Research Article www.ijcps.com

International Journal of
Chemical and Pharmaceutical Sciences
2019, Aug., Vol. 10 (2)

ISSN: 0976-9390
IJCPS

Assemblage of pyrazoline heterocyclic frameworks through michael- addition mediated cyclization

[1] Barathi S, [2] Suresh G and [1] Prabhu NV*

[1] Department of Chemistry, School of Arts and Science, PRIST (Deemed to be University), Thanjavur, Tamilnadu, India.

[2] Department of Biotechnology, Indian Institute of Technology, Madras, Chennai, Tamilnadu, India.

***Corresponding Author:** E-Mail: info.prabhunv@gmail.com

Received: 25th Aug 2019, Revised and Accepted: 27th Aug 2019

ABSTRACT

A new and efficient construction of pyrazoline scaffolds through Michael addition mediated cyclization strategy by concomitant utilization of chalcone as requisite precursor and various carbohydrazides. All the reactions conducted in presence of AcOH/EtOH medium to afford the corresponding pyrazoline scaffolds in eco-friendly manner. The newly synthesized pyrazoleproducts **5a-j** was obtained in 73-89% yield and properly characterized through spectroscopic analyses.

Keywords: Chalcone, Carbohydrazide, Pyrazoline, Michael-addition, Cyclization.

1. INTRODUCTION

In the perspectives of organic chemistry, the synthesis of target molecules occupied a prominent position with a wide range of applications in various domains like pharmaceuticals, industry and academic would be important criteria, especially for researchers focused their attention on various factors such as simplistic, well-organized, and non-polluting synthetic techniques with minimal usage of organic solvents and toxic reagents. Besides the sustainability has become one of the greatest scientific tasks nowadays, due to eco-friendly, health and societal concerns.[1]Such methodology determines the effluence avoidance and environmental protection, and is now gaining importance. Therefore many of the chemists accomplished and satisfied the scientific and practical demands to pursuit the new methodology to synthesize the organic molecules with high potential applications.

In particular, the synthesis of heterocyclic molecules has gained wide scope of attentions due to prevalent utility in many biological and medicinal applications. Since their heterocyclic skeleton occurin several natural products, as well as many alkaloids, hormones, vitamins, antibiotics, pharmaceuticals, agro based chemicals, dye stuffs, etc.,[2]in addition to that the naturally occurring compounds, enormous synthetic heterocycles with significant properties are also recognized.[3]Such kind of heterocyclic compounds afford prospective pharmacophores, which can assemble to provide the high efficient drug scaffolds.[4] Similarlythesetypes of available heterocyclic moieties possess good solubility for oral captivation and also biocompatability.[5]

Amidst the heterocyclic compounds, exclusively the nitrogen-atom based skeletons, employed as a key substrate for numerous biological potent molecules and display abundant application in biological, chemical, and other scientific profiles.[6] Currently, several drug components have been established from pyrazoles urro gates. For instance, celecoxib has been recognized for anti-inflammatory evaluation, mean while it inhibits COX-2; fomepizole drug candidate, which constrains alcohol dehydrogenase, rimonabantact as a cannabinoid receptor and is exploited for obesity and sildenafil prevents the phosphor diesterase. Some other material chemistry based applications such aselectroluminescenceproperties.[7]Amongst some of privileged pyrazole comprising heterocycles have considerable interest due to their availability as synthetic substrates in multicomponent reaction schemes, chiral auxillary series etc. In accordance to the presence of aforementioned properties[8]of the pyrazole moiety, possess some of the medicinal /therapeutic activities[9]such asantibacterial, anticancer, antifungal, antidepressant, antioxidant, antiinflammatory, anti-tuberculosis, as well as antiviral agentsetc.

2. EXPERIMENTAL SECTION

2.1. Material Method

The chemical purchased from the Sigma Aldrich are 3,4,5-trimethoxybenzldehyde, Acetophenone, Isoniazid, benzohydrazide, 2-fluorobenzohydrazide, 2-methoxybenzohydrazide, 3-bromobenzohydrazide, 3-methoxybenzohydrazide, 4-bromobenzohydrazide, 4-chlorobenzohydrazide, 4-methylbenzohydrazide, furan-2-carbohydrazide. Solvents, such as, hexane, DCM, chloroform, ethyl acetate, methanol and ethanol, purchased from the local sources.

*Synthetic protocol for chalcone compound***3**3,4,5-trimethoxybenzaldehyde 1mmol and acetophenone 1mmol in a reaction flask have 30 mL ethanol, and 2 mL of 40% KOH are added with continuous stirring on a magnetic stirrer for 1h in rt. The reaction mixture is monitored by TLC. Subsequently, completion of the reaction, this crude is poured into crushedice; the solid is removed / filtered, add cold water, dried and finally recrystallize from ethanol.*Preparation of pyrazoline molecules***5a-j**

To a stirred solution of chalcone**3** (1mmol) and various substituted carboxy acid hydrazide (**4a-j)** 1mmol in a 15-30 mL of ethanol solvent in 100 mL round bottom flask, further the catalytic amount of acetic acid is added and allowed to reflux for 3-6h. After completion of the reaction, through successive monitoring using TLC analysis, the crude reaction mass was poured in ice, the resulting pale yellowish solid thus obtained is filtered and washed with hot ethanol.

