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# Synthesis of 1,5-benzodiazepines using catalytic Dowex-50W as a recyclable cation exchange resin under solvent-free condition

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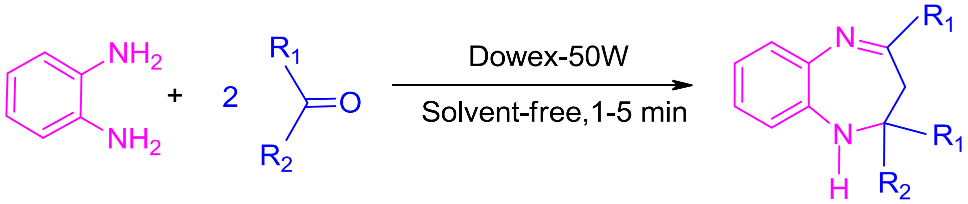
## ABSTRACT

A simple, efficient and versatile route to the synthesis of 1,5-benzodiazepines by the condensation of *o*-phenylenediamine (OPDA) with cyclic/acyclic/aromatic methyl ketones in the presence of catalytic Dowex-50W, an acidic cation exchange resin under solvent-free condition is reported. The present method affords excellent yield of the products in short reaction durations. Catalyst recovery and recyclability has broadened the scope of designing the synthesis of these privileged molecules.



Key words: 1,5-Benzodiazepines; *o*-Phenylenediamine (OPDA); Ketones; Dowex 50W; Recyclable catalyst; Solvent-free reaction.

## 1. Introduction

Development of green technologies is a major objective in the present day research scenario;[1,2] and the synthetic organic chemists on the other hand, are focusing on the strategic design of newer chemical processes to improve the environmental performance. Recycling of the catalysts and replacement or non-use of volatile organic solvents is of utmost importance to attain environmentally benign conditions and such methodologies are especially important in the organic synthesis. [3−7]

The privileged *N*-containing heterocyclic compounds: benzodiazepines are key synthons for the synthesis of various fused ring systems.[8] Some of the annulated naturally occurring benzodiazepine based heterocycles are: pyrrolo[2,1-*c*]-[1,4]benzodiazepines,[9] thiazolo[4,3-*c*]-[1,4]benzodiazepines,[10] and substituted chromeno[4,3-*b*][1,5] benzodiazepines,[11] and these molecules exhibit antitumor and antineoplastic activities. Bioactive oxadiazolo,[12a] and oxazino or furano-fused benzodiazepines[13] are derived from substituted 1,5-benzodiazepines.

1,5-Benzodiazepines also exhibit sedative, anti-convulsant, antianxiety, hypnotic, analgesic and antidepressant activities.[14−18] Their polycyclic derivatives are used in the

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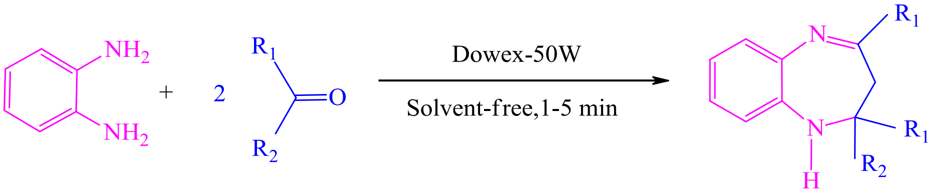
treatment of CNS disturbances.[19−22] Pharmacological studies on these drugs has revealed their applicability in the treatment of cancer, schizophrenia and cardiovascular diseases.[23] Application of this motif and its derivatives is well-documented in the dye industries for acrylic fibres and in the photography.[24] Methods are available in the literature on the synthesis of 1,5-benzodiazepines which involve the condensation of *o*-phenylenediamine with α,β-unsaturated carbonyl compounds, β-haloketones or ketones in the presence of $BF_3·OEt_2$,[25] $NaBH_4$,[26] MgO-$POCl_3$,[27] $SO_4^{2-}$-$ZrO_2$,[28] Yb(OTf)$_3$,[29] Sc(OTf)$_3$,[30] AcOH-microwaves,[31] 2,4,6-trichloro-1,3,5-triazine,[32] ionic liquids,[33,34] (L-Proline)$_2$Zn,[35] $CeCl_3$-NaI-$SiO_2$,[36] $InBr_3$,[37] glycerol,[38] Grignard reagents,[39] boric acid,[40] $Bi(NO_3)_2·5H_2O$,[41] $AgNO_3$[42] and molecular iodine.[43] Use of heterogeneous catalysts in the synthesis of benzodiazepines has driven much attention with catalysts such as: zirconia solid acid,[44] $Al_2O_3$-$P_2O_5$,[45] $Ag_3PW_{12}O_{40}$,[46] PVP-$FeCl_3$,[47] H-MCM-22,[48] amberlyst-15 immobilized in 1-butyl-3-methylimidazolium hexafluorophosphate ionic liquid,[49] $HBF_4$-$SiO_2$,[50] HY-Zeolite,[51] graphite oxide,[52] metal-organic frameworks (MOFs),[53] metal-benzenetricarboxylates,[54] Fe-containing intercalated montmorillonites[55] and other Iron-containing materials.[56]

