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STUDIES TOWARDS THE SYNTHESIS OF NOVEL *N*1- & *N*2-BENZOTRIAZOLE LINKED *C*-3 SUBSTITUTED AZETIDIN-2-ONES

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ABSTRACT
An operationally simple strategy for the synthesis of novel *C*-3 functionalized azetidin-2-ones containing *N*1- and *N*2-linked benzotriazole moiety is described. The starting *N*1 and *N*2-benzotriazole esters (in the ratio of 4 : 1, respectively) were converted into their corresponding acids, which on cycloaddition with appropriate Schiff's bases using Et_3N and $POCl_3$ in refluxing toluene afforded the *trans*-azetidin-2-ones stereoselectively. All the synthesized compounds were characterized by FT-IR, NMR spectroscopy (^1H and ^{13}C) and elemental analysis.The *trans* configuration of the β-lactam was assigned with respect to C3-H and C4-H.

KEYWORDS
trans-azetidin-2-ones, benzotriazole, β-lactams, stereoselective

INTRODUCTION
In recent years, the emergence of life threatening diseases and bacterial resistance against available drugs has become increasingly common, which spells the need for discovering new compounds with a broad spectrum of biological activity. The introduction of β-lactam antibiotics during the latter stages of World War II into the health care system was one of the most important contributions of medical sciences for society. Even today, β-lactams continue to be appreciated as the most widely utilized antibiotic[i] owing to their low cost, high effectiveness, ease of delivery and minimal side effects. The uniqueness of these antibiotics arises from its localized and specific action on bacteria with no functional and structural counterpart in the human host. The low production cost and wide availability of these antibiotics make it necessary to preserve the power of this valuable clinical resource.
Benzotriazole is another privileged and rapid developing substructure in modern heterocyclic chemistry with wide range of biological activities[ii] such as antiprotozoal, antimicrobial, anti-inflammatory, antitumor etc. The property of the benzotriazole moiety to readily bind to a variety of enzymes and receptors in biological system *via* diverse non-covalent interactions

and with metal complexes[iii] is the main cause of its broad spectrum of biological activities. For the above reasons, more potent benzotriazole derivatives with broad bioactivity, low toxicity, few side effects, and little multi-drug resistance have been frequently discovered and have shown great potential as medicinal agents[iv,v]. The structural modification of β-lactam ring by other pharmacophores could improve the bioactive efficiency and various benzotriazole substituted β-lactams[vi-viii] (Figure 1) have been reported which possess good antifungal **I**, antimicrobial **II** and antitubercular **III** activities. Zigheimat *et al.*[ix] have recently reported the synthesis of a series of *trans*- and *cis*-*C*-3 substituted *N*1-linked benzotriazolyl-β-lactams. However, to the best of our knowledge, no reports are available in the literature regarding the synthesis of *C*-3 substituted *N*2-linked benzotriazolyl-β-lactams and stereoselectively *trans*-*C*-3 substituted *N*2-linked benzotriazolyl-β-lactams.

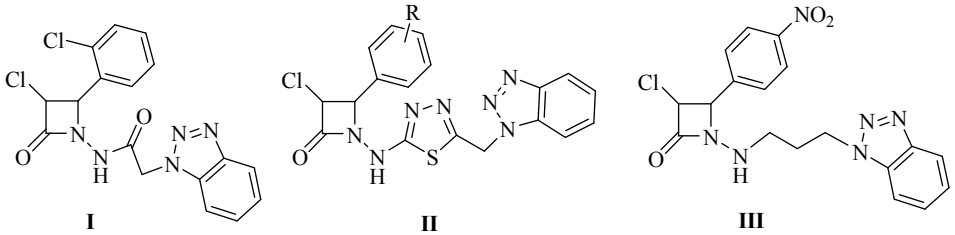


Fig. 1 Biologically potent benzotriazole substituted β-lactams

Our research group has been actively involved in the synthestic β-lactam chemistry[x] such as novel β-lactam precursors, stereoselective *cis*- and *trans*-alkoxy-β-lactams,3-thio/seleno-β-lactams and their Lewis acid mediated functionalization, novel 4-pyrazolyl-β-lactams,spirocyclic-β-lactams, α-keto-β-lactams, bicyclic-β-lactams, 4-pyrazolylspirocyclic-β-lactams and (*E*)- and (*Z*)-3-allylidene-β-lactams. In continuance of the aforementioned topics and considering the importance of benzotriazole substituted β-lactams, herein we wish to report the synthesis of *C*-3 substituted *N*1- and *N*2-linked benzotriazolyl-β-lactams.

