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One pot synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines under solvent-free conditions using anhydrous stannous chloride as catalyst

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ABSTRACT

The present work is mainly designed to synthesize a variety of new 2,3-dihydro-1H-1,5-benzodiazepine derivatives using symmetrical and unsymmetrical diamines and substituted ketones to obtain number of 1,5-benzodiazepine derivatives catalyzed by anhydrous stannous chloride. The proposed mechanism of this reaction involves an intramolecular imine enamine cyclization promoted by stannous chloride anhydrous. The remarkable advantages offered by this method are easily and inexpensive available catalyst, simple procedure, mild conditions, much faster (40–60 min) reactions and moderate to good yields of products.

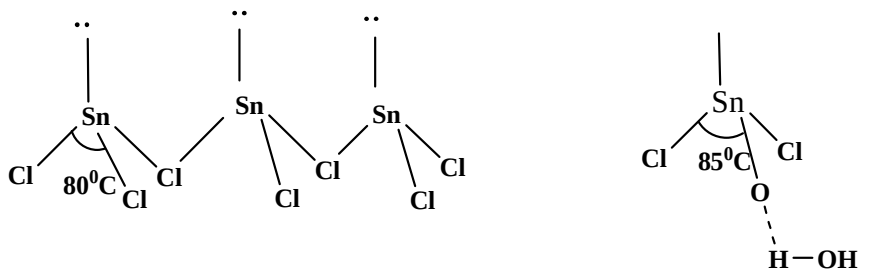
Keywords: *o*-Phenylenediamine, anhydrous stannous chloride, 3,4-Diaminotoluene, 1,5-Benzodiazepine.

INTRODUCTION

Benzodiazepine is an important class of pharmacologically active organic compounds. Considerable interest has been focused on the synthesis of benzodiazepines because of their wide range of biological activities [1] and therapeutics [2]. The discovery of diazepam followed by many other psychotropic agents sharing a 1,4 benzodiazepines skeleton has also promoted the studies on the isomeric 1,5-benzodiazepine ring system [3] along with the synthetic approaches to mono and diannelated 1,5-benzodiazepines [4]. Due to their accessibility, easily functional and potential pharmacological properties, mainly 1,5-benzodiazepines and 1,5-benzodiazepinone derivatives have received significant attention. Peripheral cholecystokinin receptor agonists [5], CCKB/gastrin receptor agonists [6], arginine vasopressin antagonists [7], CNS depressants [8-9], antiamoebics [10] and antiproliferative agents[11,12] derived from 1,5-benzodiazepinones have

been reported. Therapeutic values of benzodiazepine results to find out efficient and convenient methods for their preparation. Particularly, 1,5-benzodiazepines are useful precursors for synthesis of some fused ring benzodiazepine derivatives such as triazolo-, oxadiazolo-, oxazino- or furano-benzodiazepines. However, the most commonly employed methods involve the cyclocondensation of 1,2–diamines with ketones[13], enones[14] or β- haloketones[15], using ionic liquids[16], under microwave irradiation[17] and $SbCl_3$-Al_2O_3[18], $HClO_4$[19], acetic acid[20], PPA or SiO_2[21],$TiCl_4$:Sm[22], $Yb(OTf)_3$[23], $H_{14}[NaP_5W_{30}O_{110}]$[24]. The known method of benzodiazepine synthesis suffers from one or other limitations such as harsh reaction conditions, expensive reagents, low yields, relatively long reaction time and formations of side products. The research still continuous to have a better methodology for the synthesis of benzodiazepines in terms of simplicity, ecofriendly and economic viability which is achieved by using $SnCl_2$ anhydrous. Pasha etal [25] earlier utilized the stannous chloride dihydrate for the synthesis of 1,5-benzodiazepine. Our aim is to use anhydrous stannous chloride as catalyst and observed any change in reaction condition and percentage yield.

