IRJSE International Research Journal of Science & Engineering
Int. Res. J. of Science & Engineering, 2018; Special Issue A5 : 93-92 SJIF Impact Factor 2016:.6.68
ISSN: 2322-0015 UGC Approved Journal No. 63628
RESEARCH ARTICLE **OPEN ACCESS**

Synthesis of 1, 5-benzodiazepines by using $Fe_3O_4@SiO_2SO_3H$ nanocatalyst

Sathe BP, Phatak PS, Dalve VS, Rote AB, Tigote RM and *Haval KP

Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University Aurangabad Sub Campus Osmanabad 413 501, India
Email: havalkp@gmail.com

Manuscript Details

Available online on http://www.irjse.in
ISSN: 2322-0015

Editor: Dr. Arvind Chavhan

Cite this article as:
Sathe BP, Phatak PS, Dalve VS, Rote AB, Tigote RM and Haval KP. Synthesis of 1, 5-benzodiazepines by using $Fe_3O_4@SiO_2SO_3H$ nanocatalyst, *Int. Res. Journal of Science & Engineering,* 2018; Special Issue A5: 93-98.

ABSTRACT

The synthesis of 1, 5-benzodiazepines using $Fe_3O_4@SiO_2SO_3H$ nanocatalyst. The iron nanoparticle catalyzed condensation of *o*-phenylenediamine with several ketones in methanol at room temperature furnished corresponding 1, 5-benzodiazopines.

Keywords: Nanocatalyst, 1, 5-Benzodiazepines, *o*-Phenylenediamine, Ketones, Green Chemistry.

INTRODUCTION

Benzodiazepines are important heterocyclic compounds that have attracted much attention of many researchers in drug discovery programs because of their wide spectrum of promising biological activities. These properties make benzo-diazepines useful in the treatment of anxiety, depression, insomnia, seizures, agitation and other CNS diseases [1]. Benzodiazepines are a class of agents that work on the central nervous system, acting selectively on gamma-amino butyric acid-A (GABA-A) receptors in the brain. It enhances response to the inhibitory neurotransmitter GABA, by opening GABA-activated chloride channels and allowing chloride ions to enter the neuron, making the neuron negatively charged and resistant to excitation. Benzodiazepines are similar in pharmacological action but have different potencies and some benzodiazepine work better in treatment of particular conditions. They are used as sedatives, hypnotics, anxiolytics, anticonvulsants, analgesic, antidepressants, hypnotic, anti-inflammatory and muscle relaxant agents [2-6].

In particular, 1, 5-benzodiazepines are useful precursors for the synthesis of fused ring benzodiazepine derivatives such as triazolo, oxadiazolo, oxazino, furano benzodiazepines. More recently their use has been extended to various diseases such as cancer, viral infections (non-nucleoside inhibitors of HIV-1 reverse transcriptase) and cardiovascular diseases [7-13]. Different reagents such as BF_3-etherate, polyphosphoric acid, $NaBH_4$, $MgO/POCl_3$, $Yb(OTf)_3$, $Ga(OTf)_3$, lead nitrate, L-proline, acetic acid under microwave conditions, molecular iodine, and ionic liquids have also been used for the synthesis of benzodiazepines [14]. Recently the synthesis of benzodiazepines has also been reported using different solid acid catalysts such as sulfated zirconia, Al_2O_3/P_2O_5, Ag_3 $PW_{12}O_{40}$, $PVPFeCl_3$, and zeolite catalysts [15].

In view of their wide range of applications in biological and industrial synthetic organic chemistry, the development of mild and efficient protocols for the synthesis of 1, 5-benzodiazepine analogs continue to be a challenging endeavor [16]. However, the most commonly employed methods involve the cyclocondensation of 1, 2–diamines with *a*, *β*-unsaturated ketones, *β*-haloketones, alkynes [17]. Literature survey reveals the various catalysts and routes for the synthesis of these compounds by condensation reaction of *o*-phenylenediamine with *a*, *β*-unsaturated carbonyl compounds in the presence of protic organic and inorganic acids catalysts [18]. The majority of methods reported in literature have several limitations such as high temperature, long reaction time, use of expensive reagents, low yields of products, high catalyst loading, corrosive reagents, strongly acidic conditions and further purification of products. Therefore, the need of development of an efficient method for the preparation of 1, 5-benzodiazepines is of prime importance using nanocatalyst [19].

