



## Synthesis of 2, 4 disubstituted 1, 5 benzodiazepines promoted by efficient Silica-Alumina Catalyst

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### ABSTRACT

An efficient and environment friendly valuable synthon of 1, 5 benzodiazepine derivatives were synthesized having unique physical and medicinal properties. This reaction is performed by mesoporous binary mixed metal oxide  $\text{SiO}_2\text{-Al}_2\text{O}_3$  which is synthesized by hydrothermal method at high temperature. This mesoporous material is investigated by XRD, SEM, EDS, TEM, TPD and BET surface area. Present method offers several remarkable advantages such as non-toxic, noncorrosive and easy work-up procedure for the purification of product with non-chromatographic method, ecofriendly reaction condition.

## 1. Introduction

Heterocyclic compounds occur widely in nature and a many of the compounds are essential to life processes. The literature on heterocyclic compounds are repleted with examples of a large number of synthetic methods of naturally occurring systems which are pharmacologically active [1-11].

One of the heterocyclic compounds is a benzodiazepine sometimes colloquially "benzo"; often abbreviated as "BZD" is a mind-altering drug whose core chemical structure consist of the fusion of a benzene and a diazepine rings. Accidentally the first benzodiazepine was discovered by Leo Sternbach in 1955 [12-13].

The only 1,4- and 1,5-benzodiazepines found wide applications in medicines among all sorts of benzodiazepines (1,2-,1,3-, 1,4-, 1,5-, 2,3-, & 2,4- ) among these 1,5-benzodiazepines are the core structure of these derivatives those are having widespread biological activities. Due to this young researchers are having very much attracted towards the synthesis of this molecule [14-16]. The adequate quantity of the benzodiazepine is beneficial to the human body.

Derivatives of benzodiazepines are widely used as anticonvulsant, antianxiety, analgesic, sedative, anti-depressive, hypnotic agents [20-27] and anti-inflammatory agents [28]. 1, 5 benzodiazepines

framework has emerged as an important pharmacophore since its derivatives exhibit a wide range of medicinal applications such as anti-HIV, anticancer, angiotensin, converting enzyme inhibitor, antimicrobial compounds etc [29-31]. In the last decade, the area of biological interest of 1, 5-benzodiazepines have been extended to several diseases like cancer, viral infection and cardiovascular disorders [32-33]. In addition, to 1, 5-benzodiazepines are key intermediates for the synthesis of various fused ring systems such as triazolo-, oxadiazolo-, oxazino- or furanobenzodiazepines [34-35]. Besides, benzodiazepine derivatives are useful for commercial importance in dyes for acrylic fibers in photography [36-39].

Owing to their versatile application various methods have been developed for the synthesis of benzodiazepines has been reported in the literature [40][41]. The different type of catalyst has been utilized for the synthesis of benzodiazepine such as montmorillonite [42] and Heteropolyacid [43] magnetically retrievable  $\text{Fe}_3\text{O}_4$  nanocatalyst [44].  $\text{CeO}_2/\text{CuO}$ @Nitrogen Graphene Quantum Dots@ $\text{NH}_2$  Nanocomposite [45], Volcanic ash [46]

Moreover 1, 5-benzodiazepines derivatives are valuable synthons used in preparation of other fused ring compounds such as triazolo-, oxadiazolo-, oxazino-,or furanobenzodiazepines [47-52].

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## 2. Results and Discussion

To determine the role of solvent and catalyst, we have chosen chalcone (1) and o-phenylene diamine (2) as the model reaction. In this our study, the effect of different solvent was investigated and given in Table 1 the choice of solvent proved critical. It was observed that the ethanol has proven a much better solvent in terms of yield than all other tested solvents such as dichloromethane, acetonitrile and methanol.

**Table 1** Optimization of model reaction using several solvent.

Entry	Solvent	Time (min)	Yield (%) <sup>b</sup>
1	Solvent Free	120	78
2	CH <sub>2</sub> Cl <sub>2</sub>	160	73
3	MeCN	160	69
4	CH <sub>3</sub> OH	120	76
5	1,4 dioxane	130	traces
6	EtOH	60	93

Reaction Condition: Chalcone (1mmol), o-phenylenediamine (1mmol), catalyst 0.1g. <sup>b</sup>Isolated yield.

