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# An expeditious synthesis of 1,5-benzodiazepine derivatives catalyzed by $CdCl_2$

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2,3-Dihydro-1*H*-1,5-benzodiazepines have been synthesized by the condensation of *o*-phenylenediamine and cyclic or acyclic ketones in the presence of $CdCl_2$ as catalyst at 80-85ºC temperature. The yields are high and the reactions go to completion within 10-20 min.

**Keywords:** 2,3-Dihydro-1*H*-1,5-benzodiazepines, *o*-phenylenediamine, ketones, $CdCl_2$, solvent-free reaction

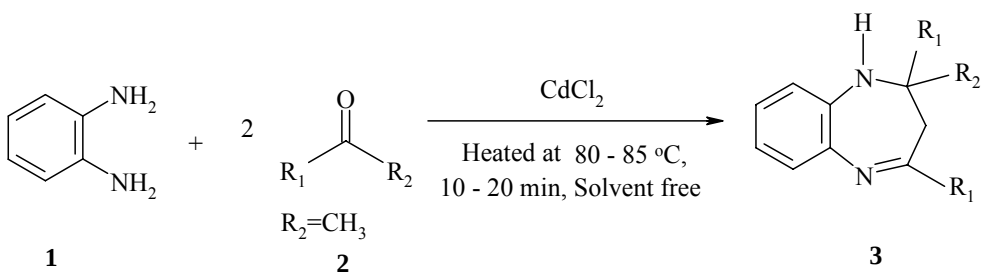
**IPC Code:** Int.Cl.[8] C07D

In 1971 Sternbach introduced benzodiazepines as drugs[1]. While some benzodiazepines are used as anti-convulsant, anti-anxiety, analgesic, sedative, antidepressive and hypnotic agents[2,3], some other benzodiazepine derivatives find application in industries such as photography, as dyes for acrylic fibers[3] and as valuable synthons for the preparation of other fused compounds such as triazolo[4a], oxadiazolo[4b], oxazino[4c] or furobenzodiazepines[4d].

Expeditious synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines and related derivatives and improvements in the syntheses have been sought continuously. Thus, the preparation of this type of heterocyclic nucleus is of much importance. Consequently, a few methods have been reported with reagents such as $InBr_3$ (ref. 5), $BF_3.OEt_2$ (ref. 6), $MgO\text{-}POCl_3$ (ref. 7), polyphosphoric acid-$SiO_2$ (ref. 8), solid superacid sulfated zirconia[9], zirconia solid acid[10], $Yb(OTf)_3$ (ref. 11), $Sc(OTf)_3$ (ref. 12), molecular iodine[13], under microwave irradiation using acetic acid[14], $Al_2O_3\text{-}P_2O_5$ (ref. 15), polymer (PVP) supported ferric chloride[16], $CeCl_3\text{-}NaI\text{-}SiO_2$[17] and ionic liquids[18]. Many of the existing methods involve expensive reagents, strongly acidic conditions, longer reaction times, high temperatures, unsatisfactory yields, cumbersome product isolation and environmental pollution. Therefore, there is a need for simple and environmentally friendly processes for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines.

## Results and Discussion

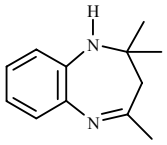
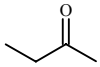
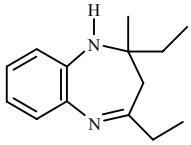
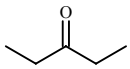
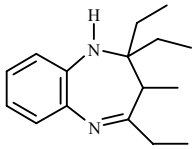
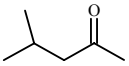
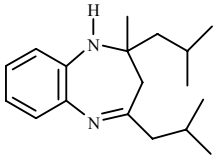
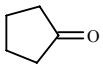
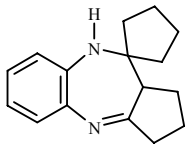
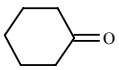
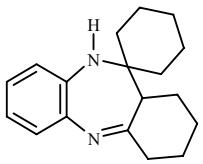
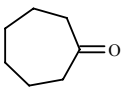
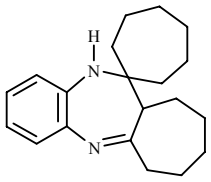
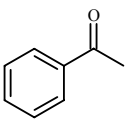
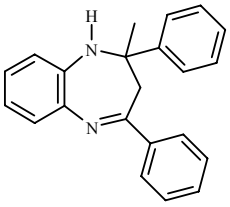
In continuation of the work on the synthesis of medicinally important molecules under environmentally safe conditions[19], it has been found that $CdCl_2$, which is an inexpensive and common chemical, can efficiently catalyze this reaction. Synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines using acyclic, cyclic and aromatic ketones and *o*-phenylenediamine (2:1 equivalents respectively) in the presence of $CdCl_2$ (catalytic amount) at 80-85ºC under solvent free condition is achieved in good to excellent yields within 10-20 min as shown in **Scheme I**.




