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Facile and Stereoselective Synthesis of Novel *trans*-3-Monosubstituted-3-benzylseleno-β-lactams

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Abstract

*A facile and stereoselective synthesis of novel trans-3-monosubstituted-3-benzylseleno-β-lactams (**5**) via Lewis acid mediated functionalization of β-lactam carbocation equivalents (**4**) with active aromatic and heterocyclic compounds (nucleophiles) is described. The structures of these novels β-lactams have been established on the basis of spectroscopic studies (FTIR, ^{1}H NMR, ^{13}C NMR, ^{77}Se NMR, GCMS) and elemental analysis. The cis or trans configuration of the hydrogen/chloro /nucleophile substitutent at C-3 was assigned with respect to C4-H.*

Keywords: β-Lactams, Lewis acid, nucleophiles, *trans*-3-monosubstituted-3-benzylseleno-β-lactams.

Introduction

β-Lactams are one of the best known and extensively investigated heterocyclic ring systems and as a result of both their biological activity as antibiotics[1] and their utility as synthetic intermediates[2]. The discoveries of monocyclic biologically active β-lactams such as cholesterol acyl transferase inhibitors **A** and **B** (figure 1)[3], thrombin inhibitors[4], human cytomegalovirus protease inhibitors[5], matrix-metalloprotease inhibitors[6], human leukocyte elastase[7], cysteine protease[8] and apoptosis inductors[9] have provided motivation for the development of new β-lactam (azetidin-2-ones) systems. Very recently, the 1,3-diketones and 4-acyl isochroman-1,3-diones have been shown to posses antibacterial and antioxidant potentialities, respectively[10-11].

The ever-increasing bacterial resistances to β-lactam antibiotics have renewed chemist's interest towards new β-lactam chemistry involving skeletal modification of naturally occurring β-lactam antibiotics. Therefore, the development of convenient approaches for the synthesis of seleno-β-lactams continues to be an area of active research. In continuation to our earlier studies[12-23] towards the synthesis of novel selenoalkanoic acids as β-lactam precursors, monocyclic 3-thio/seleno-β-lactams and their Lewis acid mediated functionalization, spirocyclic-β-lactams, 3-allylidene-β-lactams and 3-keto-β-lactams, we wish to report here the synthesis of novel *trans*-3-monosubstituted-3-benzylseleno-β-lactams.