When same reaction was carried out in the absence of catalyst very less amount of product (20%) was obtained which indicate that a catalyst is necessary for the reaction. In this connection, we carried out the reaction using different amount of SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> and the results obtained are summarized in (Table 2). With an increase in the quantity of SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> from 0.05 to 0.2g. To obtained good yield of product for 0.1g of amount of catalyst.

**Table 2** Optimization of model reaction using different amount of catalyst on the reaction condition.

Entry	Catalyst amount (g)	Time(min)	Yield (%) <sup>a</sup>
1	No Catalyst	160	20
2	0.05	130	85
3	0.1	60	93
4	0.15	90	92
5	0.2	120	90

Reaction Condition: chalcone (1mmol), o-phenylenediamine (1mmol), catalyst. <sup>b</sup>Isolated yield.

To compare the SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> catalyst activity with the another reported catalyst in the literature shown in (Table 3), to observed that SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> synthesised material shown a good yield in reported time.

**Table 3** Synthesis of 2, 4 disubstituted 1, 5, benzodiazepine derivatives catalyzed by SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub>.

Entry	Catalyst	Time(h)	Yield (%) <sup>a</sup>
1	SbCl <sub>3</sub> -Al <sub>2</sub> O <sub>3</sub>	3-4	83[53]
2	MCM-41	8	90[54]
3	HPW/SiO <sub>2</sub>	2	92[55]
4	SiO <sub>2</sub> /H <sub>2</sub> SO <sub>4</sub>	1-2	90[56]
5	SiO <sub>2</sub> -Al <sub>2</sub> O <sub>3</sub>	1	93

It was interesting noticed that the nature of substituent on the aromatic ring does not affect the yield of product. From (Table 4) it was clear that the reaction of aromatic aldehyde carrying electron-donating or electron-withdrawing groups were also successfully carried out by this method.

**Table 4** Synthesis of 2, 4 disubstituted 1, 5, benzodiazepine derivatives catalyzed by SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub>.

Product	R	R'	Time (min)	Yield (%) <sup>a</sup>	M.P.(°C) Found	Literature
3a	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	120	90	76-78	77[57]
3b	C <sub>6</sub> H <sub>4</sub>	4-OMeC <sub>6</sub> H <sub>4</sub>	145	81	160-162	160[57]
3c	C <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	125	80	116-118	117[58]
3d	C <sub>6</sub> H <sub>4</sub>	4-OHC <sub>6</sub> H <sub>4</sub>	130	80	117-119	120[57]
3e	C <sub>6</sub> H <sub>4</sub>	4-FC <sub>6</sub> H <sub>4</sub>	128	97	80-81	79[58]
3f	4-ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	120	87	129-131	130[59]
3g	2-ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	132	89	132-134	132[60]

Reaction Condition: chalcone (1mmol), o-phenylenediamine (1mmol), catalyst 0.1g. <sup>a</sup>Isolated yield.

In this study, the catalyst was recovered and reused in another run. The catalyst was recovered by simple filtration, washed with ethanol and reused for three successive reaction giving 89, 87, 83% yield of product (Table 5).

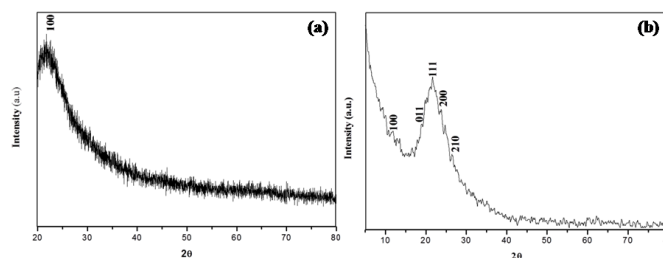
**Table 5** Studies on reusability of SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> metal oxide in the preparation of 3a.

Entry	Number of recycling	Yield (%) <sup>a</sup>
1	Fresh	93
2	1	89
3	2	87
4	3	83

Reaction Condition: Chalcone (1mmol), o-phenylenediamine (1mmol), catalyst 0.1g. <sup>b</sup>Isolated yield.