$SnCl_2$ is widely used as a reducing agent (in acid solution), Stannous (II) chloride also behaves as a Lewis acid, forming complexes with ligands such as chloride ion. $SnCl_2$ has a lone pair of electrons. In the solid state, crystalline $SnCl_2$ anhydrous forms chains linked via chloride bridges as shown in **Fig. 1.** The dihydrate is also three-coordinate, with one water coordinated on to the tin and second water coordinated to the first. The main part of the molecule stacks into double layers in the crystal lattice, with the "second" water sandwiched between the layers.

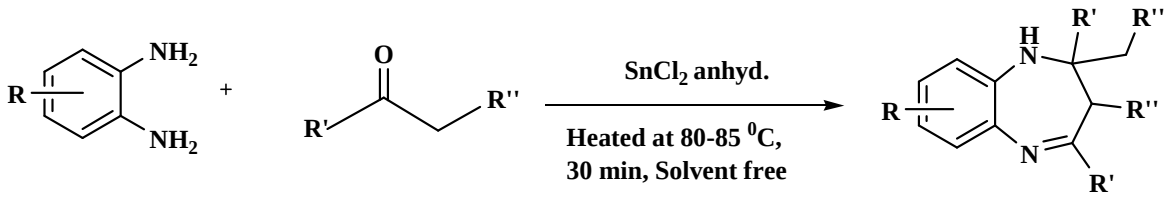


Crystalline $SnCl_2$ **$SnCl_2$ dihydrate**

Fig. 1

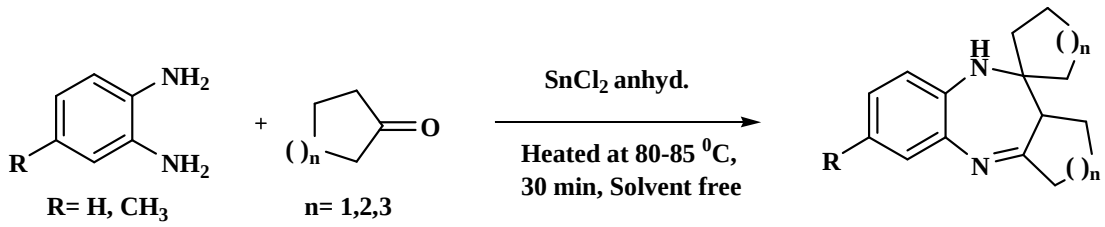
$SnCl_2$ is used to selectively reduce aromatic nitro groups to anilines. Stannous chloride can be used to test for the presence of gold compounds [26]. $SnCl_2$ is used in Friedel-Crafts reactions as a catalyst for homogeneous alkylation and cyclization. Lewis acid catalysis to increase the rate, as well as the regio- and stereoselectivity of the addition [27].

o-Phenylenediamine (OPD), ketones (in 1:2 equivalents respectively) in the presence of Stannous chloride anhydrous (catalytic amount) were ground well using mortar and pestle, at 80-85^{0}C under solvent free conditions, the corresponding 1,5-benzodiazepine and fused ring benzodiazepine derivatives were obtained in good yield within an hour. Completion of the reaction was monitored by TLC **(Scheme 1).**



Scheme 1

Interestingly, a cyclic ketone such as cyclohexanone also worked well with similar success to afford fused ring 1,5-benzodiazepines in a high yield **(Scheme 2).**



Scheme 2

EXPERIMENTAL SECTION

General procedure for the preparation of 2,3-Dihydro-1*H*-1,5-benzodiazepines: Substituted Ketone (20 mmoles) , *o*-phenylenediamine (10 mmoles), and stannous chloride anhydrous (0.5 mmoles) were ground well using mortar and pestle and transferred to a 50 ml round bottomed flask and heated at 80-85^{0}C for 40 min to 1hr. After completion of the reaction (monitored on TLC), the reaction mixture was poured into crushed ice and basified with ammonia solution. The precipitated solid was separated, washed thoroughly water and dried. The product was recrystallised from ethanol to get the pure 2,3-dihydro-2-methyl-2,4-diphenyl-1*H*-1,5-benzodiazepine.

