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High surface area SnO_2 nanoparticles as a benign catalyst for the synthesis of 1,5-benzodiazepines

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Original Research

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Abstract:

A benign and efficient promoted synthesis of 1,5-benzodiazepinederivatives *via* a simple and atom-economical reaction between 1,2-phenylenediamines as well as ketones by the usage of catalytic amount of SnO_2 nanoparticlesat room temperature in ethanol as a solvent is described. This approach results for the synthesis of various 1,5-benzodiazepines in excellent yields (93-98%). The advantages of this process are operational effortlessness, high yields products, mild reaction conditions, catalyst recyclability, high purity products and short reaction times.

Keywords: 1,5-Benzodiazepines; Nano catalyst; 1,2-Phenylenediamine; SnO_2 nanoparticles

1. Introduction

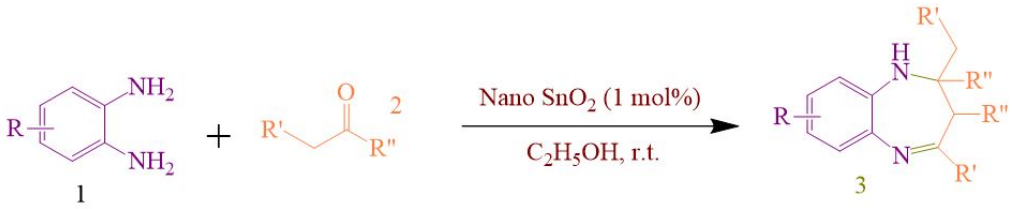
Benzodiazepine and their polycyclic derivatives are key compounds, broadly applied in as hypnotic, antianxiety, psychosis, antitumor, anticonvulsant and antipyretic agents [1]. Some these title compounds are applied in light sensitive material [2] and anti-inflammatory agents [3]. Also, these compounds are valuable precursors for the synthesis of several fused ring benzodiazepines, for example oxadiazolo-, triazolo-, oxazino-, triaxolo- or furano-benzodiazepines [4]. Therefore, investigation in this part is still active and is focused to the synthesis of compounds with improved pharmacological activity [5]. Numerous approaches have been studied for the synthesis of 1,5-benzodiazepine containing condensation reactions of 1,2-phenylenediamine with β-haloketones [6], α, β-unsaturated carbonyl compounds [7], β-aminoketones [8], or ketones by using clay-supported polyoxometalates [9], fluorous/aqueous emulsion [10], $Er(OTf)_3$ [11], AlKIT-5 [12], $H_{14}[NaP_5W_{30}O_{110}]$ [13] and Borax/phosphorous oxychloride [14].

The application of heterogeneous catalysts to achieve several organic transformations has high significance in organic synthesis. These catalysts can properly be handled and eliminated from mixture of the reaction, causing the experimental process simple and sustainable. Consequently, the performing of an organic reaction in the presence of a benign and facile catalyst will be a perfect approach, if the catalyst displays appropriate catalytically activity [15].

Metal oxide nanoparticles are fascinating significant attention since they can alter the feasible progressive to conformist materials in numerous fields of solid state chemistry. Metal oxide nanoparticles can be basically used as a heterogeneous nano catalyst in different organic transformations as they contained high surface area than their bulk counterparts [16].

Tin dioxide (SnO_2 nanoparticles) is a superb compound for a varied range of uses includes transparent conducting electrodes, gas sensors detecting leakages, optoelectronic devices, and catalyst supports [17, 18]. SnO_2 established slight consideration in the catalysis part [19] in comparison with other metal oxides. Although, SnO_2 supported catalysts have been investigated to be active for hydrogenation reaction of nitrate [20], esterification reaction [21], reducing the amount of NO/NO_2 to N_2 [22] as well as oxidation of organic compounds [23].

In our efforts to improve efficient catalyst systems and organic synthesis [24, 25], herein we study a mild and simple process on account of synthesis of 1,5-benzodiazepine

