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Some Transformations of Benzimidazolyl Chalcones Using MAOS Protocol- A Green Approach

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ABSTRACT

Benzimidazolyl Chalcones(1) were treated with isonicotinoyl hydrazide (1NH) to afford N^1 isonicotinoyl -3-benzimidazolyl -5- aryl -2- pyrazolines(2). Reactions of (1) with ethyl acetoacetate in presence of basic alumina gave 6-Carb-ethoxy-3-benzimidazolyl-5-aryl cyclohexenones(3) which on treatment of hydrazine hydrate gave 6-benzimidazolyl-4-aryl 3-oxo-2,3,4,5 tetrahydro-1H-indazoles(4). All the transformations were carried out under microwave assisted condition. The synthesized compounds were screened for their antimicrobial activity in vitro.

Keywords: Benzimidazole, Isoniazid, Hydrazine Hydrate, Antibacterial, Antifungal.

INTRODUCTION

The Chalcones are one of the most useful Michael acceptors and versatile synthons. Their reaction with Michael adducts gave resulted Michael adducts which becomes to be interesting intermediate for the synthesis of a large number of heterocyclic systems with diverse biological activities [1-11].

The chalcones undergo Michael type of reactions with ethyl acetoacetate [12] to afford a variety of products [13-19] depending on the experimental conditions. The reactions when carried out in presence of piperidine [20], anhydrous k_2co_3 and dry acetone [21] results cyclohexenone derivatives which on treatment with hydrazine hydrate can be converted into corresponding indazoles.

The indazole derivatives exhibit a variety of pharmacological activities such as anti-inflammatory [22,23] antidepressant [24] antitumor [25] antihypertensive [26] antiviral [27] and anticancer [28] activities.

Pyrazoline derivatives have been studied intrusively because of their easy accessibility, diverse chemical reactivity and variety of industrial application various 2-pyrazoline derivatives have been effectively utilized as antimicrobial, anticonvulsant, cardiovascular, anti-inflammatory and antidepressant agent [29-33].

The combination of solvent free protocol with microwave irradiation can be carried out to synthesize a variety of compounds [34,35] within a shorter reaction period & with enhanced yields, its comparison to conventional heating method. It is an easy efficient eco-friendly and economic process and turned to be e-chemistry.

Keeping in mind above facts it was decided to transform benzimidazolyl chalcones into some new pyrazole and indazole derivatives is an attempt to prepare new biodynamic compounds.

MATERIALS AND METHODS

Experimental: Starting material and reagents were procured from commercial chemical suppliers. All the chemicals used in the synthesis were of analytical grade. Melting points reported are uncorrected and were taken in open capillaries. The IR spectra (KBr, υ cm^{-1}) were recorded on a Perkin Elmer Spectrometer, PMR spectra($CDCl_3$ or DMSO-d_6, υ ppm) were taken on Brucker DRX -600 Spectrometer using TMS as internal standard and Mass spectra(FAB, m/z %) were taken on Jeol-SX-600 Mass spectrometer using m-nitrobenzyl alcohol as matrix. The matrix peaks were observed at m/z 136,137,154,289 and 307. The purity of compounds and progress of the reaction was checked by TLC using silica gel-G as absorbent. All the transformations were carried out in a domestic microwave oven (Samsung 1630 N output 800 watt 2450 MHZ frequency).

Method

The title compounds were prepared in the following steps:

(A) Conventional Method:-

(i) Synthesis of N^1 isonicotinoyl-3- benzimidazolyl -5- aryl -2- pyrazolines (2a-f)

Benzimidazolyl chalcone (0.01 mole) and isonicotinoyl hydrazide (0.012 mole) were dissolved in ethanol the reaction mixture was refluxed for 5-7 hours and left at room temperature. The solid separated was filtered washed with ice cold water and crystallization from benzene,ethyl acetate as colourless crystals of (2a-f) in 70-75% yield.

