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Stereoselective synthesis of novel monocyclic *trans*-3-halogenated-4-pyrazolyl-β-lactams: Potential Synthons and promising biologically active agents

Shiwani Berry

Department of Chemistry and Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh, India

Shamsher S. Bari

Department of Chemistry and Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh, India

Bimal K. Banik

Community Health Systems of South Texas, Edinburg, TX, USA

Aman Bhalla

Department of Chemistry and Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh, India

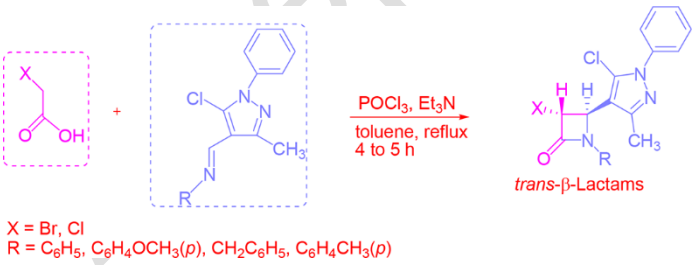
Address correspondence to Aman Bhalla, Department of Chemistry and Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh 160014, India. Tele: +91-172-253-4417/+919872659217. Fax: +91-172-254-5074. E-mail: amanbhalla@pu.ac.in

Full experimental details, their spectral data (**3a-d** and **5a-h**) and copies of ^{1}H NMR, ^{13}C NMR and FT-IR spectra of (**3d** and **5a-h**) have been included in the supplementary data. Supplementary data associated with this article can be found *via* the supplementary content section of this article's web page.

ABSTRACT

Stereoselective synthesis of novel monocyclic *trans*-3-halogenated-4-pyrazolyl-β-lactams **5** is described. The reaction of ketene derived from α-bromo/chloro ethanoic acids **4** using $POCl_3$ and Et_3N with pyrazolyl substituted imines **3a-d** in refluxing toluene resulted exclusive formation of *trans*-β-lactams *via* [2+2] through cycloaddition reaction. The chemical structures of all the newly synthesized β-lactams were verified on the basis of spectroscopic techniques such as FT-IR, ^{1}H NMR, ^{13}C NMR and elemental analysis (CHN). The *trans* configuration of β-lactams **5** was assigned with respect to position of C3-H and C4-H. The novel β-lactams **5** are potential synthons for azetidines, aziridines, 3-unsubstituted azetidinones, 3-alkyl-halo-azetidinones and promising biologically active agents.

GRAPHICAL ABSTRACT



KEYWORDS: cycloaddition, β-lactams, pyrazolyl, stereoselective, *trans*-3-halogenated-4-pyrazolyl-β-lactams

Introduction

Nitrogen-containing heterocyclic compounds, always drawn the attention of chemist over the years due to their wide occurrence in natural products, drugs and pharmaceuticals.[1],[2] Among these, pyrazole and its analogues has been appreciated in medicinal chemistry due to their potency as EP1 receptor antagonists **(I)**,[3] monoamine oxidase inhibitor,[4a] anti-COX-1 **(II)**[4b] and hypoglycaemic agent[5] (**Figure 1**). Several other substituted pyrazole derivatives have also shown diverse pharmacological properties including antirheumatoidal,[6] anti-alzheimer,[7] and hormone oxytocin agonists.[8] Synthesis of various 3-halogenated monocyclic β-lactams[9] and their hetero-substituted analogues[10] **(III-IV)** (**Figure 1**) have been greatly facilitated due to their promising medicinal properties and attendant rich chemistry.

Furthermore, 3-halo-4-functionalized β-lactams acts as an effective synthon for the synthesis of many substituted β-lactams.[11a–c] The transformation of 3-halogenated β-lactams **(V-VIII)** (**Figure 1**) into corresponding 1,4-benzothiazepines (*via* ring expansion),[11d,e] aziridines[11f]/azetidines[11g] (*via* ring opening), 3-unsubstituted azetidinones (*via* dehalogenation),[12a] and 3-alkyl/hydroxyalkyl-flouro-β-lactams (*via* aldol and direct alkylation)[12b] have been well documented. Although different methods have been reported in literature for the generation of Cα-halogen center using alkylation, reduction and metalation, however, synthesis involving cycloaddition of imine and haloketene generated *in-situ* has been still a facile, efficient and convenient route for the stereocontrolled formation of α-halo-β-lactams.[13a,b]

Encouraged by above reports and in continuation to our interest towards the synthesis of monocyclic-β-lactams, bicyclic-β-lactams, spirocyclic-β-lactams and heterocyclic-β-lactams,[14a–

[c] we further envisaged to incorporate α-halo-β-lactams with sterically constrained pyrazolyl ring system into single framework.

