SYNTHESIS OF NOVEL SUBSTITUTED PYRAZOLINES AND ISOXAZOLINES CONTAINING INDOLE AND COUMARINES

Doddappa Anekal[1] & J.S.Biradar[1,*]

**Department of Chemistry, Gulbarga University, Gulbarga-585 106, Karnataka-INDIA*
E-mail:dpanekal@gmail.com

ABSTRACT:

A novel 5-(2', 5'-disubstituted 1'H-indol-3'-yl)-3-(2"H-Chromen-2"-one-3"-yl) 4,5-dihydro-1H-pyrazoles **2a-d,** 1-acetyl 5-(2', 5'-disubstituted 1'H-indol-3'-yl)-3-(2"H-Chromen-2"-one-3"-yl) 4,5-dihydro-1H-pyrazoles **3a-d,** 1-phenyl-5-(2', 5'-disubstituted 1'H-indol-3'-yl)-3-(2"H-Chromen-2"-one-3"-yl) 4,5-dihydro-1H-pyrazoles **4a-d** and 5-(2', 5'-disubstituted 1'H-indol-3'-yl)-3-(2"H-Chromen-2"-one-3"-yl) 4,5-dihydroisoxazoles **5a-d** have been prepared by the cyclocondensation of Chalcones **1a-d** with hydroxylaminehydrochloride, hydrazinehydrate and phenylhydrazine respectively. Synthesised compounds have been characterized on the basis of elemental analysis, IR, ^{1}H NMR and mass spectral data.

Key Words: 2, 5-di substituted indole, triheterocycles, pyrazolines, isoxazolines, coumarines.

INTRODUCTION

Indole and its derivatives occupied a unique place in the chemistry of nitrogen heterocyclic compounds because of their varied biodynamic properties (1-6). Pyrazoline and isoxazole derivatives are of great interest, because of their biological and pharmacological activities (7-17). Several pyrazoline derivatives are found to have antiproteolitic (7), antifungal (8), chemotherapeutic (9) and various industrial applications (10-12). A number of substituted isoxazole derivatives are reported to possess anti-inflammatory (13), sedative (14-16) and antiviral (17) activities. A wide range of biological activities exhibited by pyrazolines and isoxazolines derivatives provide an impetus for the synthesis of some novel five membered heterocycles containing Indole and coumarine moiety with a view to achieve enhanced biological activities.

RESULTS AND DISCUSSION

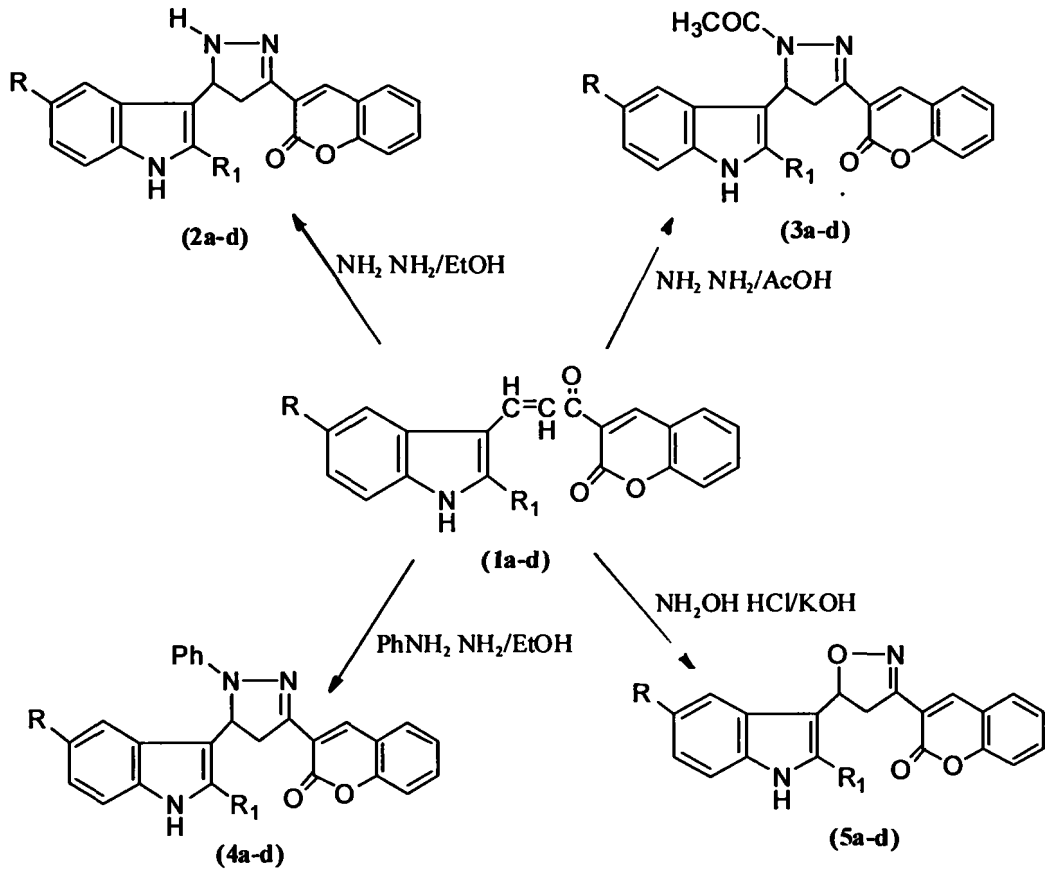
In the present investigation the cyclocondensation of chalcones **1a-d** with the hydrazinehydrate in ethanol yielded the 5-(2', 5'-disubstituted 1'H-indol-3'-yl)-3-(2"H-Chromen-2"-one-3"yl) 4,5-dihydro-1H-pyrazoles **2a-d,** The formation of the compound **2a** is confirmed by the presence of IR absorption bands at 3215 and 3111 cm^{-1} due to indole NH stretching and pyrazole NH, 1623 cm^{-1} (C=O), 1577 cm^{-1} (C=N) and 1244 cm^{-1} (-O-). The ^{1}H NMR spectrum of compound **2a** appeared at 2.4 δ (d, 2H, $-CH_2-$) of two protons in the pyrazole ring. The downfield signals at δ 12.2 (s, 1H, NH) and δ 6.4 (s, 1H, NH) are attributed to indole NH and pyrazole NH. The triplet at δ 3.3 (t, 1H, Ar-CH) accounting for one proton is due to the –CH- group (Ar-CH). A multiplet in the region δ 7.2 to δ 7.9 (m, 13H, ArH) accounting for thirteen protons is assigned for aromatic protons, suggesting the cyclocondensation. Mass spectral fragmentation of the compound **2a** has displayed the molecular ion peak at m/z 440 (10%). It has undergone into

