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A Novel Magnetic Nanocatalyst Fe_3O_4@TiO_2-H_5IO_6 for the Green Synthesis of 4-Substituted-1,5-benzodiazepine Derivatives

Fatemeh Ahmadzadeh, Bahador Karami,* Mahnaz Farahi and Jamileh Etemad
Department of Chemistry, Yasouj University, Yasouj, PO Box 353, Iran
karami@yu.ac.ir*

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Summary: In this study, periodic acid-functionalized magnetic support (Fe_3O_4@TiO_2-H_5IO_6) as a new, benign and recyclable nanocatalyst was prepared by anchoring / periodic acid onto TiO_2-coated nano-Fe_3O_4. This catalyst was applied to achieve a high-efficiency, low-cost and eco-friendly approach for synthesizing 4-substituted-1,5-benzodiazepines with the multicomponent reactions of aromatic aldehydes, *o*-phenylenediamine, and dimedone. The / periodic acid group on Fe_3O_4@TiO_2 possesses both Lewis and Brønsted acidity, which is responsible for the high catalyst activity. The obtained results show that the catalyst performance has been acceptable in the presented research. / The catalyst could be recovered and reused up to six times without any notable decrease in its activity.

Key words: Periodic acid; Fe_3O_4; TiO_2; Nanocatalyst; Benzodiazepine.

Introduction

Benzodiazepines are an outstanding class of heterocyclic compounds that find extensive use in pharmaceutical industries [1-3]. They are best known for owning a wide variety of biological properties, including antidepressive [4], antifungal [5], antiepileptic [6, 7], analgesic [8], antibiotic [9, 10], and HIV-1 protease inhibiting activities [11, 12]. Many family members have extensively applied as tranquilizing and anticonvulsant agents [13]. Specifically, 1,5-benzodiazepines, which constitute the fundamental structural units of well-known drugs, are of interest to the medicinal chemist. Its unique central nervous system (CNS) depressant activity made them one of the most widely prescribed psychotropics classes [14]. Fused or functionalized 1,5-benzodiazepines, as useful intermediates, are used to synthesize triazole-, oxadiazole-, oxazino-, and furano-benzodiazepines [15-17]. Most of the synthetic methods reported for the preparation of 1,5-benzodiazepines are related to the reactions of the *o*-phenylenediamine with α,β-unsaturated, carbonyl compounds, β-haloketones, or ketones which some of these processes suffer major or minor restrictions including high catalyst loading, unfavorable product yields, and difficulty in isolation methods of product [18]. Due to the attractive features of 1,5-benzodiazepines, in the present work, we decided to report a comfortable and practical approach for synthesizing them.

Multicomponent reactions (MCRs) are excellent strategies that offer a wide range of advantages, including being quick, simplified, and easy fulfillment, with a high atom economy. So, they have attracted significant interest owing to their impressive synthetic efficiency. Multicomponent reactions have broad applications in medicinal chemistry to produce libraries of biologically active compounds using readily available starting materials [19-23].

Homogeneous transition metal catalysts often exhibit excellent performance in organic transformations but show drawbacks regarding recovery and recyclability [24, 25]. These kinds of reusable catalysts, such as mesoporous silica or polymers in which transition metal has immobilized / solid supports from industrial and environmental viewpoints, possess many benefits [26]. Much better mild reaction conditions, easy set-up, and work-up are intrinsic features of heterogeneous catalysts over their homogenous analogs. Furthermore, after completing the reaction, the supported catalysts are ready to quickly isolate from the crude mixture through simple filtering or centrifuging and then recovered for more runs. The heterogeneous catalytic systems not only decrease the production of the waste but also show high activity and excellent selectivity [27-31].