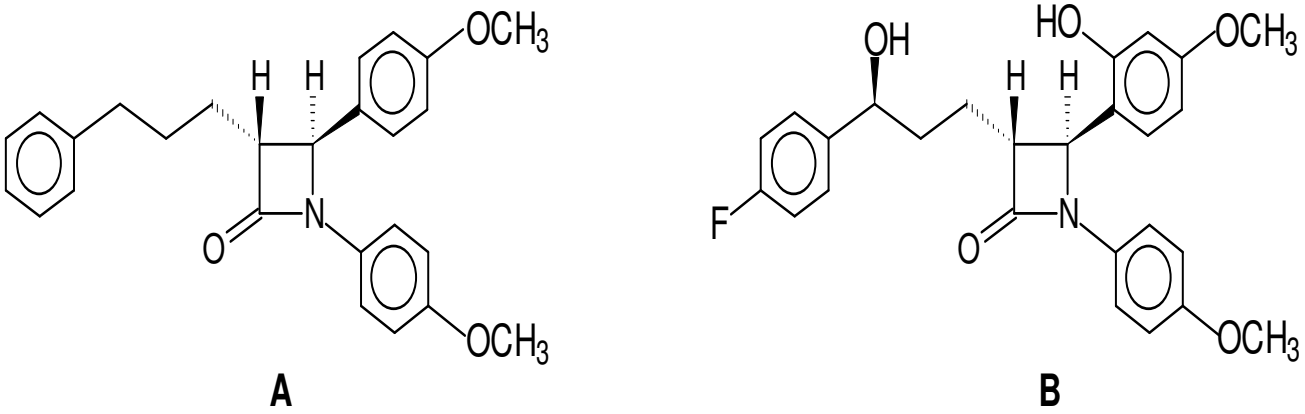


Figure-1
Cholesterol acyl transferase inhibitors

Our previous studies have revealed[12-23] *cis*-3-chloro-3-phenylthio/seleno-β-lactams on treatment with a number of active aromatic and heterocyclic compounds (nucleophiles) in the presence of a Lewis acid ($TiCl_4$ or $SnCl_4$) preferentially afforded C-3 disubstituted β-lactams. However, the presence of benzylthio ($PhCH_2S$-) group at C-3 position led to the exclusive formation of *trans*-3-monosubstited-3-benzylthio-β-lactams from *cis*-3-chloro-3-benzylthio-β-lactams[12]. Since C-3 monosubstituted β-lactams are very important synthons from the biological point of view, it is proposed to employ the above reported methodology for the stereoselective synthesis of novel *trans*-3-monosubstituted-3-benzylseleno-β-lactams. Further, to explore the comparative study of thio- and seleno-β-lactams for understanding the mechanism as well as produce new chemical entities, which might have different biological activity. The strategy involves the introduction of active aromatic and heterocyclic compounds (nucleophiles) at C-3 of *cis*-3-chloro-3-benzylseleno-β-lactams (4) in the presence of Lewis acid to furnish steroselective *trans*-3-monosubstituted-3-benzylseleno-β-lactams 5(a-e).

Material and Methods

^1H, ^{13}C NMR and ^{77}Se NMR spectra were recorded at 300, 75 and 57 MHz respectively, in $CDCl_3$ solution using JEOL 300 MHz NMR spectrometer. Chemical shifts are given in parts per million relative to tetramethylsilane as an internal standard (δ = 0 ppm) for ^1H NMR, $CDCl_3$ (δ = 77 ppm) for ^{13}C NMR and Me_2Se (δ = 0 ppm) for ^{77}Se spectra. IR spectra were taken on FTIR spectrophotometer and are reported in cm^{-1}. Mass Spectra (GCMS) were recorded on Polaris Q (MS 211858). The elemental analysis (CHN) was carried out using Elementar (VARIO EL). Column chromatography was performed using Merck silica gel (60-120 mesh). Thin layer chromatography (TLC) was performed using Merck silica gel G. For visualization, TLC plates were stained with iodine vapors. Melting points are uncorrected. All commercially available compounds/reagents were used without further purification. Dichloromethane and carbon tetrachloride distilled over P_2O_5 were redistilled over CaH_2 before use. Toluene was distilled over sodium-benzophenone immediately before use.

Synthesis of *trans*-1-(4'-methylphenyl)-3-benzylseleno-4-(4'-chlorophenyl)azetidin-2-one (2): Compound 2 was prepared by the procedure described in the cited reference12. mp: 107-108 °C. I.R. (KBr, cm^{-1}): 1764 (C=O). ^1H NMR (δ ppm): 7.22-6.93 (13H, m, Ar-*H*), 4.45 (1H, d, *J* = 1.8 Hz, C3-*H*), 3.95 (2H, s, CH_2Se), 3.90 (1H, d, *J* = 2.1 Hz, C4-*H*), 2.21 (3H, s, CH_3). ^{13}C NMR (δ ppm): 159 (*C*=O), 142-117 (Ar-*C*), 52 (*C*-3), 39 (*C*-4), 31 (*C*H_2), 28 (*C*H_3). Analysis calculated for $C_{23}H_{20}ClNOSe$: C, 62.70; H, 4.60; N, 3.20. Found: C, 62.56; H, 4.48; N, 3.10%.

Synthesis of *cis*-1-(4'-methylphenyl)-3-chloro-3-benzylseleno-4-(4'-chlorophenyl)azetidin-2-one (3): Compound 3 was prepared by the procedure described in the cited reference12. mp: 137-138 °C. I.R. (KBr, cm^{-1}): 1753 (C=O) ^1H NMR (δ ppm): 7.24-6.99 (13H, m, Ar-*H*), 5.25 (1H, s, C4-*H*), 4.41-4.38 (1H, d, *J* = 10.5 Hz, CH_aH$_b$Se), 4.12-4.08 (1H, d, *J* = 10.5 Hz, CH$_a$$H_b$Se), 2.24 (3H, s, C$H_3$). ^{13}C NMR (δ ppm): 162 (*C*=O), 136-118 (Ar-*C*), 78 (*C*-3), 70 (*C*-4), 61 (*C*H_2), 21 (*C*H_3). Analysis calculated for $C_{23}H_{19}Cl_2NOSe$: C, 58.10; H, 4.00; N, 2.90. Found: C, 57.01; H, 3.92; N, 2.88%.