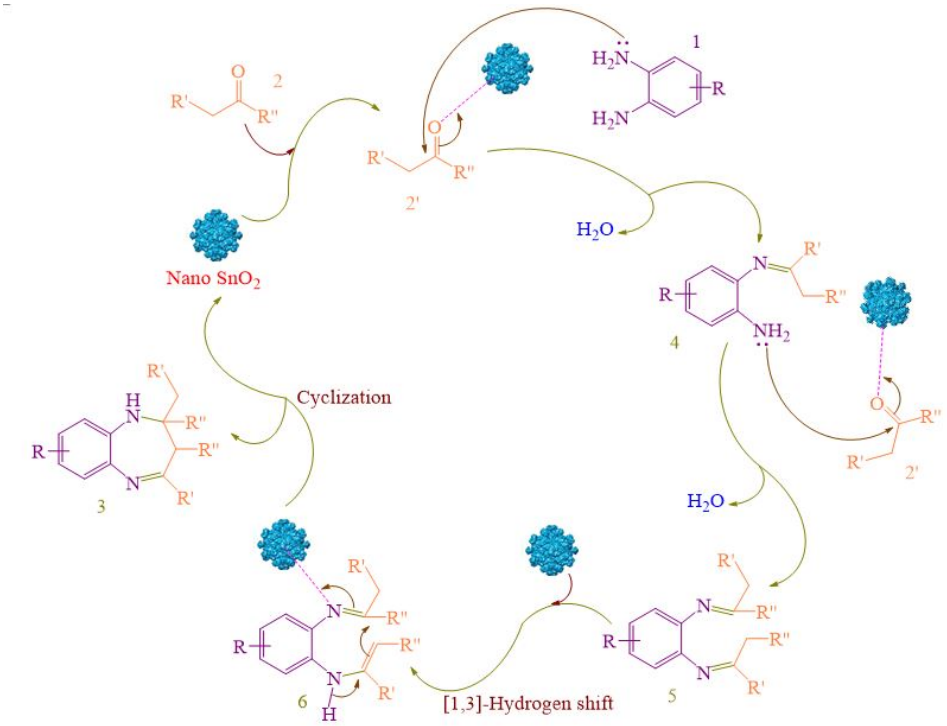


Scheme 1. SnO_2 nanoparticles catalyzed synthesis of 1,5-benzodiazepines.

derivatives from reaction of 1,2-phenylenediamines and ketones when there is catalytic amount of SnO_2 nanoparticles at room temperature in ethanol.

2. Results and discussion

Application of SnO_2 nanoparticles as a catalyst for the synthesis of 1,5-benzodiazepines In our preliminarily study, we select 1,2-phenylenediamine (1 mmol; 0.108 g) and acetone (2 mmol; 0.116 g; 0.148 mL) as the normal system to display conditions of the reaction. The impact of solvent and amount of catalyst on the typical reaction was scientifically investigated and the outcome were shortened in Table. 1. Satisfyingly, by the usage of 0.5 mol% SnO_2 nanoparticles at room temperature in ethanol, only 50% yield was attained after 40 minutes (Table. 1, entry 1). When the reaction was conducted via using 1 and 2 mol% SnO_2 nanoparticles, the finished product with the high yield (95%) was gained (Table. 1, entries 2 and 3). To our surprise, when we increase the loading amount of SnO_2 nanoparticles to 5 and 10 mol%, the chosen product was isolated in 93% and 89% yields, respectively (Table. 1, entries 4 and 5). These results showed that higher amount of SnO_2 nanoparticles did not improve the output of desired product. The reaction was very slow in the absence of SnO_2 nanoparticles and the selected product was not attained.
As can be seen from Table. 1, the solvents performance a significant part in the model reaction. It was found that ethanol is the appropriate one among the solvents confirmed, and the reaction progressed in ethanol and provided the chosen product in 95% yield,whereas water gave the product only in 48% yield. Use of CH_3CN, CH_2Cl_2, THF and toluene as solvents have result in decrease reaction yields and increase reaction times (Table. 1, entries 6–10).
Furthermore, no increase in yield was identified when the reaction time was extended. The optimized reaction conditions for the reaction were establish to be SnO_2 nanoparticles (1 mol%) in ethanol at room temperature.
Considering the improvement of reaction conditions, the overview of the 1,5-benzodiazepines synthesis catalyzed by SnO_2 nanoparticles was investigated. The reaction displayedsubstantial tolerance for substituents in 1,2-phenylenediamines andketones (Table. 2). The products were isolated and recognized as 1,5-benzodiazepines, and no side reactions were discovered. In all samples, the re-



Scheme 2. Proposed mechanism for the synthesis of 1,5-benzodiazepines catalyzed by SnO_2 nanoparticles.

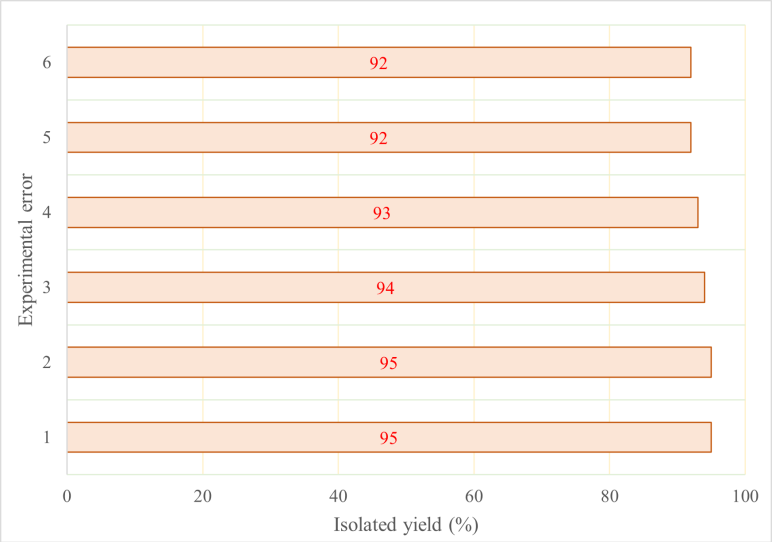


Figure 1. Recyclability of SnO_2 nanoparticles on the model reaction in 15 minutes.

