Design And Development of Pyrazole-Based Heterocycles with Potential Applications

Nagesh R. Nahate
Department of Chemistry
Shri. R.R. Lahoti Science College, Morshi, Dist.Amravati,444905
doi.org/10.64643/IJIRTV12I9-195713-459

***Abstract*—Pyrazoles have attracted considerable interest in both organic and pharmaceutical research because of their usefulness as synthetic intermediates in the development of diverse bioactive molecules. As a result, the synthesis of pyrazoles remains a central area of investigation for organic chemists. In particular, fused pyrazole systems such as pyrazolo-pyridines and pyrazolo pyrimidines have been extensively explored owing to their distinctive physicochemical and biological properties, which arise from the electronic characteristics of these nitrogen-containing heterocycles. The preparation of such fused heterocycles and their derivatives is therefore of great importance, not only for discovering new structural variants but also for identifying novel applications. Numerous synthetic strategies have been reported in recent years, with condensation reactions being the most common approach. The structures of the resulting pyrazole derivatives are typically verified using techniques such as ^{1}H NMR and GC-MS analysis.**

***Index Terms*—fused heterocycles, Pyrazole, Heterocyclic, bioactive,**

I. INTRODUCTION

Pyrazole is a heteroaromatic compound characterized by a five-membered ring containing two adjacent nitrogen atoms [1]. NH-pyrazoles exhibit both weak basic and weak acidic behaviour, as they can accept protons through the C=N group, while the N–H atom, similar to pyrrole, has the ability to donate protons [2]. The hydrogen bonding interactions between heteroatoms and hydrogen are largely influenced by the structural framework of pyrazoles [3].

In 1883, the German chemist Ludwig Knorr attempted to synthesize quinoline with antipyretic properties [4], but instead obtained pyrazole [5]. Knorr was the first to introduce pyrazole as a heterocyclic core, showing that it could be derived from pyrrole by substituting a carbon atom with nitrogen [6]. He also identified the antipyretic activity of pyrazole derivatives in humans, which sparked significant interest in this moiety [7]. Later, in 1846, Kosuge and Okeda isolated 3-n-nonylpyrazole from *Houttuynia cordata*, a plant known for antimicrobial activity, and levo-β-(1-pyrazolyl) alanine from watermelon seeds (*Citrullus vulgaris*) [8]. Prior to these discoveries, pyrazoles were not believed to occur naturally [9]. The versatility of pyrazole-based compounds in both biological and synthetic applications has since been well established, making them one of the most extensively studied members of the azole family, despite the presence of many natural products containing pyrazole units [10].

N-heterocyclic compounds such as substituted pyrazoles are particularly important due to their broad applications [11]. Many natural products feature fused pyrazole structures; for instance, pyrazolo[4,3-d] pyrimidine occurs naturally in Formicin A, which exhibits diverse biological activities including antiviral and antitumor effects. Overall, compounds containing a pyrazole core fused with five- or six-membered heterocycles demonstrate significant biological and pharmacological potential. Notably, pyrazole-based pyridines and pyrimidines have played a crucial role in drug discovery [12].

II. EXPERIMENTAL SECTION

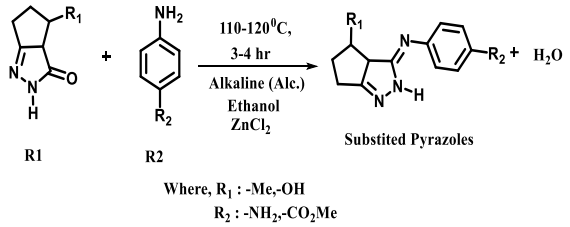
MATERIALS

Methanol (98%), Ethanol (98%) Acetonitrile (99%) and ethyl acetate (98%) were procured from Avra chemical Pvt. Ltd. Sodium hydroxide (98%) zinc chloride Were acquired from Sisco Research Laboratories Pvt. Ltd.

