Int. J. Chem. Sci.: 7(2), 2009, 805-813

AN ULTRASONICALLY ASSISTED SOLVENT-FREE SYNTHESIS OF SOME 1, 5-BENZODIAZEPINE DERIVATIVES POSSESSING SIGNIFICANT ANTI-ANXIETY ACTION USING SILICA GEL AS A CATALYST

N. R. CHATTERJEE, B. G. CHANDAK[*a], S. S. THUBE, S. D. KULKARNI[a] and A. D. DESHPANDE

Department of Pharmaceutical Chemistry, Pad. Dr. D. Y. Patil Inst. of Pharm. Sc. and Research, PIMPRI, PUNE – 411018 (M. S.) INDIA
Siddhant College of Pharmacy, Sudumbare, PUNE – 411018 (M. S.) INDIA

ABSTRACT

An efficient method for green synthesis of some 2, 3-dihydro 1*H*-1, 5-benzodiazepine derivatives has been developed by simple cyclocondensation reaction of *o*-phenylendiamine with aromatic, cyclic and acyclic ketones as well as 1, 3-β dicarbonyl compounds in presence of catalytic amount of silica gel under ultrasound irradiation. The title compounds have been characterized by physico-chemical methods and screened for anti-anxiety activity in order to evaluate for the effectivity against diazepam as standard.

Key words: 1, 5-Benzodiazepines, o-Phenylenediamine, Ketones, 1, 3-β– Dicarbonyl compounds, Silica gel, Ultrasound irradiation, Anti-anxiety

INTRODUCTION

In recent days, great emphasis has been provided upon adopting greener methodologies in most chemical reactions; primarily due to their eco-friendly nature. Hence, the importance of ultrasound accelerated organic reactions has drawn attention of medicinal chemists because of their many fold advantages over the traditional methods. [1]

Benzodiazepines are an important class of compounds finding application as anti-inflammatory, anti-anxiety, anticonvulsant, hypnotic agents[2] and also employed as valuable synthons for the preparation of many fused heterocyclic ring system[3]. The introduction of diazepam as a tranquilizer in 1971 by Sternbach followed by many other

[*] Author for correspondence; E-mail: nitharc@yahoo.com, badri_chandak30@yahoo.co.in

psychotropic agents sharing 1, 4-benzodiazepine skeleton afforded a great impetus to synthetic studies of the isomeric 1, 5-benzodiazepine ring system. Some members of this class of compound have demonstrated an array of pharmacological properties e. g. CNS depressent, antiproliferative agent, arginine vasopressin antagonists. Furthermore 1, 5-benzodiazepines are valuable synthons for the preparation of other fused ring systems such as triazolo[4a], oxazino[4b], furano [4c] or oxadiazolo-benzodiazepines[4d].

The easy accessibility of 1, 5-benzodiazepine derivatives via cycloaddition reaction of *o*-phenylenediamine with α, β-unsaturated carbonyl compounds[5], β-haloketone[6], acyclic and cyclic ketones in presence of various catalysts viz : $CdCl_2$[7], $[(L)proline]_2Zn$[8], molecular iodine[9], BF_3-etherate[10], $NaBH_4$ [11], polyphosphoric acid-SiO_2[12], $MgO/POCl_3$ [13], Yb $(OTf)_3$[14], sulfated zirconia[15], Al_2O_3/P_2O_5[16], AcOH under microwave irradiation [17], Sc $(OTf)_3$ [18], polymer (PVP) supported ferric chloride [19], $CeCl_3$-NaI-SiO_2 [20], ionic liquid medium [21] and NBS [22] are well documented. However, majority of these reactions suffer from one or other drawbacks such as expensive reagent, low to moderate yield, longer or drastic reaction conditions leading to side reactions, tedious work-up procedure for product isolation and environmental pollution.