Results and Discussion

Starting substrate, pyrazole carbaldehyde **2** was prepared *via* Vilsmeier-Haack reaction of pyrazolinone **1** which in turn were prepared by the condensation of phenyl hydrazine with ethyl acetoacetate at reflux temperature (Scheme 1).[15]

The pyrazole substituted Schiff's bases **3a-d** were prepared by stirring equivalent amount of an appropriate primary amine and pyrazole carbaldehyde **2** using molecular sieves (4Å) in dichloromethane at room temperature (Scheme 1, **Table 1**).

Following thin-layer chromatography (TLC), solvent evaporation and crystallization, the structure of pyrazole substituted Schiff's bases **3a-d** were confirmed on the basis of spectroscopic techniques viz., FTIR, NMR (^{1}H, ^{13}C) and CHN elemental analysis.

The synthesis of novel *trans*-3-bromo/chloro-4-pyrazolyl-β-lactams **5a-h** has been achieved via Staudinger cycloaddition reaction between the ketene generated from α-halo ethanoic acids **4a-b** and Schiff's bases **3a-d**. Initially, 2-bromoethanoic acid **4a** was treated with Schiff's base **3a** in the presence of phosphorus oxychloride ($POCl_3$) and triethylamine (Et_3N) under nitrogen atmosphere in dry toluene at reflux temperature. Following thin-layer chromatography (TLC), solvent evaporation and purification by column chromatography, the product was identified as *trans*-1-phenyl-3-bromo-4-(5'-chloro-3'-methyl-1'-phenyl-1*H*-pyrazol-4'-yl)azetidin-2-one **5a** (Scheme 1, **Table 2**, entry 1) on the basis of various spectroscopic techniques viz. FT-IR, ^{1}H NMR, ^{13}C NMR and elemental analysis.

Further, the reaction was performed by altering R and X substituents (R = C_6H_5, $C_6H_4OCH_3$(*p*), $CH_2C_6H_5$, $C_6H_4CH_3$(*p*); X = Br/Cl) (**Table 2**, entries 2-8). The reaction was found to be highly stereoselective and has resulted in exclusive formation of *trans*-β-lactams in all the cases. All these newly synthesized novel monocyclic *trans*-3-bromo/chloro-4-pyrazolyl β-lactams **5b-h** were purified by column chromatography and their structures were fully characterized on the basis of various spectroscopic techniques *viz.*, FT-IR, NMR (^{1}H and ^{13}C) along with elemental analysis (CHN).

FT-IR spectra of the target compounds **5a–h**, showed strong absorption bands at 1766-1758 cm^{-1} for the C=O of β-lactam ring, medium absorption at 1597-1548 cm^{-1} for C=N group and a stong absorption recorded in the range of 684-758 cm^{-1} is for C–Br/C–Cl supported the formation of β-lactams. The spatial juxtaposition of the C3-H and C4-H was assigned *trans* for the title compounds **5a-h** on the basis of the coupling constant values (*J* = 1.5-2.1 Hz; C3-H and C4-H) in ^{1}H NMR spectra.[14] CHN elemental analysis data of all the synthesized molecules **5a–h** were also in full support with their depicted structures.

It is quite noteworthy that the Staudinger [2+2] cycloaddition favours the stereospecific formation of α-bromo and α-chloro β-lactams in all cases due to steric hindrance of the bulky pyrazole group in imine moieties i.e. reaction is highly selective towards *trans*- configuration and no traces of *cis* isomer were detected. These facts can be explained according to plausible mechanism reported for ketene-imine Staudinger reaction[14] depicted in Scheme 2.

Initially, ketene **IX** is generated by the addition of phosphorus oxychloride and triethylamine to α-bromo/chloro ethanoic acids **4** in refluxing toluene. Further, zwitterionic intermediate **X** formed by nucleophilic attack of imine nitrogen at the carbonyl carbon of the ketene which isomerises to zwitterionic intermediate **XI** followed by conrotatory

electrocyclization (isomerization-ring closure) afforded *trans*-3-halogenated-4-pyrazolyl-β-lactams **5**. These 4-pyrazolyl-β-lactams **5a-h**, are air- and moisture-stable, soluble in solvents such as dichloromethane, chloroform, acetone, toluene, ethyl acetate and obtained as stable solids. In addition, studies have been underway in laboratory for the transformation of these novel 3-bromo/chloro β-lactams to diversely functionalized molecules such as azetidines, aziridines, 3-unsubstituted azetidinones, 3-alkyl-halo-azetidinones in relation to recent reports[11] (**Figure 2**).

