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## ARTICLE TYPE

# An efficient facile and one-pot synthesis of benzodiazepines and chemoselective 1,2-disubstituted benzimidazoles using magnetically retrievable Fe<sub>3</sub>O<sub>4</sub> nanocatalyst under solvent free condition

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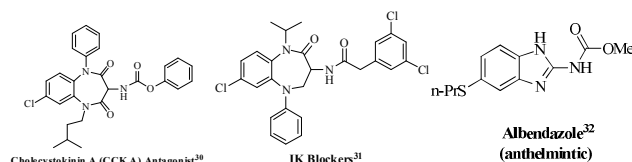
Benzodiazepine and chemoselective 1,2-disubstituted benzimidazole derivatives were synthesized by the condensation reaction of *o*-phenylenediamine with ketones and aryl aldehydes using Fe<sub>3</sub>O<sub>4</sub> nanoparticles as a recyclable catalyst under solvent free condition. This synthetic approach eliminates the use of toxic organic solvents with the added benefit of easy separation and reusability of the catalyst without compromising the yield or purity which makes the procedure green.

Green chemistry is the development of reaction processes that reduce or eliminate the use or generation of hazardous substances.<sup>1</sup> Towards the last decade emphasis has been given to developing more environmentally benign synthetic organic processes. Organic solvent pose the biggest challenge in this regard due to its hazardous impact on the environment and the human health. The design of a reaction process without the use of hazardous organic solvent would be an important step towards green chemistry. The present approach offers the advantage of eliminating the use of hazardous organic solvents.

Recently, metal nanoparticles have received much attention in the field of organic synthesis. Metal nanoparticles are much more reactive than the bulk because of their higher surface to volume ratio.<sup>2</sup> Further, the reusability of the catalyst has become an important trend in chemistry due to growing environmental and economic concern. Of the nanoparticles, Fe<sub>3</sub>O<sub>4</sub> NPs are important because of their potential uses such as in magnetic drug targeting, clinical diagnosis and as catalyst.<sup>3</sup> Fe<sub>3</sub>O<sub>4</sub> NPs, are also of interest due to its easy synthesis and magnetic property which makes it easily separable by an external magnetic field and being comparatively cheap.

Nitrogen containing [6, 7] and [6, 5] fused heterocycles like benzodiazepine and benzimidazole derivatives are important class of heterocyclic compounds having interesting pharmacological and biological properties.<sup>4,5</sup> These compounds have also been known for their analgesic, antianxiety, hypnotic, anti-inflammatory, anticonvulsant, muscle-relaxant, antitumor, antiulcer, antimicrobial, antiviral, anti-HIV and amnesic properties.<sup>6-9</sup> Benzimidazole has also been found to be effective against human cytomegalovirus (HCMV) and as efficient selective neuropeptide YY1 receptor antagonists.<sup>10,11</sup> Because of these medicinal and industrial applications, these compounds have been of wide

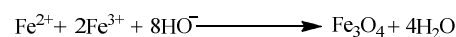
interest. These compounds can also be used for the preparation of other important heterocyclic compounds and are important intermediates in many organic reactions.<sup>12-15</sup> Benzodiazepines and benzimidazole derivatives have been prepared by the condensation or cyclization of *o*-phenylenediamine with a variety of carbonyl compounds. Various catalyst such as BF<sub>3</sub>.Et<sub>2</sub>O,<sup>16</sup> NBS,<sup>17</sup> NaBH<sub>4</sub>,<sup>18</sup> LaCl<sub>3</sub>.7H<sub>2</sub>O,<sup>19</sup> polyphosphoric acid,<sup>20</sup> AgNO<sub>3</sub>,<sup>21</sup> Yb(OTf)<sub>3</sub>,<sup>22</sup> Sc(OTf)<sub>3</sub>,<sup>23</sup> Ga(OTf)<sub>3</sub>,<sup>24</sup> ZnCl<sub>2</sub>,<sup>25</sup> and ionic liquids,<sup>26</sup> have been employed for the synthesis of benzodiazepine. Benzimidazole have also been reported with amberlite,<sup>27</sup> Fe(ClO<sub>4</sub>)<sub>3</sub>,<sup>28</sup> In<sub>2</sub>O<sub>3</sub>.<sup>29</sup> However these methods suffer from drawbacks such as the use of hazardous organic solvents, longer reaction time, low yield, harsher reaction condition and high cost. In our present approach, we have synthesized benzodiazepine and benzimidazole derivatives under solvent free condition using Fe<sub>3</sub>O<sub>4</sub> NPs which eliminates the use of toxic solvents with the added advantage of reusability of the catalyst.



