International Journal of Applied Chemistry.
ISSN 0973-1792 Volume 13, Number 2 (2017) pp. 369-376
© Research India Publications
http://www.ripublication.com

Highly Efficient Synthesis and Antibacterial of 1, 5-Benzodiazepines under Microwave Irradiation

Dr. Shrikrishna D. Tupare[1] and Dr. R. P. Pawar[2]

[1]K. E. S. Anandibai Pradhan Science College, Nagothane Raigad M S- India

[2]Dept. of Chemistry, Deogiri College, Aurangabad MS -India

Abstract

The chemistry and pharmacology of thiazoles and diazoles have of great importance. These are of great interest to medicinal chemists nowadays, because they are known to possess a wide range of pharmacological properties in the field of clinical research. Many methods of synthesis are found in literature. Literature survey promoted us to prepare simple, rapid and highly efficient synthesis of benzodiazepines under microwave irradiation using environmentally benign solvent methoxyethanol. The clean reactions, shorter reaction time and high yields and purity of product. All compounds were screened for their antibacterial. Among the synthesized compounds, the compounds were found to be the most active against bacterial human pathogens.

Keywords: benzodiazepines, o-phenylene diamine, Microwave irradiation, antibacterial activity.

INTRODUCTION:

Benzodiazepines and benzodiazepines have been attracted as an important class of heterocyclic compounds in the field of clinical research. These compounds are widely used as anticonvulsant[1], Antibacterial and antifungal[2-4] properties of 2, 4-diaryl, 2,3-dihydro-1,5-benzodiazepines have been reported. They also possess a wide range of pharmacological properties.[5-6] including anti-HIV[7], anticoagulant[8] and anti-allergenic[9]. The 1, 5 – benzodiazepines moiety is a privileged class of pharamacophore, as compounds bearing this structural unit possess a broad spectrum of biological activities. The common strategy for synthesis of the 1, 5 – benzodiazepines moiety is the reaction of Chalcones with o-phenylene diamine[10]. The various methods of synthesis involve use of ethanol as a solvent. Some methodologies

involve the use of inorganic solid supports such as silica gel, clay, alumina, TFA or few drops of piperidine under reflux condition or microwave irradiation. Many of these processes suffer from some limitations such as requiring harsh conditions. With these objectives it was decided to prepare some novel 1, 5]- benzodiazepines by using 6-(3-((E)-3-phenylacryloyl)phenyl amino)pyridazin-3(2H)-one earlier prepared biologically active chalcones[11] and o-phenylene diamine & few drops of piperidine in methoxy ethanol by microwave irradiation. TLC indicated formation of the products. The crude product was subjected to crystallization from benzene.

EXPERIMENTAL METHOD:

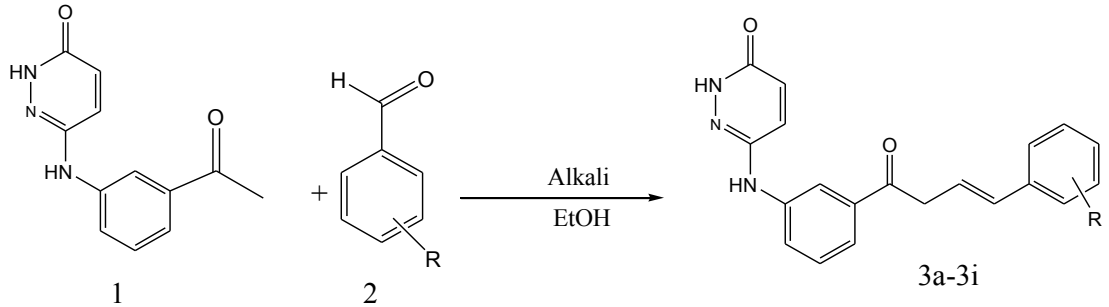
a. General: All melting points reported are uncorrected. TLC was used to monitor the progress of reactions and to test the purity of the compounds on silica gel 'G' coated glass plates with solvent system, benzene: ethanol ammonia (7:2:1), upper layer). IR spectra (KBr) were recorded a Perkin-Elmer infracord-577 spectrophotometer, 1H NMR and a Joel FT 90 MHz spectrophotometer using TMS as internal standard and mass on a Varian Match-7 instrument at 70 eV.

b. Experimental procedure for the preparation of 6-(3-((E)-4-phenylbut-3-enoyl) phenyl amino) pyridazin-3(2H)-one (Chalcones) (3a-i): Chalcones derivatives were synthesized by condensing 6-(3-((E)-4-phenylbut-3-enoyl) phenyl amine) pyridazin-3(2H)-one with various aromatic substituted aldehydes **2a-i** according to the method in the literature.[11,12]

c. Experimental procedure for the preparation 1, 5- benzodiazepines (4a-i) Equimolar quantities o-phenylene diamine (1mmol) 6-(3-((E)-3-phenylacryloyl) phenyl amino) pyridazin-3(2H)-one were dissolved in a minimum quantity of methoxyethanol (10 ml) and few drops of piperidine. The reaction mixture was irradiated in microwave oven for a period of 4-5 minutes. Reaction was monitored by thin layer, crude solid obtain, which were recrystallized from dry benzene (**4a-i**).

