International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.2, No.2, pp 860-864, April-June 2010

Microwave Assisted Synthesis and Antimicrobial Activity OF Some Schiff's Bases

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ABSTRACT: Microwave assisted synthesis, a green chemistry approach, is nowadays widely practiced in the synthetic laboratories. In the present work, some Schiff's bases were synthesized using microwaves. They were purified and characterized by means of spectral data and subsequently subjected to the *in vitro* antibacterial activity against few pathogenic strains of microbes. It was observed that para-substituted compounds like **4e, 4f** and disubstituted compound **4d** exhibited good activity against almost all the organisms.
KEYWORDS: 2-Methyl benzimidazole, Microwave synthesis, Schiff's base, antibacterial.

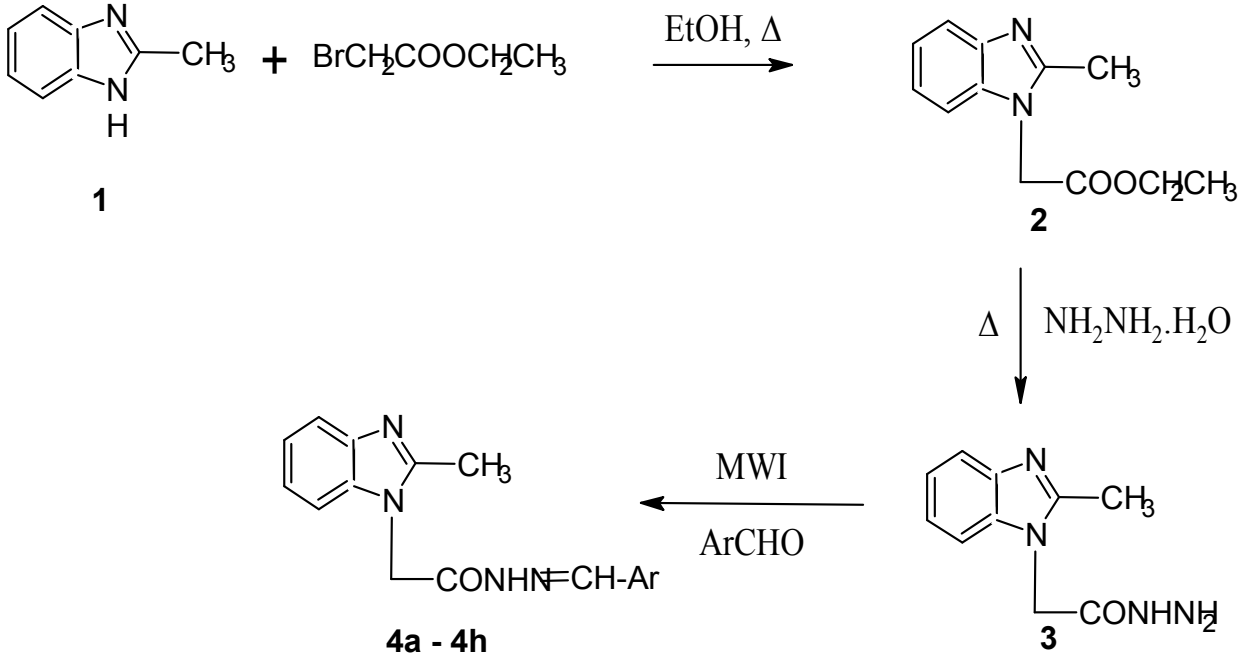
INTRODUCTION

Heterocyclic compounds constitute about sixty-five percent of organic chemistry literature. From straight chain aliphatic to branched to cyclic to aromatic, attention is currently paid to heterocyclic moieties, which are essential to life. Benzimidazoles are five membered benzoheterocyclic compounds containing two heteroatoms. Benzimidazoles (aryl and alkyl substituted) have wide variety of reported activities especially, antimicrobial, antitumor, antiviral, antifungal, antioxidant and antiulcer activity.[1-5]

2-Methyl benzimidazole has a large aromatic group substituted to the imidazole ring causing hydrophobic hydration effect, manifesting is an enhancement of the solvent structure. Recent investigation of ruthenium (III) complexes as potential anti-cancer drugs which are promising as an alternative to already applied platinum complexes, are in clinical examination.[6] The cytotoxicity of 2-methyl benzimidazole derivatives was investigated against a variety of cell lines where, introduction of various heterocyclic rings at the position 5 of 2-methyl benzimidazole led to the discovery of potent antitumor derivatives.[7-8] Traditionally organic reactions are heated using an external heat source and therefore transferred by conductance. This is comparatively slow and inefficient method for transferring energy into the system because it depends on thermal conductivity of the various material that must be penetrated and results in increasing the temperature of the reaction vessel being higher than that of the reaction mixture. By contrast microwave irradiation produces efficient internal heating by direct coupling of microwave energy with polar molecules.[9-10]

Schiff's bases possess important activities such as antimicrobial, analgesic, anti-inflammatory, anti - convulsant [11], antifungal [12] and anticancer activity.[13-14]

SCHEME OF SYNTHESIS:



1 **2** **3** **4a - 4h**

RESULTS AND DISCUSSION

All the titled compounds were synthesized in quantitative yield. The structure of compound **2** was confirmed by its analytical and spectral data. The IR spectrum showed strong absorption bands at 2987 and 2936 cm^{-1} due to Ar-CH str. at 1743 cm^{-1} characteristic for CO str of ester, at 1636 cm^{-1} equivalent to C=N str. Then, the compound **2** was reacted with hydrazine hydrate to yield the acetohydrazide **3**. The IR spectrum revealed strong absorption bands at 3305 cm^{-1} equivalent to –NH str, at1664 cm^{-1} due to CO str. of amide. The target compounds **4a-4h** were obtained by reaction with different aromatic aldehydes in presence of catalytic amount of glacial acetic acid under microwaves. It was noted that time required for microwave assisted synthesis was less and yield was optimum against conventional synthesis. *In vitro* antibacterial activity against few pathogenic strains of microbes revealed that para-substituted compounds like **4e, 4f** and disubstituted compound **4d** exhibits good activity against almost all the organisms.

MATERIALS AND METHODS:

All chemical like ethyl bromoacetate, hydrazine hydrate, various aldehydes, and solvents were purchased from S.D. Fine Chem. India Ltd. Mumbai. Solvents were used after distillation throughout this work. Melting points were determined by open capillary methods on a 'Veego' VMP-D apparatus and are uncorrected. TLC was done using silica gel G plates of size 3x8 cm (Sigma-Aldrich) and visualized by UV or in an iodine chamber. Column chromatography wherever necessary was performed on a neutral silica column (2.5 x 45 cm) using appropriate eluent. The IR spectra (KBr) were determined on FTIR 8400S, SHIMADZU spectrometer and the values are expressed in cm^{-1}. Mass spectra were recorded on Thermo Fisher Scientific Mass Spectrometry Instruments and ^1H NMR was recorded at 400 MHz in either $CDCl_3$ or DMSO-d_6 solvents using TMS as an internal reference standard. Elemental analyses were carried out on a THERMOQUEST EA-1112 elemental analyzer at IIT, Mumbai. Microwave synthesis was carried out using Catalyst Microwave System, Pune having power level in the range of 1-9 at 140-700 watt.

Synthesis of ethyl-2-(2-methyl-1H-benzimidazol-1-yl)-acetate (2):

In a mixture of 2-Methyl benzimidazole (**1**, 12.2g, 0.10 mole) and dry anhydrous K_2CO_3 (5 g) in ethanol (40 mL) was added ethyl bromoacetate (20.16 g, 0.12 mole). The reaction was refluxed till complete conversion took place, which was monitored by TLC. It took approx. 20-22 h.The reaction mixture was then cooled to room temperature and filtered to remove K_2CO_3. Solvent was removed under vaccum and residue thus obtained was recrystallised from methanol to yield the product. Yield 84 %, m.p. 112-114^{0}C, IR (KBr, cm^{-1}): 2987, 2936 (Ar-CH *str*); 1743 (CO *str)*; 1636.52 (C=N *str*); 1382(CO *bend*); 748 (CH *bend*).

Synthesis of 2-(2-methyl-1H-benzimidazol-1-yl)-acetohydrazide (3):
Ethyl-2-(2-methyl-1H-benzimidazol-1-yl)-acetate (**2**, 21.8g, 0.10 mole) was dissolved in 25 mL of ethanol and to this solution, hydrazine hydrate (7.5g, 0.15 mole) was added. This mixture was refluxed for 8-10 h, concentrated under vaccum and cooled. The residue was poured into ice cold water to yield white precipitate. It was filtered and washed twice with ice cold water and dried. Yield 85 %, m.p.160-161^{0}C, IR (KBr, cm^{-1}): 3305 (NH *str*); 3047 (CH *str*); 1664 (C=O *str* amide); 1523 (C=N *str*); 1251(CO *bend*); 738-663 (CH *bend*).