**Fig.1** Some biologically important compounds.

## RESULTS AND DISCUSSION

Fe<sub>3</sub>O<sub>4</sub> NPs was prepared by the addition of a base to an aqueous solution containing Fe<sup>3+</sup> and Fe<sup>2+</sup> in a molar ratio of 2:1, according to the procedure given by Karami et al.<sup>33</sup> The resulting solution was heated at 50-60 °C with stirring. A dark black precipitate was formed. Then the precipitate was filtered, dried and characterized by TEM, SEM, XRD, EDAX UV and IR. The equation can be expressed as



XRD patterns of Fe<sub>3</sub>O<sub>4</sub> NPs are shown in **Fig. 2**. The XRD patterns shows a number of prominent Bragg reflections by their indices (220), (311), (400), (422), (511) and (440) which indicates that the resultant nanoparticles were Fe<sub>3</sub>O<sub>4</sub> with a spinel structure. The broad peak is an indication that the particles were of nanoscale size. The size of the particles was examined by transmission electron microscope (TEM) and the TEM image (**Fig. 3a**) clearly shows a monodispersed

spherical shaped  $\text{Fe}_3\text{O}_4$  NPs. The morphology and particle size of the  $\text{Fe}_3\text{O}_4$  NPs was studied using SEM. The SEM image (Fig. 4a) indicates that the  $\text{Fe}_3\text{O}_4$  NPs are spherical in shape and in the nanometer range. Characterization of  $\text{Fe}_3\text{O}_4$  NPs was also done using EDAX. The EDAX spectra show a strong peak of Fe (Fig. 5). The characterization of the  $\text{Fe}_3\text{O}_4$  NPs was also studied using UV and IR. The UV spectra show a characteristic absorption bands at 370 nm which corresponds to the  $\text{Fe}_3\text{O}_4$  NPs (Fig. 6), which originate primarily from the absorption and scattering of UV radiation by magnetic nanoparticles. The results was found to be in good agreement with those reported in the literature.<sup>34</sup> The particles size were found to be 10- 20 nm before used. The distributions of  $\text{Fe}_3\text{O}_4$  NPs are shown in Fig. 7. The IR spectrum shows bands at  $599\text{ cm}^{-1}$  and  $3430\text{ cm}^{-1}$  which indicates Fe-O structure and OH group for spinel  $\text{Fe}_3\text{O}_4$  (Fig. S.I-1).<sup>35</sup>

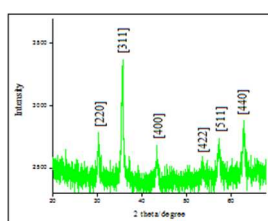
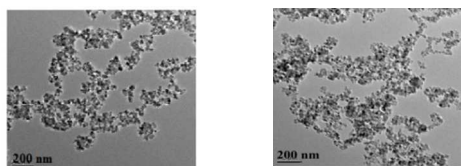
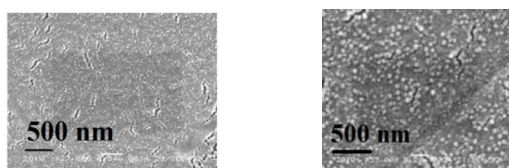


Fig.2 Powder XRD of  $\text{Fe}_3\text{O}_4$  NPs.



(a) Before used (b) After reused

Fig.3 TEM image of  $\text{Fe}_3\text{O}_4$  NPs before and after use.



