), 5.45 (s, 1H, C4-H), 4.67 (d, *J* = 15.1 Hz, 1H, CH_2Ph), 3.92 (d, *J* = 15.0 Hz, 1H, CH_2Ph), 3.75 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 2.86 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ: 170.7, 160.6, 160.0, 158.9, 157.8, 136.3, 136.0, 132.1, 130.0, 129.4, 128.9, 128.5, 127.4, 127.2, 126.9, 118.1, 103.9, 103.4, 98.9, 98.4, 69.8, 66.0, 55.2, 55.0, 53.9, 44.5.

1-(4'-Methoxyphenyl)-3,3-dimethoxy-4-phenylthio-azetidin-2-one (6a): m.p.: 105-106 °C; IR (KBr): 1735 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36-6.75 (m, 9H, ArH), 5.03 (s, 1H, C4-H), 3.73 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.15 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ: 162.1, 156.3, 133.8, 130.6, 128.7, 128.0, 118.9, 114.3, 108.3, 68.8, 55.1, 52.3, 51.3.

***cis*-1-Benzyl-3-(2',5'-dimethoxyphenyl)-4-phenyl-azetidin-2-one (7):** IR ($CHCl_3$): 1739 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38-6.33 (m, 13H, ArH), 5.16 (d, *J* = 5.7 Hz, 1H, C3-H), 4.63 (d, *J* = 15.0 Hz, 1H, CH_2Ph), 4.56 (d, *J* = 5.7 Hz, 1H, C4-H), 3.68 (d, *J* = 15.0 Hz, 1H, CH_2Ph), 3.49 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ: 171.8, 152.3, 150.6, 139.5, 137.4, 127.6, 127.0, 125.6, 120.8, 115.1, 113.7, 113.2, 59.4, 56.9, 53.7, 47.3, 39.9.

RESULTS AND DISCUSSION

Starting substrate *cis*-3-methoxy-3-phenylthio-β-lactam (**2**) was prepared by treatment of *cis*-3-chloro-3-phenylthio-β-lactam (**1**) with methanol and zinc chloride-silica using reported procedure [3] (**Scheme-I**).



Scheme-I: Synthesis of *cis*-3-methoxy-3-phenylthio-β-lactams **2a** and **2b**

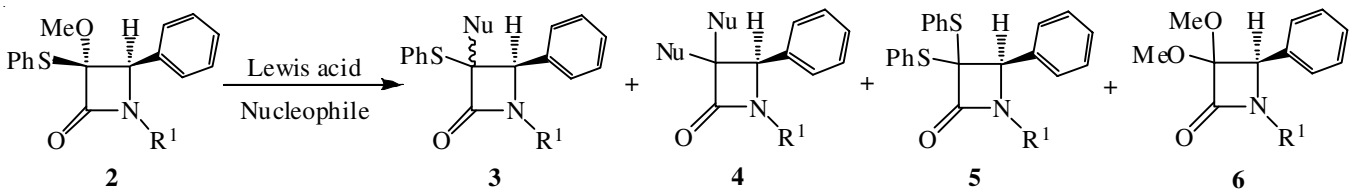
Initial study was performed by subjecting the substrate **2a** [R^1 = (*p*-OCH_3)Ph] under C3 functionalization using anisole as the active nucleophile in $TiCl_4$. The reaction afforded a mixture of disubstituted β-lactams, which were separated by column chromatography and identified (using spectroscopic studies) as **4a** and **5a**, respectively (**Scheme-II**, Table-1, entry 1). Similar results were obtained using β-lactam (**2b**) and $SnCl_4$, however, mild Lewis acid $ZnBr_2$ furnished only 3,3-*bis*(phenylthio)-β-lactam (**5a**) (Table-1, entry 2, 3). β-Lactams of type **4** and **5** have been obtained when substrate **2a** was treated with other aromatic nucleophiles such as 1,3-dimethoxy-benzene or 1,4-dimethoxybenzene (Table-1, entries 4-5, 7-9). Interestingly, β-lactam (**2b**) (R^1 = -CH_2Ph) on treatment with aromatic 1,4-dimethoxybenzene as a nucleophile in the presence of 1 equiv. of $TiCl_4$ or $SnCl_4$ furnished monosubstituted β-lactam (**3a**) as a major product along with disubstituted β-lactams of type **4** and **5** (**Scheme-II**, Table-1, entry 6).

