December 2008 Volume 4 Issue (9-11)

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 4(9-11), 2008 [447-450]

Microwave-assisted synthesis of pyrazole and thiadiazine derivatives containing indole

Jaiprakash S.Biradar*, Praveen S.Mugali

Department of Post Graduate Studies and Research in Chemistry, Gulbarga University, Gulbarga-585106, Karnataka, (INDIA)

Tel : 08472-245982

E-mail : wordofchemistry@gmail.com

Received: 13th October, 2008 ; Accepted: 18th October, 2008

ABSTRACT

Substituted indole aldehydes were condensed with substituted acetophenones in presence of base afforded the substituted indole-3-chalcones. These compounds on reaction with substituted hydrazide yielded the title compounds. The compounds were synthesized by conventional and microwave irradiation methods. The reaction rate is enhanced tremendously under microwave irradiation as compared to conventional method. The newly synthesized compounds were characterized by their analytical and spectral data. © 2008 Trade Science Inc. - INDIA

KEYWORDS

Indole aldehydes;
Chalcones;
Pyrazoles;
Thiadiazine;
Conventional;
Microwave methods.

INTRODUCTION

Indoles are the most widely distributed heterocycles in nature. Indole nucleus is a common structural feature of a wide variety of biologically active compounds[1-4]. Pyrazole and its synthetic analogues have been found to exhibit industrial, agricultural and biological applications[5,6]. Pyrazole containing compounds have been reported to show a broad spectrum of biological activities[7,11].

In recent years design of environmentally benign reactions is an important goal in organic synthesis. Due to the hazardous chemicals and byproducts of various reactions increase the pollution in the environment. Keeping in view the need for avoiding hazardous chemicals in chemical reactions, microwave technique was found to be accelerating a wide variety of transformations[12]. Microwave assisted organic reactions occur more rapidly, safely and have been gaining importance due to its remarkable advantages such as increase in yields, decrease in reaction period, improved selectivity, eco-friendly nature and easier work-up[13].

In the light of above observations it was thought of considerable interest to synthesize novel indole derivatives containing pyrazole and thiadiazine heterocyclic systems by microwave and conventional methods.

RESULTS AND DISCUSSION

The starting compounds **(1a-d)** were obtained by Simple and substituted indoles on Vilsmeier-Haack formylation[14]. These were coupled with substituted acetophenones in presence of base to obtain chalcones **(3a-l)**. The compound **(4)** was prepared by the reaction of diethylbromomalonate with thiocarbohydrazide in presence of base which undergoes cyclisation to yield the substituted hydrazide containing thiadiazine ring.

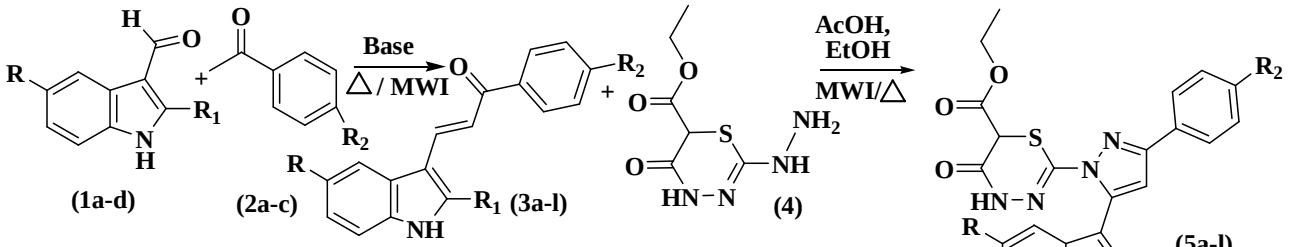
Chalcones prepared from the corresponding substituted indole-3-carboxaldehydes on reaction with substituted acetophenones in presence of base produced α, β-unsatured carbonyl compounds **(3a-l)**. The IR spectral data of compound 3k has shown a peak at 3295 cm^{-1} (NH) and the appearance of a carbonyl at 1641 cm^{-1} indicating the condensation of substituted

Full Paper

TABLE 1: Physical data and comparison of the reaction time and yields (%) of compounds (3a-l) and (5a-l) under conventional and microwave methods