3. RESULTS AND DISCUSSION

To execute our idea we have taken chalcone as key starting material for the synthesis of pyrazole frameworks through Michael addition mediated cyclization, therefore, initiallywe have taken the tri-methoxybenzaldehyde (**1**) 1mmol and acetophenone (**2**)1mmol for the construction of requisite precursor chalcone, (**3**) which was further reacted with hydrazide (**4a-j**) to yield our target pyrazoline molecular architectures (**5a-j**) in 73-89% yields as shown in Scheme and the isolated yield of the pure products **5a-j** as presented in Table 1.

The pyrazoline compounds are completely examined by IR, ^{1}H, ^{13}C NMR and mass spectral data, in which the characteristic values are properly matched, especially the comound**5a**is given in the experimental section. The stretching frequency, chemical shift / coupling constants and molecular weight for all the products analyzed with an aid of IR, NMR and mass spectroscopic techniques.

According to the IR spectral analysis for the compound **5a** has shown the characteristic stretching band for aromatic CH (3058, 2935 cm^{-1}), aliphatic CH (2837 cm^{-1}), C=O (1632 cm^{-1}), alkene (1591 cm^{-1}), C=N (1505 cm^{-1}), C-O-C (1324 cm^{-1}), C-N(1234cm^{-1}), The ^{1}H Nuclear Magnetic Resonance spectrum of compound **5a**indicated the three doublets of doublets at5.68 ppm (dd, *J*=5Hz, 15Hz, 1H-pyrazoline CH), 3.74 ppm (s, 9H-Methoxy) 3.71 ppm (dd, J=5Hz, 5Hz, 1H-pyrazoline CH_2), 3.13 ppm (dd, *J*=5Hz, 20Hz, 1H-pyrazoline CH_2) respectively.The aromatic methane protons observed at the range of 7.94-6.44 ppm for twelve hydrogen. The compound **5a** exhibit a singlet at δ 3.74 ppm for nine proton count corresponds to methoxy proton. Similarly, the ^{13}C NMR of compound **5a** afforded the aliphatic methine, methylene, and methoxy represents the carbon peak at 61.48 (pyrazoline CH), 60.73 (Methoxy), 56.10 (Methoxy), 41.77 (pyrazoline CH2) ppm respectively. The carbonyl carbon observed at 166.58ppm and aromatic carbons were observed at the range of 153.69, 137.65, 137.37, 131.24, 131.04, 130.49, 130.02, 128.76, 127.74, 126.80, 102.39 ppm respectively. The compound **5a** exhibited molecular mass peak is 388.1884 emu.

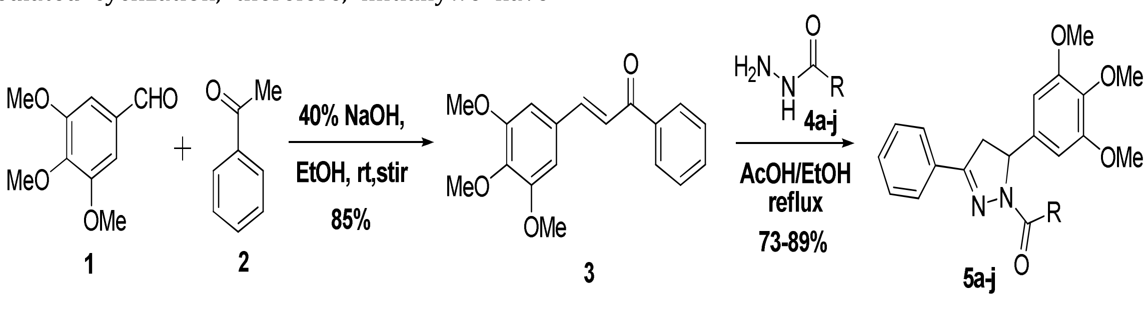
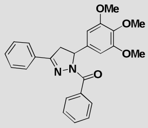
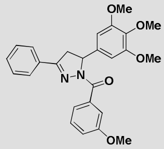
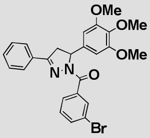
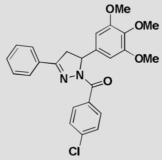
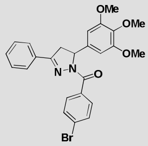
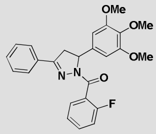
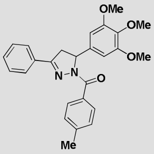
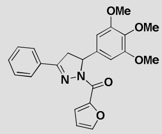
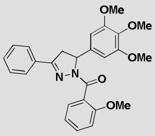
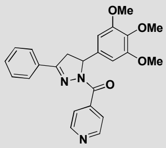


