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Synthesis of Some Benzimidazolyl Pyrazole Derivatives Under Microwave Irradiation and their Antimicrobial Activities

Shailendra Jain*

Department of Chemistry, Synthetic Organic Chemistry Laboratory, Manikya Lal Verma Government College, Bhilwara, India

Research Article

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***For Correspondence:**

Shailendra Jain, Department of Chemistry, Synthetic Organic Chemistry Laboratory, Manikya Lal Verma Government College, Bhilwara, India, Tel: +91-22-42332000;

E-mail: shailjain1@yahoo.co.in

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ABSTRACT

A simple competent method has been developed for the synthesis of some pyrazole derivatives under microwave irradiation. The reaction of benzimidazolyl chalcone (1) with bromine in chloroform gave corresponding dibromochalcones (2), which when condensed with hydrazine hydrate afforded the title compounds 3-benzimidazolyl-5-aryl-2-pyrazoles (3). All the synthesized compounds were characterized by elemental analysis, IR, NMR and MS spectra. Microwave irradiation method provided improved product yield in a very short span of time. Newly synthesized pyrazoles were screened for their antimicrobial activity *in vitro*, some of them have exhibited impressive biological activity.

INTRODUCTION

Over the years various innovative methods have been devised to speed up the chemical reactions. In the environment conscious era, the development of technology is intended for environmentally sound and eco-friendly methods. The use of microwave energy to accelerate the organic reaction is of increasing relevance and offers several advantages over conventional techniques [1].

Synthesis of the molecules which usually requires a long period of time can be achieved rapidly and conveniently in domestic microwave oven. Less reaction time, easy work up and cleaner products are the major advantages of microwave protocol. Furthermore, the reactions can be carried out under solvent free conditions which hold a strategic position as the solvents used are often very toxic, problematic and expensive. Solvent free condition is especially suitable for microwave activation. Thus, the use of microwave energy for the synthesis of organic compounds forms a part of green chemistry [2].

The chalcones having an α, β -unsaturated ketone system, serve as important Michael acceptors. They serve as a synthon in various chemical transformations for the synthesis of a variety of biodynamic molecules such as five membered (pyrazolines, isoxazolines), six membered (pyridines, pyrimidines), and seven membered (diazepines, thiazipines) heterocyclic and carbocyclic systems [3]. These systems constitute the major share of synthetic drugs, which are capable of performing a variety of functions. Much attention has been paid to the synthesis of heterocycle containing pyrazole system mainly due to its broad spectrum of pharmacological properties. Pyrazole derivatives possess variety of pharmacological activities such as analgesic, electorseisure, anti-inflammatory, antidepressant, antihypertensive, antiviral and anticancer activities [4-9].

Keeping in view the above observations and utility of benzimidazole nucleus as a potent precursor for synthesis of a variety of biodynamic heterocyclic compounds it was thought worthwhile to undertake the brominations of 1-benzimidazolyl-3-aryl-2-propen-1-ones in an attempt to prepare some new dibromo chalcones and to transform them into pyrazole derivatives which may be pharmacologically active.

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The required synthon for this transformation 1-benzimidazolyl-3-aryl-2-propenone [1a-f] was prepared by condensation of 2-acetyl benzimidazole with variously substituted aromatic aldehydes in presence of base (NaOH/KOH) under solvent free solid phase microwave irradiation condition by the literature method [10].

EXPERIMENTAL

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The purity of the compounds and progress of the reaction were monitored by thin layer chromatography on silica gel coated aluminium plates (Merck) as adsorbent and UV light was used for visualization. The progress of the reaction was also checked by UV-Vis spectrophotometer (UV-1700, Shimatzu). The structures of synthesized compounds were confirmed by elemental and spectral analysis. IR spectra (KBr in cm^{-1}) were recorded on a Perkin- Elmer spectrophotometer in the range of 4000-400 cm^{-1}. 1 H NMR spectra were recorded on an ECS 400 MHz (JEOL) NMR spectrometer using $CDCl_3$ as solvent and TMS as an internal standard (chemical shifts in δ ppm). Mass spectra (FAB) were recorded by Xevo G2-SQ, TOF(Waters). m-nitrobenzyl alcohol was used as matrix. Domestic Microwave oven (Samsung CE117ADE, output 900 W, frequency 2450 MHz) was used to prepare all compounds.