Conclusion

In conclusion, stereoselective synthesis of novel 3-bromo/chloro β-lactams bearing pyrazole ring has been achieved by treatment of α-bromo/α-chloro acetic acids and heterosubtituted imines using Et_3N. The structures and stereochemistry of all the novel compounds were established on the basis of various spectroscopic techniques such as FT-IR, ^1H NMR, ^{13}C NMR and elemental analysis. These novel *trans*-3-halogenated-4-pyrazolyl-substituted-β-lactams have been submitted for molecular modelling studies which will be followed by *in-vitro* screening of best fit molecules for potential biological activities. Further, a detailed report elaborating the results of biological evaluation and synthetic applications of these newly synthesized β-lactams will be reported in near future.

Experimental

Melting points were determined in an open capillary on melting point apparatus (Perfit GSI-MP-3) and are uncorrected. IR spectra were recorded by using Thermo scientific Nicolet iS50 (FT-IR) spectrophotometer (υ_{max} in cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on JEOL AL 300 MHz and BRUKER AVANCE II 400 MHz spectrometer using TMS as an internal standard. The elemental analysis (C, H, N) were recorded on Flash 2000 Organic elemental analyzer All the

reactions were monitored by thin layer chromatography (TLC) using precoated silica 60 F254, 0.25 mm aluminum plates (Merck) with visualization under UV light. Column chromatography was performed using Merck Silica Gel (60-120 mesh) using ethyl acetate-hexanes (10:90) as an eluant system.

Preparation of novel pyrazole linked 3-halogenated-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 and dichloromethane were dried and distilled over anhydrous calcium chloride ($CaCl_2$) and phosphorus pentoxide (P_2O_5) respectively. Toluene was distilled under N_2 from sodium-benzophenone immediately before use.

General procedure for the preparation of Schiff base 3a-d

Solution of aromatic amine (1 mmol) and pyrazole carbaldehyde (1 mmol) in the presence of molecular sieves (4 Å) in dry methylene chloride (15 mL) was stirred at room temperature. Progress of the reaction was monitored by TLC. After the completion, reaction mixture was filtered and solvent was evaporated to yield crude product which was purified by recrystallization from a mixture of methylene chloride and hexane.

N-[(5'-chloro-3'-methyl-1'-phenyl-1H-pyrazol-4'-yl)methylene]-4methyl benzenamine 3d

Yellow crystalline solid; yield: 80%; mp: 105-107 °C; FT-IR (ν_{max}, cm^{-1}): 1625, 2917; ^1H NMR (300 MHz, $CDCl_3$): δ 2.36 (3H, s, CH_3), 2.62 (3H, s, CH_3), 7.01-7.57 (9H, m, Ar-H), 8.39 (1H, s, -N=CH-); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 20.4, 20.9, 21.0, 109.5, 115.5, 115.8, 117.2,

118.8, 120.7, 121.1, 125.0, 125.2, 126.5, 128.5, 128.8, 128.9, 129.1, 129.2, 129.3, 129.7, 130.5, 135.4, 137.6, 137.7, 138.3, 150.2, 150.6, 150.9, 152.7, 161.3; Anal. Calcd. for $C_{18}H_{16}ClN_3$: C 69.79, H 5.21, N 11.44%. Found: C 69.52, H 5.08, N 11.31%.

General procedure for synthesis of 3-bromo/chloro-4-pyrazolyl-β-lactams 5a-h

A solution of phosphorus oxychloride ($POCl_3$, 0.69 mmol, 1.5 equiv.) in dry toluene was added dropwise to a stirred solution of 2-substituted ethanoic acid (0.55 mmol, 1.2 equiv.), Schiff's base (0.46 mmol, 1 equiv.) and distilled triethyl amine (1.38 mmol, 3 equiv.) in dry toluene under nitrogen atmosphere. The reaction mixture was refluxed for 3-4 h. The solvent was evaporated and crude product was extracted with CH_2Cl_2. The organic layer was washed with water (3x10 ml), 1N HCl (3x10 ml), 5% $NaHCO_3$ (3x10 ml) and brine (3x10 ml), then dried (Na_2SO_4) and concentrated. The crude product was then isolated by column chromatography over Silica gel using hexane/EtOAc (90:10) as eluent to afford pure products.

trans-1-Phenyl-3-bromo-4-(5'-chloro-3'-methyl-1'-phenyl-1H-pyrazol-4'-yl)-azetidin-2-one 5a

White solid; yield 75%; mp 118-120 °C; IR (ν_{max}, cm^{-1}): 1760 (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 2.31 (3H, s, CH_3), 4.97 (1H, d, *J* = 2.1 Hz, C4–H), 5.05 (1H, d, *J* = 2.1 Hz, C3–H), 7.11-7.52 (10H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.0, 29.8, 48.0, 57.9, 61.4, 117.0, 117.1, 124.8, 125.0, 128.5, 129.1, 129.4, 136.9, 137.7, 148.0, 159.8; Anal. Calcd. for $C_{19}H_{15}BrClN_3O$: C 54.76, H 3.63, N 10.08%. Found: C 54.62, H 3.56, N 9.82%.