(ii) Synthesis of 6-carb ethoxy-3-benzimidazolyl -5-aryl cyclohexenones (3a-f)

To a solution of benzimidazolyl chalcone (0.01 mole) in ethanol (20ml) was added ethyl acetoacetate (0.02 mole), piperidine (0.02 moles) and basic alumina (4.0 grms) were added and reaction mixture was refluxed for 6-7 hrs. The reaction was filtered off and left at room temperature. The solid separated was filtered off and crystallized from ethanol on colourless crystals of (3a-f) in 70-72% yield.

(iii)Synthesis of 6-benzamidazolyl-4-aryl3-oxo-2,3,4,5-tetrahydro-1H-Indazoles(4a-f)

To a solution of compounds (3a-f) (0.01mole) in ethanol was added hydrazine hydrate (0.015 mole). The reaction mixture was refluxed for 5-7 hrs and then left overnight at room temperature. The separated solid was filtered off, washed with water dried and crystallized from ethanol, benzene to afford analytical samples of (4a-f) in 70-72% yield.

(B) MAOS Method:-

(i) Synthesis of N^1 isonicotinoyl -3- benzimidazolyl -5- aryl -2- pyrazolines (2a-f)

Benzimidazolyl chalcone (0.01 mole) and isonicotinoyl hydrazide (0.012mole) and DMF(10ml) were mixed thoroughly to form a homogeneous paste. It was then subjected to microwave irradiation for 4-5 minutes. The reaction mixture was then cooled to room temperature, washed with ice cold water crystallised from ethanol to afford analytical sample of (2a-f) in 80-85% yield.

(ii) Synthesis of 6-carb ethoxy-3-benzimidazolyl -5-aryl cyclohexenones (3a-f)

Benzimidazolyl chalcone (0.01 mole), ethyl acetoacetate (0.02 mole), piperidine (0.02 mole) and basic alumina (4.0 gm) were mixed initially to form a slung. It was subjected to MWI for 3-5 minutes. It was then cooled and extracted with ethanol. The emergences were filtered off and filtrate obtained was left at room temperature. The solid separated was filtered off. It was recrystallised from ethanol to get the analytical samples of (3a-f).

(iii)Synthesis of 6-benzamidazolyl-4-aryl3-oxo-2,3,4,5-tetrahydro-1H-Indazoles(4a-f)

Compounds (3a-f) (0.01mole) and hydrazine hydrate (0.015 mole) were mixed thoroughly and the residue was subjected to MWI for 4-6 minutes. After completion of reaction the residue obtained was crystallised from ethanol to get analytical samples of (4a-f).

Characterization of newly synthesized compounds

(i) Characterization of synthesized compounds (2a-f):

The IR spectra of compounds (2) gave absorption bands at 3015-2930 cm^{-1} (-CH Stret), 1680-1635 cm^{-1} (-NC=O and C=N combined vibration) and 3240-3200 cm^{-1} (NH of benzimidazole ring). The PMR Spectra of these compounds gave signals at δ 2.92–3.01(dd, 1H, C_4-H_A), δ 3.42–3.50 (dd, 1H, C_4-H_B) and δ 4.89–4.94 (dd, 1H, C_5-H_X) confirming the presence of ABX pattern of pyrazoline ring system. A multiplet δ 7.90–8.70 was observed for aromatic protons where as a singlet at δ 9.50 for NH protons of benzimidazolyl ring was also obtained.

(ii) Characterization of synthesized compounds (3a-f):

The IR spectra of compounds (3) gave absorption bands at 3280-3240 cm^{-1} (-NH of benzimidazole), 3060-2920 cm^{-1} (-CH Stret), 1725-1700 cm^{-1} (>C=O of ester), 1645-1600(>C=O ketonic of cyclohexeanone ring and C=N combined vibration) 1450-1430 (CH deformation). The PMR spectra of the compounds (3) gave signals at υ 2.55–2.60 (dd, 1H, C_4-H_A), 3.37-3.40 (dd,1H, C_4-H_B), 3.51-3.54 (m,1H, C_5-H_C), 3.81-3.82(d,1H, C_6-H_d), υ 6.30(S1H, C_2), of cyclohexenone ring and a singlet at 9.92 for NH of benzimidazole ring. A triplet for methyl protons of -OCH_2CH_3 was obtained at δ 1.1-1.3 and a quartret at δ 4.1-4.2 for methylene proton was also observed.