Further studies were pursued with aliphatic nucleophile allyltrimethylsilane. Initially, exclusive formation of monosubstituted β-lactam (**3b**) was observed when the reaction of compound **2a** was performed with allyltrimethylsilane in the presence of one equivalent of $TiCl_4$ at 0 °C (Table-1, entry 10). However, the same reaction with $SnCl_4$ as Lewis acid at 0 °C surprisingly furnished disubstituted 3,3-dimethoxy-β-lactam (**6a**) as a major product along with compound **5a** as minor one (Table-1, entry 11). In addition to this, *N*-benzyl-β-lactam (**2b**) afforded monosubstituted β-lactam (**3c**) exclu-sively with Lewis acid $TiCl_4$ or $SnCl_4$ (Table-1, entry 12).

These products were separated by column chromatography and after purification were identified on the basis of their spectral (^1H and ^{13}C NMR) analysis.

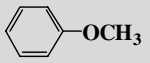
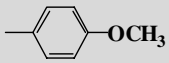
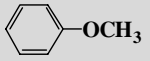
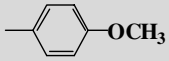
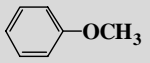
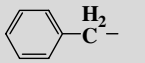
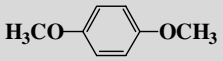
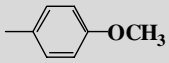
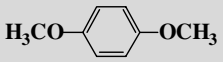
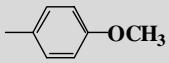
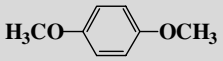
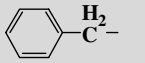
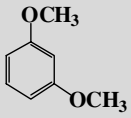
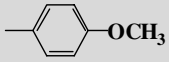
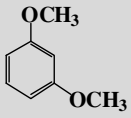
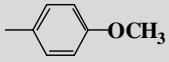
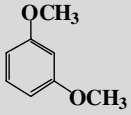
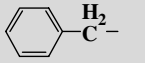
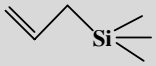
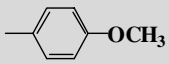
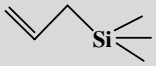
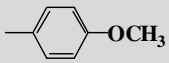
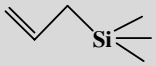
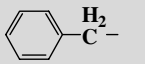
These studies reveal that the presence of R^1 group, choice of Lewis acid and nucleophile affects the formation of differently substituted products **3**, **4**, **5** and **6**. The plausible explanation for the formation of product *trans*-1-benzyl-3-(2′,5′-dimethoxyphenyl)-3-phenylthio-4-phenylazetidin-2-one (**3a**) can be explained as the Lewis acid first forms a complex with β-lactam which (complex) being bulkier in size hinders the approach of nucleophile from same side (**Scheme-III**). Therefore, the reaction probably proceeds *via* S_N^2 mechanism and results in *trans*-stereochemistry. In case of trimethylallylsilane as aliphatic nucleophile, monosubstituted products **3(b-c)** were formed but with retention of stereochemistry at C-3. Here the reaction most likely follows S_N^1 mechanism involving the formation of carbocation at C-3 as an intermediate (**Scheme-III**). Then the nucleophile approaches the carbocation from the side of hydrogen atom at C-4, which is less hindered. The assignment of α-stereochemistry to the nucleophile at C-3 of **3b** has already been established by its X-ray crystallographic studies [10].