Compound	Substitutents			M.P,	Reaction time		Yield (%)	
no.	R	R_1	R_2	(^{0}C)	Conventional	MWI (min)	Conventional	MWI
(3a)	H	H	H	164-65	240	04	58	71
(3b)	H	H	CH_3	187-89	240	04	52	74
(3c)	H	H	Cl	201-02	240	04	61	78
(3d)	H	Ph	H	170-71	240	04	49	65
(3e)	H	Ph	CH_3	180-81	240	04	59	70
(3f)	H	Ph	Cl	210-11	240	04	56	68
(3g)	CH_3	Ph	H	178-79	240	04	66	78
(3h)	CH_3	Ph	CH_3	191-92	240	04	60	76
(3i)	CH_3	Ph	Cl	230-32	240	04	58	74
(3j)	Cl	Ph	H	250-51	240	04	61	78
(3k)	Cl	Ph	CH_3	205-06	240	04	67	88
(3l)	Cl	Ph	Cl	242-43	240	04	65	81
(5a)	H	H	H	149-51	480	05	54	69
(5b)	H	H	CH_3	198-99	540	06	59	72
(5c)	H	H	Cl	174-75	540	06	60	75
(5d)	H	Ph	H	233-34	540	06	53	67
(5e)	H	Ph	CH_3	209-11	540	06	60	65
(5f)	H	Ph	Cl	227-28	540	06	57	70
(5g)	CH_3	Ph	H	203-04	540	06	63	71
(5h)	CH_3	Ph	CH_3	218-19	540	06	61	73
(5i)	CH_3	Ph	Cl	256-57	540	06	67	79
(5j)	Cl	Ph	H	215-16	540	06	56	69
(5k)	Cl	Ph	CH_3	244-45	540	06	70	82
(5l)	Cl	Ph	Cl	270-71	540	06	65	74

All compounds gave satisfactory elemental analysis



3a-l and 5a-l, a b c d e f g h i j k l

R = H H H H H H CH_3 CH_3 CH_3 Cl Cl Cl

R_1 = H H H Ph Ph Ph Ph Ph Ph Ph Ph Ph

R_2 = H CH_3 Cl H CH_3 Cl H CH_3 Cl H CH_3 Cl

SCHEME 1

acetophenones with indole-3-carboxaldehydes to give α, β-unsaturated carbonyl compounds. It is further supported by the NMR and Mass spectral data. The NMR spectrum of compound **(3k)** has shown a singlet at 2.6 (s,3H, CH_3) corresponding to three protons of methyl present on the aromatic ring system, two protons present on the methine carbons have deshielded and appeared with aromatic protons. The multiplet between 7.2 – 7.8 δ (14H, Ar- H) integrating for fourteen protons are assigned to twelve aromatic and two methine protons. Deshielded indole NH has appeared at 9.5 δ (s, 1H, indole NH). Mass spectrum of compound 3k has shown molecular ion peak at m/z, 371 corresponding to the molecular weight of the compound.

Substituted pyrazoles containing thiadiazine **(5a-l)** were obtained from the respective chalcones and substituted hydrazide in presence of catalytic amount of acetic acid using ethanol, which makes the solution homogenous and acts as energy transfer medium. IR spectrum of compound **(5k)** showed the absence of carbonyl peak at 1641 cm^{-1} and appearance of peaks at 1745, 3301 and 3150 cm^{-1} are assigned for the thiadiazine carbonyl and ester carbonyl, indole and thiadiazine-NH- respectively, and the peak at 1615 cm^{-1} for (C=N)

TABLE 2: Spectral data of synthesized compounds (3a-l) and (5a-l)