Synthesis of 1- benzimidazolyl-3-aryl-prop-2-ene-1-one-2,3- dibromides (2a-f)

To a solution of 1-benzimidazolyl-3-aryl-2-propenones (1a-f) (0.01 mole) in chloroform (25 ml) was added dropwise with stirring, a solution of bromine (0.01 mole) in chloroform (25 ml). After complete addition the reaction mixture was stirred for 30 minutes and left at room temperature. The solid separated out was filtered, washed with chloroform and crystallized from ethanol as cream colored solid (2a-f) (80-85%).

Synthesis of 3-benzimidazolyl-5-aryl-2-pyrazoles (3a-f)

To a solution of benzimidazolyl chalcone dibromides (2) (0.01 mole) in ethanol (20 ml) was added hydrazine hydrate (0.01 mole). The contents were mixed thoroughly and subjected to microwave irradiation at 300-watt power for 3-5 minutes. After completion of the reaction as indicated by TLC, the contents were cooled to room temperature and poured on to ice cold water. The separated solid was filtered, washed with water, dried and crystallized from ethanol as cream colored crystals (3a-f) in 80-88% yield.

RESULTS AND DISCUSSION

The structure of the product was then established on the basis of elemental analysis and spectral data. The IR spectra of compounds (2a-f) gave characteristic carbonyl group stretching bonds in the region 1680- 1630 cm^{-1}. Characteristic aromatic (C-H) stretching bands in the region 3000- 2900 cm^{-1} were also observed. Medium intensity absorption bands for the benzene ring vibration were observed in the region 1600-1400 cm^{-1}. The number and position of these peaks depends on the extent of substitution pattern of aromatic rings. The typical C-Br stretching was observed in the region 650-550 cm^{-1} as medium intensity peak.

The ^{1}H NMR spectra of these compounds (2a-f) exhibited doublets for C-H protons in the range of δ 5.64- 5.67 (Hα) and 6.44- 6.49 (Hβ) respectively. The aromatic proton gave a multiplet at δ 6.89- 8.01 **(Scheme 1)**.

The mass spectra (FAB) of dibromides gave molecular ion peaks corresponding for their molecular masses. The fragmentation generally takes place on expected lines on either side of the carbonyl group. The ions derived from these depend upon the substitution pattern of the parent compound.

The IR spectra of the compounds (3a-f) gave characteristic absorption bands at 3350 cm^{-1} for –NH stretching, 2986-2800 cm^{-1} for C-H stretching. Combined vibration of C=N and C=C groupings were observed as a broad band at 1444-1361 cm^{-1}.

^{1}H-NMR spectra of compounds (3a-f) gave a doublet at 2.04-2.7 indicating that presence of hydrogen atoms at C_4 of pyrazole ring. The aromatic protons gave a multiplet at δ 7.22- 7.89. The mass spectra of these compounds gave the molecular ion peaks corresponding to their molecular masses. The mass spectra indicated that the pyrazole formation probably takes place through the formation of intermediate 4-bromo-pyrazoline (3") which underwent dehydrobromination to form corresponding pyrazole **(Tables 1-3)**.

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Table 1. Physical data of 1-benzimidazolyl-3-aryl-prop-2-ene-1-one-2,3-dibromide (2a-f).