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Table 1. Synthesis of pyrazolyl substituted Schiff's bases 3a-d.

Entry	*R*	Schiff's base 3	Yield[a] (%)
1	C_6H_5	**3a**	**85**
2	$C_6H_4OCH_3(p)$	**3b**	**82**
3	$CH_2C_6H_5$	**3c**	**79**
4	$C_6H_4CH_3(p)$	**3d**	**80**

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

Table 2. 3-Bromo/chloro-4-pyrazolyl-β-lactams 5a-h.

Entry	*X*	*R*	*trans*-β-Lactams 5	Yield[a] (%)
1	Br	C_6H_5	**5a**	75
2	Br	$C_6H_4OCH_3$(*p*)	**5b**	68
3	Br	$CH_2C_6H_5$	**5c**	66
4	Br	$C_6H_4CH_3$(*p*)	**5d**	72
5	Cl	C_6H_5	**5e**	79
6	Cl	$C_6H_4OCH_3$(*p*)	**5f**	74
7	Cl	$CH_2C_6H_5$	**5g**	69
8	Cl	$C_6H_4CH_3$(*p*)	**5h**	70

[a]Yield of pure isolated product after chromatographic purification with correct analytical and spectral data.

Figure 1. Structures of biologically active pyrazoles (**I-II**), α-halo heterosubstituted β-lactams **(III-IV)**, α-halo β-lactams of synthetic utility **(V-VIII)** and title compounds **5(a-h)**.