RESULTS AND DISCUSSIONS

In continuation of our previous studies on exploration of various methods and catalysts in organic transformations [20], herein, we report a highly efficient, active and recyclable acidic magnetic nanocatalyst for the one pot synthesis of 1, 5-benzodiazepines using sulfonic acid supported on ferrite-silica supermagnetic nanoparticles ($Fe_3O_4@SiO_2SO_3H$ NPs) (Scheme 1). It is prepared according the procedure reported in literature [21]. It has been used as green catalyst in various condensation reactions [22]. There is no report available in literature describing the use of $Fe_3O_4@SiO_2SO_3H$ NPs as catalyst for the synthesis of 1, 5-benzodiazepines [23]. Initially, we study influence of $Fe_3O_4@SiO_2SO_3H$ NPs for the synthesis of 1, 5-benzodiazepine using *o*-phenylenediammine and acetophenone as a model reaction and by changing the amount of $Fe_3O_4@SiO_2SO_3H$ NPs (Table 1). The catalyst quantity was optimized to 20 mol% of $Fe_3O_4@SiO_2SO_3H$ NPs and excellent results were obtained with 84% yields. The solvent effect was studied by performing reaction in different solvents varying ketones to furnish corresponding 1, 5-benzodiazepines with 70-98% yields (Table 2). It has been observed that the better results are obtained in methanol solvent.

Table 1: Effect of concentration of $Fe_3O_4@SiO_2SO_3H$ nanopartilces

Entry	Catalyst (mol%)	Time (h)	Yields (%)
1	10	4	73
2	15	4	78
3	20	4	84
4	25	4	84

Reaction Conditions: *o*-Phenylenediamine, acetophenone and $Fe_3O_4@SiO_2SO_3H$ nanoparticles.

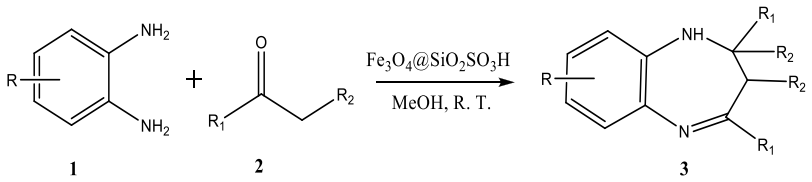
Table 2: Effect of solvent on synthesis of 1, 5-benzodiazepine.

S. N.	Solvent	Time (h)	Yield (%)
1	Ethanol	4	92
2	THF	4	86
3	Iso-propanol	3	90
4	DCM	4	87
5	Methanol	3	98
6	Ethyl acetate	5	85
7	Acetonitrile	5	85
8	Toluene	6	70

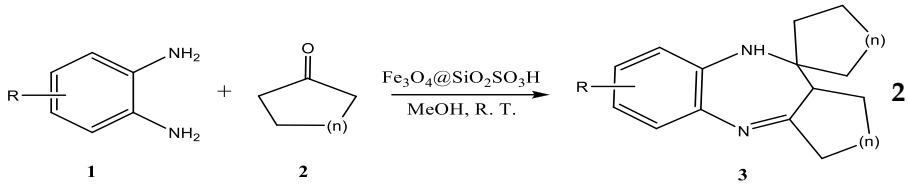
Reaction Conditions: *o*-Phenylenediamine, acetone and $Fe_3O_4@SiO_2SO_3H$ (20 mol%).

The scope of present invention checked by performing reactions between various substituted *o*-phenylenediamines (10 mmol) and ketones (20 mmol) in presence of $Fe_3O_4@SiO_2SO_3H$ (20 mol%) in methanol (**Scheme 1 & 2**). All the reactions furnished the corresponding 1, 5- benzodiazepines with 70-98% yields (**Table 3**). The present protocol is applicable to both aliphatic cyclic, acyclic and aromatic ketones without significant differences. The progress of reaction was monitored by TLC. The analytical and spectral data of obtained compounds is matching with the reported in literature.