(a) Before used (b) After reused

Fig.4 SEM image of  $\text{Fe}_3\text{O}_4$  NPs before and after use.

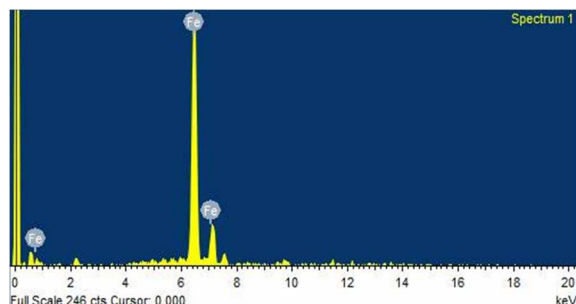


Fig.5 EDAX spectra of  $\text{Fe}_3\text{O}_4$  NPs.

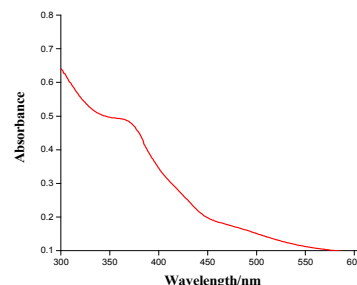


Fig.6 UV visible spectra of  $\text{Fe}_3\text{O}_4$  NPs.

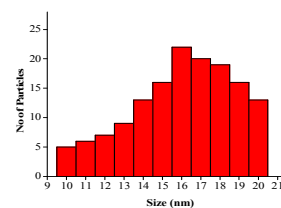


Fig. 7 Histogram diagram of  $\text{Fe}_3\text{O}_4$  NPs.

The synthesized  $\text{Fe}_3\text{O}_4$  NPs was then applied as a reusable catalyst in a condensation reaction which intern will produce biologically important heterocyclic compounds such as benzodiazepine and their derivatives. The model condensation reaction between *o*-phenylenediamine (**1**, 1 mmol) and acetophenone (**2**, 2.2 mmol) in presence of  $\text{Fe}_3\text{O}_4$  NPs was carried out under solvent free condition (Scheme 1). The reaction was carried out in various solvents, like water, THF, acetonitrile, ethanol and toluene. Significant improvement was achieved in ethanol and acetonitrile, but the best result was observed under solvent free condition (Fig. 8). However, the reaction did not proceed in water medium which might be due to poor solubility of the starting materials.

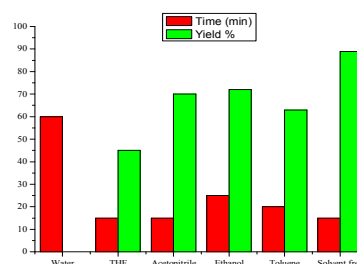


Fig.8 Chart for the optimization of solvent effect.

The amount of catalyst concentration for the model reaction was scanned. Firstly, the condensation reaction of *o*-phenylenediamine (**1**, 1 mmol) and acetophenone (**2**, 2.2 mmol) was carried out in absence of catalyst, very less conversion was observed (22 %). The reaction was then studied with various mol % of the catalyst (2-10 mol %). It was found that the product yield proportionally increased with catalyst concentration. Maximum yield was obtained by

using 6 mol % of the catalyst. Further increase in the catalyst concentration (8 mol % and 10 mol %), the yield of the product did not improve. So 6 mol % is the optimum catalyst concentration in this reaction (Fig. 9).

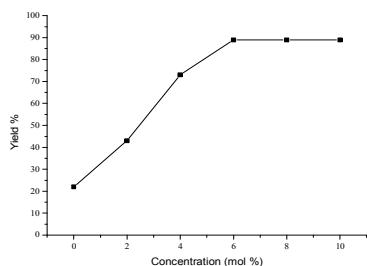


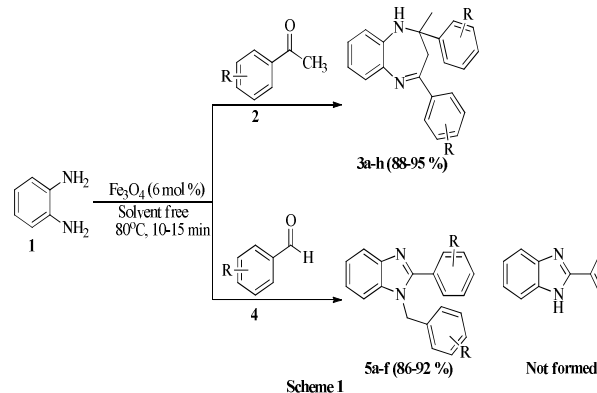
Fig. 9 Effect of catalyst loading on the reaction yield.