Synthesis of *trans*-3-monosubstituted-3-benzylseleno-β-lactams 5(a-e): Compounds **5(a-e)** were prepared by the procedure described in the cited reference12.

***trans*-1-(4'-Methylphenyl)-3-(2',5'-dimethoxyphenyl)-3-benzylseleno-4-(4'-chlorophenyl)azetidin-2-one (5a): mp:** 152-154 °C. I.R. (KBr, cm^{-1}): 1772 (C=O). ^{1}HMR (δ ppm): 7.48-6.76 (16H, m, Ar-*H*), 5.18 (1H, s, C4-*H*), 4.12-4.09 (1H, d, *J* = 10.5 Hz, CH_aH$_b$Se), 3.77 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.44-3.40 (1H, d, *J* = 10.5 Hz, CH$_a$$H_b$Se), 2.19 (3H, s, C$H_3$). ^{13}C NMR (δ ppm): 167 (*C*=O), 130-113 (Ar-*C*), 73 (*C*-3), 69 (*C*-4), 56 (O*C*H$_3$), 55 (O*C*H$_3$), 29 (*C*H$_2$), 25 (*C*H$_3$). ^{77}Se NMR (δ ppm): 439 (*Se*). Analysis calculated for $C_{31}H_{28}ClNO_3Se$: C, 64.50; H, 4.90; N, 2.40. Found: C, 63.41; H, 4.88; N, 2.37%. GCMS: m/z (assignment): 578 (M+1).

***trans*-1-(4'-Methylphenyl)-3-(4'-methoxyphenyl)-3-benzylseleno-4-(4'-chlorophenyl)azetidin-2-one (5b): mp:** 144-145 °C. I.R. (KBr, cm^{-1}): 1761 (C=O). ^{1}HMR (δ ppm): 7.62-6.92 (17H, m, Ar-*H*), 5.33 (1H, s, C4-*H*), 4.34-4.31 (1H, d, *J* = 10.2 Hz, CH_aH$_b$Se), 3.97 (3H, s, OCH_3), 3.60-3.56 (1H, d, *J* = 10.2 Hz, CH$_a$$H_b$Se), 2.40 (3H, s, C$H_3$). ^{13}C NMR (δ ppm): 168 (*C*=O), 133-113 (Ar-*C*), 71 (*C*-3), 66 (*C*-4), 55 (O*C*H$_3$), 29 (*C*H$_2$), 24 (*C*H$_3$). Analysis calculated for $C_{30}H_{26}ClNO_2Se$: C, 65.90; H, 4.80; N, 2.60. Found: C, 65.79; H, 4.69; N, 2.48%.

***trans*-1-(4'-Methylphenyl)-3-(4'-bromophenyl)-3-benzylseleno-4-(4'-chlorophenyl)azetidin-2-one (5c):** Yellowish oil. I.R. ($CHCl_3$, cm^{-1}): 1764 (C=O). ^{1}HMR (δ ppm): 7.43-6.70 (17H, m, Ar-*H*), 5.13 (1H, s, C4-*H*), 4.14-4.11 (1H, d, *J* = 10.5 Hz, CH_aH$_b$Se), 3.40-3.37 (1H, d, *J* = 10.5 Hz, CH$_a$$H_b$Se), 2.20 (3H, s, C$H_3$). ^{13}C NMR (δ ppm): 170 (*C*=O), 130-113 (Ar-*C*), 69 (*C*-3), 61 (*C*-4), 30 (*C*H$_2$), 25 (*C*H$_3$). Analysis calculated for $C_{29}H_{23}BrClNOSe$: C, 58.50; H, 3.90; N, 2.40. Found: C, 58.41; H, 3.76; N, 2.39%.