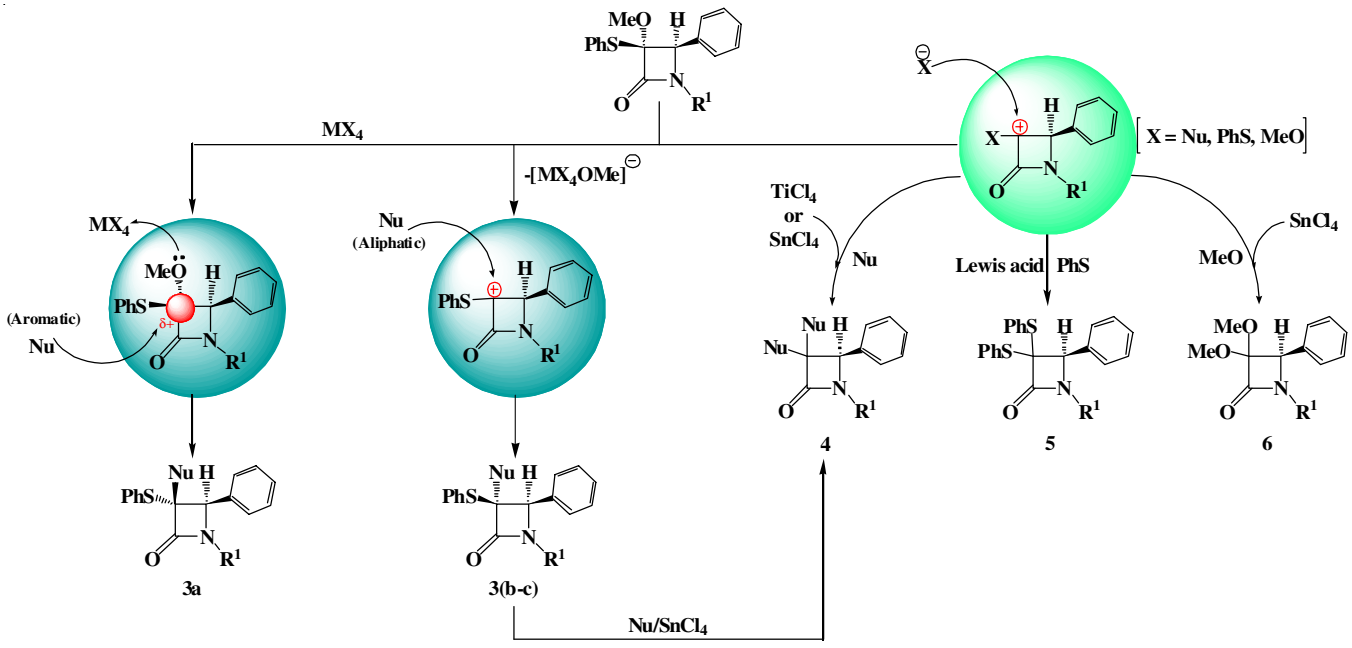
The possible role of the monosubstituted product **3** as an intermediate in the formation of disubstituted β-lacatm (**4**) was supported by the transformation of monosubstituted β-lacatm (**3c**) into disubstituted β-lactam (**4a**) on treatment with 1,4-dimethoxybenzene in the presence of $SnCl_4$. Groups PhS and MeO play dual characters for being a leaving group as well as a nucleophile at the same time and hence led to the formation of disubstituted products **5** and **6**. The group MeO is more polar and forms a better leaving group than PhS and thus we get a product of type **3** after nucleophillic substitution. Also, carbocation generated by the elimination of MeO group is resonance stabilized by PhS group and therefore favours the elimination of MeO group over PhS functionality. It has



Scheme-II: Synthesis of C3 monosubstituted/disubstituted β-lactams

TABLE-1

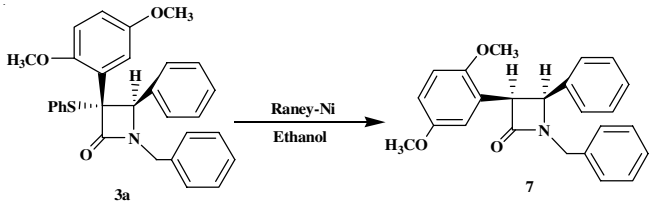
Entry	Substrate	Nucleophile	Lewis acid	R^1	Product of type, yield (%)			
					3	**4**	**5**	**6**
1	**2a**		$TiCl_4/SnCl_4$		–	**4a** (52)	**5a** (17)	–
2	**2a**		$ZnBr_2$		–	–	**5a** (58)	–
3	**2b**		$TiCl_4/SnCl_4$		–	**4b** (47)	**5b** (15)	–
4	**2a**		$TiCl_4/SnCl_4$		–	**4c** (43)	**5a** (21)	–
5	**2a**		$ZnBr_2$		–	–	**5a** (57)	–
6	**2b**		$TiCl_4/SnCl_4$		**3a** (48)	**4d** (12)	**5b** (15)	–
7	**2a**		$TiCl_4/SnCl_4$		–	**4e** (49)	**5a** (15)	–
8	**2a**		$ZnBr_2$		–	–	**5a** (46)	–
9	**2b**		$TiCl_4/SnCl_4$		–	**4f** (54)	**5b** (12)	–
10	**2a**		$TiCl_4$		**3b** (86)	–	–	–
11	**2a**		$SnCl_4$		–	–	**5a** (13)	**6a** (70)
12	**2b**		$TiCl_4/SnCl_4$		**3c** (63)	–	–	–



Scheme-III: Plausible mechanism for the monosubstituted/disubstituted β-lactams

also been observed that benzene and toluene do not undergo alkylation under these conditions. The preference of $TiCl_4$ or $SnCl_4$ as Lewis acids over $ZnBr_2$ was justified in relation to afford novel differently disubstituted β-lactams of type **4** over 3,3-*bis*(phenylthio)-β-lactam of type **5**.