Hence, it was considered worthwhile to carry out a simple expeditious synthesis of 2, 3-dihydro-1*H*-1, 5-benzodiazepine derivatives because of their variety of pharmacological activity and industrial applications. In continuation of our work on green organic synthesis of pharmacologically active heterocyclic compounds [23], we report herein solvent free synthesis of some 1, 5-benzodiazepine derivatives by cyclocondensation of *o*-phenylendiamine with ketones as well as 1, 3-β-dicarbonyl compounds under eco-friendly condition using silica gel as a catalyst **(Scheme I)** and preliminary evaluation of their anti-anxiety or anti-depressent action.

EXPERIMENTAL

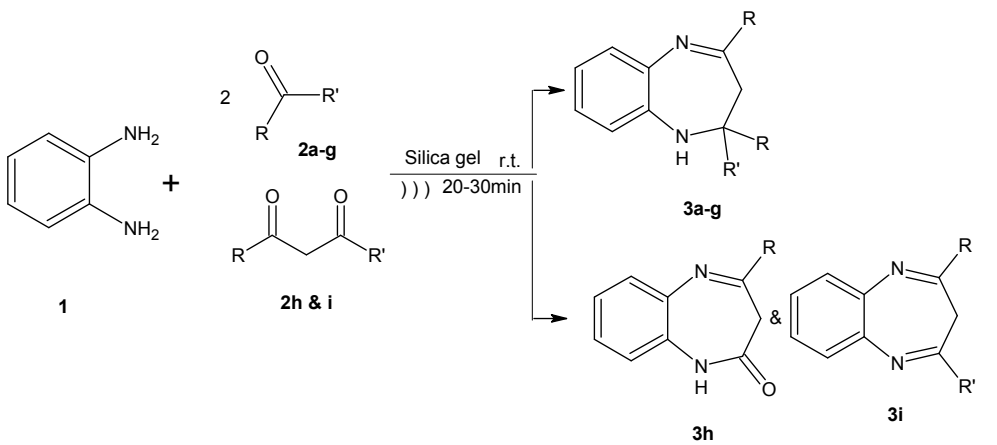
General procedure for the preparation of 1, 5-benzodiazepines

Acetophenone **(2c)** (2.6 mL, 22 mmole), o-phenylendiamine (1.08 g, 10 mmole) and silica gel (0.3 g) were taken in a 100 mL iodine flask, mixed well by gentle shaking and then stoppered. The contents of the flask were then irradiated in a sonicator bath maintaining for 25-30 min at room temperature. After completion of the reaction (confirmed by TLC) [EtOAc: pet. Ether : $CHCl_3$], chloroform (15 mL) was added in the reaction mixture and filtered to remove silica gel; which was washed twice with chloroform (3-4 mL). The combined organic layer was washed with water (4-5 mL) and

then dried over anhydrous Na_2SO_4. The dried organic layer was then concentrated under vacuo to get a thick dark liquid; which on trituration with hexane gave the crude product **(3c)** (6.35 g; 20.1 mmole) melting around 138-148ºC. A portion of this compound was recrystallized from methanol to get the pure product **3c** melting at 150-152^{o}C; whose m. m. p remained undepressed in admixture with an authentic sample. All compounds **(3a-i)** reported herein were prepared by this procedure and were characterized by comparison of their m. p. and spectral data [IR, ^{1}H NMR and mass] as well as m. m. p. with their respective authentic sample prepared by conventional procedure as reported in literature.

Anti-anxiety activity evaluation

Anti-anxiety activity was carried out by using hole board method[27]. Male/ Female albino mice weighing 20-25 g were obtained from National Institute of Toxicology, Pune. The mices were administered with respective 1, 5-BDZ compound at dose levels (20, mg/kg, p. o.), diazepam 3.0 mg/kg, i. p., and control (vehicle–propylene glycol, 5 mL /kg, p. o.) in three groups and after 1 h, each mouse was placed individually on the hole board apparatus to determine the duration of dips as well as number of dips during 5 min.