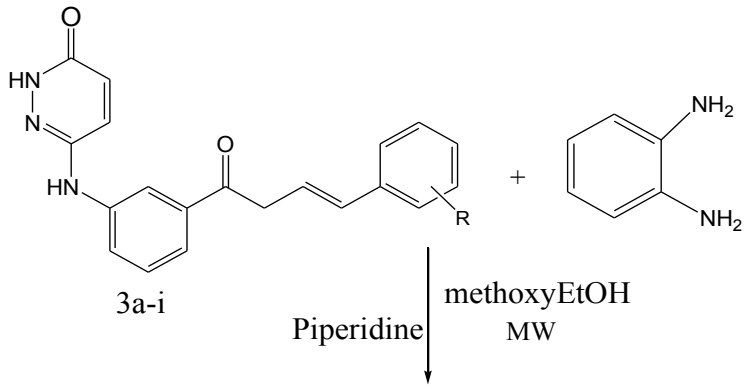
SCHEMATIC WORK:

Scheme I. Synthesis of Chalcones:



1 2 3a-3i

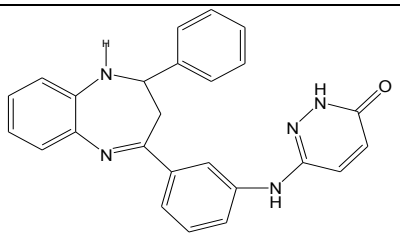
Scheme II. Synthesis of 1, 5- benzodiazepines

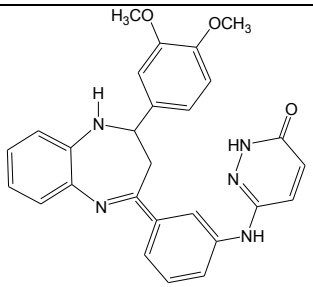
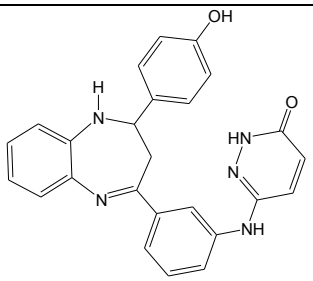
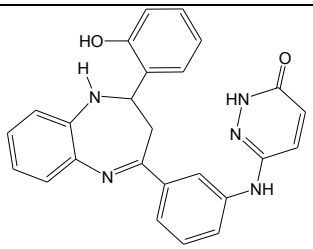
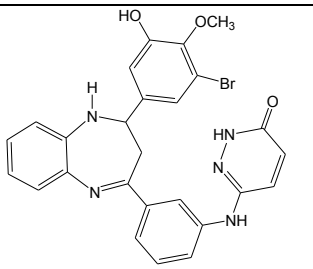
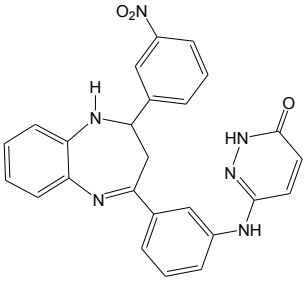


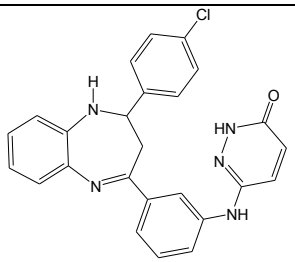
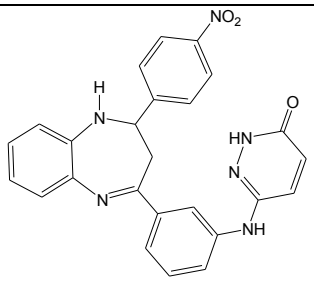
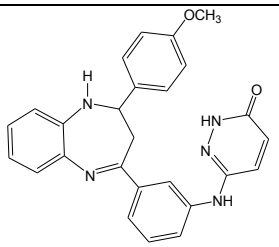
4a-i

RESULT AND DISCUSSION

Table1. Physical constants and analysis data of substituted-1, 5-benzodiazepines (**4a-i**).