Table - 1: Synthesis of pyrazoline scaffolds from chalcone and various hydrazides

S. No	Substrate	Products[a]	Yields (%)	S. No	Substrate	Products[a]	Yields (%)
1	4a	 **5a**	77	**6**	4f	 **5f**	83
2	4b	 **5b**	76	**7**	4g	 **5g**	79
3	4c	 **5c**	80	**8**	4h	 **5h**	73
4	4d	 **5d**	82	**9**	4i	 **5i**	75
5	4e	 **5e**	89	**10**	4j	 **5j**	86

[a]All compounds are characterizedusing IR, ^{1}H, ^{13}C NMR, mass spectral data.

4. CONCLUSIONS

We have successfully afforded the pyrazoline based molecules in good yields in an eco-friendly manner. The reaction, which creates five membered pyrazoline ring with a new C=C, C-C, C=N bond formation in a single step. The Michael addition mediated cyclization strategy provided the Pyrazole products with high regioselectivityand high atom efficiency.

Acknowledgements

We gratefully acknowledged IITM- Sophisticated Analytical Instruments Facility (SAIF) for the instrument facility support.

5. REFERENCES

1. B. A. de Marco, B. SaúRechelo, E. G. Tótoli, A. C. Kogawa, H. R. N. Salgado, Evolution of green chemistry and its multidimensional impacts: A review; Saudi Pharm. J. 2019; 27, 1-8.
2. Y. Ju and R. S. Varma, Aqueous N-Heterocyclization of Primary Amines and Hydrazines with Dihalides: Microwave-Assisted Syntheses of N-Azacycloalkanes, Isoindole, Pyrazole, Pyrazolidine, and Phthalazine Derivatives, J. Org. Chem., 2006; 71, 135-141.
3. D. Za´rate-Za´rate, R. Aguilar, R. I. Herna´ndez-Benitez, E. M. Labarrios, F. Delgado and J. Tamariz, Synthesis of α-ketols by functionalization of captodative alkenes and divergent preparation of heterocycles and natural products. Tetrahedron, 2015; 71, 6961–6978.
4. E. M. Gordon, R. W. Barrett, W. J. Dower, S. P. A. Fodor and M. A. Gallop, Applications of Combinatorial Technologies to Drug Discovery. 2. Combinatorial Organic Synthesis, Library Screening Strategies, and Future Directions. J. Med. Chem., 1994; 37, 1385–1401.
5. P. D. Leeson and B. Springthorpe, The influence of drug-like concepts on decision-making in medicinal chemistry. Nat. Rev. Drug Discovery, 2007; 6, 881–890.
6. A. Ansari, A. Ali, M. Asif, Shamsuzzaman, Review: biologically active pyrazolederivatives. New J. Chem., 2017; 41, 16.
7. S. Mert, R. Kasimogullari, T. Ica, F. Colak, A. Altun and S. Ok, Synthesis, structure–activity relationships, and in vitro antibacterial and antifungal activity evaluations of novel

pyrazole carboxylic and dicarboxylic acid derivatives. Eur. J. Med. Chem., 2014; 78, 86-96. (b) H. Fu and J. Yao, Size Effects on the Optical Properties of Organic Nanoparticles. J. Am. Chem. Soc., 2001; 123, 1434-1439. (c) M. Wang, J. Zhang, J. Liu, C. Xu and H. Ju, Intramolecular energy and charge transfer in 5-(9-anthryl)-3-(4-nitrophenyl)-1-phenyl-2-pyrazoline. J. Lumin., 2002; 99, 79-83. (d) F. Karci, F. Karci, A. Demirçali and M. Yamaç, Synthesis, solvatochromic properties and antimicrobial activities of some novel pyridone-based disperse disazo dyes. J. Mol. Liq., 2013; 187, 302-308. (e) X. C. Gao, H. Cao, L. Q. Zhang, B. W. Zhang, Y. Cao and C. H. Huang, Properties of a new pyrazoline derivative and its application in electroluminescence. J. Mater. Chem., 1999; 9, 1077-1080.

8. (a) X. Tu, W. Hao, Q. Ye, S. Wang, B. Jiang, G. Li and S. Tu, Four-Component Bicyclization Approaches to Skeletally Diverse Pyrazolo[3,4-b]pyridine Derivatives. J. Org. Chem., 2014; 79, 11110-11118. (b) G. Molteni and P. Del Buttero, A bicyclo[3.1.1]heptano[4,3-c]pyrazole derived chiral auxiliary for dipolar cycloadditions. Tetrahedron: Asymmetry, 2005; 16, 1983–1987.

9. Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. From 2000 to mid-2010: a fruitful decade for the synthesis of pyrazoles. Chem. Rev. 2011; 111, 6984-7034.