Scheme I

Spectral studies

All commercially available compounds were used without further purification. The reactions were followed and checked by TLC (silica gel G60) for completion using EtOAc : pet. ether : $CHCl_3$ (4 : 1 : 1) and the spots were examined by either I_2 vapor or under UV lamp; whereas the identity and purity of the final products were checked against the authentic sample using EtOAc : pet. ether (1 : 9) and their R_f-values have been reported.

The IR spectra of the products were recorded on a 300 MHz Shimadzu FTIR-8400S spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded in $CDCl_3$ on a 300 MHz Shimadzu FT-NMR (δ in ppm) relative to TMS as internal standard and mass spectra were recorded on a SSQ7000 mass spectrometer at 70 eV.

2, 2, 4-Trimethyl-2, 3-dihydro-1*H*-1, 5-benzodiazepine (3a) : Yellow crystals; m. p. 136-38°C[7]; Rf = 0.76, IR (KBr) : 3343, 1657, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 1.35 (s, 6H), 2.20 (s, 2H), 2.35(s, 3H), 2.95 (br s, 1H, NH), 6.65-7.3(m, 4H); MS : m/z 188(M^+).

2, 4-Diethyl-2-methyl-2, 3-dihydro-1*H*-1, 5-benzodiazepine (3b) : Yellow solid; m. p. 138-40°C [8], Rf = 0.71, IR (KBr); 3350, 1648, 1615 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.99 (t, 3H)), 1.25(t, 3H), 1.70(q, 2H), 2.15(m, 2H), 2.35(3H), 2.69(q, 2H), 3.25(br s, NH, 1H) 6.65-7.35 (m, 4H); MS : m/z 217 (M^+).

2-Methyl-2, 4-diphenyl-2, 3-dihydro-1*H*-1, 5-benzodiazepine (3c) : Yellow solid; m. p. 150-52°C [7]; Rf = 0.69, IR (KBr) : 3343, 3010, 1635, 1510 cm^{-1}; ^{1}HNMR ($CDCl_3$) : δ 1.65 (s, 3H), 3.15 (d, 2H), 4.1(br s, NH) 6.8-7.55(14H, Ar-H), MS : m/z 312 (M^+).

2, 4-Bis(4-chlorophenyl)-2-methyl-2, 3-dihydro-1*H*-1, 5-benzodiazepine (3d) : Yellow crystals; m. p. 160-63°C [9]; Rf = 0.71, IR (KBr) : 3343, 2950, 1624, 1518 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 1.65 (s, 3H), 2.90 (s, 2H), 3.95(br s, NH) 6.85-7.45 (m, 12H, Ar-H) MS : m/z 381 (M^+).

2, 4-Bis(4-methylphenyl)-2-methyl-2, 3-dihydro-1*H*-1, 5-benzodiazepine (3e) : Yellow crystals; m. p. 142-45°C [10]; Rf = 0.74, IR (KBr) : 3253, 1654, 1528 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 1.65 (s, 3H), 2.1(s, 9H, 3xAr-CH_3), 2.70 (s, 1H), 3.05 (d, 1H), 3.60(br s, 1H, NH)7.1-7.5(m, 11H, Ar-H); MS : m/z 378(M^+).