Compd.	Ar	Mol. Formula (Mol. wt.)	M.P (°C)	% Yield	Mean Time (hrs)
2a	Phenyl	$C_{16}H_{12}N_2OBr_2$ (408)	148	85	5.0
2b	4-methoxy phenyl	$C_{17}H_{14}N_2O_2Br_2$ (438)	166	84	5.5
2c	3-4dimethoxyphenyl	$C_{18}H_{16}N_2O_3Br_2$ (468)	228	86	5.0
2d	3,4,5-trimethoxyphenyl	$C_{19}H_{18}N_2O_4Br_2$ (498)	102	82	6.0
2e	4-chlorophenyl	$C_{16}H_{11}N_2O_5Br_2$ (442.5)	130	83	5.0
2f	2-furanyl	$C_{13}H_{10}N_2OBr_2$ (386)	110	84	5.5

Table 2. Physical data of 3-benzimidazolyl-5-aryl-2-pyrazole (3a-f).

Compd.	Ph	Molecular Formula (Mol. Wt.)	M.P. (°C)	% Yield MWI	Reaction Time MWI (min)
3a	Phenyl	$C_{16}H_{12}N_4$-260	168	88	4
3b	4-methoxyphenyl	$C_{18}H_{16}N_2O_2$-290	141	86	4.5
3c	3,4-dimethoxyphenyl	$C_{18}H_{16}N_2O_2$-320	156	86	4
3d	3,4,5-trimethoxyphenyl	$C_{19}H_{18}N_2O_3$-350	117	88	4
3e	4-chlorophenyl	$C_{16}H_{11}N_2Cl$-294.5	96	84	3
3f	2-furanyl	$C_{14}H_{10}N_4O$	122	82	4

Table 3. Biological screening results of compounds (3a-f) Zone of Inhibition (mm).

Compd.	Anti-Fungal			Anti-Bacterial		
	C. albicans	*A. niger*	*E.coli*	*K. pneumonia*	*K. pneumonia*	*P. aeruginusa*
3(a)	19	15	17	9	16	15
3(b)	12	10	12	8	14	12
3(c)	18	13	13	10	16	12
3(d)	-	-	14	9	15	10
3(e)	17	12	15	10	17	15
3(f)	16	10	13	8	16	17
Standard Diflucan	18	16	-	-	-	-
Standard Coffrioxane	-	-	20	24	21	23

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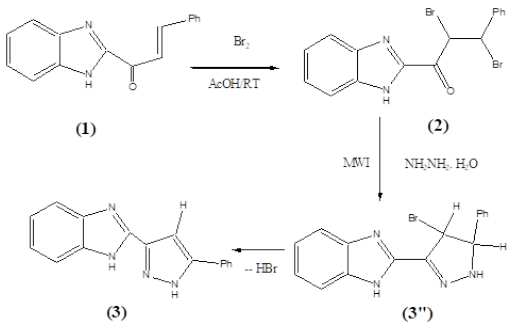

Scheme 1. Reaction of Chemicals.

The products obtained were identified on the basis of their analytical, spectral data, CO-TLC and MP (Table 1). It indicates that in MWI method the reaction can be completed with good yields and lesser time (Table 2).

Antimicrobial activity: Newly prepared compounds were screened for their antifungal against *Candida albicons* and *Aspergillus niger* and antibacterial against *E. coli*, *P. aeruginusa*, *B. subtilis* and *K. pneumoniae in vitro* at a concentration 300 mg/ml. Standard drugs used were diflucan and coffrioxane respectively. The screening results have been shown in Table 3.

CONCLUSION

The newly synthesized compounds gave agreeable elemental data. In comparison to the conventional method, microwave induced synthetic procedure showed the considerable rate enhancement bringing down the reaction time from hours to minutes with improved yields. Therefore, this method has offered new vistas towards simplification of laboratory technique without the use of standard organic laboratory peripherals such as reflux condenser, stirrer etc. Solid phase-solvent free microwave induced method was preferred over liquid phase method as it eliminates the use of hazardous and costly solvents. This method is economic, easy and eco-friendly and forms the part of green chemistry.

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