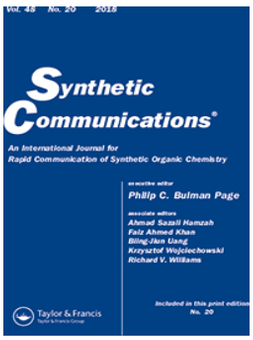

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Facile synthesis of novel benzothiazolylpyrazolyl anchored 3-thio/seleno/chloro-β-lactams: Synthetic intermediates for novel 3-sulfenyl/sulfonyl, C-3 functionalized monocyclic and spirocyclic β-lactams

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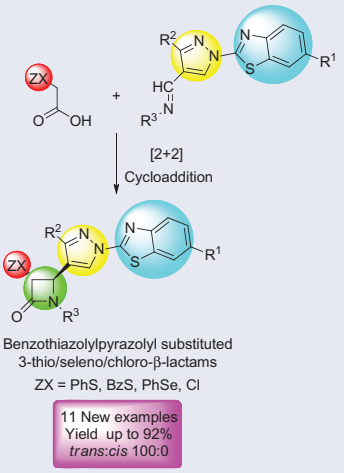
ABSTRACT

Efficient synthesis of a new series of 3-phenyl/benzylthio-4-benzothiazolylpyrazolyl-β-lactams is described. Treatment of 2-phenylthio/benzylthioacetic acid with benzothiazolylpyrazolyl substituted Schiff's bases furnished trans-β-lactams exclusively. Newly synthesized substituted Schiff's bases and β-lactams were identified using FT-IR, ^{1}H NMR, ^{13}C NMR and elemental analysis (CHN). The *trans* configuration was assigned with respect to coupling constant values of C3-H and C4-H. The novel β-lactams will be the potential synthetic intermediates to access 3-sulfenyl/sulfonyl, C-3 functionalized monocyclic and spirocyclic β-lactams of medicinal interest. The present manuscript provides first report on β-lactams linked to bulky group benzothiazolylpyrazolyl.

GRAPHICAL ABSTRACT



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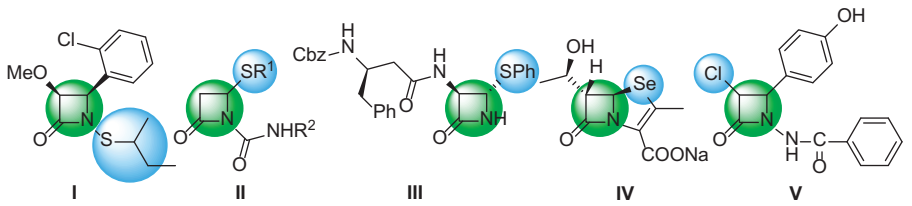


Figure 1. Biologically active thiolated-β-lactams.

Introduction

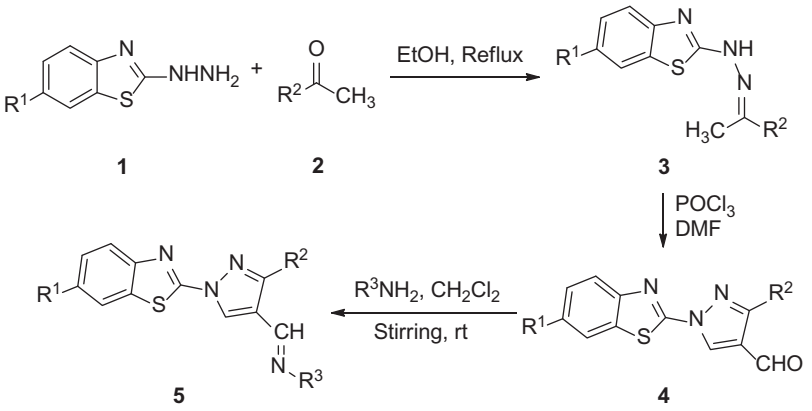
The β-lactam chemistry has always attracted the interest of both synthetic as well as medicinal chemist. Continuous efforts in this field to explore other analogs with better activity profiles, efficient synthetic methodologies, novel heterocyclic scaffolds is the prime focus of present scenario.[1] The β-lactam derivatives has shown promising applications as versatile intermediates for preparation of many valuable compounds viz. amino acids, peptides, heterocycles.[2,3] Significant interest has been shown in nitrogen containing heterocycles such as benzothiazole and pyrazole as they provided great contribution in agriculture and pharmaceutical industry.[4] Thio/seleno/chloro substituted β-lactams has found uses in various fields either as biologically active molecules or as synthetic intermediates (Fig. 1). The N1-thiolated-β-lactams **I** exhibited excellent antimicrobial activities against wide range of microbial strains,[5] and C4 thiolated β-lactams **II-III** were found as antiviral and inhibitors of cystein protease (Fig. 1).[6,7] Additionally, seleno and chloro substituted β-lactams **IV-V** were also found to exhibit antibacterial activity.[8–10]

