International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.7, pp 94-98, 2017

Synthesis of Some Novel Pyrazolines Containing Pyrazole Moiety

Amol J. Shirsat[1]*, Sunil S. Bhagat[1], Gopal K. Kakade[2]

[1]Department of Chemistry, R. B. Attal Arts, Science & Commerce College, Georai, Beed, Maharashtra, India.
[2]Department of Chemistry, Arts, Commerce & Science College, Kille- Dharur, Beed, Maharashtra, India.

Abstract : To synthesize pyrazolines containing pyrazole moiety, a simple, efficient and green procedure was used. When acrolein, and α, β- enone reacted with phenylhydrazine provided the simple pyrazoline formation via. Cyclization. This method has the advantages of operational simplicity, and high yield of products via a simple experimental and work-up procedure. Further the structures of pyrazoline derivatives were confirmed on the basis of spectral data. The compounds were screened for their in vitro antibacterial activity using Gram - positive and Gram - negative bacteria.
Keywords : Chalcone, Pyrazoline, Novel, spectral data, antibacterial activity.

Introduction

Among the five membered heterocyclic compounds containing two hetero atoms in its ring structure, pyrazole is one of the most important as large variety of biological activities such as anti-inflammatory, antimicrobial[2,3,4,5] antimycobacterial[6,7], antiamoebic[8,9], anti-inflammatory[10], analgesic[11], anticonvulsant[12], antidepressant[13], anticancer [14], acyl-CoA inhibitory [15], neuroprotective[16], antiviral [17], amine oxidase inhibitory [18] etc. have been reported for various pyrazole derivatives. Pyrazoline is dihydropyrazole, a five membered heterocyclic compound containing two nitrogen atoms in adjacent positions and one endocyclic double bond[1].

Experimental

All the chemicals required were obtained from Sigma Aldrich and SD Fine chemicals. Melting points were recorded in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on BrukerAvance II 400 MHz NMR Spectrophotometer in DMSO-d_6 and TMS as an internal standard. The infra-red spectra were recorded as potassium bromide disk using FT-IR Spectrophotometer Model RZX (Perkin Elmer). Mass spectra were recorded on Macromass mass spectrophotometer (Waters) by electro-spray method (ES). The purity of the synthesized compounds was checked by TLC silica gel coated plates obtained from Merck as stationary phase and solvent mixture of ethyl acetate/hexane (20:80) as mobile phase.

General procedure

Compound **1c**Chalcone(0.01mol) was dissolved in 15ml ethanol. To this reaction mixture, 0.02 mol of hydrazine hydrate was added. Contents were heated under mild reflux for 4 hr and then to the reaction mixture 4-5 drops of glacial acetic acid was added and heating was continued further for 3hr and then cooled to room

temperature. Cold water (50ml) was slowly added to the flask and separated product was filtered, washed with cold water for several times and crystallized from ethanol. The compounds **2(a-g)**were prepared by following the general procedure. Physical data are recorded in **Table 1**. Their structures have been confirmed by IR, ^{1}HNMR and Mass spectra.

IR (2c) (cm^{-1}):961(C-Cl), 1061(Ar-Br), 1552(C=C), 1596(C=N), 3106(O-H), 3335(N-H).

^{1}H NMR (2c) (DMSO-d_6)δppm: 3.1211-3.1881(dd, 1H, -CH_a-,*J*=10.04 Hz&*J*=10.12Hz),

