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SYNTHESIS AND CHARACTERIZATION OF SOME NEW SERIES OF PYRAZOLINE DERIVATIVES

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Abstract: Pyrazolines are well known and important nitrogen containing five membered heterocyclic compounds. Pyrazoline derivatives have been extensively studied because of their ready accessibility through synthesis, diverse chemical reactivity, various biological activities and variety of industrial applications. In the present study, Novel pyrazoline derivatives were carried out by cyclization of acrylamide derivatives with hydrazine hydrate in the presence of benzoic acid. Structures of the newly synthesized compounds were assigned on the basis of elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR.

Keyword: Pyrazoline derivatives, spectral analysis, Substituted pyrazoline, Synthesis.

INTRODUCTION

Heterocyclic compounds are acquiring more importance in recent years because of their immense biological and pharmacological potency. Various biologically active synthetic compounds have five membered nitrogen containing heterocyclic ring in their structures. Pyrazoline is a dihydro form of pyrazole which is 5-membered ring containing adjacent nitrogen atoms[1]. It displays various different pharmacological activities such as anti-inflammatory, antipyretic, analgesic[2] , antimicrobial[3], anticancer[4] ,antiviral[5], antihypertensive[6] , antiglaucoma[7] , antioxidant[8] , antidepressant, anxiolytic, neuroprotective[9] and antidiabetic[10] activity.

Pyrazolines were also found as effective chemical bleaching agents, luminescent and fluorescent agents[11-12]. Literature survey reveals several synthetic protocols for the synthesis of these compounds and the presence of this core in any molecule plays a key role in enhancing the activity. In view of these observations and in continuation of our research programme on the synthesis of five membered hetero cyclic compounds, we report here in the synthesis of some new pyrazoline derivatives, which have been found to possess an interesting profile of anti inflammatory, analgesic, anti bacterial activity, with significant reduction in their ulcerogenic potential. Therefore there is always demand for new molecules, methodologies and improved protocols for synthesis. The present study deals with the synthesis of pyrazoline derivatives by cyclization of the acrylamide derivatives with hydrazine hydrate in the presence of the benzoic acid.

RESULTS AND DISCUSSION

The main objective of the study was to synthesize novel pyrazoline derivative via Claisen–Schmidt-type aldol-crotonic condensation of 4-Acetamidocyclohexanone **(1)** with various aromatic aldehydes **(2)** was used for the preparation of α,β-Unsaturated carbonyl compound **(3a-h)**. Cyclization of the latter with hydrazine hydrate and benzoic acid afforded the corresponding pyrazoline derivatives **(4a-h) scheme 1.**

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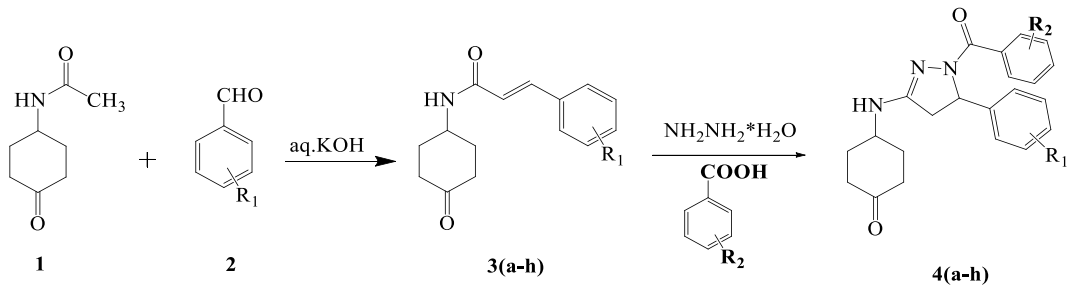
Scheme 1: Synthetic route of the titled compounds 4(a-h)



The effect of several protic and aprotic solvents on the yield of the reaction was studied (**Table no. 1**). Ethanol gave best yield of the product as compared to other solvents.