## 2.1 XRD Analysis

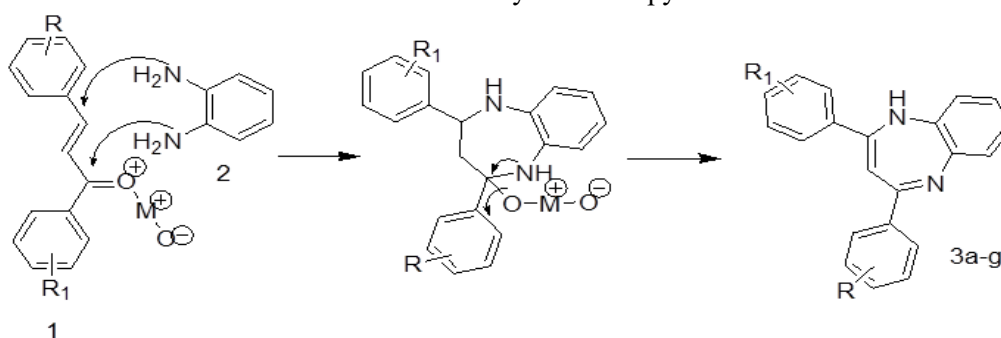
The XRD pattern is useful to investigate the geometry and crystallinity of synthesized material. The powder X-ray diffraction pattern of SiO<sub>2</sub> shows the broad peak at 21.74° with a 100 plane indicating the amorphous nature of silicon dioxide (JCPDS card no 01-086-1561) as shown in Fig.1(a). The XRD pattern of synthesized SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> is shown in Fig.1(b) the XRD pattern shows the orthorhombic crystal structure which is matched with JCPDS card no 84-1566 having lattice parameters a=7.503, b=7.738, c=5.804. Here broad peak at 21.74° indicates 111 plane with sharp point that signifies enhancement in the crystalline nature of SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> enhanced.



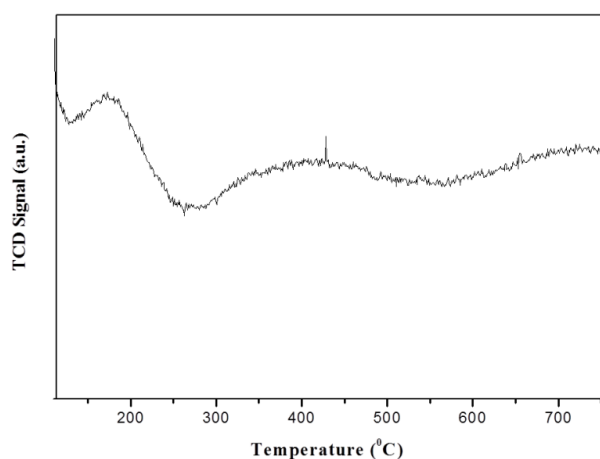
**Figure 1:** XRD pattern of a) SiO<sub>2</sub>, b) SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> mixed metal oxides.

## 2.2 TPD Analysis

NH<sub>3</sub>-TPD provides information about the total concentration and strength of Bronsted and Lewis acidic sites [61]. From NH<sub>3</sub>-TPD analysis, it was found that the ammonia desorbed in three different regions. In first region 0.00155 mmol/gm of NH<sub>3</sub> desorbed at 185.3°C to presence of Lewis acidic sites, while in the second and third region 0.00394 mmol/gm, 0.00552 mmol/gm of NH<sub>3</sub> desorbed at 428.1°C and 691.0°C Bronsted acidic sites respectively. Hence the total strength of acidic sites present in SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> was found to be 0.01101 mmol/gm (Fig. 2). The presence of both weak Lewis and strong Bronsted acidic sites in SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> can be attributed to the Ammonia-TPD. Increased numbers of Bronsted acidic sites play a significant role in the synthesis of pyrazole derivatives.



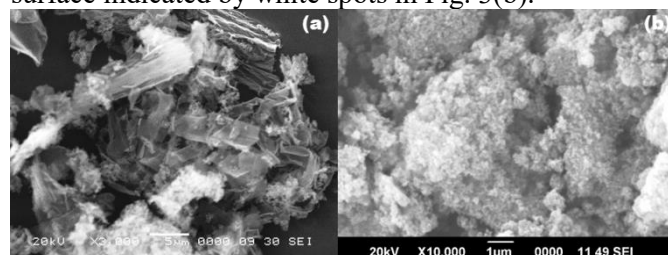
Schematic representation of plausible mechanism of 2, 4 disubstituted 1, 5, benzodiazepine.



