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AN EFFICIENT MICROWAVE ASSISTED SYNTHESIS OF SOME NOVEL 1, 4 DIZEPINE DERIVATIVES AS POSSIBLE ANTIMICROBIAL AGENTS

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ABSTRACT

The reaction of 2-acetyl benzimidazoles (1) with substituted aldehydes(2) in methanol in presence of base afforded corresponding benzimidazolyl chalcones (3) which on treatment with ethylenediamine afforded the title compound (4) under MWI condition. The newly synthesized compound have been characterized on the basis of their elemental analysis and spectral data. Compounds (4) were screened for the antibacterial and antifungal activity in vitro. Results showed that all the compounds possess promising activity.

Keywords: Benzimidazole, ethylenediamine, antibacterial, antifungal.

INTRODUCTION

Benzodizepine are well known CNS depressant agents and constitute an important area of research for the treatment of traumatic conditions. 1,4 dizepines are heterocyclic rings exhibiting a vide variety of pharmacological activities. Benzimidazole derivatives have evoked considerable attention in recent years as these are endowed with a wide range of pharmaceutical activities like antifungal[1], antihypertansive[2], antioxidant[3], cardiotonic[4], antithrombiotic[5], HIV-IPR inhibitor[6], IL-1 inhibitor[7], anticonvasulent[8], antihepatitis B and C and antiviral activity[9].

A number of benzimidazole derivative have been described for their chemotherapeutic importance[10-15].

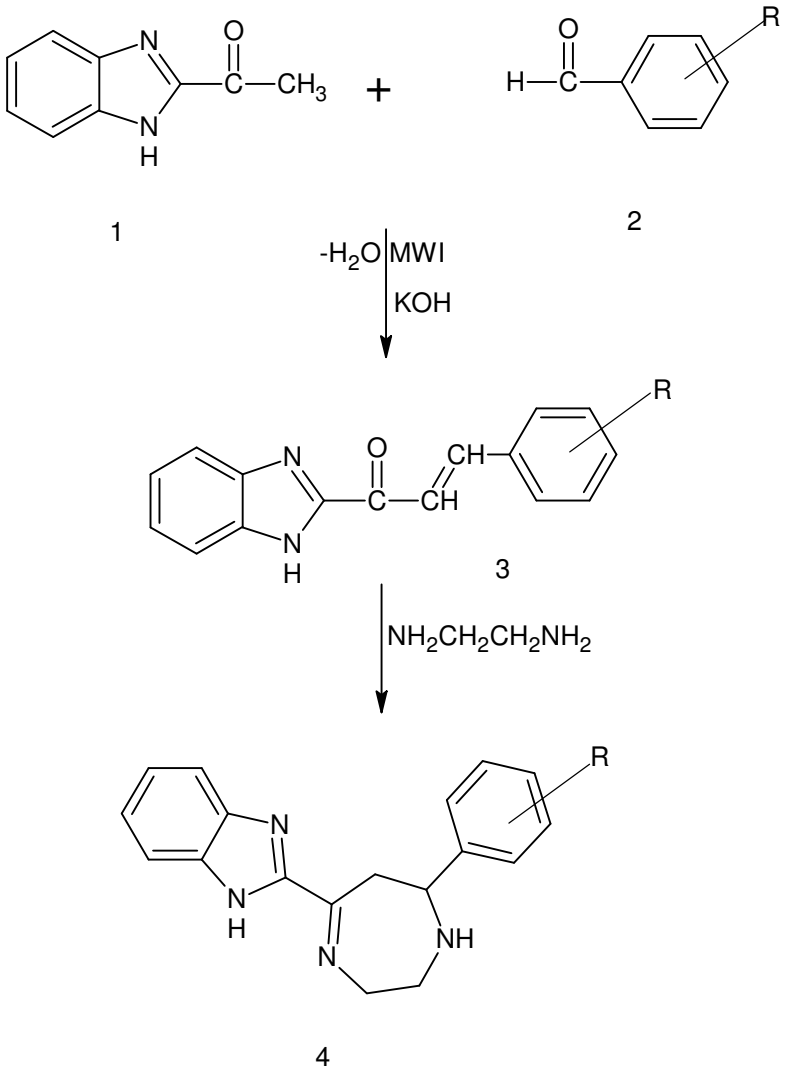
Thus, either synthesis of this heterocyclic nucleus or its incorporation into an established pharmacophore system like benzodiazepine is of continuing interest and has been the aim of the present investigation.