A successful synthesis of a variety of β-lactam precursors, 4-pyrazolyl-β-lactams, spirocyclic β-lactams, 3-allylidene-β-lactams and pyrimidine linked β-lactams have been reported by our research group.[11–15] In continuation to synthesis of 3-thio/seleno-β-lactams, their C3 functionalization and heteroaryl substituted β-lactams,[12,13,15] we envisaged to synthesize a new class of benzothiazolylpyrazolyl anchored 3-thiolated-β-lactams. The significance of this manuscript lies in the fact that this is the first report on benzothiazolylpyrazolyl linked 3-thiolated-β-lactams having multiple heterocycles in single system viz. pyrazole, benzothiazole and β-lactam. In addition to this, chemical transformation of these β-lactams into β-lactam sulfoxides/sulfones, C-3 functionalized monocyclic and spirocyclic β-lactams along with biological evaluation is presently underway in our laboratory.

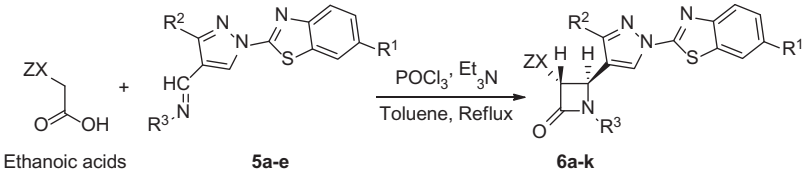
Results and discussion

Initially, benzothiazolylpyrazolyl linked Schiff's bases **5** were prepared by treatment of 1-(benzo[*d*]thiazol-2'-yl)-1*H*-pyrazole-4-carbaldehydes **4** with differently substituted amines using our earlier reported strategy (Scheme 1).[16]

3-Phenylthio/benzylthio/phenylseleno/chloro-4-benzothiazolylpyrazolyl-β-lactams **6a-f** were prepared by treatment of various ketenes derived from 2-phenylthio/benzylthio/phenylseleno/chloroacetic acids and benzothiazolylpyrazolyl substituted Schiff's bases **5a-e** (Scheme 2). Initially, 2-phenylthioacetic acid was treated with *N*-[{1-(6′-methoxybenzo[*d*]thiazol-2′-yl)-3-phenyl-1*H*-pyrazol-4-yl}methylene]-4-methoxybenzenamine **5a**



Scheme 1. Synthesis of benzothiazolylpyrazolyl substituted imines **5**.



Scheme 2. Synthesis of 3-phenylthio/phenylseleno/chloro-4-benzothiazolylpyrazolyl-β-lactams **6a–k**.

in the presence of phosphorous oxychloride and triethylamine using toluene (dry) as a solvent at refluxing. The progress of the reaction was monitored by TLC. On completion, the solvent was evaporated under vacuum and crude product was obtained which was purified by efficient silica gel column chromatography using 10% EtOAc/hexane as eluant. The product was identified as *trans*-1-(4′-methoxyphenyl)-4-[1-(6′-methoxybenzo[*d*]thiazol-2′-yl)-3-phenyl-1*H*-pyrazol-4-yl]-3-phenylthioazetidin-2-one **6a** (Scheme 2) on the basis of various spectroscopic techniques viz. FT-IR, ^{1}H NMR, ^{13}C NMR and elemental analysis.

Further, scope of the reaction was checked by using differently substituted ethanoic acids (ZX = PhS, BzS, PhSe, Cl) and Schiff's bases (R^1, R^2, R^3 i.e. R^1 = OMe, Cl; R^2 = Ph, 4-MeC_6H_4; R^3 = 4-OMeC_6H_4, Bz, ^{i}Bu) (Table 1, entries 2–6).