Compd. no.	IR (cm^{-1})	^{1}H NMR (δ ppm)
(3a)	3275 (NH) and 1634 (C=O),	9.3 (s, 1H, indole NH) and 7.1-7.8 (m, 13H, Ar-H).
(3b)	3280 (NH) and 1641 (C=O),	9.5 (s, 1H, indole NH), 7.2-7.9 (m, 12H, Ar-H). and 2.5 (s, 3H, CH_3).
(3c)	3270 (NH) and 1640 (C=O),	9.2 (s, 1H, indole NH) and 7.2-7.8 (m, 12H, Ar-H).
(3d)	3295 (NH) and 1645 (C=O),	9.6 (s, 1H, indole NH) and 7.3-7.9 (m, 17H, Ar-H).
(3e)	3301 (NH) and 1641 (C=O),	9.8 (s, 1H, indole NH), 7.1-7.9 (m, 16H, Ar-H) and 2.6 (s, 3H, CH_3).
(3f)	3290 (NH) and 1647 (C=O),	9.6 (s, 1H, indole NH) and 7.3-7.8 (m, 16H, Ar-H).
(3g)	3270 (NH) and 1636 (C=O),	9.4 (s, 1H, indole NH), 7.2-7.8(m, 16H, Ar-H) and 2.5 (s, 3H, CH_3).
(3h)	3285 (NH) and 1640 (C=O),	9.1 (s, 1H, indole NH), 7.1-7.8 (m, 15H, Ar-H) and 2.7(s, 6H, CH_3).
(3i)	3300 (NH) and 1645 (C=O),	9.5 (s, 1H, indole NH), 7.2-7.9 (m, 15H, Ar-H) and 2.6 (s, 3H, CH_3).
(3j)	3290 (NH) and 1635 (C=O),	9.2 (s, 1H, indole NH) and 7.1-7.9 (m, 16H, Ar-H).
(3k)	3295 (NH) and 1641 (C=O),	9.5 (s, 1H, indole NH), 7.2-7.8 (m, 14H, Ar-H) and 2.6 (s, 3H, CH_3).
(3l)	3300 (NH) and 1640 (C=O),	9.6 (s, 1H, indole NH) and 7.2-7.9 (m, 15H, Ar-H).
(5a)	3301, 3155 (NH/NH), 1740 (C=O/C=O) and 1620 (C=N),	9.5 (s, 1H, indole NH), 8.7 (s, 1H, thiadiazine NH), 7.2-8 (m, 11H, Ar-H), 4.6(s, 1H, CH) thiadiazine, 4.3 (q, 2H,CH_2) and 1.2 (t, 3H, CH_3) ester.
(5b)	3305, 3150 (NH/NH), 1745 (C=O/C=O) and 1615 (C=N)	9.6 (s, 1H, indole NH), 8.8 (s, 1H, thiadiazine NH), 7.1-7.9 (m, 10H, Ar-H), 4.7(s, 1H, CH) thiadiazine, 4.3 (q, 2H, CH_2), 1.3 (t, 3H, CH_3) ester, and 2.5 (s, 3H CH_3).
(5c)	3295, 3160 (NH/NH), 1750 (C=O/C=O) and 1610 (C=N),	9.7 (s, 1H, indole NH), 8.9 (s, 1H, thiadiazine NH), 7.1-8 (m, 10H, Ar-H), 4.6 (s, 1H, CH) thiadiazine, 4.4 (q, 2H, CH_2) and 1.4 (t, 3H, CH_3) ester.
(5d)	3310, 3170 (NH/NH), 1740 (C=O/C=O) and 1620 (C=N),	9.9 (s, 1H, indole NH), 9 (s, 1H, thiadiazine NH), 7.3-8 (m, 15H, Ar-H), 4.7(s, 1H, CH) thiadiazine, 4.3 (q, 2H, CH_2) and 1.3 (t, 3H, CH_3) ester.
(5e)	3300, 3150 (NH/NH), 1740 (C=O/C=O) and 1615 (C=N),	9.7 (s, 1H, indole NH), 8.7 (s, 1H, thiadiazine NH), 7.2-7.9 (m, 14H, Ar-H), 4.5(s, 1H, CH) thiadiazine, 4.3 (q, 2H, CH_2), 1.2 (t, 3H, CH_3) ester and 2.6 (s, 3H CH_3).
(5f)	3305, 3170 (NH/NH), 1745 (C=O/C=O) and 1615 (C=N),	9.8 (s, 1H, indole NH), 8.9 (s, 1H, thiadiazine NH), 7.1-7.9 (m, 14H, Ar-H), 4.7(s, 1H, CH) thiadiazine, 4.4 (q, 2H, CH_2) and 1.3 (t, 3H, CH_3) ester.
(5g)	3301, 3160 (NH/NH), 1741 (C=O/C=O) and 1610 (C=N),	9.6 (s, 1H, indole NH), 8.8 (s, 1H, thiadiazine NH), 7.2-8 (m, 14H, Ar-H), 4.7(s, 1H, CH) thiadiazine, 4.4 (q, 2H, CH_2), 1.2 (t, 3H, CH_3) ester and 2.6(s, 3H CH_3).
(5h)	3290, 3150 (NH/NH), 1750 (C=O/C=O) and 1620 (C=N),	9.7 (s, 1H, indole NH), 8.5 (s, 1H, thiadiazine NH), 7.1-7.8 (m, 13H, Ar-H), 4.6(s, 1H, CH) thiadiazine, 4.3 (q, 2H,CH_2), 1.3 (t, 3H, CH_3) ester and 2.6 (s, 6H CH_3).
(5i)	3300, 3165 (NH/NH), 1741 (C=O/C=O) and 1610 (C=N),	9.9 (s, 1H, indole NH), 8.8 (s, 1H, thiadiazine NH), 7.2-7.9 (m, 13H, Ar-H), 4.7(s, 1H, CH) thiadiazine, 4.4 (q, 2H, CH_2), 1.2 (t, 3H, CH_3) ester and 2.5 (s, 3H CH_3).
(5j)	3300, 3170 (NH/NH), 1750 (C=O/C=O) and 1620 (C=N),	9.8 (s, 1H, indole NH), 9.1 (s, 1H, thiadiazine NH), 7.2-8 (m, 14H, Ar-H), 4.7(s, 1H, CH) thiadiazine, 4.4 (q, 2H, CH_2) and 1.3 (t, 3H, CH_3) ester.
(5k)	3301, 3150 (NH/NH), 1745 (C=O/C=O) and 1615 (C=N),	9.6 (s, 1H, indole NH), 8.9 (s, 1H, thiadiazine NH), 7.1-7.9 (m, 13H, Ar-H), 4.7(s, 1H, CH) thiadiazine, 4.3 (q, 2H, CH_2), 1.3 (t, 3H, CH_3) ester and 2.6 (s, 3H, CH_3).
(5l)	3315, 3170 (NH/NH), 1750 (C=O/C=O) and 1615 (C=N),	9.8 (s, 1H, indole NH), 8.9 (s, 1H, thiadiazine NH), 7.1-8 (m, 13H, Ar-H), 4.7(s, 1H, CH) thiadiazine, 4.4 (q, 2H, CH_2) and 1.3 (t, 3H, CH_3) ester.

