Tetrahedron Letters 57 (2016) 2822–2828

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Facile synthesis of novel halogenated 4-pyrazolylspirocyclic-β-lactams: versatile heterocyclic synthons

Aman Bhalla [a,*], Shamsher S. Bari [a], Jitender Bhalla [a], Sadhika Khullar [b], Sanjay Mandal [b]

[a] Department of Chemistry and Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh 160014, India
[b] Indian Institute of Science Education and Research (IISER), Mohali 160062, India

ARTICLE INFO

Article history:
Received 21 April 2016
Revised 10 May 2016
Accepted 13 May 2016
Available online 13 May 2016

Keywords:
β-Lactams
Spirocyclic
Halogenated
Rotamers
X-ray crystal structures

ABSTRACT

A mild approach for the synthesis of halogenated 4-pyrazolylspirocyclic-β-lactams via halogen (I_2, Br_2, ICl) mediated intrasulfenyl cyclisation of *cis*-3-(prop-2′-ynyloxy)-4-pyrazolyl-β-lactams is described. The behaviour of the substrate towards the nature and variable amount of halogen was investigated. The structural and stereochemical analysis of novel β-lactams were carried out using FT-IR, NMR (^{1}H and ^{13}C), 2D-NMR (COSY and HSQC), elemental analysis (CHNS), mass spectrometry (EIMS) and single crystal X-ray crystallographic studies (**3a**, **6a**, **7a**). NMR experiments were also performed on *cis*-3-chloro-4-pyrazolyl-β-lactams to establish the relationship between isomeric ratio of rotamers and nature of solvents. The *cis* or *trans* configuration of the hydrogen/chloro/nucleophile substituent at C-3 was assigned with respect to C4-H.

Polyfunctional heterocyclic derivatives are well known for their wide range of applications in the field of therapeutics[1] and molecular recognition[2] along with their utilities as building blocks for many natural products[3] and materials having defined properties.[4] The bromine and iodine substituted compounds act as effective synthons for polyfunctional arenes and heteroarenes.[5] Heterocycles containing β-lactam and pyrazole moieties in their structures have occupied a prime place in the pharma sector due to their diverse pharmacological activities.[6,7]

Further, the synthesis of spirocyclic β-lactams has gained the interest of researchers due to their distinctive characteristics such as antidiabetic, anti-inflammatory, anticancer, peptidomimetics, inhibitors of acetyl-CoA cholesterol acyl transferase and picornaviruses.[8] In addition to this, mono and polyhalogenated compounds are useful as agrochemicals, pharmaceuticals, flame retardants and speciality chemicals.[9] These type of heterocyclic constructs have expressed their utilities as diagnostic agent I, anti-infective II, analgesic and anti-inflammatory agent III, antibacterial agent IV and biologically important marine natural product like chartelline V (Fig. 1).

Several syntheses of spiro-β-lactams have been described in the literature and presently Singh et al. have extensively discussed the syntheses including various methodologies (cycloaddition, cyclisation and transformation of attached groups) and biological relevance of different types of spiro-β-lactams.[10] Very recently, Xu et al.[11] have synthesised 4-spiro-β-lactams via intramolecular cyclisation of *N*-(*p*-hydroxyphenyl)cyanoacetamides using IBD as oxidant and KOH as base. Pinho e Melo and co-workers[12,13] have carried out the synthesis of spiropyrazoline penicillanates with different diazomethane and spiropyrazoline β-lactams via 1,3-dipolar cycloaddition. Halogen mediated cyclisations utilising carbon–carbon multiple bond is one of the pioneering methods for constructing heterocyclic rings[14,15] and in relevance to this, Turos et al. have reported halocyclisation reactions of unsaturated sulfides.[16]

Our research group has been extensively engaged in the synthesis of novel β-lactam precursors,[17,18] 3-thio/seleno-β-lactams and their Lewis acid mediated functionalisation,[19–24] stereoselective *cis*- and *trans*-alkoxy-β-lactams,[25] (*Z*)- and (*E*)-3-allylidene-β-lactams,[26] 3-keto-β-lactams[27] and bicyclic-β-lactams.[28] Further, synthesis of novel spirocyclic β-lactams[29–31] and 4-pyrazolyl-β-lactams[32] have been pursued by our research group. The need for an easy access to halogenated molecules aiming at highly functionalised chemical entities, diverse biological applications of β-lactams and pyrazole moieties, led us to investigate the synthesis of halogenated 4-pyrazolylspirocyclic-β-lactams.