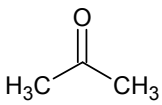
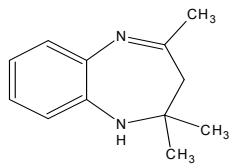
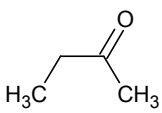
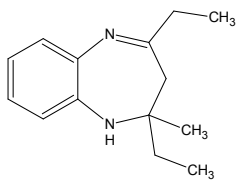
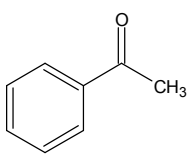
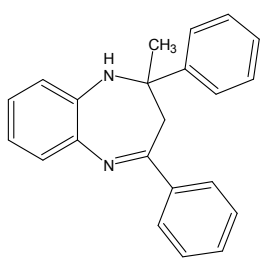
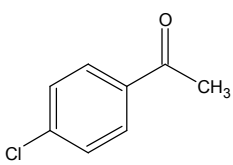
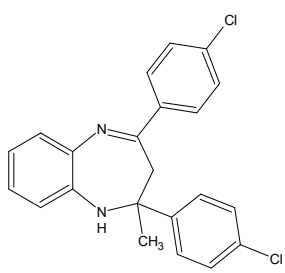
10-Spirocyclohexane-2, 3, 4, 10, 11, 11a-hexahydro 1*H*-dibenzo [b, e] [1, 4]diazepine (3f) : Yellow crystals; m. p. 138-40°C [9], Rf =. 072, IR (KBr); 3290, 2980, 1645, 1525 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.96-2.75 (m, 16H), 2.80-2.90 (m, 3H), 3.80(br s, NH, 1H) 7.0-7.35 (m, 4H); MS : m/z 268 (M^+).

10-Spirocyclopentane-1, 2, 3, 9, 10, 10a-hexahydro benzo[b] cyclopenta[e] [1, 4]diazepine (3g) : Yellow solid; m. p. 138-40°C [8], Rf = 0.73, IR (KBr); 3335, 1665, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30-190 (m, 12H), 2.30-2.60 (m, 3H) 4.45 (br s, NH, 1H) 6.65-

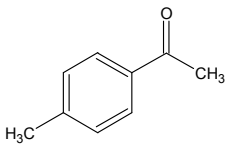
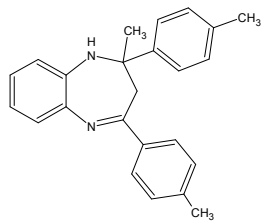
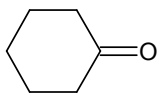
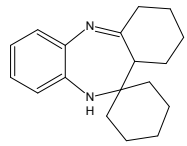
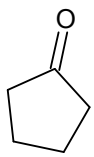
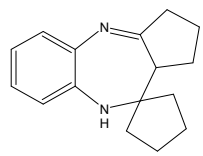
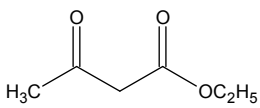
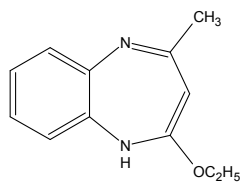
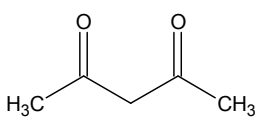
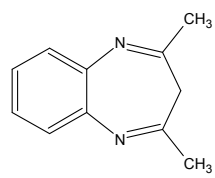
7.35 (m, 4H); MS : m/z 240 (M^+).

4-Methyl-2, 3-dihydro-1*H*-1, 5-benzodiazepin-2-one (3h) : Yellow crystals; m. p. 142-44°C[24] Rf = 0.72 IR(KBr); 3300, 3010, 1675, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.50 (s, 1H, NH), 7.5-7.0 (m, 4H arom.), 3.30 (s, 2H, CH_2), 2.40 (s, 3H, CH_3); MS : m/z 180(M^+).

Table 1. Silica gel catalyzed cyclocondensation of o-phenylendiamine with acyclic, cyclic and aromatic ketones and 1, 3-β-dicarbonyl compound.

Comp.	Ketone	[a]Yield (%)	Product[b]	Ref.	M. P. (°C)
3a		89		4	126-28
3b		78		5	138-40
3c		92		4	156-58
3d		75		6	136-38

Cont…

Comp.	Ketone	[a]Yield (%)	Product[b]	Ref.	M. P. (°C)
3e		87		7	142.4
3f		92		6	138-4
3g		85		5	133-3
3h		82		21	142-4
3i		80		22	184-8

2, 4-Dimethyl-3*H*-1, 5-benzodiazepine (3i) : Yellowish crystals; m. p. 184-86°C[25], Rf = 0.74 IR (KBr); 3010, 1675, 1605 CM^{-1}; ^1H NMR ($CDCl_3$) δ 7.5-7.0 (m, 4H arom.), 3.30 (s, 2H, CH_2), 2.40 (s, 3H, CH_3); MS : m/z 183 (M^+).