**1** **2** **3**

**Scheme I**

**Table I —** Condensation of *o*-phenylenediamine with acyclic, cyclic and aromatic ketones in the presence of catalytic $CdCl_2$

| Compd | Ketone **2** | Yield (%)[a] | Product[b] **3** |
|---|---|---|---|
| **a** |  | 94 |  |
| **b** |  | 80 |  |
| **c** |  | 92 |  |
| **d** |  | 70 |  |
| **e** |  | 80 |  |
| **f** |  | 82 |  |
| **g** |  | 75 |  |
| **h** |  | 92 |  |

[a] Isolated yields.

[b] All the products are known, characterized by IR, MS and NMR spectral analysis and compared with the authentic samples.

The same process was successfully extended to other 1,5-benzodiazepine derivatives and the results are summarized in **Table I**. Treatment of *o*-phenylenediamine with acetone (Compd. **2a**, **Table I**) in the presence of $CdCl_2$ at 80-85ºC (a water condenser was fixed and ice-cold water was circulated to condense acetone) gave 2,2,4-trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine in 94% yield within 10 min. Similarly acyclic ketones: 2-butanone, 3-pentanone and isobutylmethylketone (**Table I**, Compd. **2b**, **c** and **d**) and cyclic ketones: cyclopentanone, cyclohexanone and cycloheptanone (Compd. **2e**, **f** and **g**) reacted smoothly to give the corresponding 1,5-benzodiazepines in 70-92% yield. Acetophenone (Compd. **2h**) also reacted easily with *o*-phenylenediamine within 20 min to give 2-methyl-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine in 92% yield.

**Experimental Section**

Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR, $^1H$ and $^{13}C$ NMR and GC-MS were recorded on Nicolet 400D FT-IR spectrophotometer, 200 MHz Brucker spectrometer and Shimadzu GC-MS QP 5050A respectively. Ketones, *o*-phenylenediamine and $CdCl_2$ were all commercial products and were used without further purification.

**General procedure for the preparation of 1,5-benzodiazepines**. 3-Pentanone (1.72 g, 20 mmoles), *o*-phenylenediamine (1.08 g, 10 mmoles) and $CdCl_2$ (0.12 g, 0.5 mmole) were ground well using mortar and pestle and transferred to a 50 mL round bottomed flask and heated at 80-85ºC for 10-20 min. After completion of the reaction {monitored on TLC [eluant; EtOAc: Pet.ether (1:6)]}, the reaction mixture was diluted with water and extracted with EtOAc (2 × 10 mL). The combined organic layer was dried over anhydrous $Na_2SO_4$, concentrated *in vacuo* and subjected to silica gel column chromatography to get 2,2,4-triethyl-3-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine (2.24 g, 92%). The aqueous layer was disposed after treatment with 10% sodium sulphide solution. Yellow precipitate of CdS was filtered and kept aside for future use. All the products prepared by this procedure were characterized by comparison of their IR, NMR spectra and GC-MS spectral analysis with authentic samples.

**2,2,4-trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine**, **3a**: Yellow crystals; m.p. Found 137-38ºC, Reported:136-38ºC[5] ; IR (KBr): 3343, 1657, 1610 $cm^{-1}$; $^1H$ 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); $^{13}C$ NMR ($CDCl_3$): δ 29.7, 30.4, 45.0, 67.8, 121.6, 122.0, 125.4, 126.7, 137.8, 140.6, 171.8; MS: m/z 188 ($M^+$).

**2,4-Diethyl-2-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine**, **3b**: Yellow solid; m.p. Found 138ºC, Reported 137-39ºC[5] ; IR (KBr): 3335, 1648, 1605 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 0.99 (t, 3H, *J* = 6.9 Hz), 1.25 (t, 3H, *J* = 7.0 Hz), 1.70 (q, 2H, *J*=6.9 Hz), 2.15 (m, 2H), 2.35 (s, 3H), 2.69 (q, 2H, *J*= 7.0 Hz), 3.25 (br s, 1H, NH), 6.78-7.35 (m, 4H); $^{13}C$ NMR ($CDCl_3$): δ 8.7, 10.8, 26.9, 35.5, 35.7, 42.1, 70.5, 121.8, 125.4, 126.2, 127.0, 137.9, 140.8, 175.6; MS: m/z 216 ($M^+$).