Starting substrate, i.e., β-lactams **1a–c** were prepared from 2-benzylthioethanoic acid and pyrazole substituted imines and after purification, further transformed into *cis*-3-chloro-4-pyrazolyl-β-lactams **2a–c** using our earlier reported methodology[32,19] respectively (Scheme 1, Table 1). *cis*-3-(Prop-2′-ynyloxy)-4-pyrazolyl-β-lactams **3a–c** were synthesised successfully by treating

* Corresponding author. Tel.: +91 172 253 4417; fax: +91 172 2545074.
E-mail address: amanbhalla@pu.ac.in (A. Bhalla).

http://dx.doi.org/10.1016/j.tetlet.2016.05.047
0040-4039/

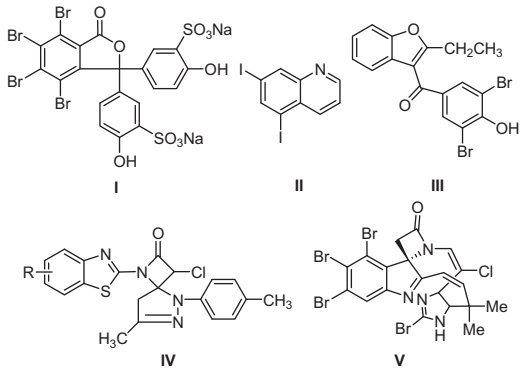


Figure 1. Biologically active halogenated heterocycles.

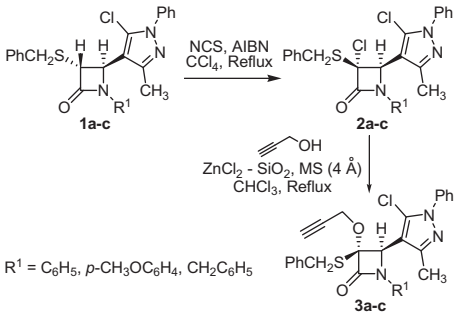
β-lactams **2a–c** with propargyl alcohol using $ZnCl_2$ as Lewis acid and chloroform as solvent in good yields (Scheme 1, Table 2).[25]

The structures, stereochemistry and plausible mechanisms for the formation of β-lactams **1–3** were established on the basis of elemental analysis, spectroscopic techniques, X-ray crystallographic analysis and are listed in the cited references and notes.[33] Earlier, all the *cis*-3-phenyl/benzyl-3-propargyloxy-β-lactams were obtained as oils or semisolids.[25] However, here the stereochemistry at C3 of β-lactams **3a–c** was established by single crystal X-ray structural analysis of *cis*-1-phenyl-3-(prop-2′-ynyloxy)-3-benzylthio-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)-azetidin-2-one **3a** (Fig. 2).[34]

Due to dynamic activity profile of spiro fused azetidin-2-ones, we envisaged the synthesis of 4-pyrazolylspirocyclic-β-lactams. Initially, **3a** was subjected to intrasulfenyl cyclisation (ISC) using 1 equiv of bromine in dichloromethane. The reaction resulted in the formation of five-membered ring spiro-β-lactams which were separated by column chromatographic purification and were identified as **4a** (higher R_f value) and **5a** (lower R_f value) on the basis of spectroscopic data (Scheme 2).[39] In **5a**, *para* position of the phenyl ring at N1 was substituted with bromine atom (Scheme 2, Table 3, entry 1).

Further, the reaction was examined by treating 2 equiv of bromine with **3a** which resulted in the formation of three products, i.e., **6a**, **7a** and **8a** (Scheme 2, Table 3, entry 2). All the three products were separated by column chromatography and were identified using various spectroscopic techniques (FT-IR, ^{1}H NMR, ^{13}C NMR, elemental analysis and mass spectrometry).[39] The structure of **6a** and **7a** was confirmed by X-ray crystallographic analysis (Figs. 3 and 4 respectively).