Microwave assisted organic enhancement is now a well established technique for synthesis of various carbon-hetero atom bonds. Almost all thermally driven can be accelerated by microwaves. Several advantages [16-20] such as shorter reaction time, cleaner products, easy workup, selectivity of products and synthesis under solvent free solid phase condition makes this procedure environmentally begin and hence it become a part of green chemistry.

Led by above fact and our continuous interest in synthesis of new benzimidazole derivatives herein we report the synthesis of some diazepine derivatives using bezimidazolyl chaclone as synthon. Substituted benzimidazole on treatment with substituted aldehyde under MWI offords[21] benzimidazolyl chalcone.

EXPERIMENTAL

All the melting points reported are uncorrected and were taken in open capillaries. The purity of newly synthesized compounds and progress of reaction was checked by TLC using silica gel G as adsorbent and benzene – ethyle acetate as eluent. IR spectra (KBr, ν cm^{-1}) were recorded on Perkin-Elmer 1600 spectrophotometer. ^1H NMR spectra were taken on brucker DRX - 600 spectrophotometer using TMS as internal standard and $CDCl_3$ as solvent. Mass spectra were recorded on Jeol-SX-DA 600 mass spectrometer using m-nitrobenzylalcohol as matrix. All the transformation were carried out in domestic microwave oven (Samsung 1630N, output 800 watt, 2450MHz).



Scheme-1

MWI Process

Synthesis of benzimidazolyl chalcones (3a-f)

A solution of substituted benzimidazole (0.01 mol) and appropriately substituted aldehyde (0.02 mol) in methanol were taken in a beaker. Potassium hydroxide was added in 4.0 gm and the reaction mixture was subjected to microwave oven over for 30 seconds to 2 minutes at 300 watts power. After completion of reaction as indicated by TLC, the reaction mixture was cooled to RT, poured in ice cold water, the products obtained was filtered washed with water and recrystillization from methanol to get analytical samples of (3a-f).

Synthesis of 2-(7-phenyl-2,2,6,7-tetra hydro-1H-1,4-dizepine-5-yl)-1H-benzimidazole(4a-f)

An ultimate mixture of chalcone (3a-f) (0.001 mol) and ethylenediamine (0.001) was subjected to microwave irradiation for 4 to 6 min at 800 watts and then cooled to RT. The products was recrystallized by methanol or acetone to get analytical samples of (4a-f).

Conventional process

Synthesis of benzimidazolyl chalcone (3a-f)

Solution of substituted benzimidazole (0.01mol) and substituted aldehyde (0.02mol) in methanol were taken in flask. Potassium hydroxide 4.0 gm was added and the reaction mixture refluxed for 3-4 houres on

water wath. After completion of reaction the mixture was cooled RT. It was poured in ice cold water, filtered, washed and recrystillised with methanol or acetone to get analytical sample of (3a-f).

Synthesis of 2-(7-phenyl-2,2,6,7-tetra hydro-1H-1,4-dizepine-5-yl)-1H-benzimidazole(4a-f)

Benzimidazole chalcone (3a-f) (0.001mole) and ethylenediamide (0.001mol) were dissolved in methanol 30ml and reaction mixture was for refluxed for 8 to 10 hours on water bath. It was then cooled at RT. The product obtained was recrystallized from methanol or acetone to get analytical samples of (4a-f).

