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SYNTHESIS AND SPECTRAL CHARACTERIZATION OF PYRAZOLE BASED 2-AZETIDINONES

S. V. Manohare[a], *, S. S. Thakare[b]

[a]*Department of Chemistry, Adarsha Science, J. B. Arts and Birla Commerce Mahavidyalaya, Dhamangaon Rly., 444709, Maharashtra, India*
[b]*Rajarshee Shahu Science College, Chandur Rly., 444704, Maharashtra*
smanohare@gmail.com

ABSTRACT:
In current study, we report the synthesis of 2-azetidinone containing pyrazole scaffold, i.e. 4-(3-(5-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-3-chloro-1-(aryl) azetidin-2-one from reaction of 1-(3-(5-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-N-(aryl) methamine with chloroacetyl chloride in 1,4-dioxane as a solvent in presence of triethylamine. The 1-(3-(5-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-N-(aryl) methamine was prepared from 3-**(**5-bromothiophen-2-yl)-1-phenyl-1-H-pyrazole-4-carbaldehyde and aromatic amines in ethanol in presence of glacial acetic acid. The newly synthesized compounds were characterized on the basis of IR, ^{1}H NMR and Mass spectroscopy.

KEYWORDS: Pyrazole, Schiff bases, 2-Azetidinones, Spectral characterization.

INTRODUCTION:

Heterocyclic compounds containing nitrogen are well investigated due their wide spectrum of biological activities [i]. Nitrogen containing heterocyclic compounds are found to be present in natural products like vitamins, hormones and alkaloids [ii, iii]. Among them, pyrazoles and their derivatives constitute an important class of heterocyclic compounds which have exhibited a broad spectrum of biological activities for instance, antibacterial [iv,v], anti-inflammatory [vi], anti-tubercular [vii], anti-AIDS [viii], anti-malarial [ix], antitumor [x,xi], and antifungal [xii].

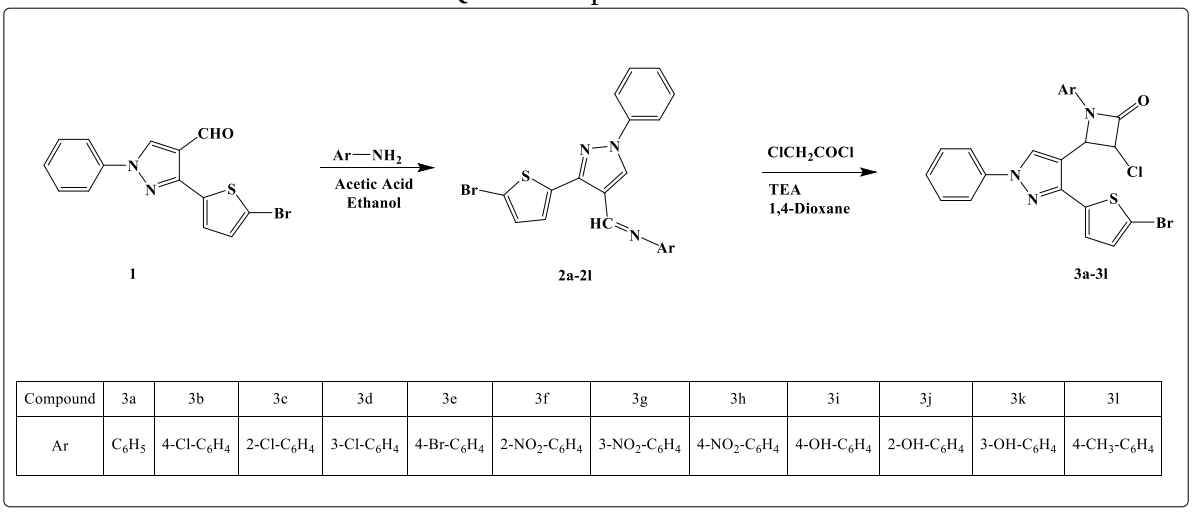
2-Azetidinone scaffold is a member of a number of biologically active compounds. *β*-lactam antibiotics are the important therapeutic drugs that have gained the interest of chemists and pharmacists for synthetic, pharmaceutical applications as well as for being a starting material and reaction intermediate in organic synthesis. Penams, cephams, penems, monobactams, carbapenems and trinems are the important members of *β*-lactam antibiotics [xiii]. Penicillins, cephalosporins, carbapenems, nocardicins, monobactams, clavulanic acid, sulbactams and tazobactams are the drugs with 2-azetidinone structure and these are the chemotherapeutic agents that had been used to treat a number of infectious diseases [xiv]. 2-Azetidinone is an important structural moiety for the synthesis of important biological compounds which show