Table No. 1.
Optimization of solvent for the reaction of acrylamide derivatives (1mmol) benzoic acid (1mmol), hydrazine hydrate (3mmol).

Sr. No.	Solvent (10ml)	Time(hr)	Yield of product(%)
1	H_2O	15	88
2	**EtOH**	**06**	**95**
3	MeOH	05	86
4	DMF	11	69
5	DMSO	13	65
6	Toluene	18	18
7	DCM	13	25

Table No. 2: Synthesis of pyrazoline derivatives 4(a-h)

Compound code	R_1	R_2	Time (hrs)	Yield (%)	Melting point
4a	H	H	6	95	240-245
4b	4-Cl	H	7	89	270-275
4c	2-Cl	H	9	82	250-255
4d	4-Br	H	10	90	252-257
4e	3-OCH_3	H	6.5	91	242-247
4f	4-OCH_3	H	8	88	243-248
4g	3-NO_2	H	10	92	251-256
4h	4-NO_2	H	8.5	89	256-260

CONCLUSION

1. In Summary, we have described new series of Pyrazolines compound derived from 4-Acetamidocyclohexanone, aromatic aldehydes, hydrazine hydrate and benzoic acid in various solvent to afford better yield.
2. After that the compounds were purified by crystallization. The structures of the synthesized compounds were established on the basis of spectral data from 1H NMR, IR spectroscopic techniques.

EXPERIMENTAL SECTION

Unless and otherwise noted, all Chemicals used were of commercial grade and they were used without any further purification. All reactions were monitored by thin layer chromatography using aluminium sheets precoated with silica gel 60 F254 (Merck) using either UV light or iodine vapours as visualizing agents. The products were identified fully or by comparison of melting points and spectroscopic data with the previously reported ones.

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General procedure for the synthesis of acrylamide derivatives 3(a-g)

To a solution of 4-Acetamidocyclohexanone **(3 mmol)** and substituted aldehyde **(3 mmol)** dissolves in ethanol (10 ml). To that mixture add catalytic amount of aq. NaOH was added and the reaction mixture was stirred for about 5 h 0-5°C. The reaction was monitored on Merck pre-coated aluminum TLC plates 60F-254 and product was visualized by UV-light using n-hexane and ethyl acetate as solvent system. After completion of the reaction, the reaction mixture was poured into ice cold water the precipitate was filtered, dried and crystalized from ethanol.

General Procedure for Preparation of Pyrazoline Derivatives from acrylamide derivatives 4(a-g)

To a solution of acrylamide derivatives **3(a-g) (1mmol)** and benzoic acid **(1mmol)** dissolves in ethanol(5ml). To that mixture add hydrazine hydrate **(3mmol)** drop wise. The reaction mixture was heated at 80°C under reflux for 5-10h on oil bath. The reaction was monitored on Merck pre-coated aluminum TLC plates 60F254 and product was visualized by UV-light using n-hexane and ethyl acetate as solvent system. After completion of reaction, the reaction mixture poured into ice cold water the precipitate was settle down at a bottom, precipitate filtered, dried and crystallized from ethanol.

CHARACTERIZATION

Melting points were measured in open capillaries and are uncorrected. IR spectra was recorded on Bruker FTIR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker FTNMR (500MHz) spectrophotometer with DMSO-d6 as solvent and TMS as internal standard. Solvent peaks in ^{1}H-NMR and ^{13}C-NMR spectra have been removed in tracing. The chemical shifts in parts per million (δ) are reported downfield from TMS (0 ppm). The abbreviations s, d, t, q, m and dd refer to singlet, doublet, triplet, quartet, multiplet and doublet of doublet respectively.