**Figure 2:** NH<sub>3</sub>-TPD profile of SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> mixed metal oxide.

## 2.3 SEM-EDS Analysis

Surface morphology of the synthesized SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> catalyst was studied by SEM image. In the Fig.3(a) shows the flakes like structure of SiO<sub>2</sub> oxide. When Al<sub>2</sub>O<sub>3</sub> doped on the surface of SiO<sub>2</sub> which is seen on the surface indicated by white spots in Fig. 3(b).



**Figure 3:** SEM image of a) SiO<sub>2</sub> b) SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> of mixed metal oxide.

Elemental composition of  $\text{SiO}_2\text{-Al}_2\text{O}_3$  catalysts is represented in Fig.4 intense peaks in the figure show the presence of Si, Al and O with 44.41, 1.55 and 54.05 atom% respectively. The minimum expected stoichiometric ratio was maintained.

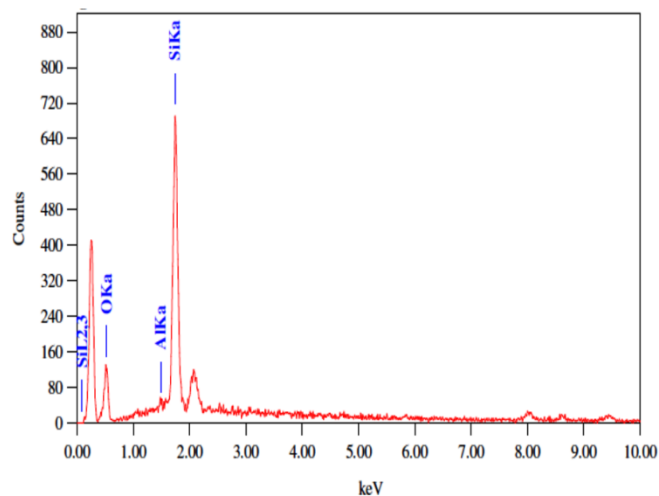


Figure 4: EDS spectrum of  $\text{SiO}_2\text{-Al}_2\text{O}_3$  mixed metal oxide.

## 2.4 TEM Analysis

In Fig.5(a) shows TEM image of  $\text{SiO}_2\text{-Al}_2\text{O}_3$ , which were used to calculate size distributions and average particle size of catalyst. The maximum and minimum size of particles was found 127 nm and 9.51 nm respectively. Size distribution was shown in Fig.5 (b). Asymmetric histograms of these images due to the lack of detection of particles are less than 1nm. The powder XRD patterns also confirm the presence of a crystalline phase.

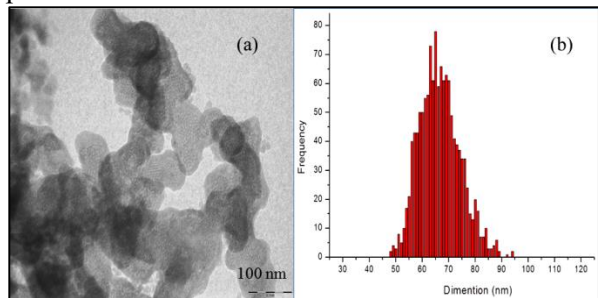


Figure 5: TEM image of a) calcined  $\text{SiO}_2\text{-Al}_2\text{O}_3$  b) Associate particle histogram of  $\text{SiO}_2\text{-Al}_2\text{O}_3$ .

## 2.5 BET Surface Area And Porosity Analysis

The surface area and pore size of  $\text{SiO}_2\text{-Al}_2\text{O}_3$  nanocomposite material was characterized by the  $\text{N}_2$ -BET method. The  $\text{N}_2$  adsorption-desorption isotherms provide information on the textural properties of  $\text{SiO}_2\text{-Al}_2\text{O}_3$  and the specific surface area shown in Fig 6. The BET Surface area, average pore diameter and pore volume of  $\text{SiO}_2\text{-Al}_2\text{O}_3$  depicted in Table 5.

The amount of  $\text{N}_2$  gas adsorbed-desorbed at a given pressure allows determining the surface area of material. The isotherm curve indicates large volume was adsorbed on the surface of the material. Single point BET surface area at  $P/P_0$  is 80.3224  $\text{m}^2/\text{g}$ , it signifies that the

synthesized material has a higher surface area. Due to this, the material gives higher catalytic activity.