Synthesis and applications of nanocatalysts have been undergoing fascinating developments in recent years as a result of their unique chemical and physical properties. The proficiency of nanocatalysts to accelerate the organic reactions and prevent the side routes from obtaining undesired products represents the interest to utilize lower amounts of inexpensive and drastic catalysts [32]. Because of the high surface area and high dispersion of metal nanoparticles (MNPs), they have been used as catalysts in many reactions [33]. The MNP-based catalysts are usually preserved by organic ligands, such as polymers, surfactants, and phosphines, to prevent coalescence. They are used inhomogeneous systems similar to those in which metal-complex catalysts are used [34]. Iron oxide nanoparticles (Fe_3O_4 NPs) are used

*To whom all correspondence should be addressed.

as a practical support for many heterogeneous nanocatalysts owing to their features such as a good imbibition magnetization value, low cost, easy renewability, and recovery by magnetic separation, non-toxicity, and surface changeability [35-38]. These nanoparticles tend to agglomerate to form larger particles. Another limitation of Fe_3O_4 nanoparticles is their sensitivity to oxidation [39]. To inhibit this accumulation and oxidation, a layer is placed on them. In this regard, coatings such as SiO_2 [40, 41], TiO_2 [42-44], graphene, and graphene oxide [45, 46] have been used in various articles recently. In this study, Fe_3O_4 nanoparticles have been coated by a TiO_2 layer to chemically stabilize bare iron oxide nanoparticles against damage during or after the subsequent application. Furthermore, the TiO_2 shell is straightforward to be functionalized and suitable for binding / various catalytic species.

The purpose of this research is to highlight the use of reusable nanocatalysts with inherent magnetic properties for the preparation of some biologically active heterocycles. Herein, in recent analysis [47-58], we prepared a solid acid catalyst via anchoring periodic acid on Fe_3O_4@TiO_2 by a simple procedure whose catalytic activity on the one-pot synthesis of benzodiazepines has been investigated.

Experimental

General materials and instruments

All chemicals used in this research were purchased from Fluka and Merck chemical companies. The monitoring of the reaction progress was accomplished using thin-layer chromatography (TLC) performed with silica gel SIL G/UV254 plates (hexane:EtOAc). Ultrasonic irradiation was performed in an ultrasound cleaning bath KQ-250 DE with a frequency of 40 kHz, and power of 250 W. Melting points were determined by an electrothermal KSB1N apparatus. The NMR spectra of ^1H were recorded in DMSO-d_6 on Bruker Avance UltraShield 400 MHz instrument spectrometers, and ^{13}C NMR spectra were recorded at 100 MHz. Fourier transforms infrared (FT-IR) spectra were obtained with a JASCO FT-IR/680 instrument spectrometer using KBr pellets. X-ray powder diffraction (XRD) patterns were recorded using a Bruker AXS (D8 Advance) X-ray diffractometer with Cu Kα radiation (λ = 0.15418 nm). The measurement was made in 2θ ranging from 10° to 80° at the speed of 0.05° min^{-1}. Energy dispersive spectroscopy (EDS) was obtained using the TESCAN vega model instrument. The particle size and morphology of the particles were studied by scanning electron microscopy (SEM: KYKY-EM3200) experiments under an acceleration voltage of 26 kV. The magnetic measurement was carried out in a vibrating sample magnetometer (VSM; Kashan University, Kashan, Iran) at room/temperature.

Procedure for the synthesis of Fe_3O_4 NPs

Nano-Fe_3O_4 was fabricated according to a reported method [59]. The mixture of $FeCl_3 \cdot 6H_2O$ (2.7 g, 10 mmol) and $FeCl_2.4H_2O$ (1 g, 5 mmol) in distilled water (45 mL) was stirred for 15 min under an argon atmosphere at 80 °C. Followed by NaOH solution (5 mL, 10 M) was added drop-wise until the color darkened. The mixture was stirred vigorously for 1 hour and then the attained black products were collected and washed several times with deionized water and ethanol, and then dried at 60 °C.

Preparation of Fe_3O_4@TiO_2

The prepared Fe_3O_4 MNPs were dispersed in a mixture of ethanol and acetonitrile (125:45 mL) ultrasonically for 15 min. A particular NH_3 aqueous solution (0.75 mL, 25%) was added to the mixture under stirring. After the continuous mechanical stirring for 30 min, tetraethyl orthotitanate (TEOT) (1.5 mL) dissolved in absolute ethanol (20 mL) was added drop-wise to the above suspension. In the end, Fe_3O_4@TiO_2 was separated by an external magnet, washed/ three times by EtOH, and dried at room/temperature for one day [60].