4-((1-benzoyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)amino)cyclohexanone **(4a)**

Molecular Formula: $C_{22}H_{23}N_3O_2$
Molecular Weight (gmol-1): 361.44
Melting Point (ºC): 240-245

IR (KBr, cm-1): 3235(N-H), 1620 and 1630 (C=O), 1675(C=N)
^{1}H NMR (500 MHz, DMSO, δ ppm): 1.91-1.94(m, 4H, CH2), 2.30-2.36(m, 4H, CH2), 3.23(dd, 2H, CH2), 3.9(m, 1H, CH), 4.5(dd, 1H, CH), 6.0(s, 1H, NH), 7.28-7.45(m, 10H, Ar-H),
^{13}C NMR (500 MHz, DMSO, δ ppm): 28.4, 28.5, 39.3, 40.3, 40.9, 53.3, 59.3, 125.3, 128.0, 128.1, 128.7, 128.9, 131.9, 134.5, 140.3, 151.1, 168.6, 210.8.

4-((1-benzoyl-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)amino)cyclohexanone **(4b)**

Molecular Formula: $C_{22}H_{22}ClN_3O_2$
Molecular Weight (gmol-1): 395.88
Melting Point (ºC): 270-275

IR (KBr, cm-1): 3125(N-H), 1610 and 1620 (C=O), 1665(C=N)
^{1}H NMR (500 MHz, DMSO, δ ppm): 1.95-2.10(m, 4H, CH2), 2.30-2.36(m, 4H, CH2), 3.27(dd, 2H, CH2), 3.6(m, 1H, CH), 4.5(dd, 1H, CH), 6.0(s, 1H, NH), 7.30-7.48(m, 9H, Ar-H).
^{13}C NMR (500 MHz, DMSO, δ ppm): 29.4, 29.5, 38.3, 41.3, 42.9, 54.3, 59.5, 125.7, 128.2, 128.3, 129.7, 129.9, 130.9, 133.5, 141.3, 150.1, 167.6, 209.9.

4-((1-benzoyl-5-(2-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)amino)cyclohexanone **(4c)**

Molecular Formula: $C_{22}H_{22}ClN_3O_2$
Molecular Weight (gmol-1): 395.88
Melting Point (ºC): 250-257

IR (KBr, cm-1): 3325(N-H), 1615 and 1630 (C=O), 1680(C=N)
^{1}H NMR (500 MHz, DMSO, δ ppm): 1.89-1.93(m, 4H, CH2), 2.30-2.36(m, 4H, CH2), 3.25(dd, 2H, CH2), 3.62(m, 1H, CH), 4.1(dd, 1H, CH), 6.1(s, 1H, NH), 7.20-7.40 (m, 9H, Ar-H).
^{13}C NMR (500 MHz, DMSO, δ ppm): 27.4, 26.5, 37.3, 40.3, 41.9, 53.3, 58.5, 121.7, 127.2, 127.3, 128.7, 128.9, 129.9, 132.5, 140.3, 151.1, 168.6, 208.9.

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4-((1-benzoyl-5-(4-bromophenyl)-4,5-dihydro-1H-pyrazol-3-yl)amino)cyclohexanone **(4d)**

Molecular Formula: $C_{22}H_{22}BrN_3O_2$
Molecular Weight (gmol-1): 440.33
Melting Point (ºC): 252-257

IR (KBr, cm-1): 3225(N-H), 1650 and 1617 (C=O), 1678(C=N)
^{1}H NMR (500 MHz, DMSO, δ ppm): 1.89-1.93(m, 4H, CH2), 2.30-2.36(m, 4H, CH2), 3.25(dd, 2H, CH2), 3.62(m, 1H, CH), 4.1(dd, 1H, CH), 6.1(s, 1H, NH), 7.25-7.32 (m, 9H, Ar-H).
^{13}C NMR (500 MHz, DMSO, δ ppm): 28.4, 28.5, 38.3, 41.3, 41.9, 54.3, 58.5, 120.7, 127.2, 127.3, 128.7, 128.9, 130.9, 132.5, 141.3, 151.1, 169.6, 207.9.

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