Biological studies

Compound **3a-h** were tested at dose levels (20 mg/kg, p. o.) for anti-anxiety activity by following hole board method [27] using diazepam as a standard [28] and the results

are summarized in Table 2.

Table 2. Anti-anxiety activity evaluation of 3a-h.

Groups (n = 3)	Treatment	Duration of dips in 5 min.	No. of dips in 5 min.
Control (vehicle)	5 mL/kg, p. o	26.2 ± 2.45	20.6 ± 1.50
Diazepam	3 mg/kg, i. p	45.0 ± 6.0**	33.2 ± 3.59*
1, 5-BDZ- **3a**	20 mg/kg, p. o	32.8 ± 1.56*	18.8 ± 1.56
1, 5-BDZ- **3b**	20 mg/kg, p. o	38.6 ± 1.72*	23.8 ± 1.10*
1, 5-BDZ-**3c**	20 mg/kg, p. o	42.2 ± 1.46**	28.4 ± 0.92*
1, 5-BDZ-**3d**	20 mg/kg, p. o	36.4 ± 5.3*	21.7 ± 1.68*
1, 5-BDZ- **3e**	20 mg/kg, p. o	29.8 ± 1.56*	18.8 ± 1.56*
1, 5-BDZ- **3f**	20 mg/kg, p. o	29.6 ± 1.72*	18.8 ± 1.10*
1, 5-BDZ-**3g**	20 mg/kg, p. o	29.2 ± 1.46*	20.4 ± 0.92*
1, 5-BDZ-**3h**	20 mg/kg, p. o	31.4 ± 5.3*	19.7 ± 1.68*

Values are Mean ± S. E. M., *P<0.05, ** p<0.01 vs. vehicle (one- way ANOVA followed by Dunnett's test).

Out of the entire compound reported in Table 2**, (3b) and (3c)** exhibited promising anti-anxiety activity. However for compounds **(3b)** and **(3c)** further investigations using more specific behavioral and biochemical screening models should be considered.

RESULTS AND DISCUSSION

An expeditious solvent free synthesis of 2, 3-dihydro-1H-1, 5-benzodiazepine derivatives has been carried out by reacting *o*-phenylenediamine with a variety of acyclic (**2a and b**), aromatic (**2c-e**), cyclic (**2f and g**) ketones and 1, 3-dicarbonyl compounds **(2h and i**) in presence of a catalytic amount (<10%) of silica gel under ultrasonic cavitation affording very good to excellent yield with in 25-30 min as shown in **Scheme I** and the results are summarized in Table 2.

ACKNOWLEDGEMENT

The author sincerely thanks Prin. A. D. Deshpande for providing all facilities for

this work as well as for his valuable advice and constant encouragement during this work. Our sincere thanks are also due to pharmacology section of our Institute for all help in carrying out pharmacological screening of the compounds.