RESULTS AND DISCUSSION

The reaction of substituted benzimidazolyl chalcones with ethylenediamine afforded 2-(7-phenyl-2,2,6,7-tetra hydro-1H-1,4-dizepine-5-yl)-1H-benzimidazoles (4a-f) by both MWI and conventional methods. The identify of newly prepared dizepines was established on the basis of their elemental analysis and spectral data.

1-(Benzimidazol-2-yl) -3- phenyl prop-2-en-1- one (3a):

IR (KBr): 3264-3444 (N-H str.), 3080 (C-H Str., Ar-H), 1667 (C=O Str.), 1597 cm^{-1} (C=N Str.); ^1H NMR ($CDCl_3$): δ 9.32 (S, 1H, NH), 7.8-7.1 (m,9H, Ar-H), 5.6 (d,1H, =CH-Ar)

1-(Benzimidazol-2-yl) -3(-4 methoxy phenyl) prop-2-en-1- one (3b):

IR (KBr): 3400 (N-H str.), 1654 (C=O Str.), 1575 (C=N Str.), 1088 cm^{-1} (C=O Str.); ^1H NMR ($CDCl_3$): δ 9.08 (S, 1H, NH), 7.88-7.32 (m,8H, Ar-H), 5.57 (d,1H, =CH-Ar) 3.3(S,3H, OCH_3).

1-(Benzimidazol-2-yl) -3[-4 (dimethylamino) phenyl] prop-2-en-1- one (3f):

IR (KBr): 3430 (N-H str.), 2913 (C-H Str., CH_3), 1663 (C=O Str.), 1601 cm^{-1} (C=NStr.); ^1H NMR ($CDCl_3$): δ 9.21 (S, 1H, NH), 7.79-7.27 (m,8H, Ar-H), 5.61 (d,1H, =CH-Ar) 3.19 (S,6H, $N(CH_3)_2$).

2-(7-Phenyl-2,3,6,7-tetrahydro-1*H*-1,4-diazepin-5-yl)-1*H*-benzimidazole (4a):

IR (KBr): 3070 (N-H), 1500 (C=N); ^1H NMR ($CDCl_3$): δ 6.0 (d, 1H, C_2-H), 7.35 (d,1H,C_3-H), 6.05-7.3 (m,11H, Ar-H),3.76 (S, 1H, NH)

2-[7-(4-Methoxyphenyl)-2,3,6,7-tetrahydro-1*H*-1,4-diazepin-5-yl]-1*H*-benzimidazole (4b):

IR (KBr): 3092 (N-H), 1490 (C=N), 1260 (C-O); ^1H NMR ($CDCl_3$): δ 6.15 (d, 1H, C_2-H), 7.37 (d,1H,C_3-H), 6.15-7.24 (m,11H, Ar-H),3.75 (S, 1H, NH), 3.95 (S,3H,OCH_3)

2-[7-(3,4-Dimethoxyphenyl)-2,3,6,7-tetrahydro-1*H*-1,4-diazepin-5-yl]-1*H*-benzimidazole (4c):

IR (KBr): 3095 (N-H), 1495 (C=N), 1270 (C-O); ^1H NMR ($CDCl_3$): δ 6.10 (d, 1H, C_2-H), 7.30 (d,1H,C_3-H), 6.12-7.24 (m,9H, Ar-H),3.75 (S, 1H, NH), 3.98 (S,9H,2X-OCH_3)

2-[7-(3,4,5-Trimethoxyphenyl)-2,3,6,7-tetrahydro-1*H*-1,4-diazepin-5-yl]-1*H*-benzimidazole(4d):

IR (KBr): 3060 (N-H), 1490(C=N), 1215 (C-O); ^1H NMR ($CDCl_3$): δ 6.22 (d, 1H, C_2-H), 7.25 (d,1H,C_3-H), 6.11-7.23 (m,8H, Ar-H),3.76 (S, 1H, NH), 3.96 (S,9H,3X-OCH_3)