Characterization data for 1,5- benzodiazepines:

2,2,4- Trimethyl- 2,3-dihydro -1*H*-1,5-benzodiazepine: (Entry 1)
UVmax (MeOH): 312.20 and 236.80 nm; **IR (KBr), ν_{max}/ cm^{-1}:** 3292 cm^{-1} (NH), 2955 cm^{-1} (Aromatic CH), 1632 cm^{-1} (Alkene C=C), 1474 cm^{-1} (Aromatic C=C); **^{1}H-NMR ($CDCl_3$):** δ 1.3 (s, 6H, -C*H*$_2$), δ 2.2 (s, 2H, -C*H*$_2$), δ 2.4 (s, 3H, -C*H*$_3$), δ 6.7-7.2 (m, 4H, Ar*H*)

2,3- Dihydro-2- Methyl- 2,4- diphenyl-1H-1,5- benzodiazepine: (Entry 2)
UVmax (MeOH): 357 nm and 273 nm; **IR (KBr)), ν_{max}/ cm^{-1} :** 3277 cm^{-1} (Sec N-H), 3061 cm^{-1} (Aromatic C-H), 2972cm^{-1} (Aliphatic C-H), 1559cm^{-1} (Aromatic C=C); **^{1}H-NMR ($CDCl_3$), δ/ ppm:** δ 1.8 (s, 3H, -C*H*$_3$), δ 3 (d, 1H, *J* = 13.1 Hz, -C*H*), δ 3.2 (d, 1H, *J* = 13.0 Hz, -C*H*), δ 6.8-7.7 (m, 14H, Ar*H*).

2,4- Diethyl-2-methyl-2,3-dihydro-1*H*-1,5- benzodiazepine: (Entry 3)
UVmax (EtOH): 316 nm and 280 nm; **IR (KBr), ν_{max}/ cm^{-1}:** 3339 cm^{-1} (Sec N-H), 3058 cm^{-1} (Aromatic C-H), 2968 cm^{-1} (Aliphatic C-H), 1639 cm^{-1} (C=N), 1472 cm^{-1}(Aromatic C=C), 1253

cm^{-1} (C-N); **^{1}H-NMR ($CDCl_3$), δ/ ppm:** δ 0.8 (t, 3H, -C*H*$_3$), δ 1.3 (m, 6H, -C*H*$_3$, -C*H*$_3$), δ 1.7 (q, 2H, -C*H*$_2$), δ 2.2 (m, 2H, -C*H*$_2$), δ 2.6 (q, 2H, -C*H*$_2$), δ 3.3 (br, 1H, -N*H*), δ 6.5-7.3 (m, 4H, Ar*H*).

11-Spirocyclocyclohexane-2,3,4,10,11,11a-hexahydro-1H-dibenzo[*b,e*][1,4] diazepine: (Entry 4)
UVmax.(EtOH): 342 nm and 282 nm; **IR (KBr), ν_{max}/ cm^{-1}:** 3278 cm^{-1} (Sec. NH), 3059 cm^{-1} (Aromatic CH), 2859 cm^{-1} (Alkane CH), 1635 cm^{-1} (Imine C=N), 1481 cm^{-1} (Aromatic C=C), 751 cm^{-1} (Ortho substituted oop); **^{1}H-NMR ($CDCl_3$), δ/ ppm:** δ 1.2-1.9 (m, 16H, -C*H*$_2$), δ 2.3-2.6 (m, 3H, -C*H*), δ 4.5 (1H, br, N*H*), δ 6.8-7.9 (m, 4H, Ar*H*).