While homogeneous catalysts are not reusable, due to constraints over environmental safety, heterogeneous catalysts find application in the synthesis of these privileged molecules. However, the procedures for preparation of some of the heterogeneous catalysts pose economic issues; and some of the reported methods of preparing benzodiazepines suffer due to the harsh reaction conditions, high catalyst loading, occurrence of several side products, use of toxic and/or hazardous transition metal incorporated materials and use of organic solvents. Therefore, there exists a scope for the development of clean and efficient method for the synthesis of benzodiazepines. We have reported the use of zinc chloride[57] and catalytic *p*-TSA[58] in the cyclization of *o*-phenylenediamine (OPDA) and aryl alkyl ketones/cyclic or acyclic alkyl ketones earlier from our laboratory.

A strong acidic cation exchange resin designated as “Dowex 50W” is readily available in the market in the form of spherical beads; it is a sulfonated polystyrene resin cross-linked with divinyl benzene, with varied degree of cross-linking; it has found application in water technology, and in conducting the size-in-solution evaluations and has been found to be the optimum resin in several chemical reactions. Dowex 50W can expedite a variety of synthetic organic transformations as a metal-free catalyst without product contamination. Synthesis of *iso*propyl lactate,[59] 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes and 1,8-dioxo-octahydroxanthenes[60] and *N*,*N'*-disubstituted-4-aryl-3,4-dihydropyrimidinones[61] are catalyzed by Dowex 50W resin. Also, there is a report on the study of behavior of Cu(II)- and Co(II)-amine complexes in the decomposition of hydrogen peroxide using Dowex 50W.[62] The main advantages of the use of Dowex 50W as a catalyst are: its ready availability, biocompatibility and reusability. Furthermore, the catalyst can tolerate a wide range of inorganic and organic/non-oxidizing reagents, chemical conditions and it can be washed easily and reused for several times. Thus, we decided to exploit the acidic nature of Dowex 50W resin in the present catalytic reaction which may benefit the academia, medicinal and pharmaceutical industries; and, herein, we report a metal free, Dowex 50W catalysed sustainable synthesis of 1,5-benzodiazepines from *o*-phenylenediamine and suitable ketones under solvent-free condition at 110 °C within 5 min as shown in the **Scheme 1**.



**Scheme 1:** Synthesis of 1,5-benzodiazepines

## 2. Results and Discussion

Different acyclic/cyclic, aryl methyl ketones and *o*-phenylenediamine were selected for the study. Blank experiments in the absence of any catalyst or solvent were performed at 26 °C, and it was observed that, the reaction between the substrates did not occur at this condition. Thereafter, the reaction was attempted in the presence of various solvents such as: EtOH, 1,2-dichloroethane, $CH_2Cl_2$, $CHCl_3$ and $CH_3CN$; and it was found that, only a trace amount of product was formed in the EtOH after 7 h (**Table 1**, entry 1) and the reaction did not occur in 1,2-dichloroethane, $CH_2Cl_2$, $CHCl_3$ and $CH_3CN$ (entries 2−5).