Rationalising the above results, we carried out the said condensation reaction of *o*-phenylenediamine (**1**, 1 mmol) and acetophenone (**2**, 2.2 mmol) in presence of Fe<sub>3</sub>O<sub>4</sub> NPs (6 mol %) under solvent free condition at 80 °C (Scheme 1). The reaction went to completion within 15 min yielding a solid pale white product in high yield (89 %). The structure of the compound was established by analytical and spectroscopic methods. The presence of peaks in <sup>1</sup>H NMR at 3.4 (brs, 1H), 3.08 (d, *J* = 13.2 Hz, 1H) and 2.92 (d, *J* = 13.2 Hz, 1H) due to NH and methylene protons and peak at 3281 cm<sup>-1</sup> due to NH stretching in IR spectra clearly indicates the

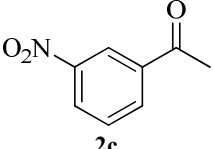
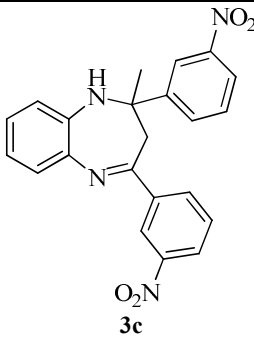
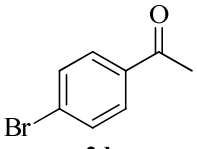
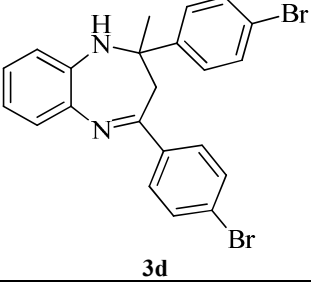
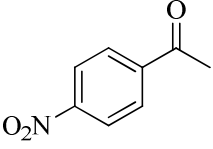
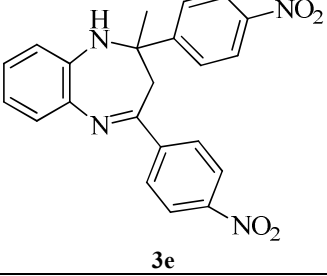
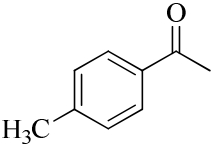
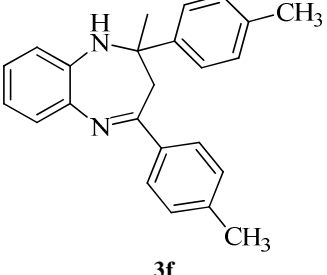
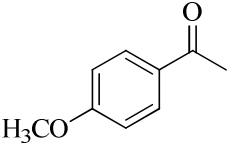
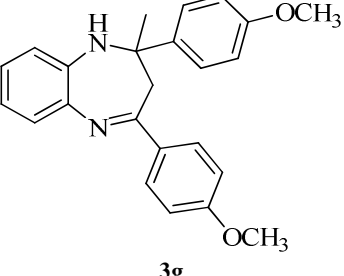
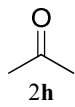
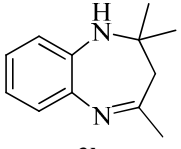
Table 1. Synthesis of compounds **3a-h** and **5a-f**.