10-Spirocycloheptan-6,7,8,9,10,10a,11,12-octahydrobenzo[*b*]cyclohepta[*e*] [1,4]diazepine: (Entry 5)
UVmax (MeOH): 398 nm and 344 nm; **IR (KBr), ν_{max}/ cm^{-1}:** 3266 cm^{-1} (Sec N-H), 2916 cm^{-1} (Aromatic C-H), 2972 cm^{-1} (Aliphatic C-H), 1634 cm^{-1} (Alkene C=C), 1484 cm^{-1} (Aromatic C=C); **^{1}H-NMR ($CDCl_3$), δ/ ppm:** δ 1.5-2.4 (m, 21H, -C*H*$_2$, -N*H*), δ 2.6 (m, 2H, -C*H*$_2$), δ 2.8 (m, 1H, -C*H*), δ 6.6-7.4 (m, 4H, Ar*H*).

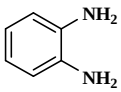
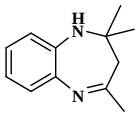
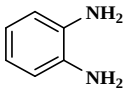
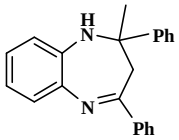
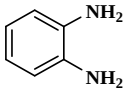
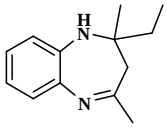
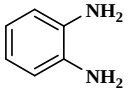
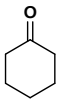
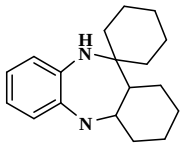
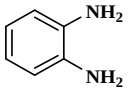
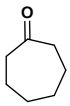
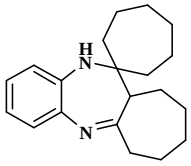
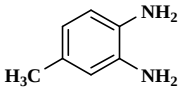
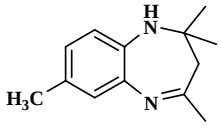
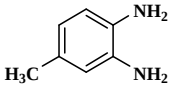
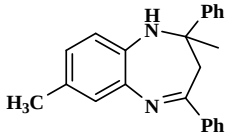
2,2,4-Trimethyl-2,3-dihydro-8-methyl-1H-1,5-Benzodiazepine: (Entry 6)
UVmax (EtOH): 349 nm and 347.5 nm; **IR (KBr) ν_{max}/ cm^{-1}:** 3454 cm^{-1} (Sec. NH), 2924 cm^{-1}(Aromatic CH), 2853 cm^{-1}(Alkane CH), 1437 cm^{-1} (Aromatic C=C), 1237 cm^{-1} (C-N), 947 (1,2,4-substituted oop); **^{1}H-NMR ($CDCl_3$), δ/ ppm:** δ 1.2 (s, 6H, -C*H*$_3$), δ 1.35 (s, 3H, -C*H*$_3$), δ 2.3 (m, 5H,-C*H*$_3$, -C*H*, -C*H*), δ 6.5 (s, 1H, Ar*H*), δ 6.79 (d, 1H, *J* = 7.4, Ar*H*), δ 7.0 (d, 1H, *J* = 8.7, Ar*H*).