actions are good selective and are concluded in 5–15 minutes. The nano SnO_2 catalyst presented appropriate activity in all the specimens, displaying 93–98% isolated yield of the corresponding products. All the above-mentioned reactions carriedsuperb product yields and accommodate a broadvariety of 1,2-phenylenediamines and ketones having electrondonating and electron-withdrawing substituents.1,2-Phenylenediamines having electron-donatingsubstituents have provided the corresponding productin 95–97% yields (Table. 2, entries 14–19). Moreover, 1,2-phenylenediamines having electron-donating substituents gave the corresponding productin 97% and 98% yields (Table. 2, entries 20–22). The probability of recycling the SnO_2 nanoparticles catalyst was studied *via* the typical reaction under the optimized conditions. Upon finishing point, the reaction mixture was filtered and the crude solid was washed with hot ethanol, dried in air, and the catalyst was reused for the upcoming reaction (the crude solid was soluble in hot ethanol and SnO_2 nanoparticles was unsolvable). The recycled catalyst can be recycled five times without any noticeable changes in its structure. No substantial loss of catalytic activity was identified (Figure. 1).

The proposed mechanism for the producing of 1,5-benzodiazepines catalyzed via SnO_2 nanoparticles, as displayed in schemes 1 and 2 [12]. Firstly, the amine moiety of 1,2-phenylenediamines**1** *via* nucleophilic attack to carbonyl moiety of the activated ketones**2** (activated by SnO_2 nanoparticles), affording intermediate **4** by eliminating one molecule of water. Then, nucleophilic attack of second amine moiety of intermediate **4** to carbonyl moiety of the second activated ketones **2**, provides diamine intermediate **5** through removal of second molecule of water. In the next step, the methyl group was attached by, a 1,3-shift of the hydrogen which happens in order to produce an enamine intermediate **6**, that cyclizes to give the seven membered ring in 1,5-benzodiazepines **3**.

The advantage of current method over reported methods was investigated by comparing the attained results with those reported previously (Table. 3). The reaction conditions for the synthesize of target molecule (Table. 2, Entry 1), were compared considering mol% of the catalyst, reaction time, temperature, and yields.

3. Conclusion

In summary, a rapid, mild and effective process for generating the 1,5-benzodiazepines *via* the reaction between1,2-phenylenediamines and ketones has been established, which includes the application of nano SnO_2 as a catalyst. As well as the purity of the products, recyclability of catalyst, short reaction times and high isolated yields generate the process advantageous. Some products were characterized by melting point, FT-IR, ^{1}H NMR and ^{13}C NMR spectra.

4. Experimental

4.1 General method

SnO_2 nanoparticles was purchased from commercial center [26]. The measure of Melting points on a Thermo Scientific apparatus and are uncorrected. FT-IR spectra were recorded on a FT-IR Bruker (WQF-510) spectrometer. ^{1}H as well as ^{13}C NMR spectra were recorded on a Bruker DRX-400 MHz spectrometer at 400 and 100MHz. NMR spectra were achieved on solution in DMSO-d_6 via applying TMS as internal standard. The usage of chemicals in this work were made by Merck and Fluka Chemical Companies.

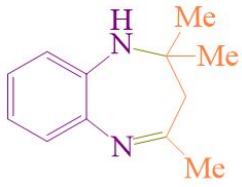
4.2 Regular procedure for the synthesis of 1,5-benzodiazepines

To a mixture of 1,2-phenylenediamines (1 mmol), ketones (2 mmol), C_2H_5OH (2 mL), SnO_2 nanoparticles (1 mol%) was added and stirred at room temperature for the suitable time (Table. 2). When the reaction was completed as showed by TLC (*n*-hexane/ethyl acetate; 3:1), the solvent was removed under reduced pressure. Then the residuum was washed in hot ethanol, dried in air, and the catalyst was reused in the following reaction (the precipitated solid was soluble in hot ethanol and SnO_2 nanoparticles is

insoluble). Finally, the solvent was removed under vacuum and precipitated solid was crystallized from ethanol and *n*-hexane (1:1) and then washed with ether (3 × 5 mL) and the titled product was achieved in good to excellent yield.