CHARACTERIZATION TECHNIQUE

The Chemical structure of synthesized compounds was confirmed by spectral data. ^{1}H-NMR spectra were recorded on BRUKER AVANCE NEO 500 MHz spectrometer using DMSO and $CDCl_3$ solvent and TMS as internal standards at SAIF, Punjab University, Chandigarh (India). Chemical shifts are expressed in ppm. Mass spectrums were recorded on Thermo Scientific TSQ 8000 Gas Chromatograph

GENERAL REACTION



Scheme 1. General Reaction for Synthesis of Substituted Pyrazoles

Reactant (R1) (0.1 mmol) was heated with reactant (R2) (0.15 mmol) in oil bath at 110 ºC to 120 ºC, till complete removal of dehydrated water is ensured. The solid cream color precipitate was obtained and it filtered, washed with methanol and recrystallized by ethanol with preferable yield, m.p.-181ºC as cream-white colored crystalline solid. (Scheme 1.)

Table 1. Synthesis of N-heterocyclic Pyrazoles Derivatives

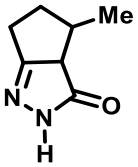
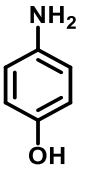
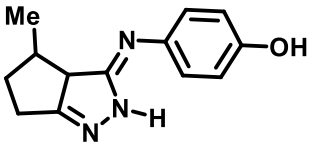
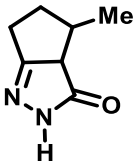
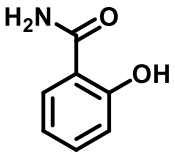
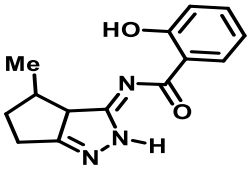
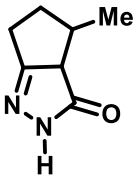
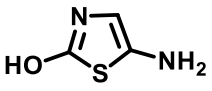
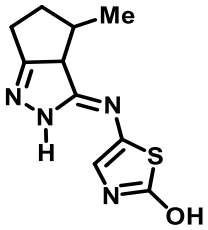
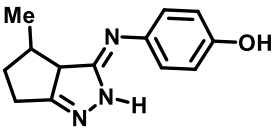
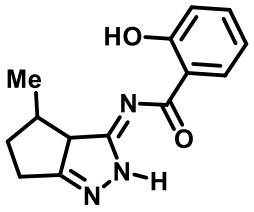
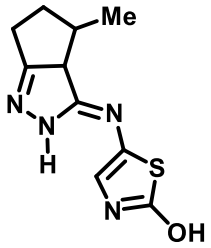
Sr. No	R1	R2	Product	Time in Hrs.	Yield
1				6	88
2				6	84
3				6	85

Table 2. Structural characterization of derivatives

Sr. No	Structure of Products	Structural analysis by ^{1}HNMR and GCMS
1		^{1}HNMR (500MHz, $CDCl_3$):δ9.42(s,1H),6.757.20(m,4H),3.43(s,3H),3.21(q,1H),2.0-2.19(t,2H),1.58-1.82 (t,2H), 1.3(t,1H) GCMS: Cal m/z: 229.28, Found m/z: 228.16

2		^{1}HNMR (500MHz, $CDCl_3$):δ9.40(s,1H),6.847.69(m,5H),3.44(s,3H),3.3(d,1H),2.0-2.18(t,2H),1.58-1.84(t,2H),1.3(t,1H) GCMS: Cal m/z: 257.29, Found m/z: 257.15
3		^{1}HNMR (500MHz, $CDCl_3$):δ9.79(s,1H),7.66(s,1H),6.65(s,1H),3.44(s,3H),3.5(q,1H),2.06-2.15(q,2H),1.55-1.85(m,2H),1.3(t,1H) GCMS: Cal m/z: 236.29, Found m/z: 236.21

III. CONCLUSION

The synthesis of pyrazole derivatives, along with their diverse functional group substitutions, is now well established. Extensive studies have focused on the biological activities of these compounds, and recent research has sought to explore their broader properties. However, several challenges remain, including achieving high synthetic yields, designing novel pyrazole derivatives with potent bioactivity in the sub-micromolar range, and accurately characterizing their structural and functional features. Consequently, there is a strong need to develop new synthetic methodologies, investigate additional properties, and identify innovative applications particularly in combination with polymeric systems. Looking ahead, the emerging direction for pyrazole derivatives is their utilization across a wider range of fields.

ACKNOWLEDGEMENT

The author is thankful to Department of chemistry, Shri, R.R. Lahoti Science College, for providing research facilities Authors are very much thankful to the Director, SAIF, Punjab University Chandigarh for providing spectral data.

CONFLICT OF INTEREST:
None

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