**2,2,4-triethyl-3-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine**, **3c**: Colorless solid; m.p. Found 142- 44ºC, Reported 143-44ºC[11]; IR (KBr): 3325, 1640, 1610 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 0.75-1.05 (m, 10H), 1.20-1.38 (m, 4H), 1.50-1.65 (m, 2H), 2.40-2.60 (m, 2H), 2.87 (q,1H, *J* = 6.9 Hz ), 3.75 (br s,1H, NH), 6.57 (d, 1H, *J* = 8.0 Hz), 6.65 (t, 1H, *J* = 8.0 Hz), 6.90 (t, 1H, *J* = 8.0 Hz), 7.38 (d, 1H, *J* =8.0 Hz); $^{13}C$ NMR ($CDCl_3$): δ 7.5, 7.9, 11.5, 12.3, 28.0, 28.4, 35.6, 46.2, 68.6, 117.5, 118.0, 126.6, 132.8, 139.0, 142.4, 173.4; MS: m/z 244 ($M^+$).

**2-Methyl-2,4-diisobutyl-2,3-dihydro-1*H*-1,5-benzodiazepine**, **3d**: Yellow solid; m.p. Found 119ºC, Reported 118-20ºC[11]; IR (KBr): 3335, 1645, 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 0.95-1.05(m, 12H), 1.32 (s, 3H), 1.49-1.52 (m, 2H), 1.65-1.75 (m, 1H), 2.05-2.25 (m, 3H), 2.24 (d, 2H, *J* = 12.7Hz), 6.60-6.65 (m, 1H), 6.85-6.95 (m, 2H), 7.05-7.15 (m, 1H); $^{13}C$ NMR($CDCl_3$): δ 22.5, 22.7, 24.2, 24.9, 25.0, 26.3, 28.1, 43.5, 51.7, 51.9, 70.8, 121.4, 121.5, 125.2, 127.2, 137.8, 140.4, 173.9; MS: m/z 272 ($M^+$).

**10-Spirocyclopentane-1,2,3,9,10,10*a*-hexahydrobenzo[*b*]cyclopenta[*e*][1,4]diazepine**, **3e**: Yellow solid; m.p. Found 136-38ºC, Reported 137-38ºC[5]; IR (KBr): 3335, 1660, 1610 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.30-1.90 (m, 12H), 2.30-2.60 (m, 3H), 4.50 (br s, NH, 1H), 6.70-7.39 (m, 4H); $^{13}C$ NMR ($CDCl_3$): δ 23.4, 24.1, 24.3, 28.7, 33.4, 38.5, 39.2, 54.4, 67.3, 118.6, 119.3, 126.9, 132.1, 139.2, 143.4, 178.0; MS: m/z 240 ($M^+$).

**10-Spirocyclohexane-2,3,4,10,11,11*a*-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepine**, **3f**: Yellow solid; m.p. Found 136-38ºC, Reported 136-37ºC[5]; IR (KBr): 3290, 1645, 1605 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.23-1.85 (m, 16 H), 2.30-2.70 (m, 3H), 4.45 (br s, NH, 1H), 6.65-7.35 (m, 4H); $^{13}C$ NMR ($CDCl_3$): δ 21.6, 21.7, 23.2, 24.5, 25.3, 33.5, 34.4, 39.3, 40.5, 52.4,

63.1, 121.3, 121.5,126.3,129.6, 138.1,142.6, 178.9; MS: m/z 268 ($M^+$).

**10-Spirocycloheptan-6, 7, 8, 9, 10, 10*a*, 11, 12-octahydrobenzo[*b*] cyclohepta[*e*] [1,4]diazepine**, **3g**: Yellow solid; m.p. Found 136ºC, Reported 135-36ºC[5]; IR (KBr): 3235, 3280, 1645, 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 0.90-1.95 (m, 20H), 2.25-2.95 (m, 3H), 3.60 (br s, NH, 1 H), 6.60-7.38 (m, 4H); $^{13}C$ NMR ($CDCl_3$): δ 22.5, 23.2, 26.5, 28.4, 28.9, 29.5, 29.7, 30.1, 38.5, 40.9, 54.3, 72.5, 121.3, 121.5, 125.5, 127.6, 137.5, 139.8, 179.1; MS: m/z = 296 ($M^+$).

**2-Methyl-2, 4-diphenyl-2, 3-dihydro-1*H*-1, 5-benzodiazepine**, **3h**: Yellow solid; m.p. Found 150-52ºC, Reported 151-52ºC[11]; IR (KBr): 3345, 1635 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.80 (s, 3H), 2.95 (d, 1H, *J* = 12.8 Hz), 3.15 (d, 1H, *J* = 12.8 Hz) 3.45 (br s, NH), 6.55-7.0 (m, 3H), 7.15-7.35 (m, 7H), 7.55-7.65 (m, 4H); $^{13}C$ NMR ($CDCl_3$): δ 167.5, 146.6, 140.1, 139.5, 138.2, 129.8, 128.6,128.4, 121.1, 127.1, 126.4, 125.5, 121.7, 121.5, 73.9, 43.2, 29.9; MS: m/z 312 ($M^+$).

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