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MICROWAVE ASSISTED SYNTHESIS AND BIOLOGICAL EVALUATION OF FLOUROSUBSTITUTED BENZIMIDAZOLE DERIVATIVES

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ABSTRACT

In the present study, a series of benzimidazole derivatives were synthesized in domestic microwave oven as well as by conventional procedures. These benzimidazole derivatives were also screened for insecticidal activity by MES (maximum electroshock) method. Most of these biologically active compounds were free of toxicity in irritation, sensitivity and immunology. The structures of all synthesized compounds have been determined by FTIR and ^{1}H NMR spectral methods.

Key words: Synthesis, Benzimidazole, Insecticidal activity, Microwave, NMR Spectroscopy, IR spectroscopy, Mass spectroscopy.

INTRODUCTION

Numerous papers dealing with the applications of microwave technology in organic synthesis have been published. Since the original works of chemists,[1,2] now microwave heating is commonly used to accelerate thermal reactions (or) control the kinetics of such synthesis. The utilization of mono mode systems led the microwave beam to be focused on the sample and the application of these ovens should be favoured inspite of being more expensive. Benzimidazole is a very potent nucleus, having various important biological activities. From the literature, it was concluded that benzimidazole derivatives had many activities viz. insecticidal, herbicidal, antiirucidal etc. and variety of industrial applications. In the present investigation, we have attempted to synthesize some biologically active imidazole derivatives by microwave method.

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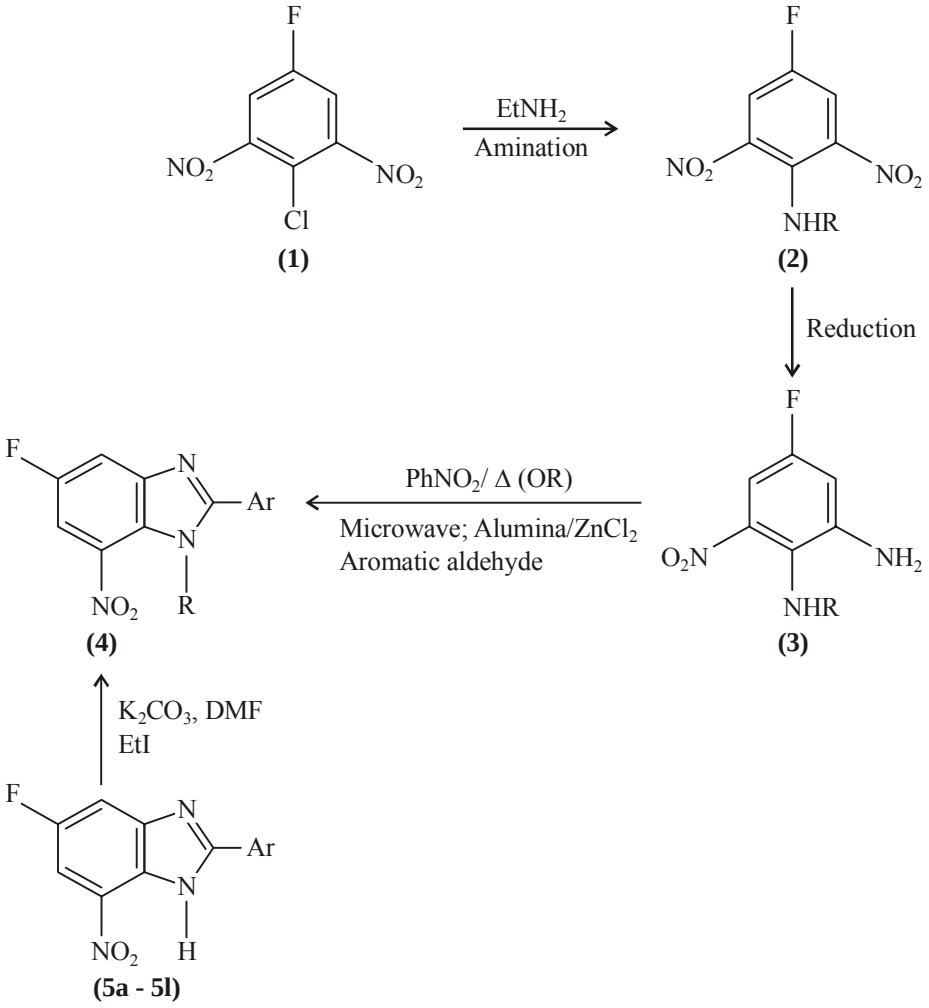
EXPERIMENTAL