Synthesis of periodic acid-functionalized magnetic TiO_2 nanoparticles (Fe_3O_4@TiO_2@H_5IO_6)

A mixture of Fe_3O_4@TiO_2 (0.5 g) and H_5IO_6 (2.50 g, 10.96 mmol) in DMSO (15 mL) was stirred at reflux under argon atmosphere for 24 hours. Then, the obtained Fe_3O_4@TiO_2@H_5IO_6 nanocatalyst was filtered and washed two times with ethanol, once with distilled water, and dried at 60 ºC for 6 hours and dried in the oven at 100 °C.

General procedure for the synthesis of 4-substituted-1,5-benzodiazepines

Fe_3O_4@TiO_2-H_5IO_6 (0.002 g) was added to a mixture of aldehyde (1 mmol), *o*-phenylenediamine (1 mmol), and dimedone (1 mmol). The resulting mixture was stirred in an oil bath (80 °C) under solvent-free conditions. Stirring was continued till complete conversion was achieved, as confirmed by TLC. When the reaction was finished, the mixture was dissolved in acetonitrile, and the catalyst was separated by an external magnetic field. The loose end solvent vaporized and eventually obtained precipitate was crystallized from hot ethanol.

Spectral data

Compound ***5l***. Yield 96%; m.p. 278-280 ° C. FT-IR (KBr): υ_{max} 3465, 3304, 3242, 3114, 2966, 1600, 1415, 1381, 1278, 758 cm^{-1}, ^1H NMR (DMSO-d_6, 400 MHz) δ = 1.09 (s, 3H), 1.11 (s, 3H), 2.17 (q, 2H, J = 15.1 Hz), 2.65 (s, 2H), 3.35 (s, 1H), 5.42 (d, 1H, J = 7.6 Hz), 5.86 (d, 1H, J = 7.6 Hz), 6.47-7.05 (m, 7H), 8.89 (s, 1H), 10.12 (s, 1H) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 27.60, 29.14, 32.36, 44.54, 49.94, 56.50, 109.09, 109.88, 117.41, 120.41, 120.75, 120.97, 123.29, 129.61, 130.35, 131.44, 133.09, 138.66, 154.97, 156.05, 192.59 ppm. Anal. Calcd. for $C_{21}H_{21}BrN_2O_2$: C, 61.03; H, 5.12; N, 6.78. Found: C, 61.09; H, 5.10; N, 6.75.

Results and Discussion

The synthetic pathway for the preparation of Fe_3O_4@TiO_2-H_5IO_6 magnetic nanocatalyst is shown in Scheme-1. Fe_3O_4 nanoparticles were prepared by chemical coprecipitation of Fe^{2+} and Fe^{3+} ions in a basic solution. Then, the modification of Fe_3O_4 nanoparticles surface was accomplished via a coating layer of TiO_2 employing tetraethyl orthotitanate (TEOT) to obtain Fe_3O_4@TiO_2. Finally, periodic acid can be immobilized on TiO_2-coated Fe_3O_4 to get our desired magnetic nanocatalyst **1**. Identification and characterization of the physicochemical properties of this catalyst were conducted by applying various analyzes methods such as FT-IR, XRD, FE-SEM, and EDX techniques.

Fig. 1, shows the X-ray diffraction (XRD) patterns of the synthesized Fe_3O_4@TiO_2 and Fe_3O_4@TiO_2@H_5IO_6. As exhibited in Fig. 1 the structure of the crystal is cubic inverse spinel and remains constant after encapsulation and functionalization [61]. In this XRD pattern, the peaks at 2θ values of 30.1, 35.4, 43.05, 57.94, and 62.56 are consistent with the standard XRD data for the structure of Fe_3O_4, and these peaks are present in two patterns [62]. Moreover, the peaks at 36.4, 53.9, and 63 belong to TiO_2 [63], the two peaks at 36.4 and 63 being overlaid the Fe_3O_4 peaks. According to the Debye-Scherrer equation, the average particle size is estimated at /30 nm.