Entry	Structure of Compound	**Yield[a] (%)**	**Time (Minutes)**	**M.P. (°C)**
4a		70%	4.5	194

4b		85%	4.0	218
4c		69%	5.0	191
4d		65%	5.0	185
4e		70%	4.0	192
4f		72%	4.5	182

4g		82%	5.0	205
4h		70%	5.5	170
4i		76%	4.5	215

[a] Isolated yield after column chromatography.

Under this reaction condition, a series of experiments for synthesis of 1, 5-benzodiazipines were performed with bioactive Chalcones. Various 1, 5-benzodiazepine derivatives obtained with excellent yields without formation of undesirable side products. Many of them were active against human pathogens like bacteria.

Microbial Activity: - The antimicrobial activity of these [1, 5]- benzodiazepines (4a-i) was tested by "paper disc diffusion plate method.[13,14] For the determination of antifungal activity, about 20 ml of sterilized PDA –(potato-dextrose-agar) and in case of antibacterial screening, oxoid nutrient medium was poured in each sterilized Petridis and before gelation of the media, about 2 ml of homogeneous mixture of fungi/bacteria in cool sterilize broth of potato and dextrose/beef extract and peptone respectively was mixed in each Petridis. After half an hour, when the media was gelatinized, discs of 6 mm size prepared from Whatman filter paper (No.1) thoroughly moistened with the solution of diazepines (4%) in ethylene glycol were placed over the seeded media and incubated at 32 ±1oC and 28 ±1oC for 24 hours in case of bacteria. Activity of standard antibacterial drug, penicillin was also checked under the same conditions and concentration. Solvent DMSO also tested for their antimicrobial activity and has shown no activity.

The experiments were performed in duplicate and average zones of inhibition in mm (including the size of the discs have been recorded and tabulated in Tables II).

Table II - Microbial Activity of Synthesized 1, 5-benzodiazepines

Entry	Compounds	Bacteria	
		E. Coli ATCC 8739	S. a. ATCC6538
1	4a	12mm	10mm
2	4b	7mm	8mm
3	4c	11mm	10mm
4	4d	8mm	-ve
5	4e	10mm	6mm
6	4f	9mm	7mm
7	4g	8mm	9mm
8	4h	11mm	7mm
9	4i	11.5mm	9mm
10	Penicillin	10.5mm	8.5mm

Legends –ve indicates No activity

Spectral Analysis: Spectral analysis of selected compounds is given.

i. 6-(3-((E)-2,3-dihydro-2-(3,4-dimethoxyphenyl) benzo [b][1,4] diazepin-4-yl) phenyl amino)pyridazin-3(2H)-one (4b). Yield 85%, M. P. 218^{0}C; **Time** 4 minutes; **FTIR(KBr):** 3250 (Ar. C=C Stre.), 3200 (N-H Stre.),1675,1670,(2 C=O), 2840 (OCH_3);1545(NH), ^{1}H NMR (DMSO-d_6): δ3.95 (s, 3H, -OCH_3), δ3.98 (s, 3H, -OCH_3), 7.14-7.89(m,7H, Ar-H), 6.20(s,1H,-CH of diazole),5.259s,1H,-NH), 7. 26 (d, 1H, Jα,β=16Hz, H β), 6.90-7.30(m, 5H, Ar-H), 6.63-7.95 (s, 1H, Ar-H), 6.83-6.90(d. 1H J=9.8 Hz, CH pyridazine), 7.17-7.22 (d. 1H. J=9.9Hz CH Pyridazine), 7.51-7.54 (t. 1H, NH pyridazine D_2O exchangeable); **Mass**;(m/z) ,467 Analysis (% for) $C_{27}H_{25}N_4O_3S$ **Calcd.** C, 66.92; H, 4.99; N, 18.18; O,9.91; **Found**.C,67.00; H, 5.10; N, 18.64; O,9.98;

ii. 6-(3-((E)-2, 3-dihydro-2-(4-hydroxyphenyl) benzo[b][1,4]diazepin-4-yl) phenyl amino) pyridazin-3(2H)-one (4c). Yield 69%, M. P. 191^{0}C; **Time** 5 minutes; **FTIR** (KBr): 3250 (Ar. C=C Stre.), 3215 (N-H Stre.),1672,1672,(2 C=O),

;1545(NH),630(C-S); ^{1}H NMR (DMSO-d_6): 7.14-7.89(m,7H, Ar-H), 6.20(s,1H,-CH of diazole),5.259s,1H,-NH), 7. 26 (d, 1H, Jα,β=16Hz, H β), 6.90-7.30(m, 5H, Ar-H), 6.83-6.90(d. 1H J=9.8 Hz, CH pyridazine), 7.17-7.22 (d. 1H. J=9.9Hz CH Pyridazine), 7.51-7.54 (t. 1H, NH pyridazine D2O exchangeable); 4.17(d,1 H,-OH). Mass; (m/z) ,440 Analysis (% for) $C_{25}H_{21}N_5O_2$ **Calcd.**
C, 68.12; H,4.59; N,19.82; O,7.21; **Found**.C,68.10; H, 4.61; N, 18.02; O,7.18.