Microwave system MG-607 APR is a domestic oven, which was used in synthesis of benzimidazole derivatives. The reaction is given in **Scheme 1**. All melting points (m.p.) were



Where R = –H or – C_2H_5

Scheme 1: Synthesis of benzimidazole derivatives

determined in open capillaries on Jindal melting point apparatus and are uncorrected. The purity of the compounds were routinely checked by thinlayer chromatography (T.L.C.) using silica gel. G (Merck). The instrument used for spectroscopic data are I.R. Jasco IR-470

spectrophotometer (KBr) with diffuse reflectance method : JEOL SX 102 mass spectrometer was used for running mass spectra by using Argon/Xenon (6kv, 10mA) as the FAB gas and m-nitrobenzyl alcohol as the matrix. ^{1}H NMR were recorded on, JEOL GSX-400, 200 MHz spectrometer in $CDCl_3$ taking TMS (Tetramethlysilane) as an internal standard. ^{1}H NMR, I.R. and mass spectra were consistent with the assigned structures. Analytical data of all campounds are given in Table 1.

Table 1: Physical characterization of flourine substituted benzimidazoles

Compd.	Ar	Molecular formula	M.P (^{o}C)	Time (min)		Yield (%)	
				Micro-wave	Thermal	Micro-wave	Thermal
5a	4-Methoxyphenyl	C_7H_7O	235	3	110	71	63
5b	Phenyl	C_6H_5	215	3	120	82	80
5c	4-N,N-Dimethyl phenyl	$C_8H_{10}N$	202	3	120	86	66
5d	4-Flourophenyl	C_6H_4F	210	3	120	84	75
5e	4-Chlorophenyl	C_6H_4Cl	208	3	120	90	58
5f	4-Methylphenyl	C_7H_7	218	3	120	86	68
5g	3-Methoxyphenyl	C_7H_7O	229	3	120	80	71
5h	4-Nitrophenyl	$C_6H_4N_2O$	> 260	3	120	87	63
5i	Naphthyl	$C_{10}H_8$	> 260	3	120	82	60
5j	4-Hydroxyphenyl	C_6H_5O	> 260	3	120	87	80
5k	2-Flourophenyl	C_6H_4F	215	3	120	82	68
5l	Furyl	C_4H_3O	205	3	120	81	65

Synthetic procedure for flourosubstituted benzimidazole derivatives

The starting materials 4-chloro-3,5-dinitroflourobenzenes were prepared by a known procedure and all other reagents were obtained from commercial sources. 3,5-Dinitro 4-chloro-flourobenzene (3 g, 11 mmoles) was dissolved in benzene (15 mL), and 70%

ethylamine (or liquid ammonia for amination) solution was added with constant stirring at room temperature for 4 hours. The reaction mixture was allowed to settle in two layers. The organic layer was separated and concentrated. The obtained solid was washed with water, filtered and dried to give compound (2 g). To a solution of sodium sulphide (2.7 g, 10 mmole) in water (20 mL), sodium carbonate (0.86 g, 10 mmole) was added with stirring. To the homogeneous mixture, methanol (30 mL) was added. The separated solid sodium carbonate was filtered and filterate was preserved. To this, a solution of 3,5-dinitro-4-ethylaminoflourobenzene (1.5 g, 5 mmole) in methanol (10 mL) was added and heated at 70^{o}C for 10 min. The aqueous methanol was removed under reduced pressure and the residue was poured on to ice. The solid was dried and recrystallised in aqueous methanol to give the compound **(3)**. A mixture of diammine (2.0 g, 10 mmole), aromatic aldehyde and anhydrous $ZnCl_2$ (0.13 g, 1 mmole) was adsorbed on alumina; transferred into a tube and subjected to microwave irradiation for 3 min. in a domestic oven. For the cyclization of Schiff's base (10 mmole) and anhydrous $ZnCl_2$ (0.15 g, 1 mmole) were adsorbed on alumina and heated for 1 min in a microwave oven. The solid was cooled to room temperature, extracted with EtOH and filtered. Column chromatrgraphy was used to get the corresponding aryl benzimidazoles. In conventional procedure, compound **(3)** (0.07 g, 0.25 mmoles) and 4-methoxy benzaldelyde (0.08 g 0.5 mmoles) were dissolved in nitrobenzene (6 mL) and heated at 160^{o}C for 1 ½ hour. The reaction mixture was cooled and diluted with pentane. The separated compound was filtered, washed with pentane, dried and purified by passing through a column of silica gel using dichloromethane as eluant to give 1,2-disubstituted benzimidazole **(4)**. To a solution of compound (0.1 g, 3 mmole) in dry dimethylformamide (5.2 g), potassium carbonate (0.52 g, 30 mmole) and ethyl iodide (0.08 g, 50 mmole) was added. The mixture was heated at 120^{o}C for 15 hours. This reaction mixture was poured on to the crushed ice and on filtration, a solid compound i.e second isomer of compound **(4)** was obtained. It is an alternate method instead of following ethyl amine route on compound **(1)**, to get our targeted molecule i.e second isomer of compound **(4)**. Results are given seperately as **(5a-l)** series.