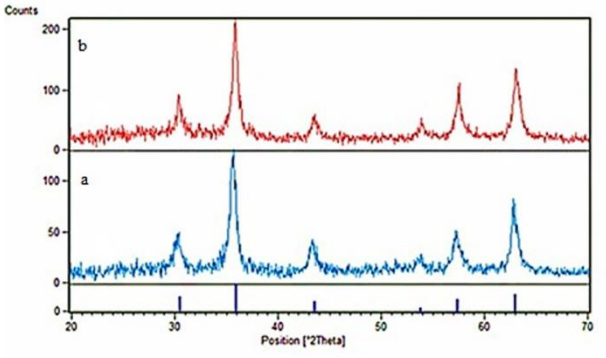


Fig. 1: The XRD pattern of a) Fe_3O_4@TiO_2 and b) Fe_3O_4@TiO_2@H_5IO_6.

The FT-IR spectra of Fe_3O_4, Fe_3O_4@TiO_2, and Fe_3O_4@TiO_2@H_5IO_6 are demonstrated in Fig. 2. This spectrum helped to confirm the stepwise formation of nanocatalysts. The peak observed at 585 cm^{-1} shows the stretching vibrational modes of Fe-O / are maintained in all samples. In Fig. 2b and 2c, the vibration frequency of Ti-O is located at 500-600 cm^{-1} but could not be recognized meticulously due to overlapping with the vibrational stretching of Fe-O in this region. The broad peak in this region in Fig. 1c is related to the O-H stretching vibration of periodic acid. Also, I=O functional groups corresponding to periodic acid have been identified by the appearance of vibrating band at 815 cm^{-1} in Fig. 2c, which is not seen in the two spectrums 2a and 2b and emphasize the stabilization of this acid on the surface of the TiO_2-coated Fe_3O_4 NPs.

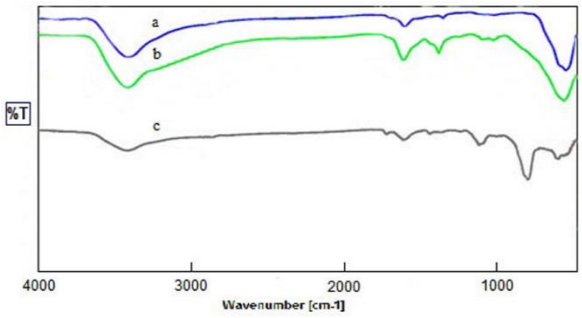
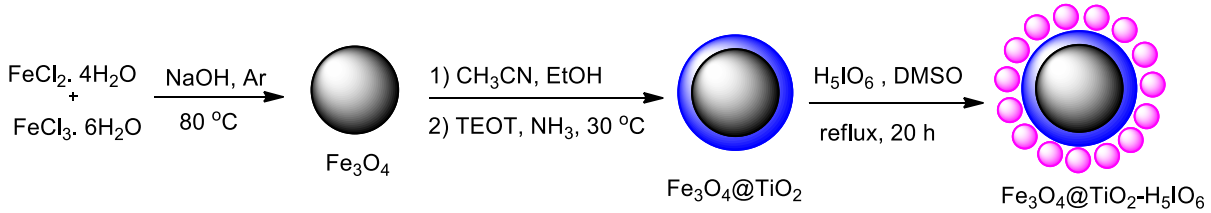


Fig. 2: The FT-IR spectra of a) Fe_3O_4, b) Fe_3O_4@TiO_2, and c) Fe_3O_4@TiO_2-H_5IO_6.



Scheme-1. Preparation of Fe_3O_4@TiO_2-H_5IO_6 (**1**).

Energy-dispersive X-ray spectroscopy (EDS) is often used to obtain useful information about the elemental composition of the objects. Herein, the EDS analysis confirmed the presence of Fe, O, Ti, C, H, and I in magnetic nanocatalyst **1,** which guarantees the successful anchoring of periodic acid on Fe_3O_4@TiO_2 (Fig. 3).

