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Microwave Assisted Synthesis, Spectral Studies and Antibacterial Activity of 1, 5-benzodiazepines Derivatives on a Solid Surface†

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Chalcones are well known intermediates for synthesizing various heterocyclic compounds. They have been utilized for the synthesis of various substituted benzodiazepines by the reaction of *o*-phenylenediamine. In present investigation we have carried out the reaction under both conventional method and microwave assisted organic synthesis technique in presence of basic alumina. The procedure lead to improved efficiency of basic alumina, better conversion within shorter period, clean, efficient, safe methodology with higher selectivity, yield and purity of compounds in comparision to conventional methods. The structures of compounds are supported by spectral and analytical data. The structure-activity relationships of synthesized compounds have also been studied.

Key Words: Microwave irradiation, Solid-phase synthesis, Antibacterial activity.

INTRODUCTION

Recently microwave radiation has gained the attention of chemists due to its unique advantages, such as shorter reaction times, cleaner reaction products, higher yields and better selectivity, being a valuable alternative to accomplish more efficient syntheses of a variety of organic compounds with a considerable simplicity of operation and milder reaction conditions, when combined with the solvent-free approach, as it provides an opportunity to work with open vessels[1,2]. Keeping in view of these findings, herein we describe a simple and convenient method for the synthesis of chalcones under microwave irradiation in solvent free environment, with improved yields and short reaction time.

Chalcones having an α,β-unsaturated carbonyl system is one of the most useful Michael acceptor and undergo Michael type nucleophillic addition followed by intramolecular cyclization and aromatization resulting a large number of heterocyclic and cyclic potentially useful system. Benzodiazepines and its derivatives constitute an important class of heterocyclic compounds which possess a wide range of therapeutic and pharmacological properties. Derivatives of benzodiazepines are widely used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive and hypnotic agents[3]. Diazepines which are a seven membered heterocyclic compounds, having two nitrogen atoms at various positions in the ring, with a maximum degree of unsaturation (*i.e.* a total of three double bonds) are classified on the basis of the positions of nitrogen atoms. Numbering is done in such a way that the least possible number is given to the second nitrogen atom. Fusion of aromatic system to diazepine system results in benzodiazepines, dibenzodiazepines and pyrimidobenzodiazepines, *etc*.

EXPERIMENTAL

All melting points were determined in open capillaries on electrically heated metal blocks and are uncorrected, IR spectra (KBr, ν_{max}, cm^{-1}) were recorded on a Perkin-Elmer 16 pc (FTIR) spectrophotometer. Mass spectra were taken on a Jeol D-300 (EI) and VG-70S mass spectrometer and ^{1}H NMR spectra on a Bruker DRX-300 (300 MHz, FT NMR) spectrometer [chemical shifts in δ (ppm) downfield from TMS using DMSO as solvent]. The reactions were carried out in unmodified microwave oven (Kenstar, Output energy 1200 W, frequency 2450 MHz model no. M69706).

Antibacterial activity: Synthesized compounds **3a-f** was screened for their antibacterial activity against gram positive (*S. aureus* and *S. fecalis*) and gram negative (*E. coli* and *P. merabillis*) bacteria,using DMF as solvent at 200 μg/mL concentration by paper disc diffusion method. The zone of inhibition after 18 h of incubation at 37 ºC was compared with the standard drugs (**3a-f**). The zone of inhibition was measured in mm. Standard drugs amicacin and linzolid for

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Gram-positive and amoxyclav and amoxycillin for Gram-negative bacteria were used as reference compound. All the compounds (**3a-f**) exhibited moderate to good activity against the test organism. Among the 1,5-benzodiazepines (**5 d,e,f**) showed good activity against *S. aureus* and *S. fecalis*. Compound (**5 d, e, f**) showed excellent activity against *E. coli*. The observed antibacterial activities have been attributed to dibromo, hydroxyl, chloro, nitro or methoxy substitution in 4-phenyl and mono/di/trimethoxy substitution in 6-phenyl group in the synthesized 1,5-benzodiazepines (Table-1).

TABLE-1
ANTIBACTERIAL SCREENING RESULTS OF SYNTHESIZED COMPOUNDS (**3a-f**)

Compd. no.	Zone of Inhibition			
	Gram positive		Gram negative	
	S. aureus	*S. Fecalis*	*E. coli*	*P. mirabiles*
3a	+	-	-	-
3b	+	+	+	-
3c	+	++	+	-
3d	++	++	+++	-
3e	+++	++	+++	-
3f	-	++	+++	-
Amicacin	++++	++++	-	-
Linzolid	++++	++++	-	-
Amoxyclav	-	-	++++	++++
Amoxycillin	-	-	++++	++++

++++ = zone size 23-30 mm, +++ = zone size 15-21 mm, ++ = zone size 8-14 mm, + = zone size 5-7 mm

Synthesis of 2,4-diaryl-2,3-dihydro-1*H*-1,5-benzodiazepine (3a-f): The synthesis of substituted chalcones was performed by the most convenient method which involves the Claisen-Schmidt condensation of equimolar quantities of a substituted acetophenone with substituted benzaldehyde in presence of base.