Spectroscopic data

(5a) 2-(4-Methoxyphenyl)-5-flouro-7-nitrobenzimidazole

IR (KBr/cm^{-1}) : 3390, 1645, 1524, 1339, 1291, **^{1}H NMR ($CDCl_3$) :** δ 3.9 (s, 3H, -OCH_3), 7.1 (d, 2H, ArH), 8.1 (d, 2H, Ar-H), 8.3 (s, 1H, Ar-H), 8.4 (s, 1H, Ar-H) 10.7 (s, 1H, - NH), **Mass (EI m/z) :** 287, 268, 222.

(5b) 2-(phenyl)-5-flouro-7-nitrobenzimidazole

IR (KBr/cm^{-1}) : 3384, 1645, 1524, 1338, 1290, **^{1}H NMR ($CDCl_3$) :** δ7.6 (m, 3H, Ar), 8.2 (m, 2H, Ar), 8.4 (s, 1H, Ar), 8.5 (s, 1H, Ar), 10.9 (s, 1H, NH), **Mass (EI m/z) :** 257, 238, 192, 105, 77

(5c) 2-(4-N,N-Dimethyl)-5-flouro-7-nitrobenzimidazole

IR (KBr/cm^{-1}) : 3350, 1606, 1520, 1330, 1291, **^{1}H NMR ($CDCl_3$) :** δ3.1 (s, 6H, CH_3), 6.8 (d, 2H, Ar-H), 8.0 (d, 2H, ArH), 8.2 (s, 1H, Ar-H) 8.4 (s, 1H, Ar-H), 10.6 (s, 1H,-NH), **Mass (EI m/z) :** 300, 281, 235

(5d) 2-(4-Flourophenyl)-5-flouro-7-nitrobenzimidazole

IR (KBr/cm^{-1}) : 3394, 1645, 1524, 1339, 1291, **^{1}H NMR ($CDCl_3$) :** δ 7.2 (d, 2H, Ar-H), 8.2 (d, 2H, Ar-H), 8.5 (s, 1H, Ar-H), 8.6 (s, 1H, Ar-H), 13.2 (1H, -NH), **Mass (EI m/z) :** 275, 237, 191

(5e) 2-(4-Chlorophenyl)-5-flouro-7-nitrobenzimidazole

IR (KBr/cm^{-1}) : 3392, 1644, 1523, 1335, 1290, **^{1}H NMR ($CDCl_3$) :** δ 7.2 (d, 2H, Ar-H), 8.2 (d, 2H, Ar-H), 8.4 (s, H, Ar-H), 8.5 (s, H, -Ar-H), 10.8 (s, 1H, -NH), **Mass (EI m/z) :** 291, 272, 237, 191

(5f) 2-(4-Methyl))-5-flouro-7-nitrobenzimidazole

IR (KBr/cm^{-1}) : 3357, 1608, 1520, 1332, 1292, **^{1}H NMR ($CDCl_3$) :** δ 2 (Ar-H), 3 (s, 3H, -$CH_{3),}$7.4 (d, 2H, Ar-H), 8.1 (d, 2H, Ar-H), 8.4 (s, 1H, Ar-H), 8.5 (s, 1H, Ar-H), 10.8 (s, 1H, -NH), **Mass (EI m/z) :** 271, 252, 206

(5g) 2-(3-Methoxyphenyl)-5-flouro-7-nitrobenzimidazole

IR (KBr/cm^{-1}) : 3390, 1640, 1534, 1337, **^{1}H NMR ($CDCl_3$) :** δ 3.9 (s, 3H, -OCH_3), 7.1 (s, 1H, Ar-H), 7.4 (s, 1H, Ar-H), 7.5 (m, 2H, Ar-H), 8.4 (s, 1H A Ar-H), 8.6 (s, 1H, Ar-H), 10.8 (s, 1H, NH), **Mass (EI m/z) :** 287, 268, 222