Scheme 1

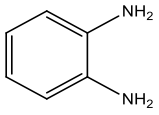
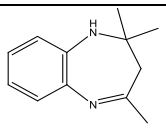
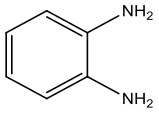
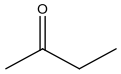
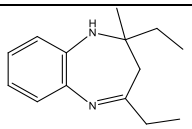
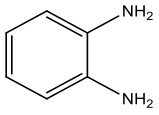
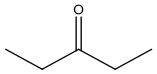
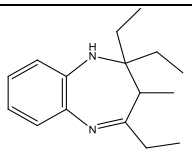
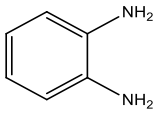
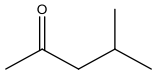
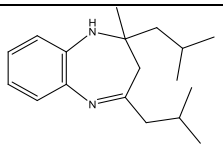
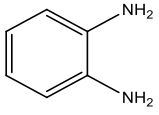
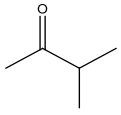
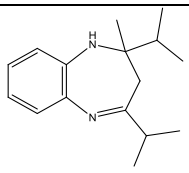
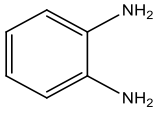
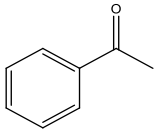
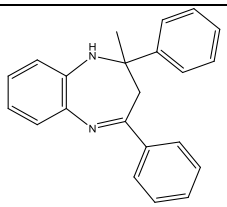


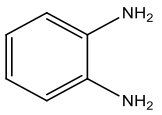
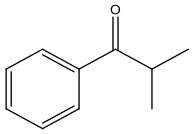
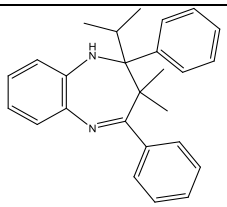
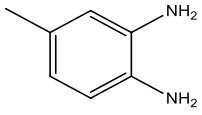
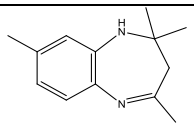
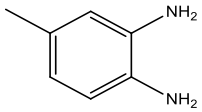
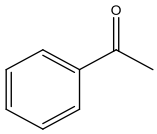
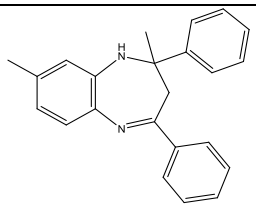
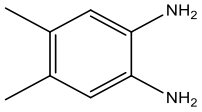
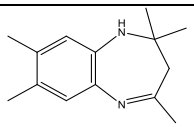
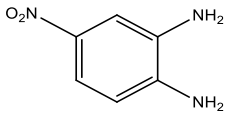
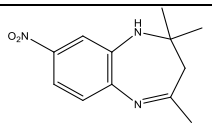
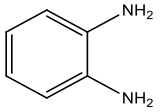
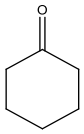
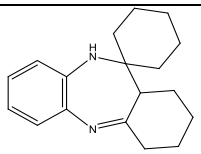
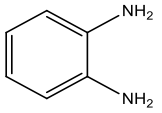
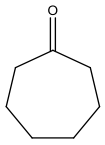
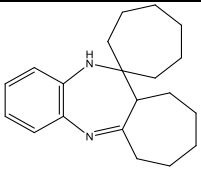
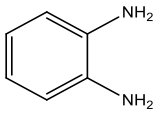
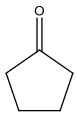
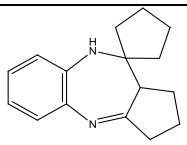
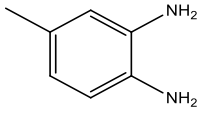
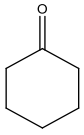
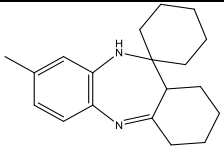
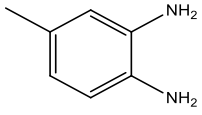
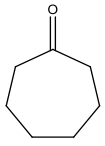
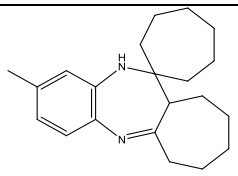
Scheme