EXPERIMENTAL

General

^{1}H NMR (400 MHz and 300 MHz) spectra were 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 a 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 : hexane mixtures. Thin-layer chromatography (TLC) was performed using Merck Silica Gel G. For visualization, TLC plates were stained with iodine vapors. All melting points are uncorrected and were determined with a Thomas-Hoover capillary melting point apparatus. The synthesis of benzotriazole esters and reactions of β-lactams were 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 phosphorus pentoxide. Toluene was distilled under N_2 from sodium-benzophenone respectively immediately before use.

Compounds **2/2′** and **3/3′** were prepared by the procedures described in the cited references.[xi-xiii]. The spectroscopic data of compounds **2/2′** and **3/3′** were also reported in the cited references.[xi-xiii]

General procedure for the synthesis of *C*-3 substituted *N*1- and *N*2-linked benzotriazolyl-β-lactams 5(a-e) and **5′(a-e)**.

To a solution of imine **4(a-e)** (1.20 mmol) and triethylamine (5.98 mmol) in 20 mL dry toluene was added dropwise under nitrogen atmosphere at reflux a solution of ethyl 2-(1H/2H-benzo[d][1,2,3]triazol-1/2-yl) acetic acids **3**/**3′** (1.19 mmol) in 5 mL of dry solvent with constant stirring. The reactants were stirred at refux temperature and the progress of the reaction was monitored by TLC. After completion of the reaction, solvent was evaporated under vacuum, followed by washing the content successively with 1N HCl (3 × 10 mL) water (3 × 10 mL), 5% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude products were purified by column chromatography using silica gel eluting with ethyl acetate : hexane (10 : 90).

***trans*-3-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1,4-bis(4-fluorophenyl)azetidin-2-one [(5a)** 45%**]** was obtained as a yellow solid, m.p. 108-110 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (d, J = 2.1Hz, 1H, C4-H), 5.77 (d, J = 2.1Hz, 1H, C3-H), 6.98-8.10 (m, 12H, ArH); FT-IR 1742 cm^{-1} (C=O); (Found C, 66.92; H, 3.79; N, 14.78; $C_{21}H_{14}F_2N_4O$ requires C, 67.02; H, 3.75; N, 14.89 %).

***trans*-3-(2*H*-benzo[d][1,2,3]triazol-2-yl)-1,4-bis(4-fluorophenyl)azetidin-2-one [(5′a)** 41%**]** was obtained as pale a yellow solid, m.p. 176-178 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H, OCH_3), 5.51-5.52 (d, J = 2.1Hz, 1H, C4-H), 5.73-5.74 (d, J= 2.1Hz, 1H, C3-H), 6.74-8.04 (m, 12H, ArH); FT-IR 1749 cm^{-1} (C=O); (Found C, 66.96; H, 3.82; N, 14.75; $C_{21}H_{14}F_2N_4O$ requires C, 67.02; H, 3.75; N, 14.89 %).

***trans*-3-(1*H*-benzo[d][1,2,3]triazol-1-yl)-4-(4-fluorophenyl)-1-(4-methoxyphenyl)azetidin-2-one [(5b)** 56%**]** was obtained as a yellow solid, m.p. 86-88 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H, OCH_3), 5.46-5.47 (d, J = 1.8Hz, 1H, C4-H), 5.83-5.84 (d, J = 2.1Hz, 1H, C3-H), 6.83-7.88 (m, 12H, ArH); FT-IR 1752 cm^{-1} (C=O); (Found C, 68.05; H, 4.39; N, 14.48; $C_{22}H_{17}FN_4O_2$ requires C, 68.03; H, 4.41; N, 14.43 %).

***trans*-3-(2*H*-benzo[d][1,2,3]triazol-2-yl)-4-(4-fluorophenyl)-1-(4-methoxyphenyl)azetidin-2-one [(5′b)** 52%**]** was obtained as a yellow solid, m.p. 164-165 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H, OCH_3), 5.44-5.45 (d, J = 2.1Hz, 1H, C4-H), 5.80-5.81 (d, J = 2.1Hz, 1H, C3-H), 6.72-7.80 (m, 12H, ArH); FT-IR 1754 cm^{-1} (C=O); (Found C, 68.01; H, 4.36; N, 14.41; $C_{22}H_{17}FN_4O_2$ requires C, 68.03; H, 4.41; N, 14.43 %).