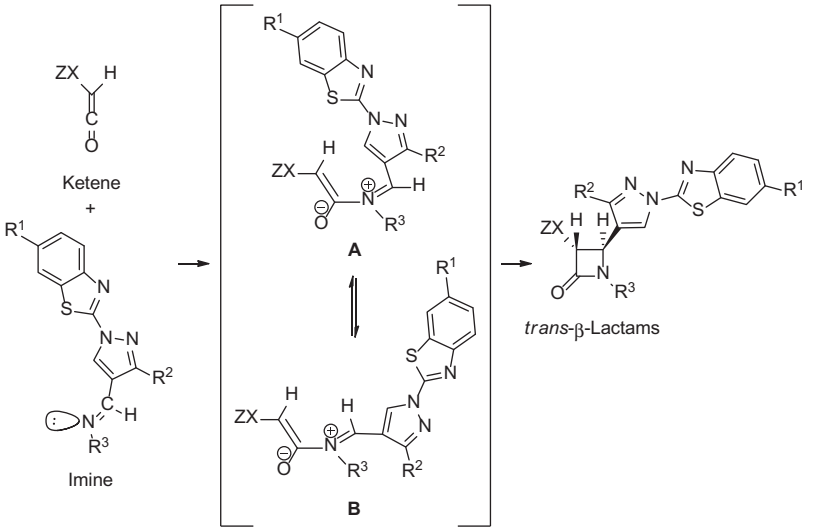
This reaction was successful in accommodating benzothiazolylpyrazolyl (big steric bulk) in the azetidin-2-one ring and furnished exclusively the *trans*- product in all cases. Benzothiazolylpyrazolyl tethered thio/seleno/chloro-β-lactams has been efficiently purified by column chromatography using 10% EtOAc/hexane as eluant were obtained as solids, soluble in various solvents (methylene chloride, chloroform, toluene, acetone and ethyl acetate) and quite stable towards air- and moisture.

The structures of these β-lactams (**6a–k**) were established using various spectroscopic studies such as FT-IR, ^{1}H NMR, ^{13}C NMR and elemental analysis (CHN). The presence of C=O group was confirmed on the basis of IR absorptions in the range of 1742-

Table 1. Synthesis of benzothiazolylpyrazolyl anchored 3-phenylthio/benzylthio/phenyl seleno/chloro-*β*-lactams **6a–k**.

Entry	–XZ	R^1	R^2	R^3	Product, **6**	Yield[a] (%)
1	$-SC_6H_5$	$-OCH_3$	$-C_6H_5$	$-C_6H_4OCH_3(p)$	**6a**	76
2	$-SCH_2C_6H_5$	$-OCH_3$	$-C_6H_5$	$-C_6H_4OCH_3(p)$	**6b**	80
3	$-SC_6H_5$	$-OCH_3$	$-C_6H_5$	$-CH_2C_6H_5$	**6c**[b]	82
4	$-SC_6H_5$	$-OCH_3$	$-C_6H_5$	$-C_4H_9(iso)$	**6d**	81
5	$-SC_6H_5$	–Cl	$-C_6H_5$	$-C_6H_4OCH_3(p)$	**6e**	88
6	$-SC_6H_5$	$-OCH_3$	$-C_6H_4CH_3(p)$	$-C_6H_4OCH_3(p)$	**6f**	92
7	$-SeC_6H_5$	$-OCH_3$	$-C_6H_5$	$-C_6H_4OCH_3(p)$	**6g**	67
8	$-SeC_6H_5$	$-OCH_3$	$-C_6H_5$	$-CH_2C_6H_5$	**6h**	80
9	$-SeC_6H_5$	$-OCH_3$	$-C_6H_5$	$-C_4H_9(iso)$	**6i**	64
10	–Cl	$-OCH_3$	$-C_6H_5$	$-CH_2C_6H_5$	**6j**	84
11	–Cl	$-OCH_3$	$-C_6H_5$	$-C_4H_9(iso)$	**6k**	83

[a]Yield of pure isolated product with correct analytical and spectral data.
[b]Structure established on the basis of EIMS.



Scheme 3. Plausible mechanism for the formation of *trans*-β-lactams **6a–k**.

1757 cm^{-1} whereas *trans*- configuration in all the β-lactams (**6a–k**) was assigned by analyzing the coupling constant values ($J = 1.7–2.7$ Hz; C3-H and C4-H) in ^1H NMR spectra.[12] In addition, CHN elemental analysis established the accomplishment of the novel β-lactams.