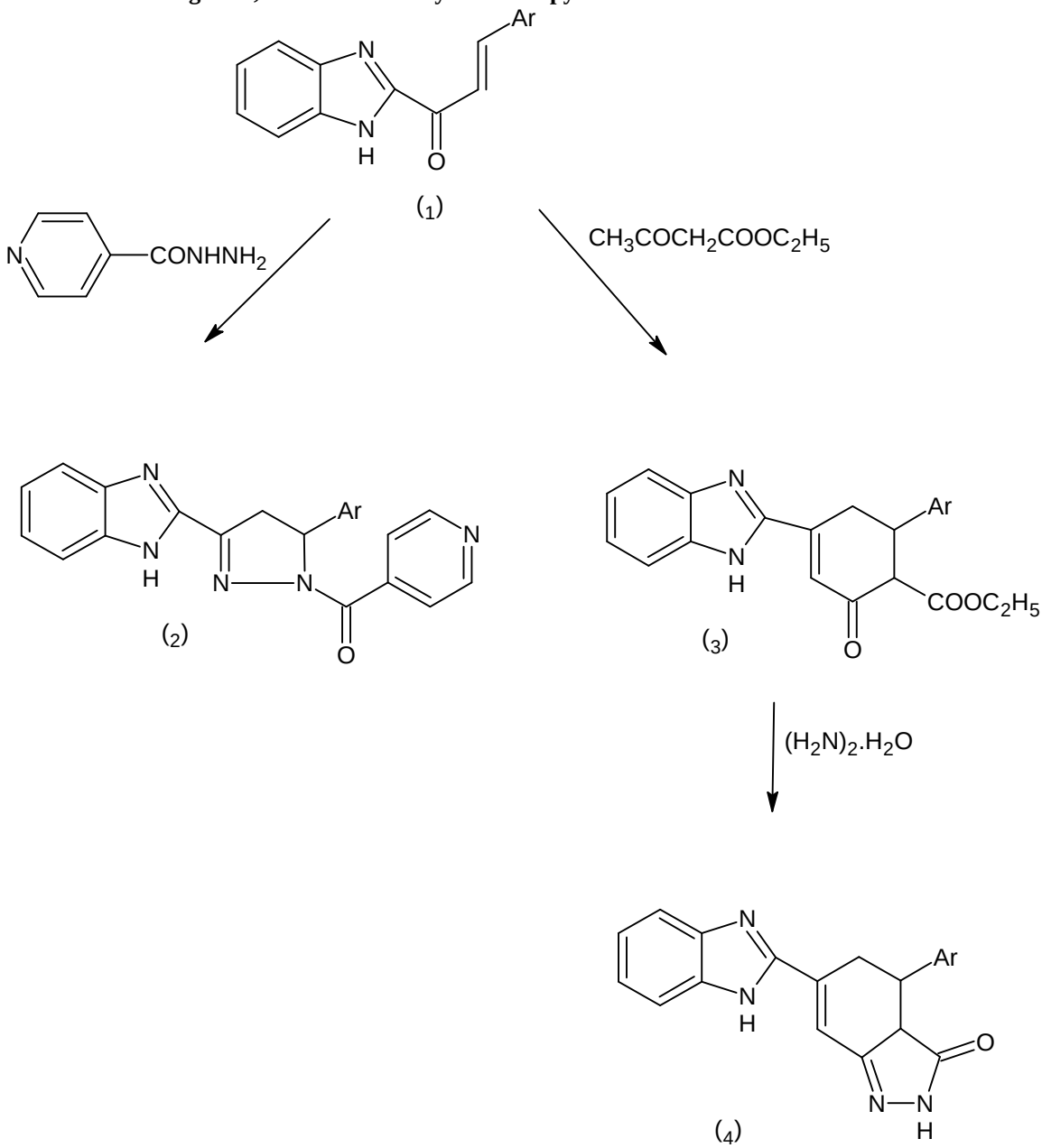
(iii) Characterization of synthesized compounds (4a-f):