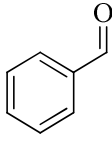
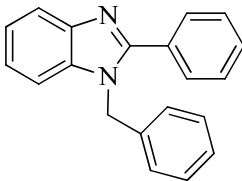
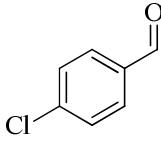
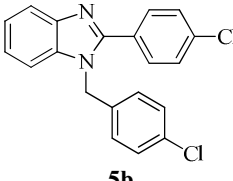
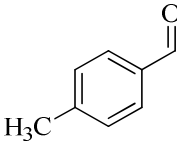
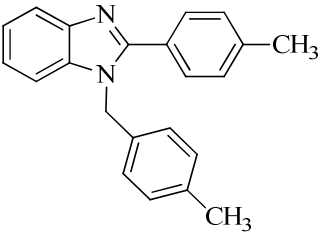
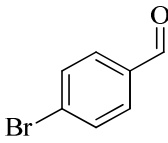
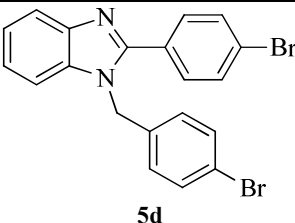
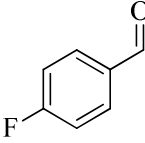
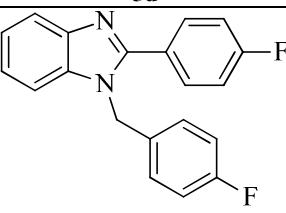
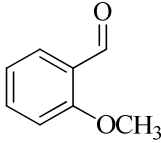
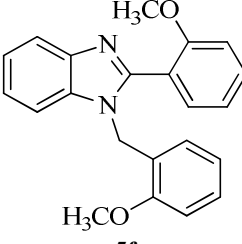
	Carbonyl compound	Product	Time (min)	Yield(%) <sup>a</sup>	M. p (°C) [Found]	M. p (°C) [Lit.]
1			15	89	150-152	[151-152] <sup>22</sup>
2			12	93	137-139	[147-149] <sup>24</sup>

formation of **3a**. The effect of temperature on the product yield was also studied. The reaction was carried out at room temperature but no desired product was obtained only starting materials were recovered after 1 h. With increase in the temperature, yield of the desired product increases and maximum yield was achieved at 80 °C (Table 1).



To make the process more general, the model reaction was carried out with different substituted ketones. In all the cases, the reactions were completed within very short period and furnished the corresponding products (**3a-h**) in higher yield (Table 1).

3	 2c	 3c	10	90	154-156	[164-166] <sup>24</sup>
4	 2d	 3d	14	91	135-137	[145-146] <sup>19</sup>
5	 2e	 3e	10	95	152-154	[154-155] <sup>24</sup>
6	 2f	 3f	15	88	97-100	[99-101] <sup>24</sup>
7	 2g	 3g	15	89	113-116	[115-116] <sup>24</sup>
8	 2h	 3h	13	89	133-135	[137-139] <sup>22</sup>

9	 4a	 5a	15	87	129-130	[134] <sup>28</sup>
10	 4b	 5b	10	91	131-135	[137] <sup>28</sup>
11	 4c	 5c	10	89	125-127	[125] <sup>28</sup>
12	 4d	 5d	15	92	157-159	[157-158] <sup>27</sup>
13	 4e	 5e	15	86	116-119	NF
14	 4f	 5f	10	90	149-150	[150] <sup>28</sup>