General procedure for Microwave Synthesis of Schiff's bases (4a-4h):
2-(2-Methyl-1H-benzimidazol-1-yl)-acetohydrazide (**3**, 2.04g, 0.01 mole) was dissolved in 10 mL of ethanol and to this solution various aromatic aldehydes (0.012
mole) were added, in presence of catalytic amount of glacial acetic acid (2-3 mL). The resultant mixture was refluxed under microwave for 30-40 minutes and monitored by TLC. Then it was poured into ice cold water to afford the corresponding Schiff's bases. The physicochemical data of these compounds are reported in **Table 2.** The analytical data is as follows:
4a: ^{1}H NMR ($CDCl_3$): δ 9.69 (s, 1H, NH), 8.68 (s, 1H, N=CH), 7.87-7.66 (m, 4H, Phenyl of benzimidazole ring), 7.48-7.22 (m, 4H, Phenyl), 5.32 (s, 2H, NCH_2), 2.63(s, 3H, CH_3).
4b: ^{1}H NMR (DMSO-D_6): δ 11.12 (s, 1H, NH), 9.00 (s, 1H, N=CH), 7.85-7.68 (m, 4H, Phenyl of benzimidazole ring), 7.43-7.37 (m, 4H, Phenyl), 6.99-9.94 (m, 2H, NCH_2), 2.50-2.49(s,3H,CH_3).
4c: ^{1}H NMR (DMSO-D_6): δ 9.0 (s, 1H, NH), 9.09 (s, 1H, N=CH), 8.33-8.20 (m, 4H, Phenyl of benzimidazole ring), 7.84-7.40 (m, 4H, Phenyl), 7.39-7.26 (m, 2H, NCH_2), 1.25-1.33(s, 3H, CH_3).
4h: ^{1}H NMR (DMSO-D_6): δ 11.68 (s, 1H, NH), 8.01 (s, 1H, N=CH), 7.87-7.60 (m, 4H, Phenyl of benzimidazole ring), 7.50-7.02 (m, 4H, Phenyl), 5.32 (s, 2H, NCH_2), 2.63(s, 3H, CH_3).
4a: M/S: m/z (Rel .Int. %): 293 (M+1, 100%); 294 (M+2, 20%).
4g: M/S: m/z (Rel .Int. %): 336 (M+1, 100%), 171, 143.

ANTIBACTERIAL ACTIVITY:
All compounds were screened *in vitro* for their antibacterial activity against *E. coli, S. aureus, S. typhii* and *P. aeruginosa* using cup-plate agar diffusion method .[15] DMSO was used as standard and the activity is expressed as zone of inhibition in mm. It is reported as the average of three readings.

Table 1: Substitutions on titled compounds (4a-4h)

Compound	Ar
4a	Phenyl
4b	2-Hydroxyphenyl
4c	2-Chlorophenyl
4d	3-Methoxy-4-Hydroxyphenyl
4e	4-Hydroxyphenyl
4f	4-Methoxyphenyl
4g	3-Nitrophenyl
4h	Cinnamyl

Table 2: Physiochemical data of titled compounds (4a-4h):

Compd.	Mol. Formula (Mol. Wt.)	% Yield	M.P. (^{0}C)	IR (KBr, cm^{-1})
4a	$C_{17}H_{16}ON_4$ (292)	84	204-207	3236 (NH *str*); 3029, 2920 (CH *str*); 1693 (CO *str*); 1614 (C=N *str*); 1527 (NH *bend*); 1392 (CO *bend*); 759,692 (CH *bend*).
4b	$C_{17}H_{16}O_2N_4$ (308)	78	210-212	3359 (OH *str*); 3218 (NH *str*); 2951 (CH *str*); 1660(CO *str*); 1623 (C=N *str*); 1571(NH *bend*); 1386(CO *bend*); 894-680(CH *bend*).
4c	$C_{17}H_{15}ON_4Cl$ (326)	85	241-243	3440, 3436 (NH *str*); 2977 (CH *str*); 1693 (CO *str*); 1564 (C=N *str*); 1471 (NH *bend*); 1394(CO *bend*); 842,757 (CH *bend*), 547 (C-Cl *str*).
4d	$C_{18}H_{18}O_3N_4$ (338)	69	247-249	3218 (NH *str*); 3074 (CH *str*); 1670 (CO *str*); 1596 (C=N *str*);1514 (NH *bend*); 1379 (CO *bend*); 827,757 (CH *bend*)
4e	$C_{17}H_{16}O_2N_4$ (308)	60	231-233	3218 (NH *str*); 3074 (CH *str*); 1677 (CO *str*); 1600 (C=N *str*); 1514 (NH *bend*); 1386 (CO *bend*); 827,757 (CH *bend*).
4f	$C_{18}H_{18}O_2N_4$ (322)	52	135-138	3359 (OH *str*); 3230 (NH *str*); 3153, 2923 (CH *str*); 1693 (CO *str*); 1606 (C=N *str*); 1515 (NH *bend*); 1396 (CO *bend*); 827,759 (CH *bend*).
4g	$C_{17}H_{15}O_3N_5$ (334)	55	243-245	3232 (NH *str*); 3083 (CH *str*); 1695 (CO *str);* 1614(C=N *str*); 1527 (NH *bend*); 1450(NO *bend*); 1267 (CO *bend*); 734,675 (CH *bend*).
4h	$C_{19}H_{18}ON_4$ (318)	71	236-238	3053(NH *str*), 2914, 2777 (CH *str*); 1697 (CO *str*); 1558 (C=N *str*); 1510 (NH(CO *str*); 1558 (C=N *str*); 1510 (NH *bend*); 1388 (CO *bend*); 844,744, 696 (CH *bend*).

Table 3: Antimicrobial activity of titled compounds (4a-4h):

Compd.	Zone of inhibition in mm			
	E. Coli	***S. aureus***	***S. typhi***	***P. aeruginosa***
4a	17	17	14	15
4b	15	12	16	15
4c	20	14	18	16
4d	25	24	20	22
4e	22	23	27	24
4f	26	25	23	23
4g	20	18	17	15
4h	11	12	16	13
Streptomycin	27	26	26	25
DMSO	-	-	-	-

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