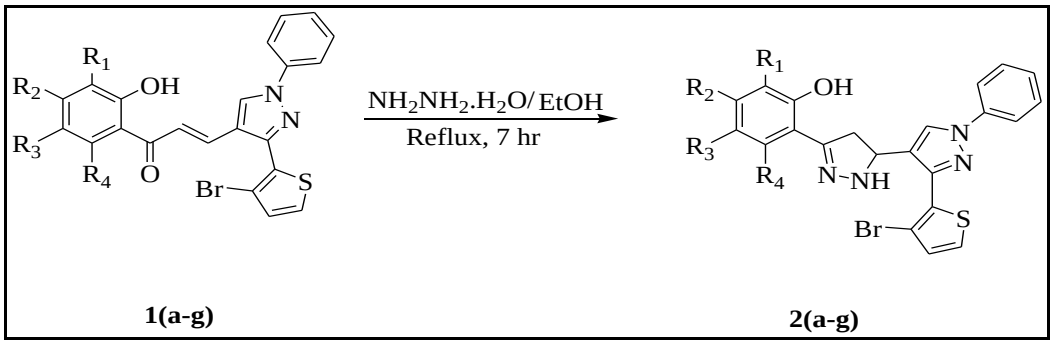
3.6119-3.6813(dd,1H,-CH_b-, *J*= 10.92Hz&*J*=10.96Hz), 4.8381-4.8982(ddd,1H, -CH_c-, *J*=3.08Hz, *J*=3.04Hz &*J*=3.12Hz), 6.9210-6.9428(d, 1H, -NH-, *J*=8.72Hz), 7.2351-7.2699(m, 2H, Ar-H), 7.3323-7.3664(m, 2H, Ar-H), 7.4996-7.5393(dd, 2H, *J*=8.24 Hz), 7.8135(s, 1H, Ar-H), 7.8135-7.8270(d, 1H, Ar-H, *J*=5.4Hz), 7.8729(s,1H,Ar-H), 7.8923(s, 1H, Ar-H), 8.6926(s,1H, pyrazole-H),11.1715(s, 1H, Ar–OH).

ES-MS (2c) (m/z):499.2(M+1), 501.2(M+2), 503.2(M+3), 504.2(M+5).

IR (2f) (cm^{-1}):959(C-Cl), 1062(Ar-Br), 1548(C=C), 1586(C=N), 3126(O-H), 3325(N-H).

^{1}H NMR (2f) (DMSO-d_6)δ ppm: 2.3755-2.5278(s, 3H, -CH_3), 3.1022-3.1678(dd, 1H, -CH_a-, *J*=10.01 Hz &*J*=10.11Hz), 3.5819-3.5911(dd,1H,-CH_b-, *J*= 10.82Hz &*J*=10.85Hz), 4.9191-4.9745(ddd,1H, -CH_c-, *J*=3.12Hz, *J*=3.11Hz &*J*=3.13Hz), 6.9623-6.9828(d, 1H, -NH-, *J*=8.2Hz), 7.2431-7.2712(m, 2H, Ar-H), 7.3513-7.3809(m, 2H, Ar-H), 7.5525-7.5893(dd, 2H, *J*=8.28 Hz), 7.7935(s, 1H, Ar-H), 7.8264-7.8409(d, 1H, Ar-H, *J*=5.8Hz), 7.8836(s,1H, Ar-H), 7.9223(s, 1H, Ar-H),8.7225(s,1H, pyrazole-H),12.1237(s, 1H, Ar–OH).

ES-MS (2f) (m/z): 513.25(M+1), 514.25(M+2), 515.25(M+3), 517.25(M+5).



Scheme 1: Synthesis of various 2-(5-(3-(3-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenol

Table 1: Physical data of compounds (2a-g)

Comp.	R_1	R_2	R_3	M.P. (^{o}C)	Yield (%)
2a	H	H	H	196-198	67
2b	H	H	CH_3	200-202	66
2c	H	H	Cl	218-220	78
2d	Cl	H	Cl	188-190	82
2e	H	H	F	222-224	73
2f	H	CH_3	Cl	206-208	79
2g	H	H	Br	212-214	72

Result and Discussion

The Pyrazoline derivatives were synthesized successfully in moderate to good yields. The newly synthesized compounds were identified on the basis of melting point range, IR, ^{1}H NMR, Mass spectral analysis. All the newly synthesized derivatives were screened for antimicrobial activity using disc diffusion method.