2

Table 3: Synthesis of 1, 5-benzodiazepines using $Fe_3O_4@SiO_2SO_3H$ Nano catalyst

S. N.	Diamine (1)	Ketone (2)	Product (3)	Time (h)	Yield (%)	MP (°C)	MP^{lit} (°C)
1				3	98	118-120	120-122
2				3.5	82	138-140	138-139
3				3	84	140-142	142-144
4				4	79	120-122	118-120
5				5	77	118-120	118-120
6				4	84	149-151	150-152

7				6	82	120-122	121-122
8				3	84	126-128	127-128
9				5	80	91-93	92-93
10				6	87	110-112	112-114
11				5	82	112-114	113-114
12				4	75	136-138	136-137
13				5	70	134-136	135-136
14				6	80	136-138	136-138
15				6	72	122-124	124-125
16				5	78	136-137	138-139

EXPERIMENTAL

The commercially available chemicals were used without further purification. The progress of the reactions was monitored by TLC. The melting points are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C (100 MHz) spectra were recorded with tetramethylsilane as the internal standard.

General procedure for 1, 5-benzodiazepines.
A mixture of *o*-phenylenediamine (10 mmol), Ketone (20 mmol) and $Fe_3O_4@SiO_2SO_3H$ (20 mol%) in methanol (10 ml) was taken in a round bottom flask. The reaction mixture was stirred at room temperature for an appropriate time as mentioned in Table 3. After completion of the reaction, the catalyst was removed easily by adsorbing onto the magnetic stirring bar when the stirring was stopped. Then, the reaction solution was filtered off and the residue was purified by washing further with water, to give crude crystalline product. The crude product was purified by recrystallization by using ethanol to gives the corresponding 1, 5- benzodiazepines with 70-98% yields. The $Fe_3O_4@SiO_2SO_3H$ nano-catalyst was then washed with ethanol, air-dried and used directly several times in other fresh reactions without loss of efficiency.

2, 3-Dihydro-2, 2, 4-Trimethyl-1H-1, 5-benzodiazepine (Entry 1): IR ($CHCl_3$) νmax: 3345, 2109, 1630, 1456, 1246, 1051, 945, 713 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.35 (s, 6H), 2.23 (s, 2H), 2.37 (s, 3H), 2.99 (bs, 1H), 6.73-6.75 (m, 1H), 6.98-7.01 (m, 2H), 7.13-7.15 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 29.9, 30.5, 45.1, 68.4, 121.8, 122.1, 125.5, 126.9, 137.9, 140.8, 172.4.

2,3-Dihydro-2, 4-diethyl-2-methyl-1H-1, 5-benzodiazepine (Entry 2): IR (KBr) νmax: 3329, 1637,1605 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.99 (t, 3H, *J* = 6.9 Hz), 1.25 (t, 3H, *J* = 6.9 Hz), 1.70 (q, 2H, *J* = 6.9 Hz), 2.15 (m, 2H), 2.35 (s, 3H), 2.69 (q, 2H, *J* = 6.9 Hz), 3.25 (br s, 1H, NH), 6.78–7.35 (m, 4H); **^{13}C NMR** (CDCl3, 100 MHz): *δ* 8.7, 10.6, 26.9, 35.5, 35.7, 42.0, 70.7, 121.7, 125.2, 126.2, 27.1, 138.0, 140.9, 175.5.

2, 3-Dihydro-2-methyl-2, 4-diphenyl-1*H*-1, 5-benzodiazepine (Entry 6): **IR** (KBr) νmax: 3277, 3061, 2972, 1559 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.8 (s, 3H), 3.1 (d, 1H), 3.2 (d,1H), 6.8-7.7 (m, 14H)

.