fragmentation to generate a fragment of peaks at m/z 384 (100%), which is the base peak of the compound. Further fragmentation is generated peaks at m/z 293 (32%), m/z 265 (55%), m/z 237 (12%), m/z 223(10%) and m/z 152 (20%). These spectral data supports the proposed structure of compound **2a**.

The cyclocondensation of chalcone **1a-d** with hydrazinehydrate in glacial acetic acid has produced the compounds 1-acetyl-5-(2', 5'-disubstituted 1'H-indol-3'-yl)-3-(2"H-Chromen-2"-one-3"-yl) 4, 5-dihydro-1H-pyrazoles **3a-d.** The IR spectrum of **3a** showed characteristic absorption peaks at 3138 (NH), 1627 (C=O), 1579 (C=O) for acetyl ketone, 1456 (C=N) and 1244 cm^{-1} (-O-). In the ^1H NMR spectrum of compound **3a** displayed a singlet at δ 2.3 (s, 3H, CH3) corresponding to three protons of methyl group. Dishielded methylene appeared as a doublet at 2.0 δ (d, 2H, -CH_2-) accounting for two protons. The triplet at δ 2.5 (t, 1H, NH) accounting for one proton is due to the –CH- group (Ar-CH). A multiplet appeared in the region δ7.2 to 8.4 (m, 13H, ArH) integrating for thirteen protons is accounting for aromatic protons. The Dishielded indole NH exhibited a singlet at δ 10.6 (s, 1H, NH). This further supported by the mass spectrum. Mass spectral fragmentation of the compound **3a** has not displayed the molecular ion peak. Compound **3a** has undergone into fragmentation to generate a fragment of peaks at m/z 270 (100%), which is the base peak of the compound. other fragmented peaks are at m/z 440(2%), m/z 410 (18%), m/z 254(13%) and m/z 190(3%). These spectral data supports the proposed structure of compound **3a**.