REFERENCES

1. R. S. Varma, Ind. J Chem., **45B**, 2305 (2006).
2. (a) J. K. Landquist, in Comprehensive Heterocyclic Chemistry A. R. Katritzky and C. W. Ress (Eds.) Ergamon, Oxford, (1984) p. 166. (b) L. O. Randall, B. Kappel, in Benzodiazepines, S. Garattini, E. Mussini and L. O. Randall (Eds.), Raven Press, New York, (1973) p. 27, (c) J. R. De Baun, F. M. Pallos and D. R. Baker, US Patent 3, 978, 227, (1976) Chem. Abstr **86,** 5498d (1977).
3. R. C. Harris and J. M. Straley, US Patent 1, 537, 757, (1968) Chem. Abstr **73,** 100054w (1970).
4. (a) M. C. Aversa, A. Ferlazzo, P. Giannetto and F. H. Kohnke, Synthesis, 230 (1986). (b) A. M. El-Sayed, H. Abdel-Ghany and A. M. El-Saghier, Synth Commun., **29**, 3561 (1999). (c) K. V. Reddy, P. S. Rao and D. Ashok, Synth Commun., **30,** 1825 (2000). (d) A. Chimini, S. Grasso, R. Ottana, G. Romeo and M. Zappala, J. Heterocycles Chem., **27,** 3561 (1991)
5. P. Stahlhofen and W. Ried, Chem. Ber., **90,** 815 (1957).
6. W. Ried and E. Torinus, Chem. Ber., **92,** 2902 (1957).
7. M. A. Pasha and V. P. Jayashankara, Indian J. Chem., **45B**, 2716 (2006).
8. V. Sivamurugan, K. Deepa, M. Palanichamy and V. Murugesan, Synthetic Communication, **34,** 3833 (2004).
9. B. P. Bandgar, V. Sampada, Bettigeri and S. N. Joshi, Synth. Commun., **34,** 1447 (2004).
10. J. A. Herbert and L. H. Suschitzky, J. Chem. Soc., Perkin Trans **1**, 2657 (1974).
11. H. R. Morales, A. Bulbarela and R. Contreras, Heterocycles, **24**, 135 (1986).
12. D. I. Jung, T. W. Choi, Y. Y. Kim, I. S. Kim, Y. M. Park, Y. G. Lee and D. H. Jung, Synth. Commun., **29**, 1941 (1999).
13. M. S. Balakrishna and B. Kaboudin, Tetrahedron Lett., **42**, 1127 (2001).
14. M. Curini, F. Epifano, M. C. Marcotullio and O. Rosati, Tetrahedron Lett., **42,** 3193 (2001).
15. B. M. Reddy and P. M. Sreekanth, Tetrahedron Lett., **44,** 4447 (2003).

16. B. Kaboudin and K. Navaee, Heterocycles, **55,** 1443 (2001).

17. P. Minothora, S. S. Julia and A. Constantinos, Tetrahedron Lett., **43**, 1755 (2002).

18. K. D. Surya and A. G. Richard, Tetrahedron Lett., **46**, 1811 (2005).

19. M. Adharvana and C. K. Syamasundar, Catal. Commun., **6**, 67 (2005).

20. S. Gowravaram, K. B. Reddy, N. M. Reddy and J. S. Yadav, Adv. Synth. Catal., **346**, 921 (2004).

21. D. V. Jarikote, S. A. Siddiqui, R. Rajagopal, T. Daniel, R. J. Lahoti and K. V. Srinivasan, Tetrahedron Lett., **44**, 1835 (2003).

22. K. Chun-Wei, V. M. Shivaji and Y. Ching-Fa, Tetrahedron Lett., **47**, 8523 (2006).

23. N. R. Chatterjee, D. C. Sharma, Y. D. Choudhary and A. D. Despandande, Ind. J Heterocyclic Chem., **16** (3), 293 (2007).

24. C. Guidon, P. Greiveldinger, B. Balette and V. Loppinet, Soc. Pharm. Biol. Lorraine, **1**, 29 (1975).

25. A. Mannschreck, G. Rissmann, F. Vogtle and D. Wild, Chem. Ber., **100**, 335 (1967).

26. K. De Surya and A. G. Richard, Tetrahedron Lett., **46,** 1811 (2005).

27. C. Fernandes, S. E. File and D. Berry, Evidence against Oppositional and Pharmacokinetic Mechanisms of Tolerance to Diazepam's Sedative Effects., Brain Research, **734** 236 (1996).

28. Xiu-Yan Wei, Jing-Yu Yang, Jin-Hui Wang and Chun-Fu Wu, J. Ethnopharmacol., **111(3)**, 613 (2007).

Accepted : 25.09.2008