2, 3-Dihydro-2, 2, 4-trimethyl-8-nitro-1*H*-1, 5-benzodiazepine (Entry 11): **IR** (KBr) νmax: 3280, 1645, 1600 cm^{-1};. **^{1}H NMR** ($CDCl_3$, 400 MHz), 1.90 (s, 6H), 2.95 (s, 3H), 3.20 (s, 2H), 7.18 (s, 1H), 8.0–8.10 (m, 1H), 8.5–8.9 (m, 1H).

CONCLUSION

In conclusion, we have reported green synthesis of various substituted 1, 5 benzodiazepines from *o*-phenylenediamine and ketones in presence of catalytic amount of $Fe_3O_4@SiO_2SO_3H$ in methanol. The present protocol has several advantages over earlier reported. The present protocol will be highly useful method for preparation of substituted 1, 5 benzodiazepines.

Acknowledgements: PSP gratefully acknowledge the financial support of CSIR New Delhi.

REFERENCES

1) a) Sternbach LH. *Angew. Chem., Int. Ed. Engl.10,***1971**, 34. b) Randall LO. *Psychopharmacological Agents,3,* **1974**, 175. c) Massah AR, Gharaghani S, Lordejani HA, Asakere N. *Med. Chem. Res.*,25, **2016**,1538.
2) Pasha MA, Jayashankara VP. *Ind. J. Chem*., 45B, **2006**, 2716.
3) Radatz CS, Silva RB, Perin G, Lenardao EJ, Jacob RG, Alves D. *Tetrahedron Lett.*, 52, **2011**,4132.
4) Naga Prashant K, Ravi Kumar K. *Int. J. Pharm Tech Res., 8,* **2015**, 60.
5) Kumar R, Joshi YC. *ARKIVOC* **2007**, 142.
6) Pasha MA, Jayashankara VP. *J. Pharmacol. Toxicol*.,1, **2006**, 573.
7) Sharma S, Prasad DN, Singh RK. *J. Chem. Pharm. Res., 3,* **2011**, 382.
8) Zhao Y, Sharma S, Huang M, Sandhar A, Singh RK, Ma Y. *Asian J. Chem.,26,* **2014**,5116.
9) Torres SY, Robolledo *F. Synthesis, 48,* **2016**,A-G.
10) Mazimba O, Molefe T. *Int. J. Chem. Studies, 3,* **2015**, 46.
11) Ashok D, Rao VH, Kavita RJ*. Serb. Chem. Soc.,81,* **2016**, 851.
12) Varvounis G. *Molecules, 21,* **2016**, 154.
13) Salve PS, Mali DS, *Int. J. Pharm. Bio. Sci., 4,* **2013**, 345.

14) a) Herbert JAL, Suschitzky HJ. *Chem. Soc.,* **1974**, 2657. b) Morales HR, Bulbarela A, Contreras R. *Heterocycles, 24,* **1986**, 135. c) Jung DI, Choi TW, Kim YY. *Synth. Commun., 29,* **1999**, 1941. d) Balakrishna MS, Kaboudin B. *Tetrahedron Lett.,42,* **2001,**1127. e) Curini M, Epifano F, Marcotullio MC, Rosati O. *Tetrahedron Lett., 42,* **2001**, 3193. f) Pan XQ, Zou JP, Huang ZH, Zhang W. *Tetrahedron Lett.,49,* **2008**, 5302. g) Kumar R, Chaudhary P, Nimesh S, Verma AK, Chandra R. *Green Chem., 8,* **2006**,519. h) Sivamurugan V, Deepa K, Palanichamy M, Murugesan V. *Synth. Commun., 34,* **2004**, 3833. i) Minothora P, Julia SS, Constantinos AT. *Tetrahedron Lett.,43,* **2002**, 1755. j) Chen WY, Lu J. *Synlett, 8,* **2005**, 1337.

15) a) Reddy BM, Sreekamth PM, Reddy VR. *J. Mol. Cat. A.*, 225, **2005**, 71. b) Kaboudin B, Navaee K. *Heterocycle, 55,* **2001**, 1443. c) Yadav JS, Reddy BVS, Praveenkumar S, Nagaiah K, Lingaiah N, Saiprasad PS. *Synthesis, 6,* **2004**, 901. d) Chari MA, Syamasundar K. *Cat. Commun., 6,* **2005**, 67. e) Heged¨us A, Hell Z, Potor A. *Cat. Lett., 105,* **2005**, 229.