<sup>a</sup> isolated yields

NF = Not Found

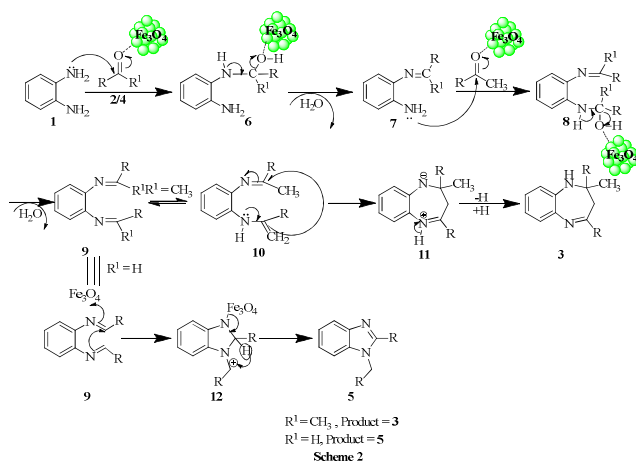
Encouraged by the initial success, next we decided to explore the synthesis of biologically important benzimidazole and their derivatives using the present protocol. To our delight, it was observed that the reaction worked well and furnished chemoselectively the 1,2-disubstituted benzimidazoles (**5a-f**) instead of a mixture of monosubstituted and disubstituted product irrespective of the molar ratio used (**Scheme 1**).<sup>36</sup> We also carried out the reaction using various aryl aldehydes having electron donating or electron withdrawing groups. In

all the cases, desired product was achieved in good yields (**Table 1**).

The plausible mechanism for the formation of compounds **3a-h** and **5a-f** is given below (**Scheme 2**). Initially the Fe<sub>3</sub>O<sub>4</sub> NPs facilitated the reaction between diamine **1** and ketones **2** or aldehyde **4**, which generates the common intermediate **9**. The intermediate **9** undergoes tautomerism to form intermediate **10**. The intermediate **10** then undergoes intramolecular cyclization followed by hydride shift to



furnish the final benzodiazepine products **3a-h**.<sup>37</sup> In case of aryl aldehydes, intermediate **9** undergoes cyclization (**12**) followed by 1,3-hydride shift to produce the disubstituted benzimidazole products **5a-f**.<sup>38</sup>



Reusability is one of the most important properties of a good catalyst. So, we checked the reusability of the catalyst in our present protocol. After the completion of the reaction, the reaction mixture was dissolved in 10 mL of ethyl acetate and the catalyst was separated using external magnetic field. The separated catalyst was then dried and reused for another set of reaction. To our excitement, it was found that the Fe<sub>3</sub>O<sub>4</sub> NPs can be reused for four consecutive runs without any appreciable decrease in its catalytic activity (Fig. 10).

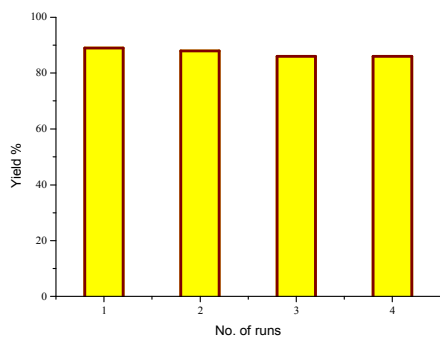


Fig. 10 Reusability chart.

Structure of the compound **3b** was further confirmed by X-ray crystallography. The compound **3b** was carefully recrystallized from ethanol. Fig. 11 shows the ORTEP diagram of compound **3b** (CCDC 933681).

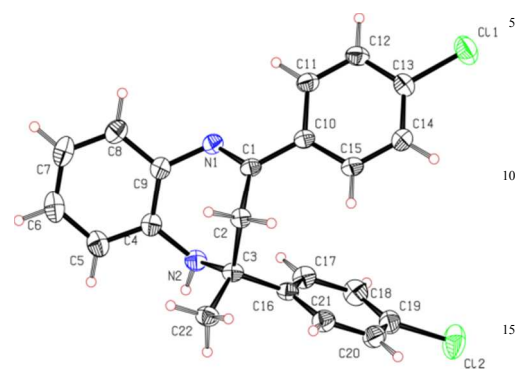


Fig. 11 ORTEP diagram of **3b** (CCDC 933681).

## Conclusions

In conclusion, we have developed a new efficient and simple method for the synthesis of benzodiazepine and chemoselective 1,2-disubstituted benzimidazole derivatives. This method will be very useful in industrial point of view because it is high yielding, solvent free and catalyst can be separated by external magnetic field and reused for several runs.