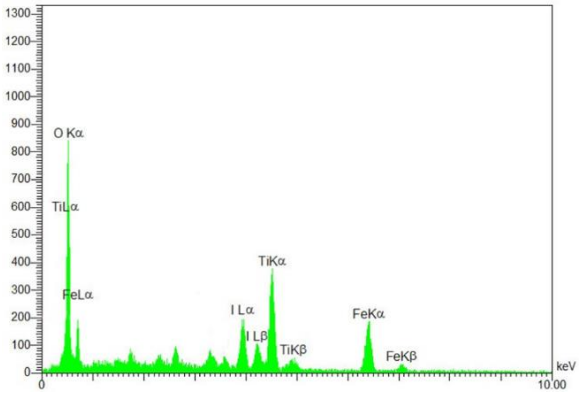


Fig. 3: EDS spectrum of nano Fe_3O_4@TiO_2-H_5IO_6.

The morphology of Fe_3O_4@TiO_2-H_5IO_6 nanocatalyst was investigated by acquiring a scanning electron microscopy (SEM) image of it, as shown in Fig. 4. The nanoparticles with a narrow distribution of diameters averaging approximately 30 nm were observed in this image.

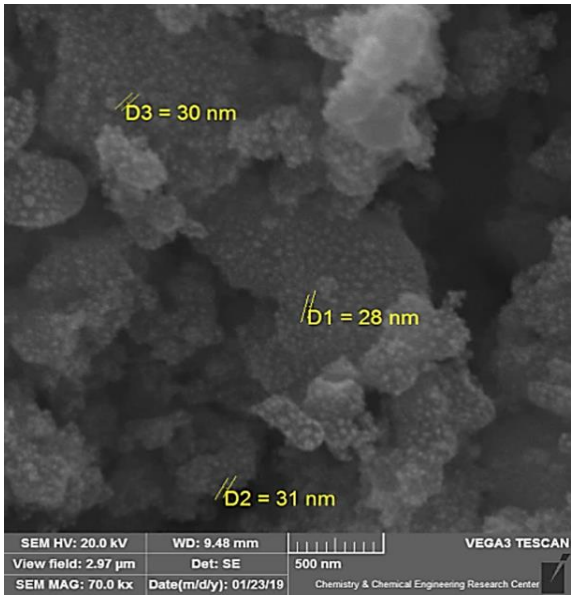


Fig. 4: SEM image of nano Fe_3O_4@TiO_2-H_5IO_6.

The below magnetization curves show the saturation magnetization of Fe_3O_4@TiO_2 nanoparticles (Fig. 5a) and Fe_3O_4@TiO_2-H_5IO_6 (Fig. 5b), which were reduced to 23emu g1 from 70 emu g1 for Fe_3O_4@TiO_2. As can be seen, the difference in saturation magnetization between Fe_3O_4@TiO_2 nanoparticles and Fe_3O_4@TiO_2-H_5IO_6 was small. Despite the reduction in the magnetic value, the catalyst still has a magnetic property and can be easily separated from the reaction by an external magnet.

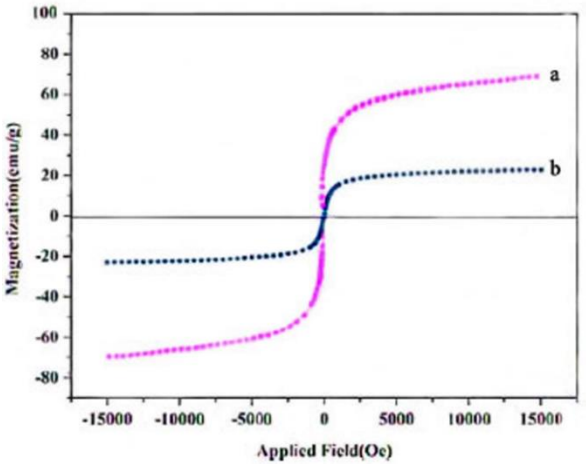
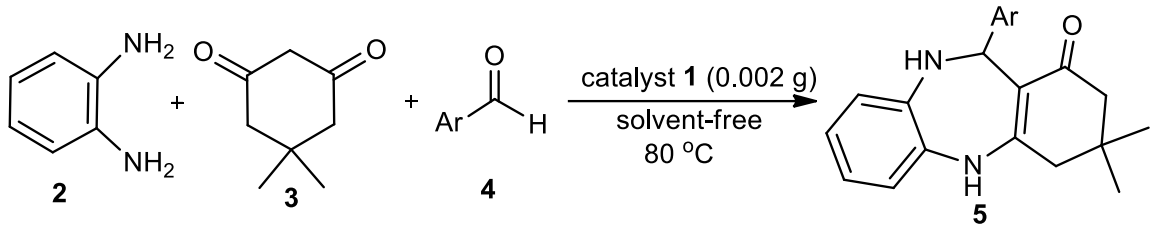