16) a) Sangshetti JN, Kokare ND, Shinde DB. *Chin. Chem. Lett., 18,* **2007**, 1305. b) Nagaraja GK, Vaidya VP, Rai KS, Mahadevan KM. *Phosphorous Sulphur Silicon Relat. Elem.*, 181, **2006,** 2797. c) Nabih K, Baouid A, Hasnaoui A, Kenz A. *Synth. Commun.*, 30, **2006**, 1825. d) Ahmad S, Ali M, *Iran J. Chem. Eng., 26,* **2007**, 93. e) Shinde DB, Sangshetti JN, Kokare ND. *Chin. Chem .Lett.,18,* **2007**,1305.

17) Huang Y, Khoury K, Chanas T, Domling *A. Org. Lett.,14,* **2012**, 5916.

18) a) Quin J, Liu Y, Cui J, Xu Z. *J. Org. Chem.,77,* **2012**, 4484. b) Li Z, Sun Y, Ren X, Li W, Shi Y, Ouyang P. *Synth. Commun., 37,* **2007,** 1609. c) Krishnan GR, Radhakrishnan S, Krishnapillai S. *Lett. Org. Chem.*,6, **2009**, 17. d) Parveen AP, Vishal A, Baseer MA, Ahmed S. *Int. J. Ind. Chem.*, 2, **2010**, 144. e) Vijayashankar AV, Deepa S, Venugopal BR, Nagaraju N. *Chin. J. Catal.*, 31, **2010**, 1321. f) Langade M, Pachpinde A, *J. Chem. Pharm. Res.*, 5, **2013**, 37. g) Konda SG, Shaikh BM, Chavan SA, Dawane BS. *Chin. Chem .Lett., 22,* **2011**, 65. h) More UB, Kharat RS, Mahulikar PP. *Asian J. Chem.,23,* **2011,** 4311. i) Jarikote DV, Siddiqui SA, Rajagopal R, Daniel T, Lahoti RJ, Srinivasan KV. *Tetrahedron Lett.*,44, **2003**, 1835. j) Das B, Ramu R, Ravikanth B, Reddy VS. *J. Mol. Catal.*,76, **2006**, 246. k) Li X-Q, Wang L-Z. *Chin. Chem. Lett.*,25, **2014**, 327. l) Ilango SS, Remya PU, Ponnuswamy S. *Ind. J. Chem.*,52B, **2013**, 136.

19) a) Neukom JD, Aquino AS, Wolfe JP. *Org. Lett.,13,* **2011**, 2196. b) Simon MO, Li C*J. Chem. Soc. Rev., 41,* **2012**, 1415.

20) a) Haval KP, Argade NP. *Synthesis*, **2007**, 2198. b) Haval KP, Argade NP. *J. Org. Chem.,73,***2008**,6936. c) Haval KP, Mhaske SB, Argade NP. *Tetrahedron, 62,* **2006**,937. d) Haval KP, Argade NP. *Tetrahedron*, 62, **2006**, 3557. e) Shinde NV, Dhake AS, Haval KP. *Oriental Journal of Chemistry*, 32, **2016**, 515. f) Shinde NV, Dhake AS, Haval KP. *Der Pharma Chemica*, 7, **2015**, 251. g) Tigote RM, Haval KP, Kazi SK. *J. Med. Chem. & Drug Discovery*, 2, **2017**,654.

21) Hassani H, Nasseri MA, Zakerinasab B, Rafiee F. *Appl. Organometal. Chem.*, 30, **2016**,408.

22) Kathirvelan D, Yuvraj P, Babu K, Nagarjun AS, Reddy SR. *Ind. J. Chem.*,52B, **2013**,1152.

23) a) Chari MA, Syamasundar K. *Catal. Commun., 6,* **2005**, 67. b) Singh RK, Saini M, Kumar S. *Ind. J. Chem.*,25, **2015**, 151.