## Acknowledgement

We thank the Department of Chemistry, Sophisticated Analytical and Instrumentation Facility (SAIF) of North-Eastern Hill University, SAIF-CDRI Lucknow, UGC for supporting this work under Special Assistance Programme (SAP) and DST-Purse programme of NEHU Shillong. We are also thankful to DST for financial support (sanctioned no: SERC/F/0293/2012-13), Dr. S. Khatua and Dr. S. L. Nongbri.

## Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Spectrum BX FT-IR, Perkin Elmer ( $\nu_{\max}$  in  $\text{cm}^{-1}$ ) on KBr disks. <sup>1</sup>H NMR and <sup>13</sup>C NMR (400/300 MHz and 100/75 MHz respectively) spectra were recorded on Bruker Avance II-400 and 300 spectrometer in CDCl<sub>3</sub> (chemical shifts in  $\delta$  with TMS as internal standard). Mass spectra were recorded on Waters ZQ-4000. Transmission Electron Microscope (TEM) was recorded on JEOL JSM 100CX. Scanning electron microscope (SEM) was recorded on JSM-6360 (JEOL). XRD was recorded on Bruker D8 XRD instrument SWAX. CHN were recorded on CHN-OS analyzer (Perkin Elmer 2400, Series II). Silica gel G (E-mark, India) was used for TLC. Hexane refers to the fraction boiling between 60 °C and 80 °C. Absorption spectra were recorded in Lambda25 (PerkinElmer Inc.) spectrometers.

X-ray crystallography

The X-ray diffraction data were collected at 293 K with Mo K $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ) using Agilent Xcalibur (Eos, Gemini) diffractometer equipped with a graphite monochromator. The software used for data collection CrysAlis PRO (Agilent, 2011), data reduction CrysAlis PRO and cell refinement CrysAlis PRO. The structure were solved by direct methods and refined by full-matrix least-squares calculation using SHELXS-97<sup>39</sup> and SHELXL-97<sup>40</sup> (CCDC 933681).

#### General procedure for the synthesis of 3a-h.

Fe<sub>3</sub>O<sub>4</sub> (6 mol %) was added to a mixture of *o*-phenylenediamine **1** (1mmol) and acetophenone **2a-h** (2.2 mmol) and heated at 80 °C under solvent free condition. After completion of the reaction, monitored by TLC, the reaction mixture was cooled to room temperature and dissolved in 10 mL ethyl acetate. The Fe<sub>3</sub>O<sub>4</sub> NPs was then separated by external magnetic field. The separated Fe<sub>3</sub>O<sub>4</sub> NPs was washed with ethyl acetate and dried. Then it was used for another set of reaction under similar condition. The reaction mixture was then washed with water (3  $\times$  5mL), brine (1  $\times$  5 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The reaction mass was concentrated under vacuum and the pure product was obtained by purification through column chromatography using ethyl acetate: hexane as eluent.

#### General procedure for the synthesis of 5a-f.

In a round bottom flask, *o*-phenylenediamine **1** (1mmol) and aldehyde **4a-f** (2.2 mmol), was taken and Fe<sub>3</sub>O<sub>4</sub> NPs (6 mol %) was added. The reaction was carried out at 80 °C under solvent free condition. After completion (TLC), the reaction mixture was cooled to room temperature and dissolved in 10 mL ethyl acetate. The Fe<sub>3</sub>O<sub>4</sub> NPs was then separated by external magnetic field and washed with ethyl acetate and dried. The separated Fe<sub>3</sub>O<sub>4</sub> NPs was then used for another set of reaction under similar condition. The reaction mixture was then washed with water (3  $\times$  5mL), brine (1  $\times$  5 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The reaction mass was concentrated under vacuum. The crude mixture was purified by column chromatography using ethyl acetate: hexane as eluent.