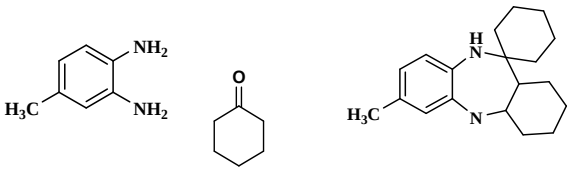
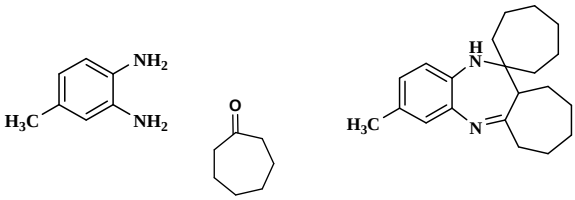
2,3- Dihydro-2,8- dimethyl- 2,4- diphenyl-1H-1,5- benzodiazepine: (Entry 7)
UVmax.(MeOH): 362 nm and 360 nm; **IR (KBr):** 3335 cm^{-1} (Sec. NH), 3058 cm^{-1}(Aromatic CH), 2969 cm^{-1}(Alkene CH), 2858 cm^{-1}(Alkane CH), 1612 cm^{-1} (Imine C=N), 1493 cm^{-1} (Aromatic C=C), 1328 cm^{-1} (C-N), 759 cm^{-1} (Ortho substituted oop); **^{1}H-NMR ($CDCl_3$), δ/ ppm:** δ 1.75 (s, 3H, -C*H*$_3$), δ 2.6 (s, 4H, -C*H*$_3$, -N*H*), δ 2.9 (d, 1H, -C*H*), δ 3.1 (d, 1H, -C*H*), δ 7.2-7.9 (m, 14H, Ar*H*).

11-Spirocyclocyclohexane-2,3,4,10,11,11a-hexahydro-8-methyl-1H-dibenzo[*b,e*][1,4] diazepine: (Entry 8)
UVmax.(EtOH): 258 nm and 279 nm.; **IR (KBr):** 3351 cm^{-1} (Sec. NH), 2931 cm^{-1} (Alkene CH), 2857 cm^{-1} (Alkane CH), 1634 cm^{-1} (Imine C=N), 1484 cm^{-1} (Aromatic C=C); **^{1}H-NMR ($CDCl_3$), δ/ ppm:** δ 1.7-2.5 (m, 18H, -C*H*$_2$), δ 3 (m, 4H, -C*H*$_3$, -C*H*), δ 7.3-7.9 (m, 3H, Ar*H*).

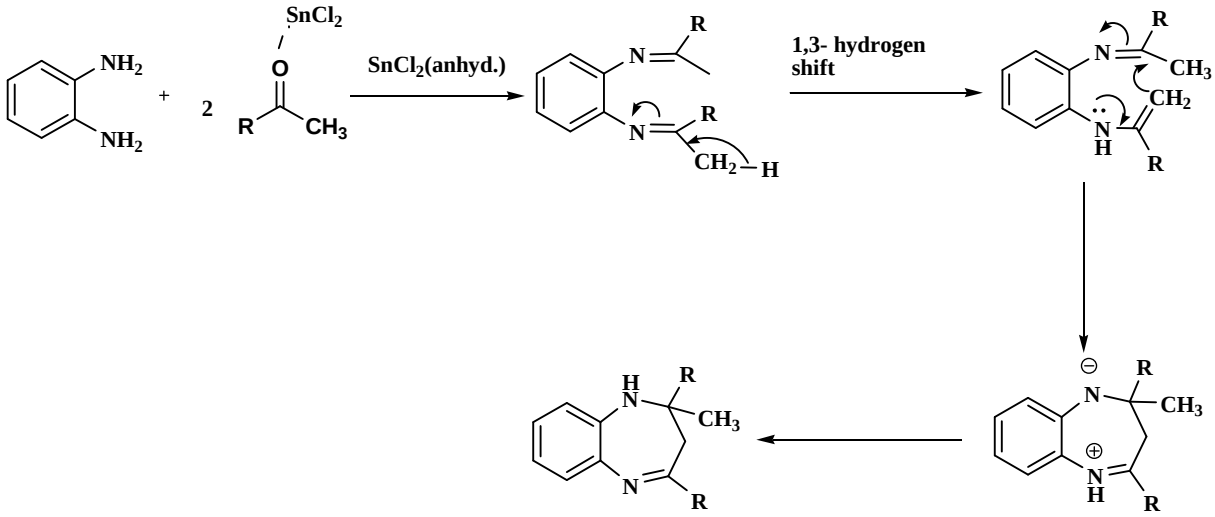
10-Spirocycloheptan-6,7,8,9,10,10a,11,12-octahydro-8-methylbenzo[*b*]cyclo hepta [*e*] [1,4]diazepine: (Entry 9)
UVmax.(MeOH): 345 nm and 286 nm; **IR (KBr):** 3328 cm^{-1} (Sec N-H), 3060 cm^{-1} (Aromatic C-H), 2923 cm^{-1} (Alkene C-H), 2852 cm^{-1} (Aliphatic C-H), 1617 cm^{-1} (Alkene C=C), 1493 cm^{-1} (Aromatic C=C); **^{1}H-NMR ($CDCl_3$), δ/ ppm:** δ 1.6 (m, 22H, -C*H*$_2$), δ 2.2 (s, 3H, -C*H*$_3$), δ 3.1 (br, 2H, -N*H*, -C*H*), δ 6.5 (s, 1H, -C*H*), δ 6.76 (d, 1H, *J* = 7.8, -C*H*), δ 7.1 (d, 1H, *J* = 7.9, Ar*H*).