Similarly, the adsorption average pore diameter for the same material is 27.39 nm, and BJH pore volume is 0.32  $\text{cm}^3/\text{gm}$ . Smaller the pore volume of material, the greater the catalytic activity.

Table 5. BET surface area, average pore diameter and microspore volume of  $\text{SiO}_2\text{-Al}_2\text{O}_3$ .

Sample	Surface Area ( $\text{m}^2/\text{g}$ )	Average pore diameter (nm)	Micro pore volume ( $\text{cm}^3/\text{g}$ )
$\text{SiO}_2\text{-Al}_2\text{O}_3$	80.3224	27.39	0.32

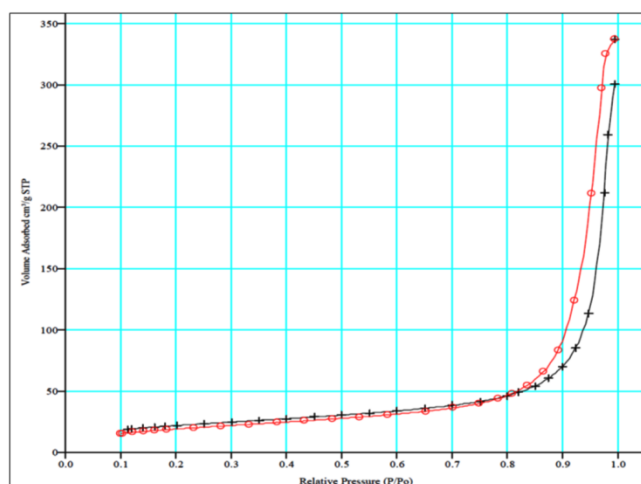


Figure 6:  $\text{N}_2$  adsorption/ desorption isotherm of  $\text{SiO}_2\text{-Al}_2\text{O}_3$ .

## 3. Experimental

### 3.1. General

All chemicals were purchased from Sigma Aldrich chemical and Molychem suppliers and used as received. Reaction monitoring was accompanied by thin layer chromatography (TLC) and visualized under ultraviolet (UV) light.

### 3.2 Preparation Of Catalyst

The Mesoporous  $\text{SiO}_2\text{-Al}_2\text{O}_3$  mixed metal oxide prepared by hydrothermal method. In a typical procedure 1gm cetyl trimethyl ammonium bromide (CTAB) was added in mixture of 8.33mL of tetraethyl ortho silicate (TEOS), aqueous solution of 0.25 gm of aluminum nitrate ( $\text{Al}(\text{NO}_3)_3$ ). Add 5 mL 1:1 aqueous sodium hydroxide (aq. NaOH) to maintain PH up to 9-10 and stirred this mixture at room temperature for 24 h to obtain precipitate. Then this mixture of precipitate hydrothermally treated at  $150^\circ\text{C}$  for 5 h in high pressure autoclave at 400 rpm having autogeneous pressure 54 psi at the volume 250 mL of mixture. After this the mixture was cooled at room temperature solid material obtained was filtered and washed with deionised water, dried at  $80^\circ\text{C}$  for 6 h and calcined at  $500^\circ\text{C}$  for 3 h.

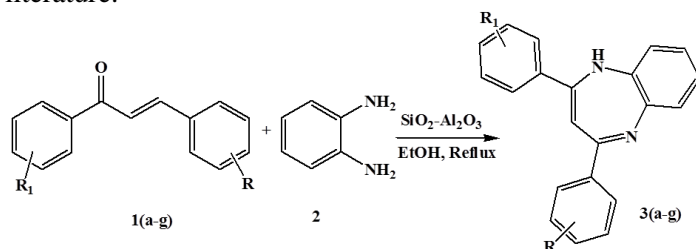


### 3.3 Catalyst Characterization

The prepared  $\text{SiO}_2\text{-Al}_2\text{O}_3$  mixed metal oxide characterized by analytical instrumental techniques such as XRD, SEM, EDS, TEM, FTIR, TPD and BET surface area. These techniques were used to get the morphology, size, porosity and composition of synthetic material [62]. X-ray diffraction (XRD) analysis of the calcined  $\text{SiO}_2\text{-Al}_2\text{O}_3$  was carried out with a Phillips X-ray diffractometer in a diffraction angle range  $2\theta(^{\circ})=20$  to  $80$  using  $\text{Cu-K}\alpha$  radiation with a wavelength of  $1.540598 \text{ \AA}$ . Surface morphology and elemental analysis of the  $\text{SiO}_2\text{-Al}_2\text{O}_3$  were carried out using a JEOL-JEM 2300 (LA) scanning electron microscope with an electron dispersion spectroscopy (SEM-EDS) attached. Fourier transform infrared (FT-IR) spectra were recorded on a FT-IR spectrometer (JASCO FTIR/4100, Japan) from  $4000$  to  $400 \text{ cm}^{-1}$ .