iii. 6-(3-((E)-2-(4-chlorophenyl)-2, 3-dihydro-1h-benzo[b][1,4]diazepin-4-yl) phenyl amino) pyridazin-3(2H)-one (4g). Yield 82%; M. P. 205^{0}C**; Time** 5 minutes**; FTIR** (KBr): 3250 (Ar C=C Stre.), 3200 (N-H Stre.),1675(C=O), 820 (C-Cl),1543(NH), **^{1}H NMR** (DMSO-d_6): δ7.14-7.89(m,7H, Ar-H), δ6.22(s,1H,-CH of diazole), δ 5.262 (s,1H,-NH), δ 7. 42 (d, 1H, Jα,β=16Hz, H β), δ 6.90-7.30(m, 5H, Ar-H), δ 6.63-7.95 (s, 1H, Ar-H), δ 6.79-6.84 (d. 1H J=9.8 Hz, CH pyridazine), δ 7.17-7.22 (d. 1H. J=9.9Hz CH Pyridazine), δ 7.49-7.52 (t. 1H, NH pyridazine D2O exchangeable); **Mass**; (m/z) ,442 Analysis (% for) $C_{25}H_{20}ClN_5O$ Calcd. C, 65.92; H, 4.25; N,19.48; O,3.51.; **Found**.C,65.60; H, 4.50; N, 19.63; O,3.58.

CONCLUSION:

We have synthesised 1, 5- benzodiazepines by microwave irradiation method by using few drops of piperidine in methoxyethanol as a solvent. This method of synthesis has many advantages over conventional methods of synthesis, including high yield, simple work-up shorter reaction span, no side reactions. So, it represents a convenient, economic, green, highly efficient process for synthesis of 1, 5-Benzodiazepines under microwave irradiation. It also shows moderate to batter antibacterial activities.

ACKNOWLEDGEMENTS:

We are grateful to the Principal Dr. Sandesh S. Gurav, The Head Department of Chemistry, K. E. S. Anandibai Pradhan Science College, Nagothane-Raigad (MS), India for providing the laboratory facility to carry the research work. I also grateful to SAIF, IIT Bombay, Pawai Mumbai for providing spectra.

REFERENCES:

[1] A. Levai, *Trends Heterocylic Chem.*, **1995**, 4, 51.

[2] G.R. Subbanwad, M.A. Baseer and Y.B. Vibhute, *Ind. J. Pharm. Sc.,* **2002**, 264.

[3] V. M. Barot, M.R. Patel and H.B. Naik, *Asian J. Chem.,* **2001**, 13(1), 347.

[4] V.M. Barot. S.R. Modi and H.B. Naik, *Oriental J. Chem.,* **2000**,16 (3), 569 and V.M

[5] Gurav and S.V. Agarkar, *Ind. J. Chem.,* **1998**, 37B, 161-162.

[6] Bigi, F. *Tetrahedron Lett*. **2001**,42,5203
[7] Warad, D. U.; Satish. C. D.; Kulkarni, V. H.; Bajgur, C. S. *Indian J. Chem*.**2000**,39A,415.
[8] Xie,L.; Tukeuchi, Y.; Consetino, L. M.; Lee, K. *J. med. Chem*. **1999**,42, 2662.
[9] Desai. H. K.; Gawad, D. H.; joshi, B. S. *Indian J. Chem*.**1977**, 15B, 291.
[10] Bukel, D. R.; Smith, H. *J. Med. Chem.* **1975**, 18, 391.
[11] Levai, A. J. Heterocyclic Chem. **2000**, 37,199
[12] Bernstein *J, Brit Pat*, **1970**, 1 198,825 (Cl. C07d); *Chem.Abstr*,**1970**, 73, 77294.
[13] Shrikrishna D. Tupare, Satish A. Daki, Santhosh Nalge, R. P. Pawar; International J of Organic Chemistry, 2012, 2, 371-376.
[14] Grayer, R. J.; Harborne, J. B. A survey of Antifungal Compounds from Higher plants. *Phytochemistry* **1994**, 37, 19-42.
[15] Irob, O. N.; Moo-Young, M.; Anderson, W. A. Antimicrobial Activity of Annatto Extract. *Int. J. Pharm*. **1996**, 34, 87-90.