shows the formation of the product. The NMR spectrum of **(5k)** showed triplet at 1.3 δ (t, 3H, CH_3) accounts for three protons of methyl and a quartet at 4.3 δ (q, 2H, CH_2) for two protons of methylene present on ester of thiadiazine ring. Also singlet at 2.6 δ (s, 3H, CH_3) integrating for three protons is due to the methyl group on the aromatic ring, and a peak at 4.7 δ (s, 1H, CH) is due to methine proton of thiadiazine ring. Multiplet between 7.1-7.9 δ (m, 13H, Ar-H) integrating for thirteen protons is due to aromatic protons. A singlet appeared at 8.9 δ (s, 1H, NH) integrating for one proton is due to the thiadiazine NH. A deshielded proton at 9.6 δ(s, 1H, NH) integrating for one proton accounts for indole NH. Appearance of molecular ion peak at m/z, 569 in its mass spectrum gave additional support for the structure of **(5k)**.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra (cm^{-1}) were recorded using KBr disc on Perkin-Elmer FTIR spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 (chemical shift in δ ppm) using TMS as an internal standard. Mass spectra were recorded with an LCMS-2010A data Report-Shimadzu. The microwave reactions were carried out in Onida 800 W (Sl. no. MO 20SG05101262) domestic microwave oven at power level 6.

General procedure for the preparation of substituted chalcones (3a-l)

By conventional method

2, 5-disubstitutedindole-3-carboxaldehyde 1, (2

mmoles) and substituted acetophenone 2, (2 mmoles) were taken with catalytic amount of piperidine in ethylene glycol and the resulting mixture was refluxed for 4 hours. The reaction mixture was decomposed in ice cold water containing few drops of acetic acid. The solid thus separated was filtered, washed thoroughly with water, dried and recrystallised from suitable solvents.