### 3.4 General Procedure For The Synthesis Of Benzodiazepine Derivatives.

A mixture of chalcone **1** (1 mmol), o-phenylenediamine **2** (1mmol), in presence of  $\text{SiO}_2\text{-Al}_2\text{O}_3$  metal oxide (0.1g) was reflux at  $80^{\circ}\text{C}$  in ethanol as solvent with stirring for appropriate time. After completion of the reaction as indicated by TLC, filter the reaction mixture with filter paper and the catalyst was filtered off. The purity of the representative product was determined by comparison to the melting points,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, FTIR and Mass spectra in the literature.



### 3.5 Spectral Data Of Representative Compound

(**2Z**, **5E**)-**1**, **4**-dihydro-2,5-diphenylbenzo[b][1,4]diazocine (**3a**);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $300\text{MHz}$ :  $\delta = 7.70$  (d, 2H),  $7.66$  (m, 10H),  $6.55$  (d, 2H),  $5.40$  (t, 1H),  $4.32$  (s, NH),  $2.35$  (d,  $\text{CH}_2$  2H); IR (KBr,  $\nu_{\text{max}}$ ):  $2962 \text{ cm}^{-1}$  (NH),  $1589 \text{ cm}^{-1}$  ( $\text{C}=\text{C}$ ).  $^{13}\text{C}$  NMR ( $50 \text{ MHz}$ ,  $\text{CDCl}_3$ )  $\delta(\text{ppm})$ :  $29.7$ ,  $77.9$ ,  $116.7$ ,  $120.7$ ,  $121.6$ ,  $122.4$ ,  $126.9$ ,  $127.4$ ,  $128.5$ ,  $129.9$ ,  $130.2$ ,  $133.4$ ,  $134.7$ ,  $136.4$ ,  $138$ ,  $139.4$ ,  $143.3$ ,  $167.1$ . ES-MS:  $m/z$   $312.25$  ( $M+3$ )

(**2Z**, **5E**)-5-(4-chlorophenyl)-**1**, **4**-dihydro-2-phenylbenzo[b][1,4]diazocine (**3c**);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $300\text{MHz}$ :  $\delta = 7.75$  (d, 2H),  $7.55$ - $7.69$  (m, 9H),  $6.60$  (d, 2H),  $5.50$  (t, 1H),  $4.25$  (s, NH),  $2.10$  (d,  $\text{CH}_2$  2H); IR (KBr,  $\nu_{\text{max}}$ ):  $3053 \text{ cm}^{-1}$  (NH),  $1620 \text{ cm}^{-1}$  ( $\text{C}=\text{C}$ ).  $^{13}\text{C}$  NMR ( $50 \text{ MHz}$ ,  $\text{CDCl}_3$ )  $\delta(\text{ppm})$ :  $30.6$ ,  $80.9$ ,  $118.5$ ,  $121.6$ ,

$121.6$ ,  $123.1$ ,  $127.4$ ,  $128.7$ ,  $129.9$ ,  $130.2$ ,  $133.4$ ,  $134.7$ ,  $136.6$ ,  $138$ ,  $141.6$ ,  $149.8$ ,  $164.2$ . ES-MS:  $m/z$   $332.24$  ( $M+2$ ).

### 4. Conclusion

In summary  $\text{SiO}_2\text{-Al}_2\text{O}_3$  binary mixed metal oxide catalyzed an efficient synthesis of 2, 4 disubstituted 1, 5, benzodiazepine derivatives using chalcone and o-phenylenediamine in ethanol at  $80^{\circ}\text{C}$  temperature. Present method offers several remarkable advantages such as non-toxic, non corrosive and an inexpensive reaction condition.  $\text{SiO}_2\text{-Al}_2\text{O}_3$  remains unchanged in mass and chemical composition at the end of the reaction under environmentally benign conditions.

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