#### Spectral data for selected compounds

Compound **3b**: (entry 2): Yellow solid. IR (KBr): 3496, 3025, 1686, 1493, 751 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta = 7.51$ -7.45 (m, 4H), 7.30-7.25 (m, 1H), 7.20-7.17 (m, 4H), 7.07-7.01 (m, 2H), 6.82-6.76 (m, 1H), 3.41 (s, 1H), 3.07 (d,  $J = 13.3$  Hz, 1H), 2.88 (d,  $J = 13.5$ , 1H), 1.71 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta = 166.1$ , 145.7, 139.8, 137.6, 136.1, 133.0, 128.5, 128.38, 128.31, 127.0, 126.6, 122.0, 121.5, 73.5, 42.9, 29.7. ESI- MS:  $m/z$  381, 383 [M + H]<sup>+</sup>. Anal. Calcd for C<sub>22</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>2</sub>: C, 69.30; H, 4.76; N, 7.35. Found: C, 69.53; H, 4.64; N, 7.44.

Compound **3c**: (entry 3): Orange solid. IR (KBr): 3278, 3088, 1604, 1473, 1349 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta = 8.47$

(s, 1H), 8.16 (s, 1H), 8.12 (d,  $J = 8.1$  Hz, 1H), 7.99-7.96 (m, 3H), 7.42-7.32 (m, 3H), 7.18-7.08 (m, 2H), 6.93-6.91 (dd,  $J = 7.5$  Hz, 1.2 Hz, 1H), 3.55 (s, 1H), 3.28 (d,  $J = 13.5$  Hz, 1H), 3.02 (d,  $J = 13.5$ , 1H), 1.87 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta = 164.1$ , 149.0, 148.1, 148.0, 140.4, 139.2, 137.1, 132.5, 131.9, 129.5, 129.2, 128.9, 127.4, 124.4, 122.4, 122.2, 121.6, 120.8, 74.1, 42.8, 29.9. ESI- MS:  $m/z$  403 [M + H]<sup>+</sup>. Anal. Calcd for C<sub>22</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub>: C, 65.66; H, 4.51; N, 13.92. Found: C, 65.61; H, 4.62; N, 13.80.

Compound **3d**: (entry 4): Pale brown solid. IR (KBr): 3370, 2979 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta = 7.46$ -7.27 (m, 9H), 7.11-7.01 (m, 2H), 6.83-6.80 (m, 1H), 3.42 (s, 1H), 3.07 (d,  $J = 13.2$  Hz, 1H), 2.89 (d,  $J = 13.2$  Hz, 1H), 1.72 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta = 166.2$ , 146.5, 140.0, 138.3, 137.7, 131.5, 131.4, 128.8, 128.7, 127.6, 126.8, 124.7, 122.2, 121.7, 121.4, 73.7, 43.0, 29.9. ESI-MS:  $m/z$  469, 471 [M + H]<sup>+</sup>. Anal. Calcd for C<sub>22</sub>H<sub>18</sub>Br<sub>2</sub>N<sub>2</sub>: C, 56.20; H, 3.86; N, 5.96. Found: C, 56.12; H, 3.88; N, 5.77.

Compound **5b**: (entry 10): Pale white solid. IR (KBr): 3075, 2928, 2852, 1611, 1250, 744 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 7.81$  (d,  $J = 7.6$  Hz, 1H), 7.53 (d,  $J = 8.4$  Hz, 2H), 7.38 (d,  $J = 8.4$  Hz, 2H), 7.29-7.19 (m, 4H), 7.14 (d,  $J = 8$  Hz, 1H), 6.96 (d,  $J = 8$  Hz, 2H), 5.33 (s, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta = 152.8$ , 142.9, 136.3, 135.8, 134.6, 133.8, 130.4, 129.3, 129.1, 128.2, 127.2, 123.5, 123.1, 120.1, 110.3, 47.8. ESI- MS:  $m/z$  353, 355 [M + H]<sup>+</sup>. Anal. Calcd for C<sub>20</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>: C, 68.00; H, 3.99; N, 7.93. Found: C, 68.21; H, 4.03; N, 7.82.

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**GRAPHICAL ABSTRACT**

**An efficient facile and one-pot synthesis of benzodiazepines and chemoselective 1,2-disubstituted benzimidazoles using magnetically retrievable  $\text{Fe}_3\text{O}_4$  nanocatalyst under solvent free condition**

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