***trans*-1-(4'-Methylphenyl)-3-(4'-hydroxyphenyl)-3-benzylseleno-4-(4'-chlorophenyl)azetidin-2-one (5d): mp:** 137-138 °C. I.R. (KBr, cm^{-1}): 1777 (C=O). ^1H NMR (δ ppm): 7.29-6.95 (17H, m, Ar-*H*), 4.81 (1H, s, C4-*H*), 4.14-4.10 (1H, d, *J* = 10.5 Hz, CH_aH$_b$Se), 4.02-3.96 (1H, d, *J* = 10.8 Hz, CH$_a$$H_b$Se), 2.24 (3H, s, C$H_3$). ^{13}C NMR (δ ppm):

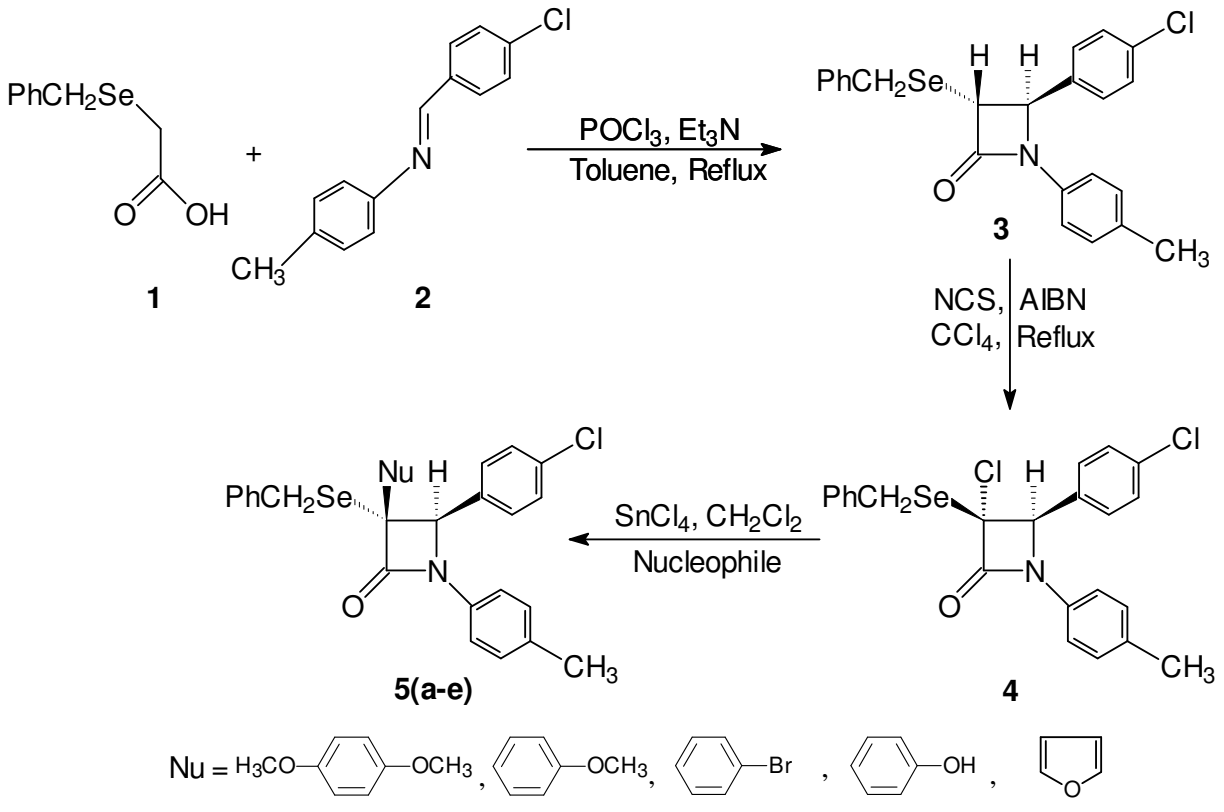
164 (*C*=O), 152-118 (Ar-*C*), 79 (*C*-3), 62 (*C*-4), 29 (CH_2), 24 (CH_3). Analysis calculated for $C_{29}H_{24}ClNO_2Se$: C, 65.40; H, 4.50; N, 2.60. Found: C, 65.21; H, 4.33; N, 2.53%.