Desulfurization studies: The stereochemistry of monosubstituted product **3b** has already been established by their X-ray crystallographic analysis reported in earlier publications [3,10]. However, compound **3a** has been obtained as a semi-solid and hence desulfurization studies have been performed to establish its stereochemistry. For this, **3a** was treated with Raney-nickel in ethanol and it led to the formation of *cis*-β-lactam **7** (**Scheme-IV**). On the basis of this stereospecific transformation, *trans* stereochemistry was assigned to β-lactam **3a** and evident from its ^{1}H NMR data which is in accordance with earlier reports on desulfurization [3,10].



3a 7

Scheme-IV: Desulfurization using Raney-Ni

Conclusion

In conclusion, synthetic investigations in monosubstituted and disubstituted β-lactams *via* C-3 functionalization of *cis*-3-methoxy-3-phenylthio-β-lactams have been explored in detail. Successive attempts were made for the exclusive formation of monosubstituted β-lactam (**3a-c**) and novel symmetrically substituted dimethoxy β-lactam (**6a**). The plausible mechanistic routes for the formation of these types of products have been incorporated and structure confirmation was achieved by using spectroscopic techniques (^{1}H NMR and ^{13}C NMR). The interesting results of these studies further extend our investigations on C-3 functionalization of differently substituted β-lactams.

ACKNOWLEDGEMENTS

One of the authors, Aman Bhalla gratefully acknowledges the financial support for this work from Department of Science and Technology (DST), New Delhi, Government of India, Project No. SR/FT/CS-037/2010 dated 28-10-2010 and FIST II grant, PURSE II grant, Panjab University, Chandigarh, India; while Kiran Sharma acknowledges the financial support from University Grants Commission (UGC), India vides sanction No. F.25.1/2013-14(BSR)/5-91/2007(BSR).

REFERENCES

1. J.C. Sheehan and K.R.H. Logan, *J. Am. Chem. Soc.*, **81**, 5838 (1959); https://doi.org/10.1021/ja01530a079.
2. D.J. Tipper and J.L. Strominger, *Proc. Natl. Acad. Sci. USA*, **54**, 1133 (1965); https://doi.org/10.1073/pnas.54.4.1133.
3. A. Bhalla, P. Venugopalan and S.S. Bari, *Tetrahedron*, **62**, 8291 (2006); https://doi.org/10.1016/j.tet.2006.06.062.
4. C. Palomo, A. Arrieta, F.P. Cossio, J.M. Aizpurua, A. Mielgo and N. Aurrekoetxea, *Tetrahedron Lett.*, **31**, 6429 (1990); https://doi.org/10.1016/S0040-4039(00)97083-7.
5. D.M. Smith, A. Kazi, L. Smith, T.E. Long, B. Heldreth, E. Turos and Q.P. Dou, *Mol. Pharmacol.*, **61**, 1348 (2002); https://doi.org/10.1124/mol.61.6.1348.
6. J.W. Skiles and D. McNeil, *Tetrahedron Lett.*, **31**, 7277 (1990); https://doi.org/10.1016/S0040-4039(00)88543-3.
7. G.S. Singh, E. Mbukwa and T. Pheko, *ARKIVOC*, 80 (2007); https://doi.org/10.3998/ark.5550190.0008.910.
8. (a) D.A. Burnett, M.A. Caplen, H.R. Davis, R.E. Burrier and J.W. Clader, *J. Med. Chem.*, **37**, 1733 (1994); https://doi.org/10.1021/jm00038a001.
(b) S. Dugar, N. Yumibe, J.W. Clader, M. Vizziano, K. Huie, M. van Heek, D.S. Compton and H.R. Davis Jr., *Bioorg. Med. Chem. Lett.*, **6**, 1271 (1996); https://doi.org/10.1016/0960-894X(96)00214-4.
(c) G.G. Wu, *Org. Process Res. Dev.*, **4**, 298 (2000); https://doi.org/10.1021/op990196r.
9. A. Bhalla, S.S. Bari, S. Vats, J. Bhalla, K. Sharma and D. Narula, *Tetrahedron Lett.*, **57**, 4763 (2016); https://doi.org/10.1016/j.tetlet.2016.09.043.
10. S.S. Bari, P. Venugopalan and R. Arora, *Tetrahedron Lett.*, **44**, 895 (2003); https://doi.org/10.1016/S0040-4039(02)02775-2.