***trans*-3-(1*H*-benzo[d][1,2,3]triazol-1-yl)-4-(4-methoxyphenyl)-1-(4-chlorophenyl)azetidin-2-one [(5c)** 48%**]** was obtained as a yellow solid, m.p. 190-192 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 3H, OCH_3), 5.49 (d, J = 2.1Hz, 1H, C4-H), 5.76-5.77 (d, J = 2.1Hz, 1H, C3-H), 6.84-8.05 (m, 12H, ArH); FT-IR 1760 cm^{-1} (C=O); (Found C, 65.19; H, 4.25; N, 13.81; $C_{22}H_{17}ClN_4O_2$ requires C, 65.27; H, 4.23; N, 13.84 %).

***trans*-3-(2*H*-benzo[d][1,2,3]triazol-2-yl)-4-(4-methoxyphenyl)-1-(4-chlorophenyl)azetidin-2-one [(5′c)** 43%**]** was obtained as a yellow solid, m.p. 76-79 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (s, 3H, OCH_3), 5.44-5.45 (d, J = 2.4Hz, 1H, C4-H), 5.90-5.91 (d, J = 2.4Hz, 1H, C3-H), 6.77-7.87 (m, 12H, ArH); FT-IR 1760 cm^{-1} (C=O); (Found C, 65.23; H, 4.21; N, 13.83; $C_{22}H_{17}ClN_4O_2$ requires C, 65.27; H, 4.23; N, 13.84 %).

***trans*-3-(1*H*-benzo[d][1,2,3]triazol-1-yl)-4-(4-chlorophenyl)-1-(4-methylphenyl)azetidin-2-one [(5d)** 51%**]** was obtained as a yellow solid, m.p. 115-117 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3H, OCH_3), 5.55-5.56 (d, J = 2.1Hz, 1H, C4-H), 5.87-5.88 (d, J = 2.1Hz,

1H, C3-H), 6.84-8.13 (m, 12H, ArH); FT-IR 1759 cm^{-1} (C=O); (Found C, 65.29; H, 4.21; N, 13.79; $C_{22}H_{17}ClN_4O_2$ requires C, 65.27; H, 4.23; N, 13.84 %).

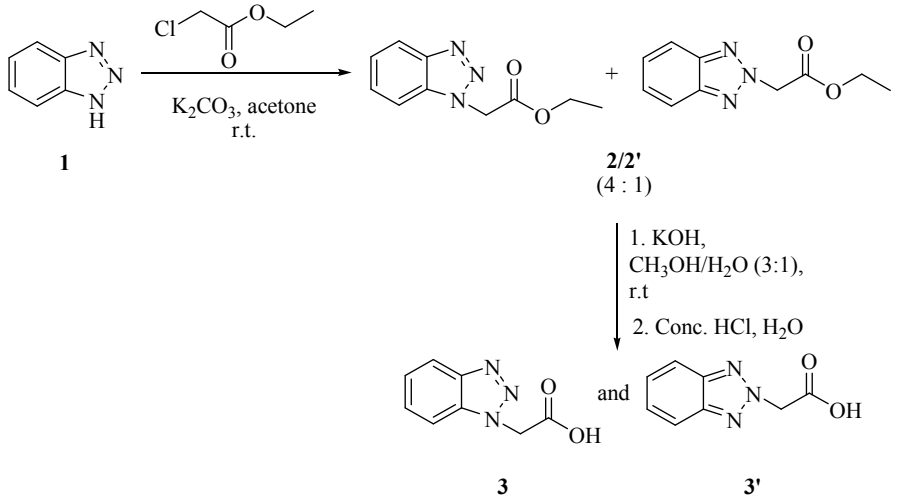
***trans*-3-(2*H*-benzo[d][1,2,3]triazol-2-yl)-4-(4-chlorophenyl)-1-(4-methoxyphenyl)azetidin-2-one [(5′d)** 43%**]** was obtained as a yellow solid, m.p. 82-84 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (s, 3H, OCH_3), 5.43-5.442(d, J = 2.1Hz, 1H, C4-H), 5.77-5.78 (d, J = 2.1Hz, 1H, C3-H), 6.38-8.63 (m, 12H, ArH); FT-IR 1745 cm^{-1} (C=O); (Found C, 65.26; H, 4.21; N, 13.86; $C_{22}H_{17}ClN_4O_2$ requires C, 65.27; H, 4.23; N, 13.84 %).