**Table 1.** Optimization of solvent in the condensation reaction[a]

| Entry | Solvent[b] | Yield (%)[c] |
|---|---|---|
| 1 | EtOH | Trace |
| 2 | 1,2-Dichloroethane | ND[d] |
| 3 | $CH_2Cl_2$ | ND[d] |
| 4 | $CHCl_3$ | ND[d] |
| 5 | $CH_3CN$ | ND[d] |

[a]Reaction condition: *o*-Phenylenediamine (1.08g, 10 mmol) and cyclohexanone (1.96g, 20 mmol) stirred for 7h; [b]5 mL; [c]Isolated yield; [d]Not detected.

In our next pursuit, a neat solvent-free condensation reaction was carried out at 110 °C with *o*-phenylenediamine (1.08g, 10 mmol) and cyclohexanone (1.96g, 20 mmol) as model substrates in the presence of different heterogeneous catalysts such as: Amberlyst-15, silica-$H_2SO_4$, silica-$HClO_4$ and $SiO_2$ to get the corresponding 1,5-benzodiazepine in 45%, 48%, 40% and 42% respectively after 5 min (**Table 2,** entries 1−4). Lewis acids such as: CuI, $Cu(OTf)_2$, $FeCl_3$ and $BiCl_3$ under solvent-free condition did not offer the desired product (entries 5−8) under the identical condition. To our fortune, in the presence of catalytic Dowex 50W, *o*-phenylenediamine and cyclohexanone reacted very well at 110 °C to give the desired 1,5-benzodiazepine in 96% yield within 2 min. Therefore, among the catalysts investigated, Dowex 50W was found to be the best in terms of yield of the product and the rate of the reaction (entry 9).

**Table 2.** Selection of the catalyst for the synthesis of 1,5-benzodiazepines[a]

| Entry | Catalyst[b] | Time (min) | Yield[d] (%) |
|---|---|---|---|
| 1 | Amberlyst-15[c] | 5 | 45 |
| 2 | Silica-$H_2SO_4$[c] | 5 | 48 |
| 3 | Silica-$HClO_4$[c] | 5 | 40 |
| 4 | $SiO_2$[c] | 5 | 42 |
| 5 | CuI | 5 | ND |
| 6 | $Cu(OTf)_2$ | 5 | ND |
| 7 | $FeCl_3$ | 5 | ND |
| 8 | $BiCl_3$ | 5 | ND |
| 9 | Dowex 50W[c] | 2 | 96 |

[a]Reaction condition: *o*-Phenylenediamine (1.08g, 10 mmol) and cyclohexanone (1.96g, 20 mmol) at 110 °C under solvent-free condition; [b]10 mol%; [c]100 mg; [d]Isolated yield; ND: Not detected.

We also studied the effect of amount of the catalyst in the present reaction and found that 100 mg per 10 mmol of OPDA and 20 mmol of ketone is essential to give the respective product in very high yield. It was also found that, the higher amount of Dowex 50W did not improve the yield of the product and the rate of the reaction. Further, maximum conversion was achieved when the reaction was carried out at 110 °C for 2 min; increasing the reaction temperature and time had no significant effect on the reaction as summarized in the **Table 3**.

**Table 3.** Dowex 50W catalyzed condensation reaction at different reaction temperatures.

| Entry | Temperature (°C) | Time(min) | Yield (%)[a] |
|---|---|---|---|
| 1 | 26 | 90 | 45 |
| 2 | 60 | 25 | 68 |
| 3 | 60 | 30 | 70 |
| 4 | 80 | 15 | 85 |
| 5 | 110 | 02 | 96 |

[a] Isolated yield.