***trans*-1-(4'-Methylphenyl)-3-(2'-furanyl)-3-benzylseleno-4-(4'-chlorophenyl)azetidin-2-one (5e): mp:** 145-147 °C. I.R. (KBr, cm^{-1}): 1769 (C=O). ^{1}H NMR (δ ppm): 7.45-7.39 (1H, dd, *J* = 0.8, 0.8 Hz, $C_4H_aH_bH_cO$), 7.40-6.65 (13H, m, Ar-*H*), 6.29-6.23 (1H, dd, *J* = 0.8, 0.8 Hz, $C_4H_aH_bH_cO$), 6.12-6.06 (1H, dd, *J* = 1.8, 1.8 Hz, $C_4H_aH_bH_cO$), 5.50 (1H, s, C4-*H*), 2.74-2.71 (1H, d, *J* = 10.5 Hz, CH_aH_bSe), 2.54-2.51 (1H, d, *J* = 10.5 Hz, CH_aH_bSe), 2.23 (3H, s, CH_3). ^{13}C NMR (δ ppm): 161 (*C*=O), 152-117 (Ar-*C* and furanyl-*C*), 74 (*C*-3), 65 (*C*-4), 29 (CH_2), 23 (CH_3). Analysis calculated for $C_{27}H_{22}ClNO_2Se$: C, 64.00; H, 4.40; N, 2.80. Found: C, 63.88; H, 4.31; N, 2.76%. GCMS: m/z (assignment): 507 (M+1).

Results and Discussion

Starting substrate, *trans*-3-benzylseleno-β-lactam (**3**) was prepared by treatment of 2-benzylselenoethanoic acid (**1**) with Schiff base (**2**) in the presence of triethylamine (Et_3N) and phosphorus oxychloride ($POCl_3$) acting as base and condensing agent respectively, according to the procedure reported in our previous publication (scheme-1)[12]. The structure of this β-lactam **3** was confirmed by spectral data (FTIR, ^{1}H NMR, ^{13}C NMR). Further, spatial juxtaposition of the C3-H and C4-H was assigned trans on the basis of coupling constant values (*J* = 1.8-2.1 Hz) and the stereochemistry was confirmed with correlation to X-ray analysis of *trans*-3-phenylseleno-β-lactam[12,17].

β-lactam carbocation equivalent, *cis*-3-chloro-3-benzylseleno-β-lactams (4), suitable substrate for Lewis acid mediated functionalization was synthesized successfully by treatment of 3 with *N*-chlorosuccinimide (NCS) and catalytic amount of AIBN in refluxing carbon tetrachloride (scheme-1)12,17. The structure of 4 was confirmed from FTIR, ^{1}H NMR and ^{13}C NMR spectroscopic analysis. The stereochemistry was assigned cis with respect to C4–H on the basis of correlation of ^{1}H and ^{13}C NMR data of 4 with that of *cis*-3-chloro-3-phenyl/benzylthio-β-lactams, whose stereochemistry has already been established by X-ray crystallographic analysis[12].

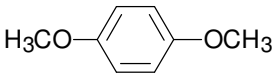
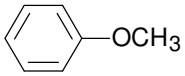
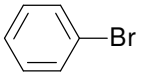
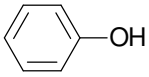


Scheme-1
Synthesis of *trans*-3-monosubstituted-3-benzylseleno-β-lactams 5(a-e)