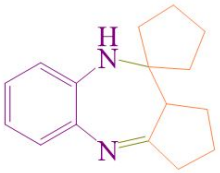
4.3 Spectral data for the selected compounds

2,2,3,4-Tetramethy l-2,3-dihydro-1H-benzo[b][1,4] diazepine



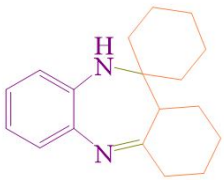
Brown solid, M.p. 137–139 °C; Yield: 95 %; FT-IR (KBr)(υ_{max}, cm^{-1}): 3293, 3093, 2952, 1648, 1483; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.33 (s, 3H), 1.56 (s, 6H), 2.51 (s, 3H), 3.35 (s, 1H),5.56 (brs, 1H, NH), 6.23-6.28 (m, 2H), 6.30-6.33 (m, 2H); (400 MHz, DMSO-d_6); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.9, 25.3, 33.5, 39.4, 80.3, 106.9, 117.9, 126.9, 133.4, 133.9, 140.8, 166.6.

2,3,9,10 a-Tetrahydro-1H-spiro[benzo[b] cyclopenta[e][1,4] diazepine-10,1' -cyclopentane



Brown solid, M.p.: 137–139 °C; Yield: 95 %; FT-IR (KBr) (υ_{max}, cm^{-1}): 3380, 3104, 2966, 1683, 1600, 1517; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.27-2.50(m, 14H, cyclopentyl), 2.61(t, *J*=8.3, 1H), 5.86(S, 1H, NH),6.54-7.12(m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ =23.6, 23.8, 24.3, 25.0, 29.3, 33.6, 38.5, 38.6, 38.7, 116.8, 119.3, 126.9, 132.4, 132.9, 140.7, 175.6.

1',2',3',4',10',11a'-Hexahydrospiro [cyclohexane-1,11' -dibenzo[b,e] diazepine



Brown solid, M.p.: 139–141 °C; Yield: 96 %; FT-IR (KBr) (υ_{max},cm^{-1}): 3380, 2967, 1654, 1517, 1349; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.12-3.96(m, 18H, cyclohexyl), 4.03 (m, 1H), 5.67(s, 1H, NH), 6.23-6.32(m,4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ =22.9, 38.2, 38.3, 38.4, 38.5, 38.6, 38.7, 38.8, 38.9, 39.0, 80.3, 107.0, 117.9, 119.3, 126.9, 132.4, 132.9, 140.8.

Supporting Information

The supporting information contains spectral images of FT-IR,1H NMR and ^{13}C NMR of selected products (Figures S1-S9) and SEM analysis of SnO_2 nanoparticle (Figure S10) [27].

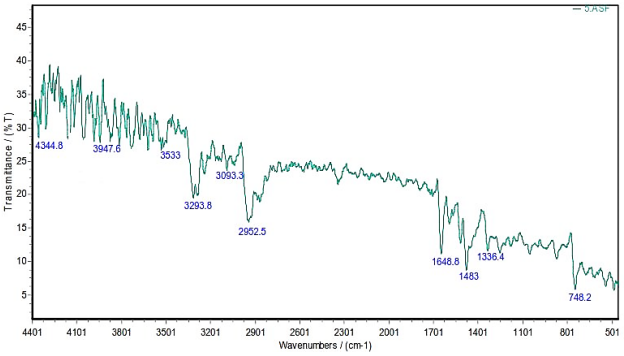


Figure S1. FT-IR spectrum of 2,2,3,4-tetramethyl-2,3-dihydro-1H-benzo[b][1,4] diazepine.

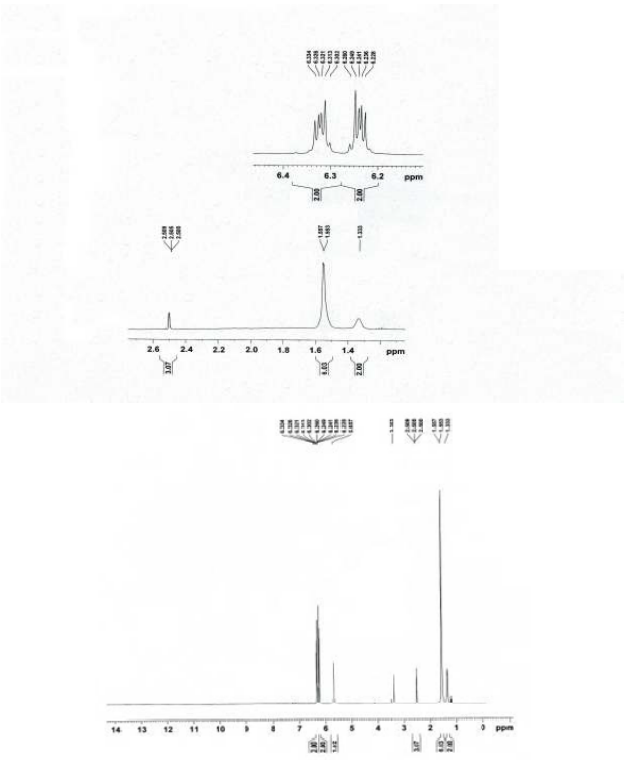


Figure S2. ^{1}HNMR spectrum of 2,2,3,4-tetramethyl-2,3-dihydro-1H-benzo[b][1,4] diazepine.