Antimicrobial activity:

Compounds **2(a-g)** were screened for their in vitro antimicrobial activity against *Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 27853), Staphylococcus aureus (ATCC 25923)* using Gentamycin as a reference standard drug by paper disc diffusion method. Antifungal activity was evaluated against *Candida sp*. using Nystatin as standard drug. All the tests were evaluated at 100 µg/ml concentration. The culture media was Muller Hinton agar. The zone of inhibition was measured in mm after 24 hr of incubation at 37^{o}C.Microbial data for corresponding compounds is summarized in **Table 2.**

Table 2:Antimicrobial Analysis Data

Sr. No.	**Comp.No.**	**Escherichia coli (ATCC 25922)**	**Pseudomonas aeruginosa (ATCC 27853)**	**Staphylococcus aureus (ATCC 25923)**	**Candida sp.**
1	2a	No Zone	No Zone	No Zone	No Zone
2	2b	No Zone	No Zone	No Zone	No Zone
3	2c	No Zone	No Zone	No Zone	No Zone
4	2d	No Zone	No Zone	No Zone	No Zone
5	2e	No Zone	No Zone	No Zone	No Zone
6	2f	No Zone	No Zone	No Zone	No Zone
7	2g	No Zone	No Zone	No Zone	No Zone
8	Gentamycin	28 mm	23 mm	32 mm	--
9	Nystatin	--	--	--	23 mm

Anti-Inflammatory Activity:

Compounds **2(a-g)** were screened for their anti-inflammatory activity. All analysis was performed using graph pad prism for Windows. All statistical analysis is expressed as mean ± standard error of the mean (SEM). Data were analyzed by one way ANOVA, where applicable $p<0.05$ was considered statistically significant, compared with vehicle followed by Dunnett's test.

Table 3.Effect of different Compounds 2a-2gon paw oedema induced by carrageenan in rat

	Treatment	**Mean Difference in Paw volume (ml)**	**Percentage Inhibition (%)**
Control	**0.1 ml of 1% (w/v)**	**1.6±0.02**	**----**
Diclofenac	30	1.5±0.01	93.75
2a	10	1.1±0.02	68.75
	20	1.2±0.01	75.00
2b	10	1.2±0.03	75.00
	20	1.3±0.01***	81.25
2c	10	1±0.02	68.75
	20	1.2±0.02*	81.25
2d	10	1±0.03	62.50
	20	1.1±0.01	68.75
2e	10	1.1±0.01	62.50
	20	1.3±0.03***	75.00
2f	10	1.1±0.03	68.75
	20	1.2±0.01*	75.00
2g	10	1±0.02	62.50
	20	1.2±0.02*	75.00

Each data suggests Mean ± SEM (n=6). One-way ANOVA using Dunnett's test is applied for statistical analysis, Treatment groups compared with Control group.

Significant at* $p < 0.01$, compared to control group.

Conclusion

Seven novel pyrazoline contain pyrazole have been synthesized, characterized byIR, 1HNMR and Mass spectral data ,Compounds 2a-g are screened for their anti-inflammatory using paw-odema method.From the results obtained it is concluded that compound 2a-2g shown good anti-inflammatory activity.

Acknowledgement

The authors are thankful to UGC, WRO, Pune for financial support & The Principal Dr. B. B. Sonwane for providing laboratory facilities. The authors are thankful to Director, SAIF/CIL, Panjab University, Chandigarh for providing spectral data & thankful to UdayKhedkar, Director, BAC-TEST Laboratory, Nashik for antimicrobial analysis.