As catalytic amounts of Dowex 50W is sufficient to bring about the present reaction under solvent-free condition, our method was then extended to various acyclic/cyclic and aryl methyl ketone to get different 1,5-benzodiazepine derivatives in excellent yields (**Table 4**, entries 1–8). Also, in the present study, we have examined the recovery and reuse of the catalyst and found that, the yield of the product in the second, third and fourth use of the catalyst was almost same as that in the first use (**Figure 1**). In every case more than 90% Dowex 50W was recovered by filtration, washed with ethyl acetate and dried in an hot air oven for 3–4 h at 120 °C and kept aside for further use.

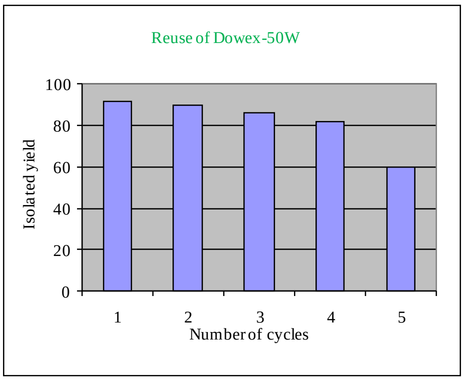
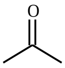
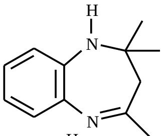
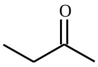
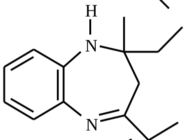
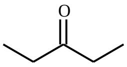
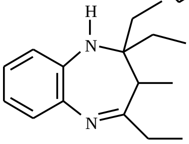
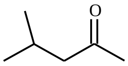
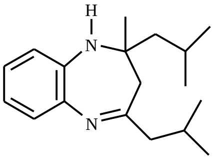
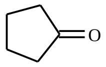
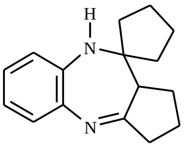
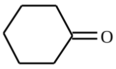
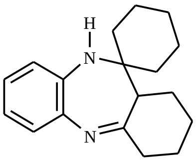
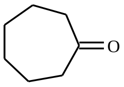
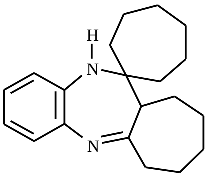
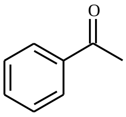
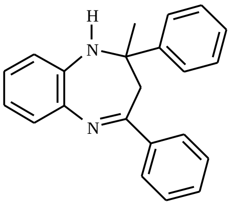


**Figure1**: Recycling of the catalyst

**Table 4.** Condensation of *o*-phenylenediamine with acyclic, cyclic and aryl methyl ketones in the presence of cat. Dowex 50W.

| Entry | Ketones | Yield (%)[a] | Product (**3**)[b] | Mp (°C) |
|---|---|---|---|---|
| 1 |  | 96 |  | 136–138 |
| 2 |  | 91 |  | 137–139 |
| 3 |  | 92 |  | 142–144 |
| 4 |  | 90 |  | 118–120 |
| 5 |  | 88 |  | 137–138 |
| 6 |  | 96 |  | 136–137 |
| 7 |  | 92 |  | 135–136 |
| 8 |  | 87 |  | 151–152 |