The IR spectra of compounds (4) gave absorption bands at 3240-3200 cm^{-1} (-NH of benzimidazole), 2930-2860 cm^{-1} (-CH stretching), 1660-1650 cm^{-1} (>C=O) and 1490-1440 cm^{-1} (C=N and N-N combined vibration).The PMR spectra of compounds (4) gave signals at δ 2.47–2.44 (dd, C_5-H_a), 2.94-2.99 (dd, C_5-H_b), 3.31-3.34 (a, C_3-H), 3.72– 3.76 (m, C_4-H), and 6.76 (S, C_2-H) of indazole system.

The mass spectra of compounds (2), (3) and (4) gave molecular ion peaks corresponding to their molecular masses. A comparison of MAOS protocol with conventional heating method reveals that the founded method is superior in the terms of higher yields, cleaner products, shorter

reaction time and easy work up and is a safe rapid and economic process. Physical data of synthesized compounds are presented in table 1&2.

Figure 1, Scheme for the synthesis of pyrazole & indazole derivatives



Antimicrobial activity

All the synthesized compounds were tested for their antibacterial and antifungal activity in vitro by disc diffusion method at a concentration of 500 µg/ml, with two gram positive bacteria S. aureus, B. subtilis and two gram negative bacteria E. coli, P. aeruginosa and fungal species like C. albicans, A. niger organisms. Cifuroxacin HCl was used as a standard drug for antibacterial screening and fluconazole was used as a standard for antifungal screening. All the synthesized compound exhibited moderate antibacterial activities and significant antifungal activities. DMSO was used as a diluents which not effected the growth of microbes. The screening results have been tabulated in table 3.

RESULTS AND DISCUSSION

N^1-Isonicotinoyl -3 benzimidazolyl-5-aryl -2- pyrazolines (2) and 6- benzimidazolyl -4- aryl 3-oxo- 2,3,4,5 tetrahydro-1H indazoles (4) were synthasized by both MAOS and conventional heating methods. The products obtained by both the methods were identified on the basis of their analytical, spectral data, CO-TLC and MP.

Table 1- Physical and analytical characterization data of compounds (2a-f), (3a-f)&(4a-f)

Compd	Ar	Molecular Formula	Molecular Wt.	MP	%N	
				°c	Cal	Found
2a	Phenyl	$C_{22}H_{17}N_5O$	367	159	19.07	19.12
2b	4-methoxy phenyl	$C_{23}H_{19}N_5O_2$	397	240	17.63	17.69
2c	3, 4-dimethoxy phenyl	$C_{24}H_{21}N_5O_3$	427	243	16.39	16.44
2d	3,4,5 trimethoxy phenyl	$C_{25}H_{23}N_5O_4$	457	249	15.31	15.36
2e	4-chloro phenyl	$C_{22}H_{16}N_5OCl$	401	238	17.45	17.49
2f	4-dimethyl amino phenyl	$C_{24}H_{22}N_6O$	410	190	20.48	20.53
3a	Phenyl	$C_{22}H_{20}N_2O_3$	360	226	07.77	07.84
3b	4-methoxy phenyl	$C_{23}H_{22}N_2O_4$	390	254	07.17	07.01
3c	3, 4-dimethoxy phenyl	$C_{24}H_{24}N_2O_5$	420	248	06.66	06.96
3d	3,4,5 trimethoxy phenyl	$C_{22}H_{26}N_2O_6$	450	232	06.22	06.09
3e	4-chloro phenyl	$C_{22}H_{19}N_2O_3Cl$	395	244	07.09	06.98
3f	4-dimethyl amino phenyl	$C_{24}H_{25}N_3O_3$	403	240	10.42	10.11
4a	Phenyl	$C_{20}H_{16}N_4O$	328	220	17.07	16.98
4b	4-methoxy phenyl	$C_{21}H_{18}N_4O_2$	358	206	15.64	15.42
4c	3, 4-dimethoxy phenyl	$C_{22}H_{20}N_4O_3$	388	196	14.43	14.40
4d	3,4,5 trimethoxy phenyl	$C_{23}H_{22}N_4O_4$	418	160	13.39	13.21
4e	4-chloro phenyl	$C_{20}H_{15}N_4OCl$	362	256	15.46	15.16
4f	4-dimethyl amino phenyl	$C_{20}H_{21}N_5O$	347	188	20.17	19.87