TABLE: 1 Condensation of *o*-phenylenediamine with various ketones catalyzed by Stannous chloride anhydrous and stannous chloride dehydrate

Entry	Diamine	Ketone	Product	Yield (%) $SnCl_2$ anhyd.	Yield (%) $SnCl_2.2H_2O$ [25]	M.P.(^{0}C)	M.P.^{lit}(^{0}C)
1.				80	92	120-122	136-138 [23]
2.				75	NR	100-102	150-152 [23]
3.				71	80	138-139	137-139 [23]
4.				74	NR	134-135	136-137 [23]
5.				63	NR	133-134	135-136 [24]
6.				77	NR	126-128	127-128 [24]
7.				68	NR	91-92	92-93 [24]

8.		65	NR	140-142	142-143 [24]
9.		71	NR	121-122	

NR=Not Reported



Scheme 2: Proposed Mechanism and possible intermediates.

RESULTS AND DISCUSSION

We investigated the reaction of a series of symmetrical and unsymmetrical ketones with *o*-phenylenediamine to get the corresponding 1,5-benzodiazepines. All synthesized derivatives were characterized using M.P., U.V., IR and ^{1}H NMR. The easy work-up of the reaction was also the advantageous aspect of this method. It includes the pouring the reaction mixture in water which on filtration gave the corresponding 2,3-dihydro-1*H*-1,5-benzodiazepines. This method was superior in regards with yield and reaction time than the previously reported methods. Especially with Stannous chloride dihydrate [25], a tedious procedure is used for proceeding the reaction mixture for the extraction of the final product in comparison with Stannous chloride anhydrous. In case of our reaction with ethylmethylketone only column chromatography was used for obtaining the pure product, whereas $SnCl_2$ dihydrate uses column chromatography for all reactions. But the yield reported earlier using stannous chloride dihydrate was high as compared with stannous chloride anhydrous. The results are summarized in **Table 1**. Both of the

linear and cyclic ketones react with the diamines containing electron donating group on aromatic rings, without any significant difference, to give the corresponding 1,5-benzodiazepine derivatives in quantitative yields. No reaction was observed when *o*-phenylenediamine was treated with ketone under similar conditions in the absence of a catalyst. As shown in **Scheme 2**, the proposed mechanism of the reaction involves an intramolecular imine enamine cyclization promoted by Stannous chloride anhydrous. Amine of *o*-phenylenediamine attacks carbonyl group of ketone giving the intermediate diimine. A 1,3-hydrogen shift of the attached methyl group then occurs to form an isomeric enamine **B**, which cyclizes to afford seven membered ring.

CONCLUSION

It can be summarized that it is a mild and efficient method for the synthesis of 2,3-dihydro-1*H*, 1,5-benzodiazepines. The work out is easy, no solvent is required, reaction condition are mild and yield are moderate to good.

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