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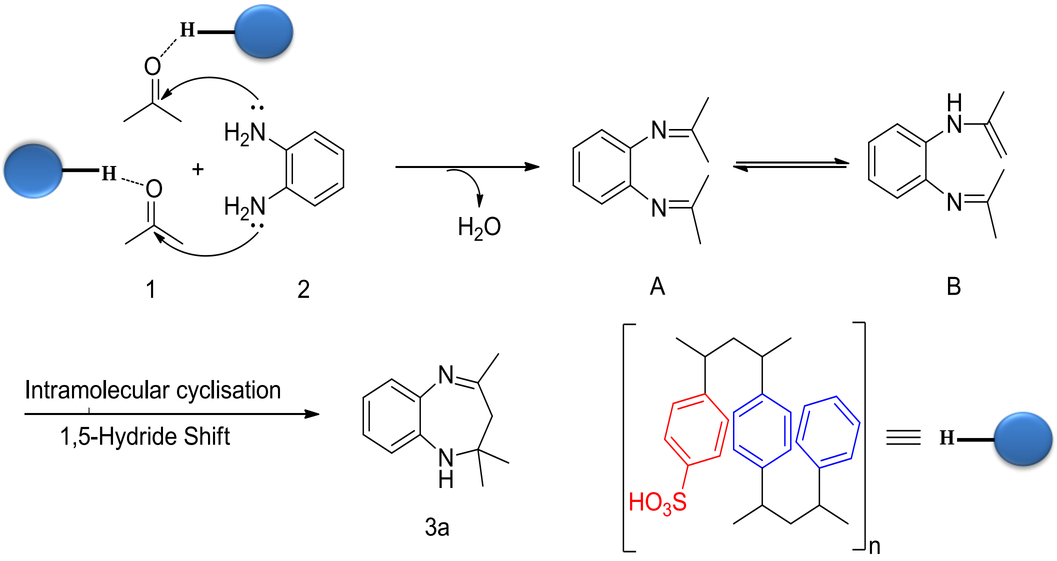
[a] Isolated yields.

## *2.1. Plausible mechanism*



**Scheme 2:** A plausible mechanism for the Dowex 50W catalysed synthesis of 1,5-benzodiazepines.

A plausible mechanism for the formation of benzodiazepines is envisaged, we suggest that, the cationic exchange resin, a $SO_3H$ functionalized catalyst: Dowex 50W, may increase the electrophilicity of the carbonyl group of a ketone (**1**) through H-bonding. The amino groups of the OPDA (**2**) may then attack two molecules of ketone simultaneously to give the intermediate diimine **A**. The intermediate **A** may then undergo an imine-enamine tautomerism to give the intermediate **B**, followed by the intramolecular cyclization to yield the desired product **3** as shown in the **Scheme 2**.

## 3. Materials and methods

All ketones, *o*-phenylenediamine and Dowex 50W resin were commercial products and were used as received without further purification. Reactions were monitored on TLC by comparison with the authentic samples of the products.[57,58] Melting points were taken in open capillaries using liquid paraffin bath. IR, $^{1}$HNMR (400 MHz), $^{13}$CNMR (100 MHz) were recorded on Nicolet 400 D FT-IR and Bruker spectrophotometers respectively and LC-Mass spectra were recorded on an Agilent LC-MSD-Trap-XCT instrument.

### *3.1. General procedure for the synthesis of substituted 1,5-benzodiazepines:*

A mixture of ketone (20 mmol), OPDA (10 mmol) and Dowex 50W (100 mg) was taken in a flat bottom glass tube and heated for 1–5 min at 110 °C in an oil bath. The completion of reaction was followed by TLC using 30% EtOAc in petroleum ether as an eluent. After the completion of the reaction, the reaction mixture was treated with ethyl acetate (5 mL) and Dowex 50W resin was removed by filtration. The filtrate was concentrated in vacuum and the resulting product was directly charged on silica gel column and eluted with a mixture of EtOAc-petroleum ether (2:8) to obtain pure 1,5-benzodiazepine. The recovered catalyst was washed with a minimum amount of ethyl acetate and activated at 120 °C for 3–4 h prior to reuse.

### *3.2 Spectral Data*

***2,2,4-Trimethyl-2,3-dihydro-(1H)-1,5-benzodiazepine***: Yellow crystals; FT-IR (KBr): ν 3343 (N-H), 1657 (C=N), 1610 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 1.34 (s, 6H), 2.21 (s, 2H), 2.38 (s, 3H), 2.93 (br s, 1H, NH), 6.64–7.4 (m, 4H) ppm; $^{13}$C NMR (100 MHz, DMSO-*d$_6$*): δ 29.6, 30.2, 45.1, 67.4, 121.3, 122.1, 125.2, 126.5, 137.7, 140.3, 171.7 ppm; *Anal.* Calcd for $C_{12}H_{15}N_2$: C, 76.66; H, 8.04; N, 14.90. Found: C, 76.60; H, 8.10; N, 14.92; MS: *m/z* = 188 (M$^+$).