By microwave irradiation

2, 5-disubstitutedindole-3-carboxaldehyde **(1)** (2 mmoles) and substituted acetophenones **(2)** (2 mmoles) and catalytic amount of piperidine were mixed well and resulting mass was taken in a borosil vessel. The reaction mixture was irradiated in a microwave oven for 4 minutes with short interruptions, on completion of reaction it was cooled, added to ice cold water and acidified with few drops of acetic acid. The product obtained was filtered, washed with water, dried and recrystallised from suitable solvents.

General procedure for the preparation of substituted pyrazoles (5a-l)

By conventional method

Substituted chalcones **(3)** (2 mmoles) and substituted hydrazide **(4)** (2 mmoles) were taken with catalytic amount of acetic acid in ethanol and the resulting mixture was refluxed for 8-9 hours. On completion of reaction, the mixture was decomposed in ice cold water. The yellow solid thus separated was filtered, washed thoroughly with water, dried and recrystallised from DMF or ethanol.

By microwave irradiation

Substituted chalcones **(3)** (2 mmoles) and substituted hydrazide **(4)** (2 mmoles) and catalytic amount of acetic acid in ethanol were taken in a borosil flask fitted with a funnel as a loose top. The reaction mixture was irradiated in a microwave oven for 5-6 minutes, with short interruptions in order to avoid the excessive evaporation of the solvent. On completion of the reaction, the reaction mixture was cooled and added to ice cold water. The solid separated was filtered, washed thoroughly with water, dried and recrystallised from DMF or ethanol.

ACKNOWLEDGMENTS

Authors are thankful to Chairman, Department of Chemistry, Gulbarga University, Gulbarga for providing facilities and encouragement. Also we are thankful to the Director, IISC, Bangalore. SGRIMS, CDRI, Lucknow. for the analytical and spectral data.

REFERENCES

[1] M.Lehr, M.Klimt, A.Schulze-Elfringhoff; Bioorg.Med.Chem.Lett., **11**, 2569 **(2001)**.
[2] B.Alcaide, P.Almendos, R.Rodriguez-Acebes; J.Org.Chem., **71**, 2346 **(2006)**.
[3] P.Wardman, L.K.Folkes, G.U.Dachs, S.Rossiter, O.Greco; PCT Int.Appl., WO, 0202110, Chem. Abstr., **136**, 102335 **(2002)**.
[4] R.J.Flower, S.Monocada, J.R.Vane, Goodman and Gilman; 'The Pharmacological Basis of Therapeutics', 7th Eds., 695 **(1985)**.
[5] C.Vicentini, G.Forlani, M.Manfrini, C.Romagnoli, D.Mares; J.Agric.Food.Chem., **50**, 4839 **(2002)**.
[6] Z.Brzozonski, F.Saczawski; Eur.J.Med.Chem., **37**, 709 **(2002)**.
[7] B.K.Karale, V.P.Chavan, A.S.Mane, R.V. Hangarge, C.H.Gill, M.S.Shingare; Korean J.Med. Chem., **10(2)**, 84 **(2000)**.
[8] S.A.F.Rostom, M.A.Shalaby, M.A.El-Demellaway; Euro.J.Med.Chem., **38**, 959 **(2003)**.
[9] A.Goal, A.K.Madan; J.Chem.Inf.Comput.Sci., **35**, 510 **(1995)**.
[10] X.L.Ren, H.B.Li, C.Wu, H.Z.Yang; ARKIVOC, **15**, 59 **(2005)**.
[11] B.Shivarama Holla, B.Sooryanarayana Rao, B.K.Sarojini, P.M.Akberali, N.Suchetha Kumari; Eur.J.Med.Chem., **41**, 657 **(2006)**.
[12] Mackie, M.Cartney; 'Practical Medicinal Microbiology', J.G.Collee, J.P.Duhuid, A.G.Fraser, Marmion (Eds.); 87 **(1989)**.
[13] T.V.Maruthikumar, V.P.Reddy, P.H.Rao; Indian J.Chem., **44B**, 1931 **(2005)**.
[14] S.P.Hiremath, J.S.Biradar, M.G.Purohit; Indian J.Chem., **21B**, 249 **(1982)**.