Conventional method: Equimolar amount (0.1 mol) of substituted chalcones and *o*-phenylenediamine (0.1 mol) was refluxed in DMF (55 mL) for 7-11 h. The progress of the reaction was monitored by TLC. Removal of the solvent under reduced pressure gave a solid which on crystallization with a mixture of acetone and petroleum ether (40-60 ºC) (2:1, v/v) afforded analytical samples.

Microwave assisted solvent phase method: A solution of chalcones (0.01 mol) and *o*-phenylenediamine (0.01 mol) in DMF (10-15 mL) was irradiated in a Pyrex conical flask (100 mL) inside the microwave oven on 35 % power (450 W) for 12-19 min, with intermittent 1 min interval after 3-4 min. The progress of reaction was monitored by TLC. The reaction mixture was further worked up as mentioned in method A to afford analytical samples.

Microwave assisted solid phase method using basic Al_2O_3: A mixture of substituted chalcone (0.01 mol) and *o*-phenylenediamine (0.01 mol) and toluene (5 mL) was adsorbed on basic alumina (5 gm) in a Pyrex conical flask and was irradiated at 50 % power for the time mentioned in Table-2. After completion of reaction was monitored by TLC. The reaction mixture was cooled at room temperature, the residue extracted with acetone (2 × 20 mL) filtered filtrate on concentration and mixed with petroleum ether (40-60 ºC), gave analytical sample of compound.

TABLE-2
COMPARISON OF REACTION TIME AND YIELDS OF COMPOUNDS (**3a-f**) UNDER CLASSICAL AND MICROWAVE ASSISTED METHODS

Comp no.	Reaction time			Yield (%)		
	Classical (h) (A)	m.w. methods (min)		Classical (A)	m.w. methods	
		B	C		B	C
3a	10	15	8	56	65	85
3b	9	16	7	55	63	75
3c	7	15	7	50	61	84
3d	8	13	7	52	64	82
3e	10	15	8	54	65	77
3f	11	18	9	51	60	72

Compound 3a: Orange crystals, m.p. 180 ºC (found: C,48.46;H,3.57;N,4.28.calcd. for $C_{24}H_{22}N_2O_5Br_2$ (578.24): C, 49.85; H, 3.83; N, 4.84 %); IR (KBr, ν_{max}, cm^{-1}): 3443-3333 (-NH str.), 3047 (=C-H), 2918, 2851 (-C-H), 1623, 1586, 1499 (C=C/C=N), 897, 749, 678 (substituted phenyl) ^{1}H NMR $^{\delta}$H (DMSO,ppm):3.98(s,Ar-C-NH), 2.98 (dd, 1H, HA, methylene), 3.08 (dd, 1H, HB methylene), 5.32 (dd, 1H, Ar-C-HX), 6.77-7.95 (m, broad and unresolved, Ar-H), 8.32, 13.40 (s.1H.OH); MS: *m/z* (%) 578 (M^+, 25), 580 (M+2, 30), 564 (10), 385 (75), 246(25), 157 (100).

Compound 3b: Pale yellow crystals, m.p. 142 ºC (found : C, 49.85; H, 3.00; N, 5.11 calcd.for $C_{21}H_{16}N_2O_3Br_2$ (504.17): C, 50.03; H, 3.20; N, 5.56 %); IR (KBr, ν_{max}, cm^{-1}): 3493-3320 (-NH str.), 3049 (=C-H), 2959, 2842 (-C-H), 1620, 1590, 1496 (C=C/C=N), 872, 763, 697 (substituted phenyl) ^{1}H NMR $^{\delta}$H (DMSO, ppm): 3.93 (s, Ar-C-NH), 2.62 (dd, 1H, HA, methylene), 3.01 (dd, 1H, HB methylene), 5.30 (dd, 1H, Ar-C-HX), 6.64-8.17 (m, broad and unresolved, Ar-H), 8.10, 13.39 (s.1H.OH).