***2,4-Diethyl-2-methyl-2,3-dihydro-(1H)-1,5-benzodiazepine***: Yellow solid; FT-IR (KBr): ν 3335 (N-H), 1648 (C=N), 1605 cm$^{-1}$ ; $^1$H NMR (400 MHz, CDCl$_3$): δ 0.98 (t, 3 H, *J* = 6.9 Hz), 1.24 (t, 3H, *J* = 7.0 Hz), 1.71 (q, 2H, *J*=6.9 Hz), 2.14 (m, 2 H), 2.36 (s, 3H), 2.68 (q, 2H, *J*= 7.0 Hz), 3.24 (br s, 1H,NH), 6.79–7.36 (m, 4H) ppm; $^{13}$C NMR (100 MHz, DMSO-*d$_6$*): δ 8.6, 10.7, 26.6, 35.6, 35.8, 42.3, 70.6, 121.9, 125.5, 126.1, 127.2, 137.9, 140.7, 175.7 ppm; *Anal.* Calcd for $C_{14}H_{20}N_2$: C, 77.80; H, 9.33; N, 12.90. Found: C, 77.77; H, 9.30; N, 12.89; MS: *m/z* = 216 (M$^+$).

***2,2,4-triethyl-3-methyl-2,3-dihydro-1H-benzo[b][1,4]diazepine*:** IR (KBr): 3325 (N-H), 1642 (C=N), 1610 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ = 0.73–1.05 (m, 10 H), 1.20–1.39 (m, 4H), 1.50–1.65(m, 2H), 2.40–2.60 (m, 2 H), 2.88 (q, 1H, *J* = 6.9 Hz), 3.77 (br s,1H, NH), 6.58 (d, 1H, *J* = 8.0 Hz), 6.69 (t, 1H, *J* = 8.0 Hz), 6.93 (t, 1H, *J* = 8.0 Hz), 7.37 (d, 1H, *J* =8.0 Hz); $^{13}$C NMR (100 MHz, DMSO-*d$_6$*): δ = 7.4, 7.9, 11.6, 12.3, 28.0, 28.7, 35.6, 46.3, 68.6, 117.6, 118.0, 126.9, 132.8, 139.2, 142.4, 173.4; *Anal.* Calcd for $C_{16}H_{24}N_2$: C, 78.76; H, 9.91; N, 11.48. Found: C, 78.70; H, 10.00; N, 11.03; MS: *m/z* = 244 (M$^+$).

***2-Methyl-2,4-diisobutyl-1H-1,5-benzodiazepine:*** Yellow solid; IR (KBr): 3335 (N-H), 1645 (C=N), 1600 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ = 0.98–1.05(m, 12H), 1.33 (s, 3 H), 1.49–1.53 (m, 2H), 1.65–1.78 (m, 1H), 2.08–2.25 (m, 3H), 2.26 (d, 2H, *J* = 12.8Hz), 6.61–6.65 (m, 1H), 6.86–6.98 (m, 2H), 7.05–7.16 (m, 1H); $^{13}$C NMR (100 MHz, DMSO-*d$_6$*): δ =22.6,22.8, 24.5, 24.9, 25.3, 26.3, 28.4, 43.5, 51.7, 51.9, 70.5, 121.4, 121.5, 128.2, 127.2, 137.8, 142.4, 174.0; *Anal.* Calcd for $C_{18}H_{28}N_2$: C, 79.48; H, 10.37; N, 10.29. Found: C, 79.52; H, 10.21; N, 10.20; MS: *m/z* =272 (M$^+$).