The present study was initiated to envisage whether the cycloaddition is possible with ketenes and imines having such a bulky group. Fortunately, azetidin-2-one ring formation occurs and cycloaddition showed selectivity towards *trans*- configuration. The exclusive formation of *trans*-β-lactams is related to presence of bulky group at C-4 and high temperature conditions which generally lowers the rate constant in case of direct ring closure or favors isomerization of the intermediate. The plausible mechanism for preparation of 3-Phenyl/benzylthio-4-benzothiazolylpyrazolyl-β-lactams **6a–k** is depicted in Scheme 3. Initially, differently substituted ethanoic acids ($Z = C_6H_5$, $CH_2C_6H_5$) generate ketene intermediates *in-situ* in the presence of $POCl_3$ and triethylamine followed by *exo*-attack of *E*-imine through lone pairs of nitrogen afforded intermediate **A**. Subsequently, intermediate **A** undergo isomerization to

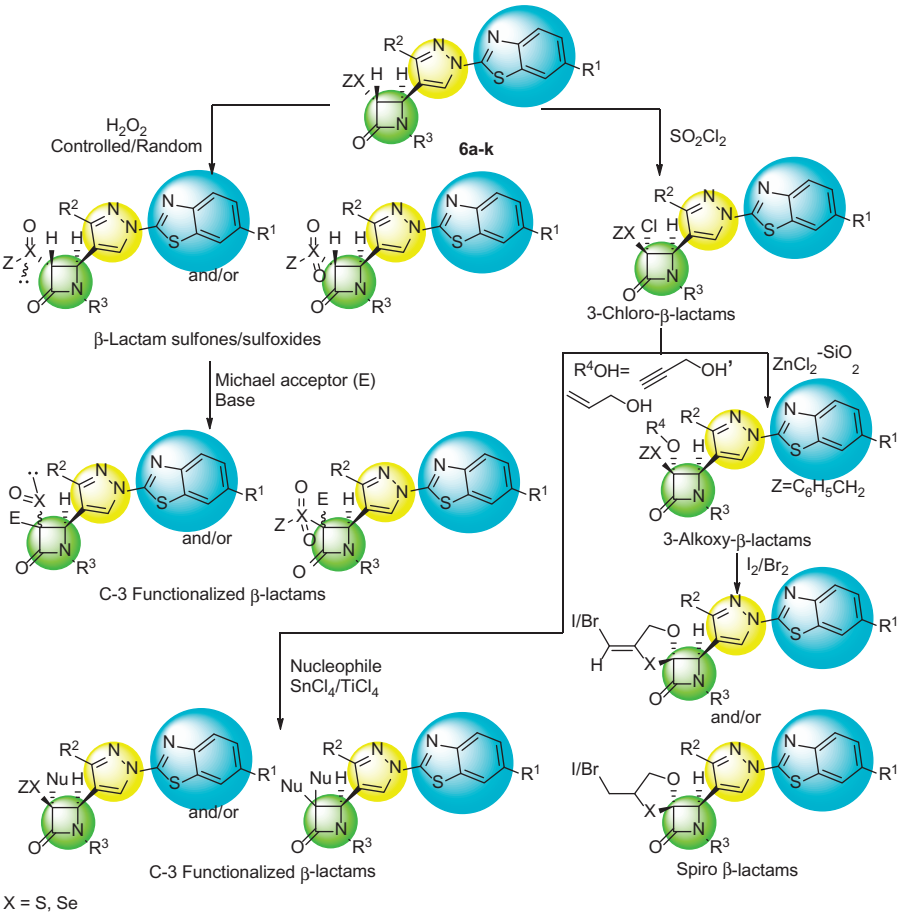


Figure 2. Synthetic utility of 4-benzothiazolylpyrazolyl-β-lactams **6**.

furnish intermediate **B** which upon direct ring closure afforded *trans*-β-lactams (**6a–k**). The mechanism is found to be totally in accordance with our earlier publication[12] and relevant literature[17] describing mechanistic aspects of β-lactam synthesis in detail.

Further, studies were pursued in transformation of these synthetically useful 3-phenylthio/benzylthio/phenylseleno/chloro-4-benzothiazolylpyrazolyl-β-lactams **6a–k** into various sulfenyl/sulfonyl, C-3 functionalized monocyclic and spirocyclic β-lactams (Figure 2).[13,19,20]

Conclusion

In conclusion, a new series of benzothiazolylpyrazolyl anchored 3-phenylthio/benzylthio-β-lactams has been synthesized using a mild, efficient and diastereoselective strategy. The complete structural analysis of all the new β-lactams have been carried out using FT-IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. In addition, novel β-lactams has been submitted for potential *in-vitro* antimicrobial/anticancer evaluation guided by *in-silico* analysis (molecular modeling). Further, synthetic utility of these novel

β-lactams to series of medicinally important scaffolds i.e. 3-sulfenyl/sulfonyl, C-3 functionalized monocyclic and spirocyclic β-lactams are underway in laboratory.