Table 2 – Comparative % yield & Rxn time

Compd	% Yield		Rxn Time	
	Conv.	MAOS	Conv (Hrs.)	MAOS (Min)
2a	73	84	7.0	5.0
2b	76	83	6.5	5.0
2c	74	84	6.5	4.5
2d	75	84	7.0	5.0
2e	74	82	7.0	4.5
2f	74	82	6.5	5.0
3a	72	82	7.0	3.0
3b	71	82	6.5	4.5
3c	72	81	6.5	4.0
3d	72	80	6.5	4.5
3e	71	82	7.0	5.5
3f	70	80	7.1	5.0
4a	70	83	6.5	4.5
4b	71	84	6.0	4.5
4c	71	84	6.0	5.0
4d	72	85	6.0	5.5
4e	71	82	6.5	5.5
4f	70	80	7.0	6.0

Table 3- Antimicrobial study of synthesized compounds (2a-f) & (4a-f)

Compd	Ar	Zone of inhibition in mm diameter					
		Anti- bacterial Activity				Anti-fungal Activity	
		Gram (-) ve		Gram (+) ve			
		E. coli	*P. aeruginosa*	*S. aureus*	*B. subtilis*	*C. albicans*	*A. niger*
2a	Phenyl	25	22	29	23	13	12
2b	4-methoxy phenyl	22	23	24	23	17	14
2c	3, 4-dimethoxy phenyl	20	20	26	22	14	13
2d	3,4,5 trimethoxy phenyl	21	24	21	21	13	15
2e	4-chloro phenyl	24	22	31	20	12	14
2f	4-dimethyl amino phenyl	23	21	28	22	15	16
4a	Phenyl	28	25	27	25	20	21
4b	4-methoxy phenyl	26	23	25	27	18	19
4c	3, 4-dimethoxy phenyl	25	27	28	23	21	17
4d	3,4,5 trimethoxy phenyl	27	24	23	26	21	20
4e	4-chloro phenyl	29	22	29	25	19	22
4f	4-dimethyl amino phenyl	26	25	26	24	23	20
S. drug	Cifuroxacin HCl	40	40	40	40	-	-
S. drug	Fluconazole	-	-	-	-	30	30

Benzimidazolyl chalcones(1) were condensed with isonicotinoyl hydrazide(1NH) to afford N^1-Isonicotinoyl 3-benzimidazolyl -5- aryl -2- pyrazolines(2), condensation of (1) with ethyl acetoacetate in presence of piperidine gave Michael adduct 6-carb-ethoxy-3-benzimidazolyl -5-aryl –cyclohexenones (3) which were treated with hydrazine hydrate to get corresponding indazoles(4). All the transformations were carried out using MAOS Protocol. For the sake of comparison the transformation were also carried out using conventional heating method.

CONCLUSION

In conclusion, an efficient, solvent free and facile one pot synthesis of substituted pyrazole & indazole derivatives from benzimidazolyl chalcone under microwave irradiation has been presented. The method is simple and requires less time for competition, making the method eco-friendly and it is felt that it is a valuable addition/alternative to the existing methods. All the newly synthesized compounds showed moderate to good potency against different bacterial strains.

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