biological activities such as antibacterial [xv-xx], anti-tubercular [xxi], anticancer [xiv, xxii], antimalarial [xxiii] and antifungal [xxiv].

Literature on the broad pharmacological activities of pyrazole and 2-azetidinone has inspired the authors to prepare a bioactive heterocycle that combines the aforementioned pyrazole and 2-azetidinone in a single molecular framework. In this study we report the synthesis and spectral characterization of a series of 2-azetidinone containing pyrazole moiety.

EXPERIMENTAL:

All chemicals used for the synthesis of the said compounds were of analytical grade and were procured from SDFCL. Melting points were determined in open capillary tube and are uncorrected. The progress and purity of compounds was checked by thin-layer chromatography using with F-252 silica gel precoated aluminium plates using petroleum ether-ethyl acetate (9:1) as a developing solvent and spots were visualised by exposing the plates in iodine vapours. Infrared spectra were recorded on Shimadzu spectrophotometer using KBr pellets technique (λ_{max} in cm^{-1}). ^1H Nuclear magnetic resonance spectra were recorded on BRUKER ADVANCE (400 FT- NMR) spectrophotometer using dimethyl sulfoxide (DMSO- d_6) as a solvent and tetramethyl silane as internal reference (chemical shifts, δ in ppm). Mass spectra were observed on Waters UPLC- TQC Mass Spectrometer.



Compound	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	3k	3l
Ar	C_6H_5	4-Cl-C_6H_4	2-Cl-C_6H_4	3-Cl-C_6H_4	4-Br-C_6H_4	2-NO_2-C_6H_4	3-NO_2-C_6H_4	4-NO_2-C_6H_4	4-OH-C_6H_4	2-OH-C_6H_4	3-OH-C_6H_4	4-CH_3-C_6H_4

Scheme

GENERAL PROCEDURE:

Synthesis of 4-(3-(5-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-3-chloro-1-(aryl) azetidin-2-one (3a - 3l).

A mixture of 1-(3-(5-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-N-(aryl) methamine (2a - 2l) (0.01 mol) and triethylamine (TEA) (0.01 mol) was dissolved in 40 ml of 1,4-dioxane, cooled and stirred at 0 – 5^{O}C. To this well-stirred cooled solution chloroacetyl chloride (0.01 mol) was added drop wise over a period of half an hour. The reaction mixture was then stirred for 5 hours. The white precipitate of amine hydrochloride thus obtained was filtered off. The filtrate was then refluxed for 8 to 15 hours. The reaction mixture was then cooled and poured into ice-cold water. The resulting solid was filtered, washed with water and purified by recrystallization in ethanol and from dioxane in some cases.

4-(3-(5-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-3-chloro-1-phenyl) azetidin-2-one (3a). IR (KBr) cm^{-1}: 1682 (C=O, *β*-lactam) 1600 (C=N), 1500 (C=C) 3101 (C-H) 686 (C-Br); ^1H NMR: δ 8.2 (s, 1H, H-pyrazole), 3.6 (d, 1H, H-C-N), 4.2 (d, 1H, H-C-Cl), 7.0-8-0 (m, 12H, Ar-H); Mass: m/z = 484 (M^+), 486 (M^+ +2).

4-(3-(5-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-3-chloro-1-(4-chloro phenyl) azetidine -2-one (3b). IR (KBr) cm^{-1}: 1682 (C=O, *β*-lactam) 1577 (C=N), 1500 (C=C) 3090 (C-H) 686 (C-Br); ^{1}H NMR: δ 8.4 (s, 1H, H-pyrazole), 3.6 (d, 1H, H-C-N), 4.1 (d, 1H, H-C-Cl), 7.0-8-3 (m, 12H, Ar-H); Mass: m/z = 528 (M^+ +9).