***10-Spirocyclopentane-1,2,3,9,10,10a-hexahydrobenzo[b]cyclopenta[e][1,4]diazepine***: Yellow solid; FT-IR (KBr): ν 3335 (N-H), 1660 (C=N), 1610 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 1.32–1.91 (m, 12 H), 2.35–2.60 (m, 3 H), 4.52 (br s, NH, 1 H), 6.74–7.39 (m, 4H) ppm; $^{13}$C NMR (100 MHz, DMSO-*d$_6$*): δ 23.5, 24.1, 24.3, 28.8, 33.4, 38.5, 39.2, 56.4, 67.3, 118.6, 119.3, 126.9, 133.1, 139.2, 143.8, 178.2 ppm; *Anal.* Calcd for $C_{16}H_{20}N_2$: C, 80.07; H, 8.39; N, 11.67. Found: C, 80.11; H, 8.03; N, 11.53; MS: *m/z* = 240 (M$^+$).

***10-Spirocyclohexane-2,3,4,10,11,11a-hexahydro-(1H)-dibenzo[b,e][1,4]diazepine***: Yellow solid; FT-IR (KBr): ν 3290 (N-H), 1646 (C=N), 1605 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 1.24–1.85 (m, 16 H), 2.30–2.74 (m, 3H), 4.48 (br s, NH, 1H), 6.69–7.35 (m, 4H) ppm; $^{13}$C NMR (100 MHz, DMSO-*d$_6$*): δ 21.8, 21.7, 23.5, 24.5, 25.3, 33.5, 34.4, 39.3, 40.8, 52.4, 63.1, 121.3, 121.6, 126.3, 129.7, 138.1, 142.6, 178.8 ppm; *Anal.* Calcd for $C_{18}H_{24}N_2$: C, 80.54; H, 9.01; N, 10.43. Found: C, 80.51; H, 9.04; N, 10.39; MS: *m/z* = 268 (M$^+$).

***10-Spirocycloheptan-6,7,8,9,10,10a,11,12-octahydrobenzo[b]cyclohepta[e][1,4]diazepine***: Yellow solid; FT-IR (KBr): ν 3280 (N-H), 1645 (C=N), 1600 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 0.92–1.95 (m, 20 H), 2.28–2.96 (m, 3 H), 3.60 (br s, NH, 1 H), 6.62–7.37 (m, 4H) ppm; $^{13}$C NMR (100 MHz, DMSO-*d$_6$*): δ 22.6, 23.2, 26.6, 28.4, 28.8, 29.5, 29.8, 30.1, 38.5, 41.0, 54.3, 72.5, 121.3, 121.6, 125.5, 127.6, 138.1, 139.8, 179.2 ppm; *Anal.* Calcd for $C_{20}H_{28}N_2$: C, 81.15; H, 9.53; N, 9.46. Found: C, 81.03; H, 9.48; N, 9.29; MS: *m/z* = 296 (M$^+$).

***2-Methyl-2,4-diphenyl-2,3-dihydro-(1H)-1,5-benzodiazepine***: Yellow solid; IR (KBr):ν 3345 (N-H), 1635 (C=N) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 1.82 (s, 3H), 2.96 (d, 1H, *J* = 12.8 Hz), 3.16 (d, 1H, *J* = 12.8 Hz) 3.45 (br s, NH), 6.56–7.0 (m, 3H), 7.15–7.38 (m, 7H), 7.55–7.67 (m, 4H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 166.5, 146.5, 140.1, 139.6, 138.1, 129.8, 128.1,128.4, 121.2, 127.1, 126.5, 125.5, 121.8, 121.5, 73.9, 43.2, 29.8; *Anal.* Calcd for $C_{22}H_{20}N_2$: C, 84.69; H, 6.46; N, 8.96. Found: C, 84.58; H, 6.38; N, 8.93; MS: *m/z* = 312 ($M^+$).

## 4. Conclusions

In conclusion, we have presented a simple, efficient and solvent-free protocol for the synthesis of a series of 1,5-benzodiazepines using catalytic amount of a readily available and recyclable Dowex 50W resin. The advantages of our method include: a simple reaction set-up not requiring specialized equipment; excellent product yields, short reaction duration, elimination of organic solvents and the catalyst can be recovered and recycled for at least five runs.

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## 6. Conflict of Interest

The authors declare that, there is no conflict of interest in the publication of this work.

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