(5h) 2-(2-Nitrophenyl)-5-flouro-7-nitrobenzimidazole

IR (KBr/cm^{-1}) : 3393, 1645, 1525, 1339, **^{1}H NMR ($CDCl_3$) :** δ 7.9 (m, 2H, Ar- H), 8.1 (m, 2H, Ar-H), 8.4 (s, 1H, Ar-H), 8.5 (s, 1H, Ar-H), 11.2 (s, 1H, -NH), **Mass (EI m/z) :** 302, 283, 237

(5i) 2-Naphthyl-5-flouro-7-nitrobenzimidazole

IR (KBr/cm^{-1}) : 3390, 1640, 1520, 1500, 1340, 1290, **^{1}H NMR ($CDCl_3$) :** δ 7.7 (m, 4H, Ar-H), 8.0 (m, 2H, Ar-H), 8.2 (d, 1H, Ar-H), 8.5 (d, 1H, Ar-H), 8.9 (d, 1H, Ar-H), 10.9 (s, 1H, -NH); **Mass (EI m/z) :** 307, 288, 242

(5j) 2-(4-Hydroxyphenyl)-5-flouro-7-nitrobenzimidazole

IR (KBr/cm^{-1}) : 3390, 3310, 1645, 1523, 1340, **^{1}H NMR ($CDCl_3$) :** δ 6.9 (d, 2H, Ar-H), 8.4 (m, 4H, Ar-H), 9.9 (s, 1H, -OH) 13.0 (s, 1H, -NH), **Mass (EI m/z) :** 273, 254, 208

(5k) 2-(2-Flourophenyl)-5-flouro-7-nitrobenzimidazole

IR (KBr/cm^{-1}) : 3384, 1643, 1524, 1339, 1290, **^{1}H NMR ($CDCl_3$) :** δ 7.2 (m, 1H, Ar-H), 7.4 (m, 1H, Ar-H),7.6 (m, 1H, Ar-H), 8.4 (s, 1H, Ar-H), 8.5 (s, 1H, Ar-H), 8.6 (m, 1H, Ar-H), 11.3 (s, 1H, -NH), **Mass (EI m/z) :** 275, 237, 191

(5l) 2-Furyl-5-flouro-7-nitrobenzimidazole

IR (KBr/cm^{-1}) : 3384, 1640, 1520, 1337, 1288, **^{1}H NMR ($CDCl_3$) :** δ 6.9 (s, 1H, Ar-HH), 7.9 (s, 1H, Ar-H), 8.2 (d, 2H, Ar-H), 13.1 (s, 1H, -NH), **Mass (EI m/z) :** 247, 228, 182

Biological activity

Biopharmacological features of flourobenzimidazoles have attracted considerable attention of many major pharmaceutical companies as an incredible number of new congeners have appeared. All the synthesized compounds have been screened for insecticidal activity. Some of them show promising activity. The enhanced therapeutic efficiency and improved pharmacological properties on incorporated fluorine group has been considered as most lipophilic of all common substituents. The change of lipophilicity in a given substrate may often be the main source of an enhanced bioactive efficiency. The lipophilicity and biological activity is due to high electronegative nature of fluorine, which alters the chemical reactivity and physical properties with the advantage of some synthetic and industrial values.

RESULTS AND DISCUSSION

The synthesized benzimidazole derivatives were physicochemical by characterized and the obtained results are given in Table 1. All the compounds gave the characteristic I.R. bands that proved the presence of particular functional groups. Mass spectroscopy ascertained the molecular weight of the synthesized compounds. Benzimidazole derivatives

showed the molecular ion peak at equivalent to molecular weight of proposed compound. Hence, m/z value confirms the molecular weight of respective synthesized compounds. As per the analytical data obtained, the presence of aromatic (Ar-C-H) unit with two heteroatom (N-C-N) and fluorine (C-F) was confirmed in all the compounds. An absorption at 3384 cm^{-1} clearly indicates the formation of product. A multiplet for ^1H NMR was observed at 8.2 and 7.6. A signal for H ortho to F and para to NO_2 groups was observed at 8.4 as singlet. A signal for H ortho to NO_2 and F was obtained at δ 8.5. Signal of NH proton of benzimidazole was found at δ 10.9.

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