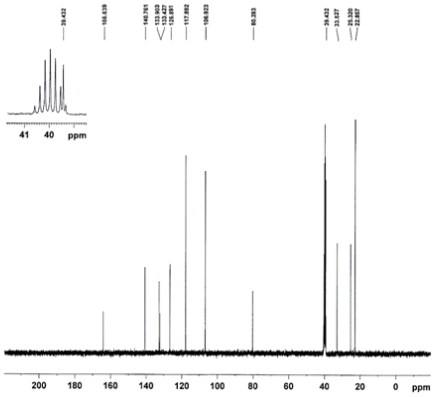


Figure S3. [13]CNMR spectrum of 2,2,3,4-tetramethyl-2,3-dihydro-1H-benzo[b][1,4] diazepine.

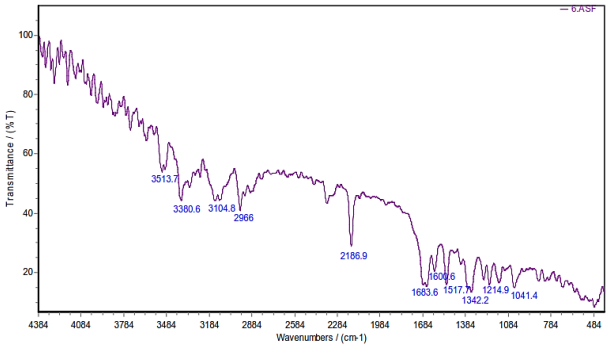


Figure S4. FT-IR spectrum of 2,3,9,10a-tetrahydro-1H-spiro[benzo [b] cyclopenta [e] [1,4] diazepine-10,1'-cyclopentane].

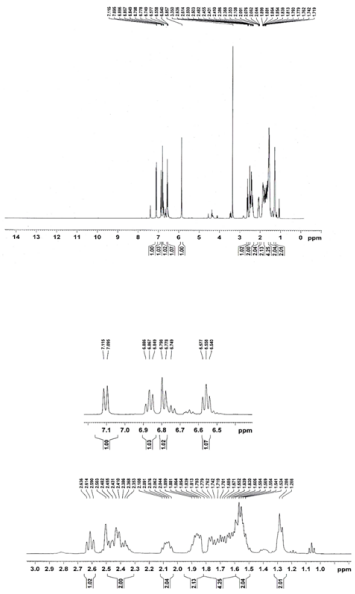


Figure S5. [1]HNMR spectrum of 2,3,9,10a-tetrahydro-1H-spiro[benzo [b] cyclopenta [e] [1,4] diazepine-10,1'-cyclopentane].

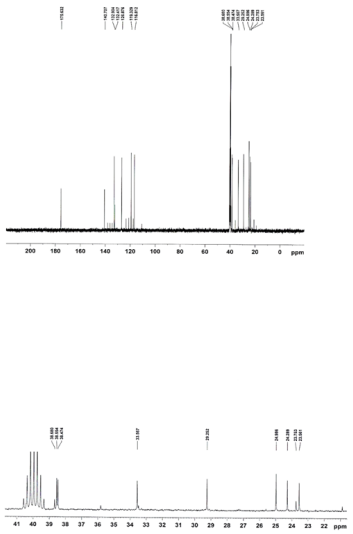
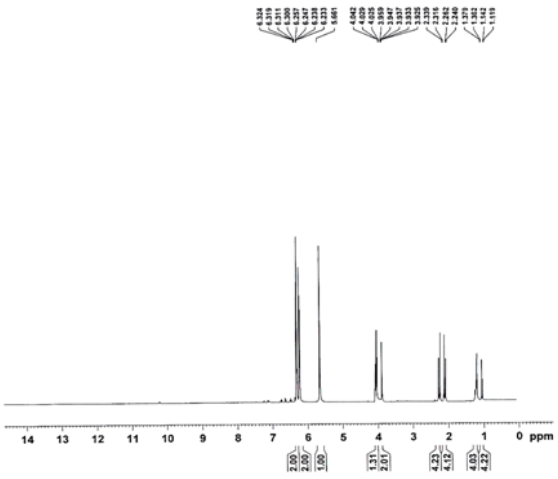


Figure S6. [13]CNMR spectrum of 2,3,9,10a-tetrahydro-1H-spiro[benzo [b] cyclopenta [e] [1,4] diazepine-10,1'-cyclopentane].

Figure S7. FT-IR spectrum of 1',2',3',4',10',11a'-hexahydrospiro[cyclohexane-1,11'-dibenzo [b,e] [1,4] diazepine].