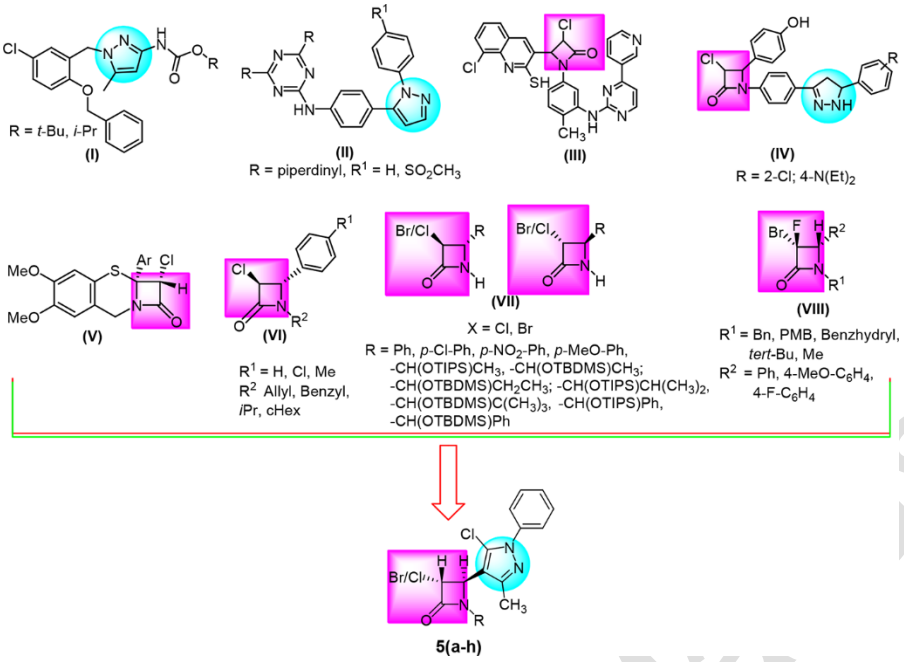
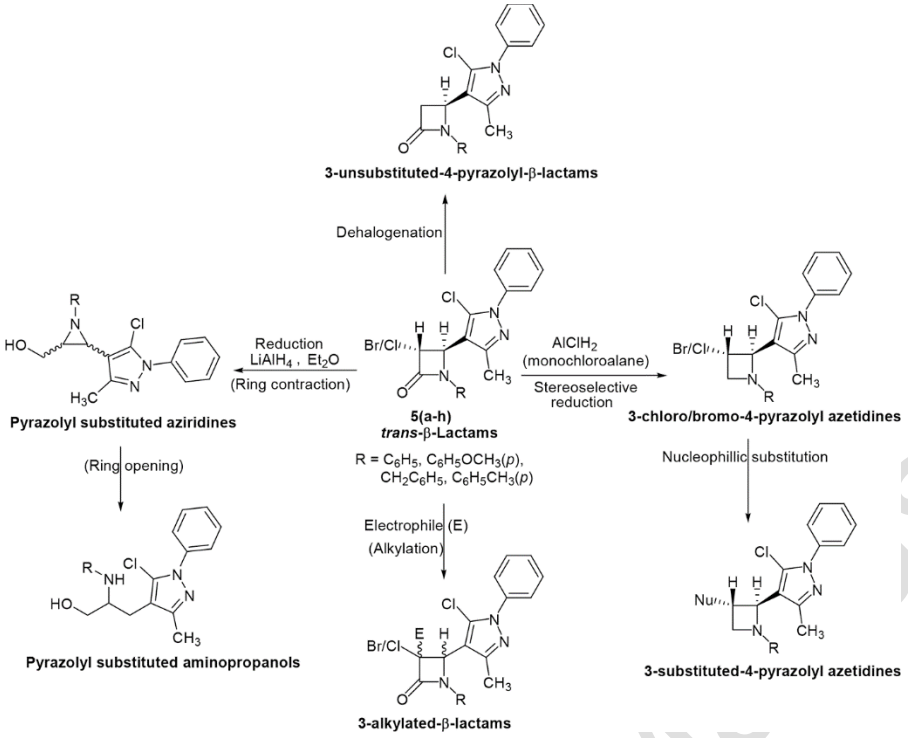
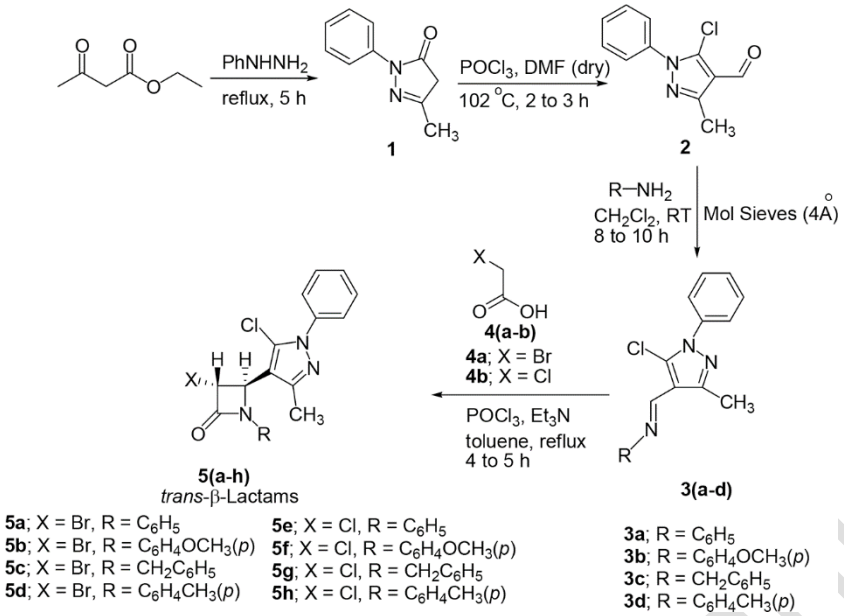


Figure 2. Synthetic utility of 3-bromo/chloro-4-pyrazolyl-β-lactams **5a-h**.



Scheme 1. Synthesis of pyrazolyl substituted Schiff's bases **3a-d** and 3-bromo/chloro-4-pyrazolyl-β-lactams **5a-h**.



5a; X = Br, R = C_6H_5
5b; X = Br, R = $C_6H_4OCH_3(p)$
5c; X = Br, R = $CH_2C_6H_5$
5d; X = Br, R = $C_6H_4CH_3(p)$
5e; X = Cl, R = C_6H_5
5f; X = Cl, R = $C_6H_4OCH_3(p)$
5g; X = Cl, R = $CH_2C_6H_5$
5h; X = Cl, R = $C_6H_4CH_3(p)$

3a; R = C_6H_5
3b; R = $C_6H_4OCH_3(p)$
3c; R = $CH_2C_6H_5$
3d; R = $C_6H_4CH_3(p)$

Scheme 2. A plausible mechanism for the formation of *trans*-3-halogenated-4- pyrazolyl-β-lactams **5**.