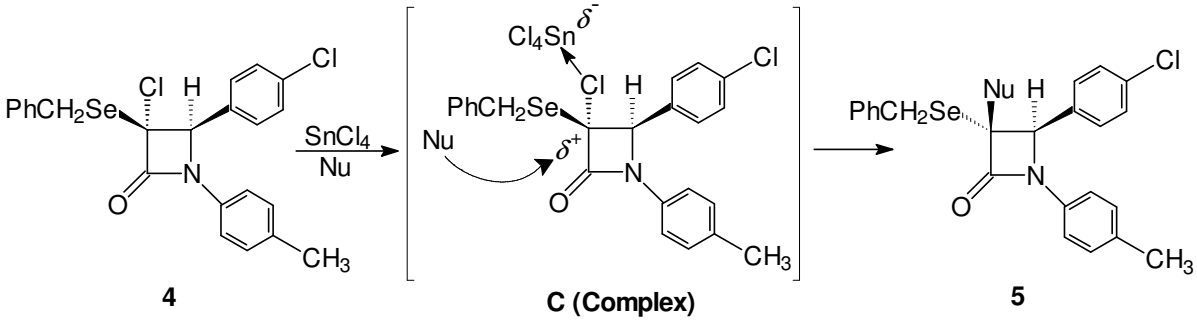
We envisaged functionalization of *cis*-3-chloro-3-benzylseleno-β-lactam employing Lewis acid catalyzed substitution reactions with different active aromatic and heterocyclic compounds (nucleophiles) to afford stereoselectively *trans*-3-monosubstituted 3-benzylseleno-β-lactams. Initial studies were carried out by reacting *cis*-3-chloro-3-benzylseleno-β-lactam 4 with 1, 4-dimethoxy-benzene as the active aromatic nucleophle in the presence of one equiv. of $SnCl_4$ in dichloromethane at 0 ^oC (scheme-1, table-1, entry-1). This reaction surprisingly resulted in the formation of only monosubstituted product, **5a**, in excellent yield. The product, after column chromatographic purification, was identified as *trans*-1-(4'-methylphenyl)-3-(2',5'-dimethoxyphenyl)-3-benzylseleno-4-(4'-chlorophenyl)azetidin-2-one on the basis of its spectral analysis such as FTIR, ^1H NMR, ^{13}C NMR, ^{77}Se NMR, GSMS and elemental analysis.

Various reactions of β-lactam carbocation equivalent 4 were performed successfully with different active aromatic and heterocyclic compounds (nucleophiles) (scheme-1) and the results are summarized in table-1. Interestingly, all the active compounds (nucleophiles) react with β-lactam 4 to give exclusively the *trans*-3-monosubstituted-3-benzylseleno-β-lactams 5(b-e) (table-1, entries 2-5). No formation of 3,3-disubstituted product was observed by ^1H NMR spectroscopy. However, earlier reports12 revealed that presence of benzylthio ($PhCH_2S$-) group at C-3 led to the formation of varying amounts of 3,3-bis(arylthio)azetidin-2-ones along with 3,3-disubstituted azetidin-2-ones. The spatial juxtaposition of the C4-H and the new substitutent at C-3 in case of 5(a-e) was assigned trans on the basis of correlation of ^1H NMR and ^{13}C NMR data with that of *trans*-3-monosubstituted-3-benzylthio-β-lactams[12].

Table-1
Reaction of 4 with various active aromatic and heterocyclic compounds (nucleophiles) using $SnCl_4$ as the Lewis acid

Entry	Compounds (Nucleophiles)	Product (5)	Yield[a-b] %
1		**5a**	81
2		**5b**	79
3		**5c**	75
4		**5d**	68
5		**5e**	76

[a] All new compounds were characterized by FTIR, ^1H NMR, ^{13}C NMR, ^{77}Se NMR, GCMS and CHN analysis.
[b] Isolated yields after purification by column chromatography.



Scheme-2
A plausible mechanism for the formation of *trans*-3-monosubstituted-3-benzylseleno-β-lactams 5(a-e)

A plausible mechanism for the formation of *trans*-3-monosubstituted-3-benzylseleno-β-lactams 5a-e is presented in scheme- 2. The Lewis acid $SnCl_4$ first forms a complex (**C**) with β-lactam 4, which being bulkier in size, prevents the approach of the incoming nucleophiles from its side. Thus, the nucleophiles attack from the opposite side of C4-H via an S_N2 mechanism.

Conclusion

In conclusion, we have developed a highly stereoselective synthesis of novel *trans*-3-monosubstituted-3-benzylseleno-β-lactams from *cis*-3-chloro-3-benzylseleno-β-lactams using various active aromatic and heterocyclic compounds (nucleophiles) in the presence of Lewis acid $SnCl_4$. Further elaboration of the *trans*-3-monosubstituted-3-benzylseleno-β-lactams to potential spirocyclic and bicyclic β-lactams is underway in our laboratory. In addition, suitably substituted novel *trans*-3-monosubstituted-3-benzylseleno-β-lactams would be evaluated for biological activity for the purpose of structure activity relationship (SAR) studies.

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