Compound 3c: Yellow crystals, m.p. 144 ºC (Found: C, 48.02; H, 2.61; N, 5.02 calcd. for $C_{21}H_{15}N_2O_2Br_2Cl$ (522.61) : C, 48.26; H, 2.89; N, 5.36 %); IR (KBr, ν_{max}, cm^{-1}): 3489, 3390 (-NH str.), 3051 (=C-H), 2950, 2834 (-C-H), 1628, 1556, 1443 (C=C/C=N), 834, 805 (substituted phenyl) ^{1}H NMR $^{\delta}$H (DMSO, ppm): 3.99 (s, Ar-C-NH), 3.15 (dd, 1H, HA, methylene), 3.27 (dd, 1H, HB methylene), 5.25 (dd, 1H, Ar-C-HX), 6.80-8.05 (m, broad and unresolved, Ar-H), 8.38, 13.36 (s.1H.OH); MS: *m/z* (%) 522 (M^+, 30), 524 (M+2, 35), 478 (2), 384 (5), 241 (45), 153 (7).

Compound 3d: Orange crystals, m.p. 158 ºC (Found: C, 49.87; H, 3.52; N, 4.97. calcd. for $C_{23}H_{20}N_2O_4Br_2$ (548.22): C, 50.39; H, 3.68; N, 5.11%); IR (KBr, ν_{max} cm^{-1}): 3462, 3381 (-NH str.), 3048 (=C-H), 2967, 2844 (-C-H), 1623, 1501, 1414 (C=C/C=N), 852, 723, 662 (substituted phenyl) ^{1}H NMR $^{\delta}$H (DMSO, ppm): 3.89 (s, Ar-C-NH), 2.51 (dd, 1H, HA, methylene), 3.02 (dd, 1H, HB methylene), 5.32 (dd, 1H, Ar-C-HX), 6.77-8.0 (m, broad and unresolved, Ar-H), 8.60, 13.34 (s.1H.OH).

Compound 3e: Yellow crystals, m.p. 174 ºC (Found: C, 50.80; H, 3.21; N, 5.20. calcd. for $C_{22}H_{18}N_2O_3Br_2$ (518.19): C, 50.99; H, 3.50; N, 5.41%); IR (KBr, ν_{max}, cm^{-1}): 3470-3025 (-NH str.), 3072 (=C-H), 2940, 2858 (-C-H), 1626, 1598, 1508 (C=C/C=N), 894, 756, 636 (substituted phenyl). ^{1}H NMR $^{\delta}$H (DMSO, ppm): 3.99 (s, Ar-C-NH), 2.56 (dd, 1H, HA, methylene), 3.83 (dd, 1H, HB methylene), 5.23 (dd, 1H, Ar-C-HX), 6.59-8.11 (m, broad and unresolved, Ar-H), 8.62, 13.35 (s.1H.OH) ; MS: m/z (%) 518 (M^+, 20), 520 (M+2, 10), 428 (25), 384 (12), 227(8).

Compound 3f: Brown crystals, m.p. 160 ºC (Found: C, 47.01; H, 2.53; N, 7.28. calcd. for $C_{21}H_{15}N_3O_4Br_2$ (533.17): C, 47.31; H, 2.84; N, 7.88 %); IR (KBr, ν_{max}, cm^{-1}): 3475, 3317 (-NH str.), 3062 (=C-H), 2934, 2865 (-C-H), 1618, 1557, 1454 (C=C/C=N), 852, 717, 678 (substituted phenyl). ^1H NMR, $^{\delta}H$ (DMSO, ppm): 3.84 (s, Ar-C-NH), 3.27 (dd, 1H, HA, methylene), 3.34 (dd, 1H, HB methylene), 5.11 (dd, 1H, Ar-C-HX), 6.91-8.01 (m, broad and unresolved, Ar-H), 8.30, 13.32 (s.1H.OH); MS: *m/z* (%) 533 (M^+, 20), 535 (M+2, 30), 312 (10),157 (100).