Fig. 5: Room-temperature magnetization curves of a) Fe_3O_4@TiO_2 and b) Fe_3O_4@TiO_2-H_5IO_6.

Next, we focused on preparing 4-substituted-1,5-benzodiazepine derivatives **5** by a three-component reaction of *o*-phenylenediamine **2**, dimedone **3,** and aryl aldehydes **4** in the presence of the prepared Fe_3O_4@TiO_2-H_5IO_6 (Scheme 2).

Initially, to determine suitable conditions, the reaction of benzaldehyde, *o*-phenylenediamine, and dimedone was selected as a model reaction. The impact of diverse parameters such as the amount of the catalyst, solvent type, and temperature were investigated and optimized (Table-1). Under catalyst and solvent-free conditions at room temperature, we could not obtain the desired product. Next, with increasing the temperature of the reaction, a trace amount of **5a** was obtained. The model reaction was conducted in the presence of various amounts of catalyst **1**. The best yield was obtained in the fact of 0.002 g of catalyst **1**. Investigation of different solvents and reaction temperatures were also done. Subsequently, different amounts of H_5IO_6 were studied. The results of several experimental conditions are summarized in Table-1. Notably, using 0.002 g of Fe_3O_4@TiO_2-H_5IO_6 under solvent-free conditions at 80 ºC was selected as the optimized reaction conditions.



Scheme-2. Synthesis of 4-substituted-1,5-benzodiazepines using Fe_3O_4@TiO_2-H_5IO_6.

Table-1: Evaluating reaction conditions on the model reaction.

Entry	Solvent	Catalyst loading	*T* (°C)	Time/Yield[a] (min/%)
1	-	-	25	360/0
2	-	-	70	360/10
3	-	Cat 1 (0.001 g)	70	30/60
4	-	Cat 1 (0.002 g)	70	30/80
5	-	Cat 1 (0.003 g)	70	30/80
6		Cat 1 (0.004 g)	70	30/65
7		Cat 1 (0.002 g)	80	10/95
8	-	Cat 1 (0.002 g)	90	10/90
9	-	Cat 1 (0.002 g)	100	10/85
10	-	Cat 1 (0.002 g)	110	10/75
11	EtOH	Cat 1 (0.002 g)	reflux	30/60
12	H_2O	Cat 1 (0.002 g)	reflux	30/50
13	$CHCl_3$	Cat 1 (0.002 g)	reflux	30/65
14	THF	Cat 1 (0.002 g)	reflux	30/70
15	-	H_5IO_6 (2 mol%)	80	100/60
16	-	H_5IO_6 (5 mol%)	80	100/65
17	-	H_5IO_6 (10 mol%)	80	100/70

[a]Isolated yields.

Table-2: Preparation of 4-substituted-1,5-benzodiazepine derivatives by using Fe_3O_4@TiO_2-H_5IO_6.[a]