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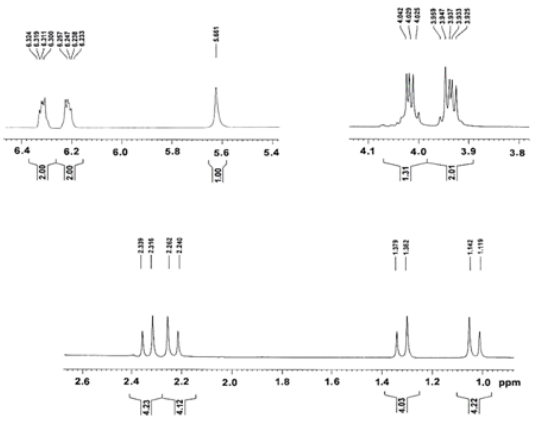

Figure S8. [1]HNMR spectrum of 1',2',3',4',10',11a'-hexahydrospiro[cyclohexane-1,11'-dibenzo [b,e] [1,4] diazepine].

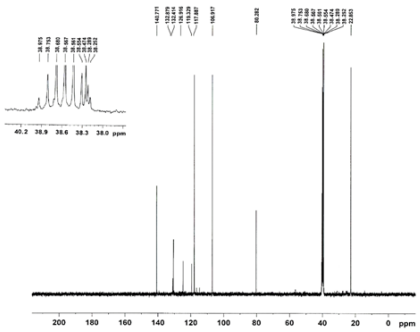

Figure S9. [13]CNMR spectrum of 1',2',3',4',10',11a'-hexahydrospiro[cyclohexane-1,11'-dibenzo [b,e] [1,4] diazepine].

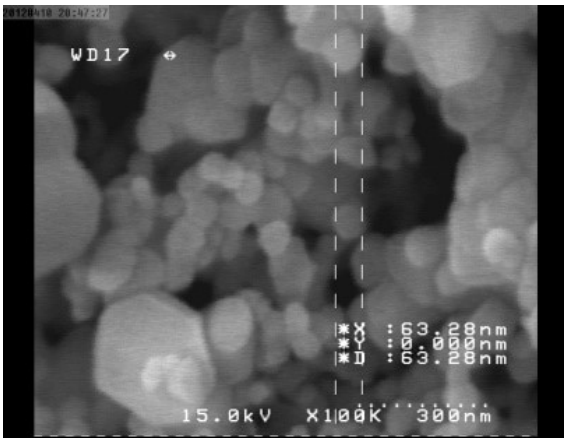

Figure S10. SEM analysis of SnO_2 nanoparticle..

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Ethical Approval
This manuscript does not report on or involve the use of any animal or human data or tissue. So the ethical approval does not applicable.

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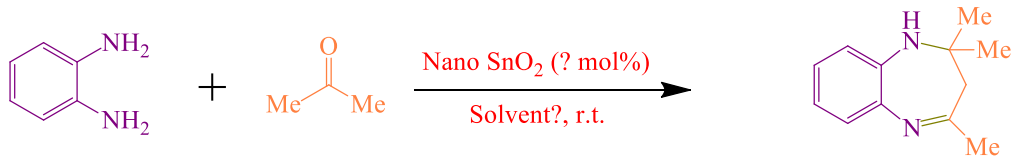
Authors Contributions
All authors have contributed equally to prepare the paper.

Availability of Data and Materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

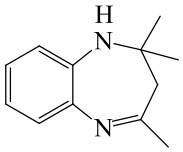
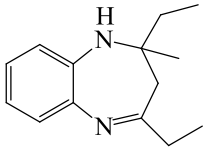
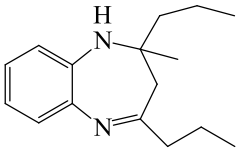
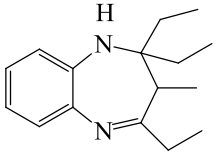
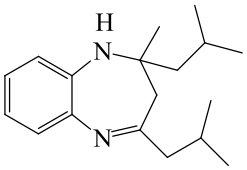
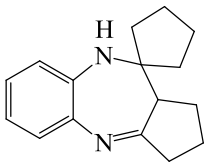
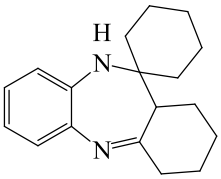
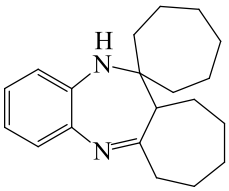
Table 1. Optimization of the reaction conditions in model at room temperature.[a]



Entry	Solvent	Catalytic amount	Reaction time (min)	Yield (%)[b]
1	C_2H_5OH	0.5	40	45
2	C_2H_5OH	1	15	95
3	C_2H_5OH	2	15	95
4	C_2H_5OH	5	20	93
5	C_2H_5OH	10	35	89
6	H_2O	1	60	48
7	CH3CN	1	15	93
8	CH_2Cl_2	1	25	93
9	THF	1	35	87
10	Toluene	1	45	85

[a] Reaction condition: 1,2-phenylenediamine (1 mmol; 0.108 g), acetone (2 mmol; 0.116 g; 0.148 mL);
[b] Isolated yield.