Compound 1-Phenyl-5-(2',5'-disubstituted 1'H-indol-3'-yl)-3-(2"H-Chromen-2"-one-3"-yl) 4,5-dihydro-1H-pyrazoles **4a-d** are obtained by the cyclocondensation of chalcones **1a-d** with the phenylhydrazine. Compound **4a** displayed peaks at 3131 (NH), 1626 (C=O), 1574 (C=N) and 1228 cm^{-1} (-O-). In the ^1H NMR spectrum of compound **4a** has shown a singlet at downfield δ 10 (s, 1H, NH) integrating for a single proton is due to resonance of deshielded proton of indole NH. A doublet at 2.3δ, (d, 2H, -CH_2-) due to the two protons of pyrazole ring. The triplet at 3.7 δ (t, 1H, Ar-CH) accounting for one proton is due to the –CH- group (Ar-CH). A multiplet extending from 7.3 to 8.2 δ (m, 18H, ArH) integrating for eighteen protons accounts for the aromatic protons. A Mass spectrum of compound **4a** has displayed molecular ion peak at m/z 516 (5%) corresponding to the molecular weight. Molecular ion has undergone into fragmentation to generate in to peaks at m/z 411 (3%), m/z 268 (5%), 253 (100%), m/z 217 (10%) and m/z 190 (3%). These spectral data supports the proposed structure of compound **4a**.

The base catalyzed cyclocondensation of chalcones **1a-d** with the hydroxylamine hydrochloride yields the 5-(2', 5'-disubstituted 1'H-indol-3'-yl)-3-(2"H-Chromen-2"-one-3"-yl)-4, 5-dihydroisoxazoles **5a-d.** In the IR spectrum of **5a** the characteristic peaks appeared at 2922 (NH), 1723 (C=O), 1580 (C=N), 1247 (-O-) for isoxazole and 1233cm^{-1} (-O-) stretching. The ^1H NMR spectrum of compound **5a** showed a peak at 2.4 δ (d, 2H, -CH_2-) of two protons in the isoxazole ring. The downfield signal at 11.9 δ (s, 1H, NH) is attributed to indole NH. The triplet at δ 3.3 (t, 1H, Ar-CH) accounting for one proton is due to the –CH- group. A multiplet in the region 7.2 to 8.8 δ (m, 13H, ArH) accounting for thirteen protons is assigned to aromatic protons. Mass spectrum of compound **5a** has not displayed the molecular ion peak. Molecule has undergone into fragmentation to generate peaks at m/z 412 (30%), m/z 376 (20%), m/z 348 (25%), 334(100%), m/z 300 (85%) and m/z 185 (60%). The peak at m/z 334 (100%) is the base peak of the compound.



	a	b	c	d
R=	Cl,	CH_3,	H,	H
R_1=	Ph,	Ph,	Ph,	H

Scheme

Table-I: Characterization data of synthesized compounds **2, 3, 4** and **5a-d.**

Compd*. No	Substituents		M.P. (°C)	Yield (%)	Spectral data (IR (KBr)ν_{max} in cm^{-1}/^{1}HNMR (DMSO) in δ / Mass in m/z)
	R	R'			
2a	Cl	Ph	340	75	3215(NH), 3111(PyrNH), 1623(C=O),1577 (C=N), 1244(-O-), 12.2 (s, 1H, NH), 6.4 (s, 1H, Pyr.NH), 7.2-7.9 (m, 13H, ArH), 3.3 (d,2H,-CH_2-) 440(10%), 412(45%), 384(100%), 293(32%), 265(55%), 152(20%)
2b	CH_3	Ph	101	55	3115 (Pyr.NH), 3211 (NH), 1643 (C=O), 1577 (C=N), 1144 (-O-).
2c	H	Ph	300	60	3126(NH), 3040(PyrNH), 1643(C=O), 1073(-O-),1621 (C=N), 3340 (NH
2d	H	H	270	65	3215 (NH), 3111 (NH Pyr.), 1623 (C=O), 1577 (C=N), 1244 (-O-).
3a	Cl	Ph	300	55	3138 (NH), 1627(C=O), 1579(C=O), 1456(C=N), 1244(-O-), 10.6 (s, 1H, NH), 2(d, 2H, -CH_2-), 2.3 (s, 3H, COCH3), 7.2-8.4 (m, 13H, ArH), 2.5(t, 1H, -CH-Ar) 440(2%), 410(18%), 270(100%), 254(15%), 190(3%),
3b	CH_3	Ph	215	58	3038 (NH), 1677(C=O), 1479(C=N), 1044(-O-),
3c	H	Ph	235	50	3063 (NH), 1627 (C=O), 1578 (C=N), 1243 (-O-).
3d	H	H	285	55	3254 (NH), 1599 (C=O), 1497 (C=N), 1244 (-O-).
4a	Cl	Ph	285	50	3131(NH), 1626 (C=O), 1574 (C=N), 1228 (-O-) 10 (s, 1H, NH), 7.3-8.2 (m, 18H, ArH), 2.3(d, 2H,-CH_2), 3.7 (t, 1H, Ar-CH) 516(5%), 411(3%), 268(5%), 253(100%), 217(10%), 190(3%),
4b	CH_3	Ph	110	65	3252 (NH), 1629 (C=O), 1600 (C=N), 1258 (-O-)
4c	H	Ph	160	70	3063 (NH), 1627 (C=O), 1578 (C=N), 1243 (–O-)
4d	H	H	145	65	3254(NH), 1599(C=O), 1497(C=N), 1244(-O-),
5a	Cl	Ph	170	64	2922(NH), 1723 (CO), 1580 (C=N), 1247(-O-),1233 (-O-) 11.9 (s, 1H, NH), 7.2-8.8 (m, 13H, ArH), 2.4 (d, 2H,-CH_2-), 3.3 (s, 1H, Ar-CH) 412(30%), 376(25%), 348(25%),334(100%), 300(85%), 185(55%).
5b	CH_3	Ph	272	65	3281 (NH), 1665 (C=O), 1520 (C=N), 1235/1079 (-O-/-O-).
5c	H	Ph	176	65	3421 (NH), 1632 (C=O), 1497 (C=N), 1075 (-O-)
5d	H	H	198	60	2781 (NH), 1645 (C=O), 1520 (C=N), 1235/1099 (-O-/-O-).