Experimental

Melting points were determined in an open capillary on melting point apparatus (Perfit GSI-MP-3) and are uncorrected. Fourier transform infrared spectra were recorded on a Thermo scientific Nicolet iS50 (FT-IR) spectrophotometer (υ_{max} in cm^{-1}). ^1H (300 and 400 MHz) and ^{13}C (75 and 100 MHz) NMR spectra were recorded on JEOL AL 300 (300 MHz) and BRUKER AVANCE II (400 MHz) spectrometer. Chemical shifts are given in ppm relative to Me_4Si as an internal standard ($\delta = 0$ ppm) for ^1H NMR, $CDCl_3$ ($\delta = 77.0$ ppm) for ^{13}C NMR. The mass spectra (EI) were obtained using Water's Q-TOF Micromass (YB361) spectrometer. The elemental analysis (C, H, N) were recorded on Flash 2000 Organic elemental analyzer. Column chromatography was performed using Merck Silica Gel (60–120 mesh) using EtOAc/hexane (10:90) as an eluant system. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel F254 aluminum plates with visualization under UV light.

Preparation of novel β-lactams was carried out under dry and deoxygenated nitrogen atmosphere. Phosphorus oxychloride (Merck), triethylamine (Qualigen), hydrazine hydrate (Qualigen) and all other commercially available compounds/reagents/solvents were of reagent grade quality and used without any further purification. Dimethylformamide (Qualigen) and dichloromethane (Qualigen) were dried and distilled over anhydrous calcium chloride ($CaCl_2$) (CDH) and phosphorus pentoxide (P_2O_5) (Qualigen), respectively. Toluene (Qualigen) was distilled under N_2 from sodium-benzophenone immediately before use.

Starting materials i.e., benzothiazolylpyrazole carbaldehydes **4**[18] and benzothiazolylpyrazolyl substituted imines **5**[16] were prepared following our laboratory methods described in cited references.

General procedure for the synthesis of benzothiazolylpyrazolyl anchored trans-3-phenylthio/benzylthio/phenylseleno/chloro-β-lactams (6a–k)

To a solution of Schiff's base **5** (1 mmol), phenylthio/benzylthio/phenylseleno/chloroacetic acid (1.2 mmol) and triethylamine (3 mmol) in 20 mL of dry toluene was added dropwise, under nitrogen atmosphere, at refluxing a solution of phosphorous oxychloride (1.5 mmol) in 25 mL of toluene with constant stirring. The reaction mixture was refluxed for 4–5 h. The progress of the reaction was monitored by TLC. After the completion, the solvent was evaporated under reduced pressure, contents were extracted with methylene chloride, washed successively with water (25 × 3 mL), 1 N HCl (25 × 3 mL), 5% $NaHCO_3$ (25 × 3 mL) and brine solution (25 × 3 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude product was purified by silica gel column chromatography using 10% EtOAc/hexane as eluant. Solvent evaporation furnished pure *trans*-β-lactams **6a–k**.

Trans-1-(4′-methoxyphenyl)-4-[1-(6′-methoxybenzo[d]thiazol-2′-yl)-3-phenyl-1H-pyrazol-4-yl]-3-phenylthioazetidin-2-one (6a)

White solid; Yield 76%; mp 176–177 °C; FT-IR (neat) ν: 1755 (C=O) cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 3.64 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 4.27 (1 H, d, J = 1.8 Hz, C4-H), 4.82 (1 H, d, J = 1.8 Hz, C3-H), 7.78–6.63 (17 H, m, ArH), 8.30 (1 H, s, =CH); ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 29.6, 53.9, 55.2, 55.7, 62.0, 104.6, 114.4, 115.5, 118.6, 119.5, 123.0, 126.7, 128.7, 128.9, 129.2, 129.8, 130.7, 131.1, 133.7, 134.5, 145.0, 153.4, 156.4, 157.3, 157.6, 162.2; Elemental analysis: found (%): C, 66.88; H, 4.29; N 9.35. $C_{33}H_{26}N_4O_3S_2$ calculated (%): C, 67.10; H, 4.44; N, 9.48.

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