***trans*-3-(1*H*-benzo[d][1,2,3]triazol-1-yl)-4-(furan-2-yl)-1-(4-methylphenyl)azetidin-2-one [(5e)** 42%**]** was obtained as a yellow solid, m.p. 145-146 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H, OCH_3), 5.61-5.62 (d, J = 2.4Hz, 1H, C4-H), 6.23 (d, J = 2.4Hz, 1H, C3-H), 6.41-8.12 (m, 9H, ArH); FT-IR 1748 cm^{-1} (C=O); (Found C, 66.62; H, 4.45; N, 15.51; $C_{20}H_{16}N_4O_3$ requires C, 66.66; H, 4.48; N, 15.55 %).

***trans*-3-(2*H*-benzo[d][1,2,3]triazol-2-yl)-4-(furan-2-yl)-1-(4-methylphenyl)azetidin-2-one (5′e). [(5′e)** 42%**]** was obtained as a yellow solid, m.p. 132-135 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H, OCH_3), 5.52-5.53 (d, J = 2.4Hz, 1H, C4-H), 6.26-6.27 (d, J = 2.4Hz, 1H, C3-H), 6.33-6.35 (dd, 1H, ArH), 6.45-6.50 (d, J = 2.4Hz, 1H, ArH) 6.77-7.83 (m, 9H, ArH); FT-IR 1751 cm^{-1} (C=O); (Found C, 66.59; H, 4.51; N, 15.57; $C_{20}H_{16}N_4O_3$ requires C, 66.66; H, 4.48; N, 15.55 %).

RESULTS AND DISCUSSION

The starting substrates ethyl 2-(1*H*-benzo[d][1,2,3]triazol-1-yl) and ethyl 2-(2H-benzo[d][1,2,3]triazol-2-yl)acetate **2** and **2'** were synthesized from benzotriazole **1** and ethylchloroacetate using a reported procedure[xi,xii] (Scheme 1). Substrates **2/2′** were obtained in the ratio of (4 : 1) respectively and separated through column chromatography. Further, **2** and **2′** were separately converted to their corresponding potassium salts followed by acidification to get the desired 2-(1H-benzo[d][1,2,3]triazol-1-yl) and ethyl 2-(2*H*-benzo[d][1,2,3]triazol-2-yl)acetic acids[xii,xiii] **3** and **3′** respectively(Scheme 1).



Scheme 1. Synthesis of *N*1- and *N*2-linked benzotriazolyl ethanoic acids **3** and **3′**

The synthesized *N*1- and *N*2-linked benzotriazolyl esters **2/2′** and acids **3/3′** were characterized using FT-IR and NMR spectroscopy (^{1}H). ^{1}H NMR spectroscopy clearly differentiates the two esters or acids on the basis of splitting pattern of aromatic protons. The more symmetrical compound **2′** and **3′** gave simple AA′BB′ splitting pattern (symmetrical) with signals from protons at C-4 and C-7 as they are deshielded by electron pairs on N-1 and

N-3, while in **2** and **3**, only one proton at C-4 is deshielded, thus giving an unsymmetrical peak distribution in NMR (Figure 2).

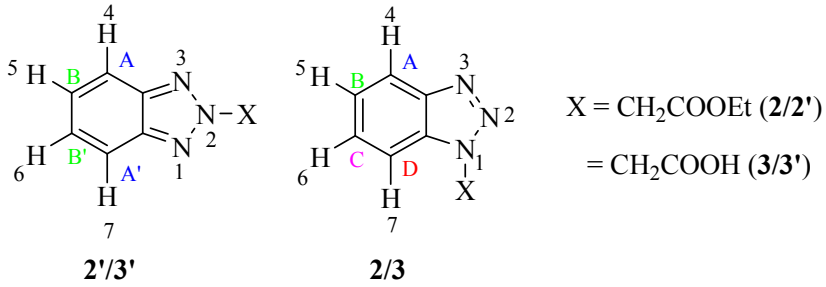
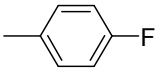
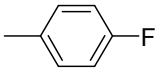
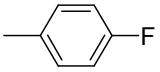
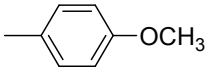
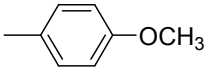
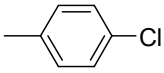
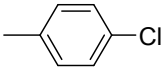
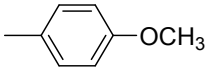
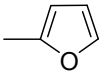
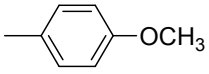