*All the compounds gave satisfactory analysis for C, H and N.

*Solvents for crystallization: For compounds **2a-d** R. spirit, **3a-d** ethanol, **4a-d** 1,4 Diaxane, **5a-d** aqueous ethanol.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in KBr on Perkin-Elmer Spectrum-one FTIR Spectrophotometer (ν max in cm^{-1}) and ^1H NMR spectra on a Joel model GSX 270 MHz FTNMR Spectrometer (Chemical shift in δ ppm down field from TMS as an internal reference). The Mass spectra were recorded on LC-MSD-Trap-SL instruments.

Preparation of 5-substituted-2-phenyl indole-3-corboxaldehydes:

The starting compounds 5-substituted-2-phenylindole-3-corboxaldehydes were prepared according to the literature method (13).

Preparation of Chalcones 1a-d.

Chalcones are prepared by the base catalyzed condensation of 2,5-disubstituted indole-3-carboxyaldehyde with 3-acetyl coumarine according to literature method (18).

Preparation of 5-(2', 5'-disubstituted 1'H-indol-3'-yl)-3-(2"H-Chromen-2"-one-3"-yl) 4,5-dihydro-1H-pyrazoles 2a-d.

A mixture of chalcones **1a-d** (1mmole) and anhydrous hydrazinehydrate (2ml, 0.1moles) in absolute alcohol (5ml) was refluxed for 1-2 hours on a water bath. On cooling, a white crystalline solid appeared, which were filtered and recrystalised from suitable solvent (***Table-I***).

Preparation of 5-(2', 5'-disubstituted 1'H-indol-3'-yl)-3-(2"H-Chromen-2"-one-3"-yl) 1-acetyl 4,5-dihydro-1H-pyrazoles 3a-d.

Chalcones **1a-d** (0.005 mole) and hydrazinehydrate (99%, 0.005 mole) in glacial acetic acid (10ml) was refluxed on water bath for 5 hours. After the completion of the reaction it was concentrated, cooled and decomposed by pouring in to ice cold water. The solids separated were filtered, washed with water, dried and recrystalised from suitable solvent (***Table-I***).

Preparation 5-(2', 5'-disubstituted 1'H-indol-3'-yl)-3-(2"H-Chromen-2"-one-3"-yl) 1-Phenyl-4, 5-dihydro-1H-pyrazoles 4a-d.

A mixture of chalcones **1a-d** (0.005 mole), Phenylhydrazine (0.005 mole) in absolute ethanol (50 ml) and catalytic amount of piperidine (1 ml) was refluxed for 10 hours. The resulting mixture was concentrated, cooled and decomposed into acidified ice-cold water. The coloured compounds separated were filtered washed with water and recrystalised from suitable solvent (***Table-I***).

Preparation of 5-(2', 5'-disubstituted 1'H-indol-3'-yl)-3-(2"H-Chromen-2"-one-3"-yl)-4,5-dihydroisoxazoles 5a-d.

Chalcones **1a-d** (1mmole), hydroxylaminehydrochloride (600 mg, 1mmole), and KOH (500mg) in ethanol was refluxed on a water bath for 3-5 hours. The reaction mixture was neutralized with acetic acid and the contents were decomposed into ice-cold water (30 ml). The pale brown precipitates separated were collected and crystallized from suitable solvent (***Table-I***).

ACKNOWLEDGMENTS

Authors are grateful to Chairman, Department of chemistry for providing laboratory facilities. Authors are also grateful to the Dr. N. D. Sathyanarayana, Post Doctoral Fellow, University of Sunderland, England. for spectral data and Dr. Manjunath S. Yalagatti for their valuable discussions in the present work.

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Received on January 29, 2009