Table 2. Synthesis of 1,5-benzodiazepines catalyzed by SnO_2nanoparticles.[a]

entry	product	time (min)	yield (%)[b]	mp (°C)	mp [lit] (°C)
1		15	95	137-139	137–139 [29]
2		15	93	136-138	137–139 [29]
3		15	94	139-141	138–140 [30]
4		15	95	146-148	144–145 [31]
5		15	95	120-122	118–119 [30]
6		15	95	137-139	138–139 [32]
7		15	96	139-141	136–137 [32]
8		15	94	136-138	134–136 [31]

[a] Reaction condition: 1,2-phenylenediamine (1 mmol), ketones (2 mmol), SnO_2 nanoparticles (1 mol%), C_2H_5OH (2 mL), r.t.; [b] Isolated yield.

Table 2. Synthesis of 1,5-benzodiazepines catalyzed by SnO_2nanoparticles.

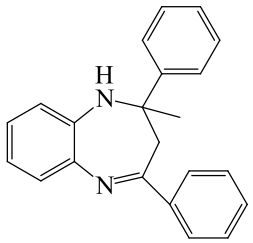
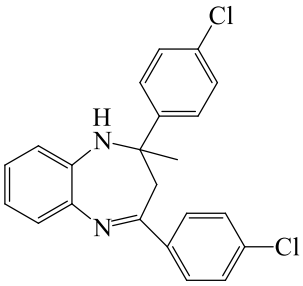
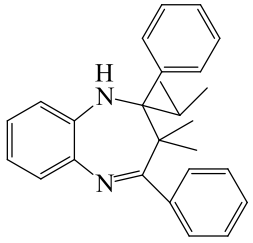
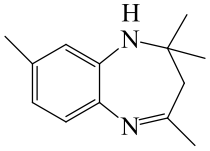
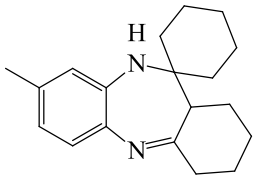
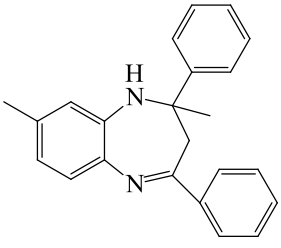
entry	product	time (min)	yield (%)	mp (°C)	mp [Lit] (°C)
9		10	95	150-152	151–152 [29]
10		5	97	139–141	138–140 [33]
11		10	97	118-120	119–120 [32]
12		10	95	128-130	127–128 [32]
13		10	95	143-145	142–143 [32]
14		10	97	94-96	92-93 [32]

Table 2. Synthesis of 1,5-benzodiazepines catalyzed by SnO_2nanoparticles.

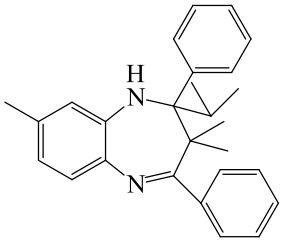
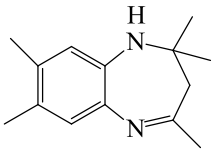
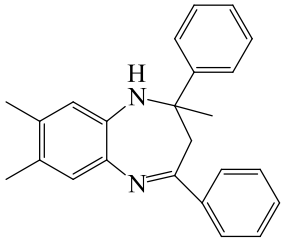
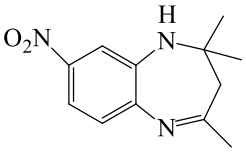
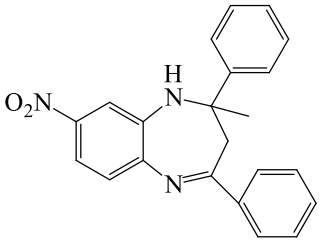
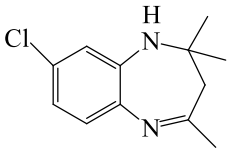
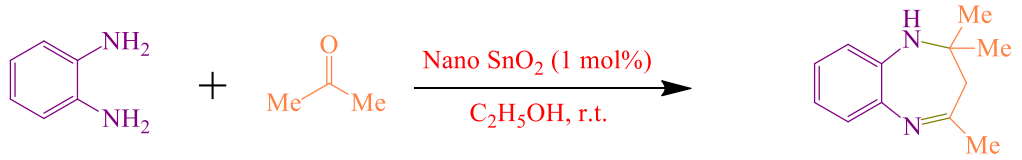
Entry	Product	Time (min)	Yield (%)	Mp (°C)	Mp [Lit] (°C)
15		10	97	121-123	119–120 [32]
16		10	96	111-113	112–114 [32]
17		10	97	114-116	115–116 [32]
18		5	98	114-116	113–114 [32]
19		5	98	137-139	136–138 [32]
20		10	97	133-135	135–136 [29]

Table 3. Comparison of this approach with further processes for the preparation of target molecule (Table. 2, Entry 1).[a]