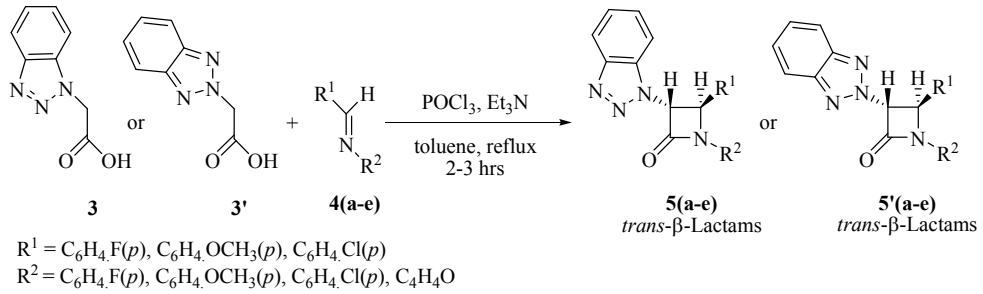
Fig. 2 NMR peaks splitting pattern in **2/2′** and **3/3′**

The synthesis of novel *trans*-3-*N*1/*N*2-linked benzotriazolyl-β-lactams **5/5′** has been achieved via Staudinger cycloaddition between the ketene generated from *N*1/*N*2-benzotriazolyl acetic acids **3** and **3′** and appropriate Schiff's bases **4** (Scheme 2). Schiff's bases **4(a-e)** required for the synthesis were prepared by stirring equivalent amounts of primary amines with the appropriate aldehyde using molecular sieves (4Å) in dichloromethane (Table 1). The structures of Schiff's bases (imines) **4** were confirmed on the basis of their NMR spectra (^{1}H, ^{13}C).

Table 1: Schiff's Bases **4(a-e)**

Entry	R^1	R^2	Imine **4(a-e)**	Yield %
1.			**4a**	95
2.			**4b**	96
3.			**4c**	94
4.			**4d**	98
5.			**4e**	91

Initially, *N*1- and *N*2-benzotriazolyl acetic acids **3** and **3′** separately were subjected to cycloaddition with Schiff's base **4a** in dry methylene chloride using phosphorus oxychloride ($POCl_3$) and triethylamine (Et_3N) at 0 °C, but this reaction failed to yield the desired product. However, when the same reaction was performed in refluxing dry toluene and the progress of the reaction was monitored by thin-layer chromatography (TLC), it resulted in the exclusive formation of *trans*-3-*N*1- and N2-linked benzotriazolyl-β-lactams **5a** and **5′a** respectively, having lower R_f value than the starting Schiff's base in excellent yields. The target β-lactams **5a**/**5′a** was purified by column chromatography and were identified as *trans*-3-(1*H*-benzo[d][1,2,3]triazol-1-yl)- and *trans*-3-(2*H*-benzo[d][1,2,3]triazol-2-yl)-1,4-bis(4-fluorophenyl)azetidin-2-ones **5a**/**5′a** on the basis of ^{1}H NMR spectroscopy.



Scheme 2. Synthesis of *trans*-3-*N*1/*N*2-linked benzotriazolyl-β-lactams **5(a-e)/5′(a-e)**

Further, to understand the nature of the various Schiff's bases **4(a-e)** towards the Staudinger reaction with benzotriazole substituted ethanoic acids **3**/**3′**, the reaction was carried out by varying the R^1 and R^2 substituents of Schiff's bases (Scheme 2, Table 2, entry 1). It was observed that the reaction is stereoselective in nature resulting into the exclusive formation of *trans*-β-lactams **5**/**5′**.