The ^{1}H NMR spectrum of **4a** and **5a** showed a triplet at δ 5.88 and 6.15 ppm respectively for bromomethylene proton at C7 which is in accordance with our earlier reported spiro-β-lactams.[30] However, in case of **6a** and **7a**, the signals appeared as singlets at δ



Scheme 1. Synthesis of *cis*-3-(prop-2′-ynyloxy)-4-pyrazolyl-β-lactams **3a–c**.

Table 1
Synthesis of *cis*-3-chloro-4-pyrazolyl-β-lactams **2a–c**

Entry	R^1	Products	Yield[a] (%)
1	C_6H_5	**2a**	72
2	p-$CH_3OC_6H_4$	**2b**	66
3	$CH_2C_6H_5$	**2c**	58

[a] Yield of pure, isolated product with correct analytical and spectral data.

6.10 and 5.81 ppm respectively. Recrystallised (methylene chloride/hexane) **6a** and **7a** were confirmed as polybrominated spiro adducts through single crystal X-ray studies (Figs. 3 and 4 respectively).[35,36] The spiro-β-lactams **6a** (higher R_f value) and **7a** (lower R_f value) differs from spiro-β-lactams **4a** and **5a** in having two extra bromine atoms and a single bond at C7 instead of an *exo*-double bond. One more product (higher R_f value than **6a**) was identified as spiro adduct **8a** on the basis of ^{1}H NMR and mass spectrometry analysis. Further increase in the amount of bromine did not cause any change in the reaction profile (Table 3, entry 3).

Afterwards, the substrate scope was analysed by varying the N1 substituent of β-lactam **3** to improve the selectivity of the target 4-pyrazolylspirocyclic-β-lactams. The reaction was performed with **3b** having *N*-PMP group and it resulted in the formation of three products (different R_f values). These were separated by column chromatography and identified as **6b**, **7b** and **8b** respectively on the basis of various spectroscopic analyses viz. FT-IR, ^{1}H NMR, ^{13}C NMR and elemental analysis (Scheme 2, Table 3, entry 4). The compound **6b** and **8b** were similar to **6a** and **8a**, but in **7b**, bromine occupied both the *ortho* positions (Scheme 2, Table 3, entry 4). Substrate **3c** having *N*-benzyl group furnished only two products. After column chromatographic separations, the products were identified as **6c** and **8c** on the basis of various spectroscopic analyses (Scheme 2, Table 3, entry 5).

The mechanism of intrasulfenyl halocyclisation is well established and reported by Turos et al. with inclusion of experimental and spectroscopic evidences.[16] The stereochemistry of products through olefinic π-complex was in accordance with the theoretical models put forth by Chamberlain and co-workers.[40] Considering the above Letters[16,40] and our earlier publication related to halocyclisation of 3-thio/seleno-β-lactams,[29,30] a plausible mechanism for the formation of halogenated 4-pyrazolylspirocyclic-β-lactams (**4a–8a**) is depicted here in Scheme 3. Firstly, two different competing paths (A and B) can be envisaged for the formation of two products (**4a** and **5a**) when 1 equiv. of bromine was used. In *Path A*, substrate **3a** underwent direct ISC via cyclic sulfonium ion intermediate (A) to furnish spiro-β-lactam **4a**. Meanwhile, substrate **3a** also converted into spiro-β-lactam **5a** which is believed to proceed via initial electrophilic aromatic substitution to afford intermediate **B** and its subsequent ISC via cyclic sulfonium ion intermediate **A** (*Path B*). In the presence of excess of bromine, **4a** and **5a** were further transformed into **6a** and **7a** by the addition of bromine at C-7 exocyclic double bond (*Path C*). The formation of 4-pyrazolylspirocyclic-β-lactam **8a** proceeds via dehydrohalogenation (removal of HBr molecule) of **6a**/**7a** (*Path D*). Reaction with β-lactam **3c**, only two spiro adducts **6c** and **8c** were formed (Table 3, entry 5). This proves the role of lone pairs of N of β-lactam

Table 2
Synthesis of *cis*-3-(prop-2′-ynyloxy)-4-pyrazolyl-β-lactams **3a–c**

Entry	R^1	Products	Yield[a] (%)
1	C_6H_5	**3a**[b]	76
2	p-$CH_3OC_6H_4$	**3b**	69
3	$CH_2C_6H_5$	**3c**	52

[a] Yield of pure, isolated product with correct analytical and spectral data.
[b] Structure established on the basis of X-ray crystallographic study.