References

1. Li J.T, Zhang X. H and Lin Z.P: An Improved Synthesis of 1, 3, 5-triaryl-2-pyrazolines in Acetic Acid Aqueous Solution under Ultrasound Irradiation. B. J. Org. Chem., 2007; vol. 3: 1860-5397.
2. Swamy P.M.G and Agasimundin Y.S: Synthesis and Antimicrobial Activity of 3-(3'-hydroxy benzofuranyl)-5-aryl-pyrazolines. Ind. J. Het. Chem., 2009; vol. 18: 275-278.
3. Sahoo A, Parida M, Sinha B.N and Venkatesan J: Antimicrobial Studies of Some New Novel Pyrazoline Derivatives. Int. J. of Res. in Pharm. Chem., 2011**;** vol. 1(3): 458-464.
4. Sahu SK, Banerjee M, Samantray A, Behera C and Azam MA: Synthesis, Analgesic, Anti-inflammatory and Antimicrobial Activities of Some Novel Pyrazoline Derivatives.Tro. J. Pharm. Res., 2008; vol. 7 (2): 961-968.
5. Mondal P, Jana S, Mahanti B, Kanthal L.K and Banerjee M: Synthesis & Evaluation of Some Novel Pyrazoline Derivatives of Indole 2-3 dione as a Potential Antioxidant & Antibacterial Agents. Int. J. Pharm. Sci. Tech., 2009; vol. 3(2): 8-11.
6. Yar M.S, Siddiqui A.A and Ali M.A: Synthesis and Evaluation of Phenoxy Acetic Acid Derivatives as a Anti-Mycobacterial Agents. Bioorg. Med. Chem. Lett., 2006; vol. 16: 4571–4574.
7. Zampieri D, Mamolo M.G, Laurini E and Scialino G: Antifungal and AntimycobacterialActivity of 1-(3,5-diaryl-4,5-dihydro-1H-pyrazol-4-yl)-1H-imidazole Derivatives. Bioorg. Med. Chem., 2008; vol. 16: 4516–4522.
8. Abid M and Azam A: Synthesis and Antiamoebic Activities of 1-N-substituted CyclisedPyrazoline Analogues of Thiosemicarbazones.Bioorg. Med. Chem., 2005; vol. 13: 2213–2220.
9. Abid M and Azam A: 1-*N*-Substituted Thiocarbamoyl-3-Phenyl-2-Pyrazolines: Synthesis and*In-Vitro* Antiamoebic Activities. Eur. J. Med. Chem., 2005; vol. 40: 935–942.
10. Khode S, Maddi V, Aragade P, Palkar M, Ronad P.K, Mamledesai S et.al: Synthesis and Pharmacological Evaluation of a Novel Series of 5-(substituted)aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines as Novel Anti-inflammatory and Analgesic Agents. 2009; vol. 44: 1682–1688.
11. Amir M, Kumar H and Khan S.A: Synthesis and Pharmacological Evaluation of Pyrazoline Derivatives as New Anti-inflammatory and Analgesic Agents.Bioorg. Med. Chem. Lett., 2008; vol. 18: 918–922.
12. Mishra R, Siddiqui A.A, Rahman M.A and Shaharyar M: Synthesis and Anticonvulsant Activity of Some Substituted 3,5-Diphenyl-2-Pyrazoline-1-Carboxamide Derivatives. Chem. Sci. J., 2010; vol. 8: 1-10.
13. Palaska E, Aytemira M, Uzbay I.T and Erola D: Synthesis and Antidepressant Activities of Some 3,5-diphenyl-2-pyrazolines. Eur. J. Med. Chem., 2001; vol. 36: 539–543.
14. Bashir R, Ovais S, Yaseen S, Hamid H, Alam MS, Samim M et.al: Synthesis of Some New 1,3,5-trisubstituted Pyrazolines Bearing Benzene Sulfonamide as Anticancer and Anti-inflammatory Agents. Bioorg. Med. Chem. Lett., 2011; vol. 21: 4301–4305.
15. Jeong T.S, Kim K.S, An S.J, Cho K.H, Lee S and Lee W.S: Novel 3,5-diaryl Pyrazolinesas Human Acyl-CoA: Cholesterol Acyltransferase Inhibitors. Bioorg. Med. Chem.Lett., 2004; vol. 14: 2715–2717.

16. Camacho M.E, Leon J and Entrena A: 4,5-Dihydro-1*H*-pyrazole Derivatives with Inhibitory nNOS Activity in Rat Brain: Synthesis and Structure-Activity Relationships. J. Med. Chem., 2004; vol. 47: 5641-5650.
17. Yar M.S, Bakht M.A, Siddiqui A.A, Abdullah M.M and Clercq E.D: Synthesis and Evaluation of *In-Vitro* Antiviral Activity of Novel Phenoxy Acetic Acid Derivatives. J. Enzym. Inhib. Med. Chem., 2009; vol. 24: 876-882.
18. Manna F, Chimenti F, Bolasco A, Secci D, Bizzarri B, Befani O et.al: Inhibition of Amine Oxidases Activity by 1-Acetyl-3,5-diphenyl-4,5-dihydro-(1H)-pyrazole Derivatives. Bioorg. Med. Chem. Lett., 2002; 12: 3629–3633.

*****