RESULTS AND DISCUSSION

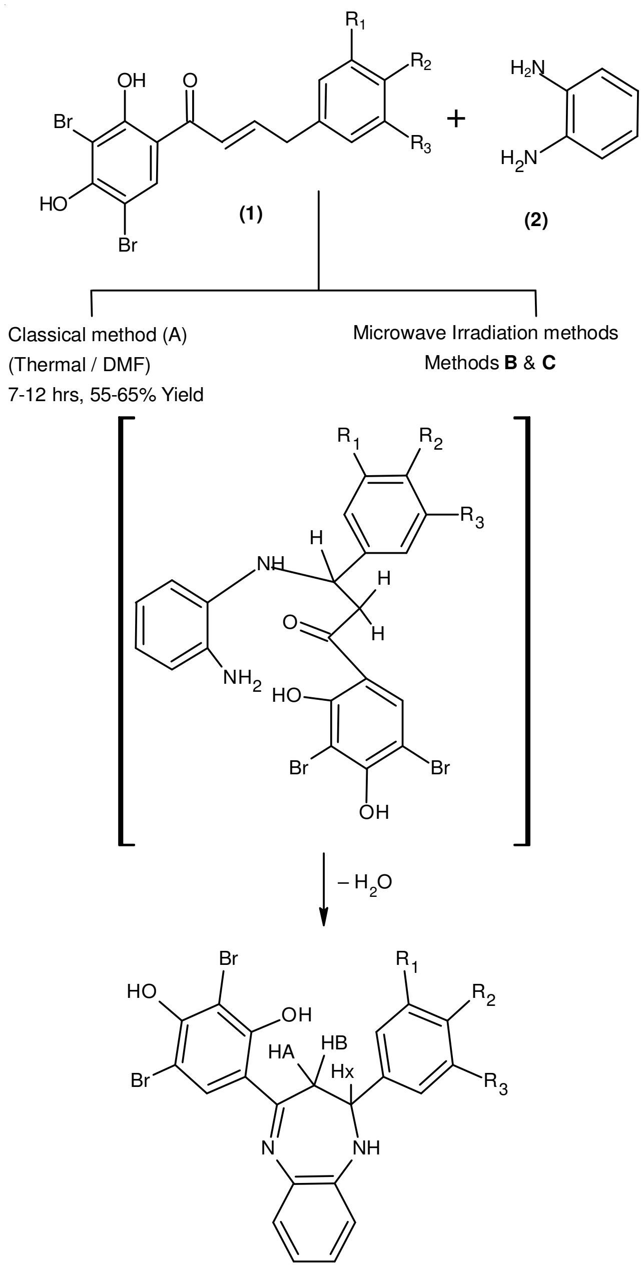
The formation of 1,5-benzodiazepines involve heterocyclization of substituted chalcones and *o*-phenylenediamine *via* conjugated Michael addition of nucleophilic $-NH_2$ group of the *o*-phenylenediamine with β-carbon atom of the chalcones followed by subsequent condensation of ortho $-NH_2$ group of the benzene ring with C=O group of the chalcones under microwave irradiation condition resulted the heterocyclic title compounds (**3a-f**) through the intermediate formation of Michael adduct in a single step (**Scheme-I**).

The structures of the synthesized compounds were established on the basis of their analytical and spectroscopic data. The IR spectra of products displayed disappearance of bands at 1650-1620 cm^{-1} due to conjugated C=O of chalcones and appearance of a band at 1620-1580 cm^{-1} due to overlap of the C=C and C=N and devoid of two peaks due to asym. and sym. stretching of NH_2 in the region 3440-3140 cm^{-1}. However in compounds (**3a-f**) due to the presence of OH group along with -NH group there was a broad band in the regions 3445-3134 cm^{-1}.

The ^1H NMR spectra of the products are characteristic of ABX pattern showing three distinct double doublets in the range of δ 2.5-5.3.The axial methylene proton (HA) of C-3 most often resonated at higher field than the geminal equitorial methylene proton (HB). Further HA and HB couples with each other to give doublets and double doublet is due to the coupling of HA and HB signals with the Hx of C-2 methine protone. Third double doublet of HX was appeared at higher d value. A broad one-proton absorption in the region above δ 3.8-4 due to NH to support the formation of 2,3-dihydro derivatives in preference to 2,5-dihydro tautomer. The molecular ion peak corresponding to molecular weight of synthesized compounds was observed along with other fragmentation pattern.

Conclusion

In conclusion, the synthesis of 2,4-diaryl-1*H*-1, 5-benzodiazepines (**3a-f**) have been carried out under conventional (thermal) and microwave irradiation solvent and solid phase condition. Microwave assisted basic alumina supported reaction resulted in improved yields with easier work up of the desired product as compares to other method. Potential significance antibacterial activity was observed with compounds **3d**, **3e** and **3f** both Gram positive and Gram negative bacteria.



(3a-f)

3a: $R_1 = R_2 = R_3 = OCH_3$; **3b:** $R_1 = R_3 = H$, $R_2 = OH$; **3c:** $R_1 = R_3 = H$, $R_2 = Cl$; **3d:** $R_3 = H$, $R_1 = R_2 = OCH_3$; **3e:** $R_1 = R_3 = H$, $R_2 = OH_3$; **3f:** $R_2 = R_3 = H$, $R_1 = NO_2$

Scheme-I

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