4-(3-(5-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-3-chloro-1-(2-chloro phenyl) azetidin-2-one (3c). IR (KBr) cm^{-1}: 1701 (C=O, *β*-lactam) 1593 (C=N), 1473 (C=C) 3043 (C-H) 678 (C-Br); ^{1}H NMR: δ 8.3 (s, 1H, H-pyrazole), 3.3 (d, 1H, H-C-N), 4.3 (d, 1H, H-C-Cl), 7.2-8-0 (m, 12H, Ar-H); Mass: m/z = 522(M^+ +3).

Analytical data of compounds (3a-3l)

Sr. No.	Compound	Ar	Molecular Formula	Colour	Melting Point in ^{0}C	% Yield
1	3a	C_6H_5	$C_{22}H_{15}BrClN_3OS$	Yellow	135	56
2	3b	4-Cl C_6H_4	$C_{22}H_{14}BrCl_2N_3OS$	Brown	118	60
3	3c	2-Cl C_6H_4	$C_{22}H_{14}BrCl_2N_3OS$	Dark brown	136	63
4	3d	3-Cl C_6H_4	$C_{22}H_{14}BrCl_2N_3OS$	Brown	148	48
5	3e	4-Br C_6H_4	$C_{22}H_{14}Br_2ClN_3OS$	Dark brown	124	64
6	3f	2-NO_2 C_6H_4	$C_{22}H_{14}BrClN_4O_3S$	Yellow	143	58
7	3g	3-NO_2 C_6H_4	$C_{22}H_{14}BrClN_4O_3S$	Yellow	162	59
8	3h	4-NO_2 C_6H_4	$C_{22}H_{14}BrClN_4O_3S$	Brown red	137	67
9	3i	4-OH C_6H_4	$C_{22}H_{15}BrClN_3O_2S$	Pale brown	152	60
10	3j	2-OH C_6H_4	$C_{22}H_{15}BrClN_3O_2S$	Brown	160	63
11	3k	3-OH C_6H_4	$C_{22}H_{15}BrClN_3O_2S$	Brown	147	60
12	3l	4-$CH_3C_6H_4$	$C_{23}H_{17}BrClN_3OS$	Pale yellow	133	54

RESULTS AND DISCUSSION:

Synthesis of title compounds, 3a-3l was accomplished in accordance with the synthetic route as depicted in scheme-1. Synthesis of 1-(3-(5-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-N-(aryl) methamine (2a - 2l) and 3-(5-bromothiophen-2-yl)-1-phenyl-1-H-pyrazole-4-carbaldehyde (1) was carried out by the reported method [xxv] and published in our previous work. The compounds 4-(3-(5-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-3-chloro-1-(aryl)azetidin-2-one (3a - 3l) were obtained by cycloaddition reaction of 1-(3-(5-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-N-(aryl) methamine (2a - 2l) with chloroacetyl chloride in presence of triethyl amine in 1,4-dioxane as a solvent. Structures of all the newly synthesized compounds were established on the basis of IR, ^{1}H NMR and Mass spectroscopy data. Spectral data of all the synthesized compounds are in full agreement with the proposed structures. In IR spectra a strong signal at 1600-1700 cm^{-1} is due to the CO stretching of β-lactam while the signal due to C=N stretching appears at around 1500 cm^{-1}. The ^{1} H NMR spectrum showed a sharp singlet at around δ 8.3 ppm for pyrazole proton while a doublet at δ 3.3ppm and δ 4.5ppm appeared for H -C-N and H-C-Cl. The aromatic protons showed the multiplet at δ 7-8 ppm. The m/z values obtained from Mass spectra for the characterized 2-azetidinones are in good agreement with the molecular weights.

CONCLUSION:

A new series of 2-azetidinones containing pyrazole scaffold from pyrazole-based Schiff bases was prepared and the structures of synthesized compounds were confirmed on the basis of spectroscopy data. Spectral data of compounds and proposed structures are in full agreement.

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