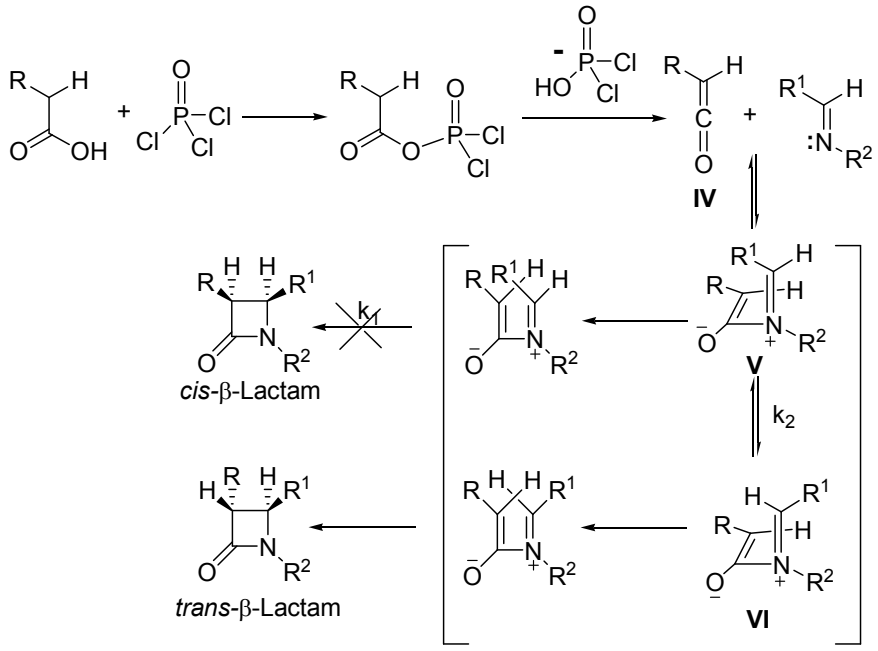
Table 2. Synthesis of *trans*-3-*N*1/*N*2-linked benzotriazolyl-β-lactams **5(a-e)/5′(a-e)**

Entry	Acids **3/3′**	Imines **4/4′**	β-Lactams **5/5′**	Yield[a] (%)
1.	**3**	**4a**	**5a**	45
2.	**3**	**4b**	**5b**	56
3.	**3**	**4c**	**5c**	48
4.	**3**	**4d**	**5d**	51
5.	**3**	**4e**	**5e**	42
6.	**3′**	**4a**	**5′a**	41
7.	**3′**	**4b**	**5′b**	52
8.	**3′**	**4c**	**5′c**	43
9.	**3′**	**4d**	**5′d**	45
10.	**3′**	**4e**	**5′e**	39

[a] Isolated yields after chromatographic purifications

All newly synthesized moncyclic *trans*-3-*N*1/*N*2-linked benzotriazolyl-β-lactams **5** or **5′** were purified by column chromatography on silica gel using ethyl acetate : hexane (10 : 90) as eluant. The structures of these β-lactams **5**/**5′** were established on the basis of various spectroscopic techniques viz., FT-IR, NMR (^{1}H, ^{13}C) and their elemental analysis (C, H, N). The IR absorption band in the range of 1724-1755 cm^{-1} for the C=O of the β-lactam ring supported the formation of benzotriazolyl-β-lactams **5**/**5′**. The spatial juxtaposition of the C3-H and C4-H was assigned *trans* on the basis of coupling constant values (J = 1.2-2.7 Hz C3-H and C4-H) in the ^{1}H NMR spectra.

The stereoselctive formation of *trans*-β-lactams can be attributed by the initial exo attack of the *E* imine to the ketene **IV**, thus generating the zwitterionic intermediate **V** followed by the isomerization of the *E* imine to less favored *Z* imine thus forming zwitterionic intermediate **VI**, which undergoes conrotatory electrocyclization to generate the thermodynamically more stable *trans*-β-lactam. The rate constants for direct ring closure and isomerization determine the relative stereoselctivity of β-lactam formation[xiv]. In addition, the presence of bulky group at C-3 position favours *trans* configuration over *cis* due to less steric crowding in case of *trans*-β-lactams (Scheme 3).



Scheme 3. Plausible mechanism for the stereoselctive formation of *trans*-β-lactams

The *trans*-3-*N*1/*N*2-linked benzotriazolyl-β-lactams **5**/**5′** are air- and moisture-stable and soluble in solvents such as methylene chloride, chloroform, acetone, toluene and ethyl acetate. All β-lactams were obtained as stable solids.

CONCLUSION

In conclusion, successful attempts have been made towards the stereoselective synthesis of novel β-lactams **5**/**5′** containing the benzotriazole moiety directly linked to the C-3 position of the β-lactam ring through *N*1 and *N*2 *via* cycloaddition reaction between ketenes generated from benzotriazolyl substituted acetic acids **3**/**3′** and Schiff's bases **4** in refluxing toluene using $POCl_3$ and Et_3N. Substrate scope was also investigated by varying R^1 and R^2 groups of imine **4**. The representative β-lactams have been submitted for their molecular docking, *in vitro* as well as *in silico* studies. Further, functionalization of these β-lactams to obtain more functionalized heterocycles is underway in our laboratory.

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