2-[7-(4-Chlorophenyl)-2,3,6,7-tetrahydro-1*H*-1,4-diazepin-5-yl]-1*H*-benzimidazole (4e):

IR (KBr): 3075 (N-H), 1490 (C=N), 780 (C-Cl); ^1H NMR ($CDCl_3$): δ 6.04 (d, 1H, C_2-H), 7.28 (d,1H,C_3-H), 6.08-7.16 (m,10H, Ar-H),3.78 (S, 1H, NH)

2-[7-(4-Dimethylamniophenyl)-2,3,6,7-tetrahydro-1*H*-1,4-diazepin-5-yl]-1*H*-benzimidazole (4f):

IR (KBr): 3090 (N-H), 1485 (C=N), 1110 (C-N); ^1H NMR ($CDCl_3$): δ 6.12(d, 1H, C_2-H), 7.36 (d,1H,C_3-H), 6.24-7.28 (m,10H, Ar-H),3.80 (S, 1H, NH), 2.46(S,6H,$N(CH_3)_2$)

The mass spectra of these compounds gave molecular ion peaks corresponding to their molecular masses.

Table-1: Physical data of compounds 3 and 4.

Compd	R	Molecular Formula	MP	Yield		Reaction Time	
			°c	Conv	MWI	Conv(Hrs)	MWI(min)
3a	H	$C_{16}H_{12}N_2O_1$(248)	205	77	82	4.0	3.0
3b	4-OCH_3	$C_{17}H_{14}N_2O2$(278)	225	75	80	4.3	3.2
3c	3, 4-OCH_3	$C_{18}H_{16}N_2O3$(308)	212	76	85	4.1	3.0
3d	3, 4,5-OCH_3	$C_{19}H_{18}N_2O4$(338)	217	73	84	4.2	3.5
3e	4-Cl	$C_{16}H_{11}N_2O_1Cl$(282)	224	75	85	4.4	3.1
3f	4-$N(CH_3)_2$	$C_{18}H_{17}N_3O_1$(291)	260	73	80	4.2	3.3
4a	H	$C_{18}H_{18}N_4$(290)	101	70	72	8.0	4.2
4b	4-OCH_3	$C_{19}H_{20}N_4O$(320)	110	68	70	9.0	4.4
4c	3, 4-OCH_3	$C_{20}H_{22}N_4O_2$(350)	130	65	69	8.3	4.3
4d	3, 4,5-OCH_3	$C_{21}H_{24}N_4O_3$(380)	91	70	75	8.4	4.1
4e	4-Cl	$C_{18}H_{17}N_4Cl$(324.5)	98	75	84	9.0	3.5
4f	4-$N(CH_3)_2$	$C_{20}H_{23}N_5$(333)	135	67	72	10.0	4.5

Antimicrobial activity

Newly synthesized compounds were screened for their antibacterial against E.coli, P. pseudomonas, B.subtilis, K. pneumoniae and antifungal activity agents Candida albicans and Aspergillus niger in vitro at a concentration 500 µg/ml. Standard drug used were cefuroxacin and Fluconazole respectively. The screening results have been tabulated in Table-2.

Table-2: Biological Screening results compounds 4 Zone of inhibition (mm)

Compd	Antibacterial				Antifungal	
	E. coli	K. pneumoniae	B. subtilis	P.pseudononas	Candida Albicans	Aspergillus Niger
4b	29	25	30	32	12	14
4c	25	18	17	25	13	12
4d	20	22	26	26	14	13
4e	33	25	24	27	13	16
4f	27	20	28	26	14	13
Standard Drug Cifuroxacin HCl	40	40	40	40	-	-
Standard Drug Fluconazole	-	-	-	-	30	30

CONCLUSION

All the transformation were carried out microwave irradiation method under solvent less condition which lead to considerable time saving better yields and environmentally benign procedure. The solvent less condition diminish the problem of waste disposal and is eco friendly. Some of synthesized compounds have shown promising antimicrobial activity.

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