Entry	Reaction condition	Time	Yield	Reported
(min)	(%)[b]	reference		
1	SnO_2 nanoparticles (1 mol%), C_2H_5OH, r.t.	15	95	This work
2	H-MCM-22 (150 Mg), C_2H_5OH, reflux	60	87	[29]
3	I2 (10 mol%), C_2H_5OH, r.t.	20	93	[32]
4	Thiamine HCl (5 mol%), Solvent free, 80°C	60	66	[33]
5	Silica sulfuric acid (0.05 gr), Solvent free, r.t.	60	98	[31]
6	$NbCl_5$ (10 mol%), n-hexane, 50°C	180	96	[30]

[a] Reaction condition: 1,2-phenylenediamines (1 mmol), Acetone (2 mmol), SnO_2 nanoparticles (1 mol%), C_2H_5OH (2 mL), r.t.; [b] Isolated yield.

References

[1] J. K. Landquist, A. R. Katritzky, and C. W. Rees. *(Eds.), Pergamon, Oxford*, **1**:166–170, 1984.

[2] R. Ricaurte, I. Braulio, A. Rodrigo, and O. Jairo. *Arkivoc*, **13**:67–71, 2014.

[3] R. C. Farges, S. R. Torres, F. Pascual, and R. M. Ribeiro do Valle. *Life Sci*, **74**:1387–1395, 2004.

[4] M. Essaber, A. Baouid, A. Hasnaoui, A. Benharref, and J. P. Lavergne. *Synth. Commun.*, **28**:4097–4104, 1998.

[5] C. W. Kuo, S. V. More, and C. F. Yao. *Tetrahedron Lett.*, **47**:8523–8528, 2006.

[6] W. Ried and E. Torinus. *Chem. Ber.*, **92**:2902–2916, 1959.

[7] P. Stahlofen and W. Ried. *Chem. Ber.*, **90**:815–824, 1957.

[8] R. Gheorghe, E. Comanita, and C. Bogdan. *ActaChim. Slov.*, **49**:575–585, 2002.

[9] R. Fazaeli and H. Aliyan. *Appl.Catal. A. Gen.*, **331**: 78–83, 2007.

[10] W. B. Yi and C. Cai. *J. Fluorine Chem.*, **130**: 1054–1058, 2009.

[11] M. Nardi, A. Cozza, L. Maiuolo, M. Oliverio, and A. Procopio. *Tetrahedron Lett.*, **52**:4827–4834, 2011.

[12] D. Shobha, M. A. Chari, S. T. Selvan, H. Oveisi, A. Mano, K. Mukkanti, and A. Vinu. *Micropor.Mesopor. Mat.*, **129**:112–117, 2010.

[13] M. M. Heravi, S. Sajedi, and H. A. Oskooie. *J. Chin. Chem. Soc.*, **55**:842–845, 2008.

[14] K. Gholivand, A. Zare, H. Jafari, and H. Adibi. *Chin. J. Chem.*, **29**:1290–1293, 2011.

[15] S. Allameh, M. Shaker, and A. Habibnia Milani. *Int. J. Ind. Chem.*, **12**, 2021.

[16] D. Salas Martell, G. Pareja Guzman, J. Tello Hijar, F. Carlos, and J. Rodriguez Reyes. *Int. J. Ind. Chem.*, **11**, 2020.

[17] Z. Peng, Z. Shi, and M. Liu. *Chem. Commun.*, **21**: 2125–2126, 2000.

[18] A. O. Neto, M. Brandalise, R. R. Dias, J. M. S. Ayoub, A. C. Silva, J. C. Penteado, M. Linardi, and E. V. Spinacé. *Int. J. Hydrogen Energy*, **35**:9177–9181, 2010.

[19] D. R. Pyke, R. T. Reid, and R. J. D. J. Tilley. *Chem. Soc. Faraday Trans. 1.*, **76**:1174–1182, 1980.

[20] R. Gavagnin, L. Biasetto, F. Pinna, and G. Strukul. *Appl. Catal. B. Env.*, **38**:91–99, 2002.

[21] A. E. R. S. Khder. *Appl. Catal. A. Gen.*, **343**:109–116, 2008.

[22] J. Li, J. Hao, L. Fu, Z. Liu, and X. Cui. *Catal. Today*, **90**:215–221, 2004.

[23] T. Kawabe, K. Tabata, E. Suzuki, Y. Ichikawa, and Y. Nagasawa. *Catal. Today*, **71**:21–29, 2001.

[24] B. Maleki, M. Baghayeri, S. M. Vahdat, A. Mohammadzadeh, and S. Akhoondi. *RSC Adv.*, **5**: 46545–46551, 2015.

[25] F. Chekin, S. M. Vahdat, and M. J. Asadi. *Russian J. Appl. Chem.(e)Comb. Chem. High Throughput Screen.*, 89(e)16:816–822(e)2–6, (a)2016(e)2013.

[26] Y. Rangraz, S. M. Vahdat, and S. Khaksar. *Heliyon. Sci.*, 9:e15135, (a)2023.