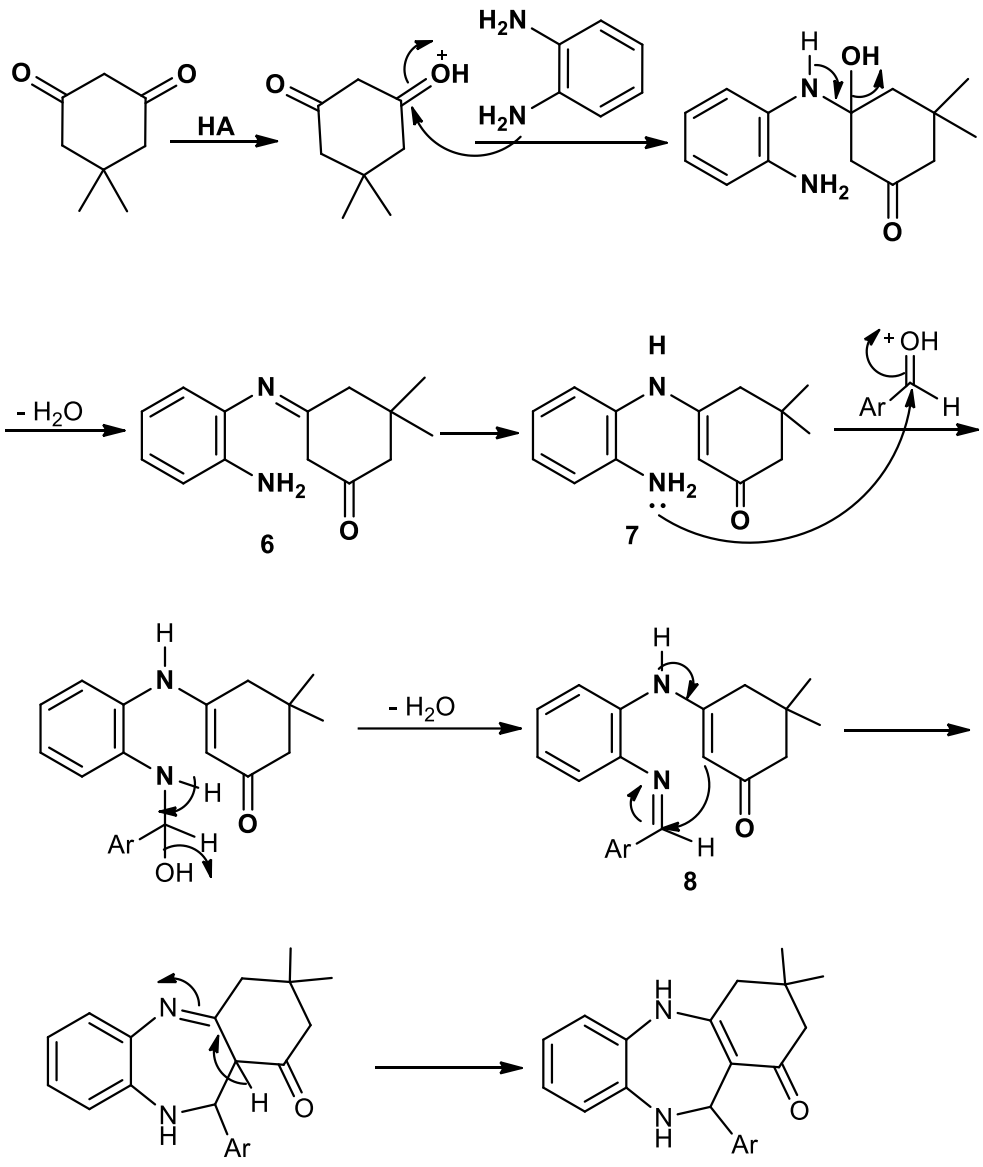
Entry	Ar	Time (min)	Yield[b] (%)	Mp (°C)
5a	C_6H_5	10	95	248-250[19]
5b	4-$NO_2C_6H_4$	7	95	272-274[64]
5c	4-ClC_6H_4	7	95	238-241[4]
5d	4-OHC_6H_4	10	92	229-232[4]
5e	4-$CH_3C_6H_4$	8	90	223-225[19]
5f	3-ClC_6H_4	7	95	230-231[1]
5g	3-$NO_2C_6H_4$	7	96	146-147[4]
5h	4-BrC_6H_4	7	93	222-224[65]
5i	4-$CH_3OC_6H_4$	8	94	249-250[4]
5j	4-Cl-5-$NO_2C_6H_3$	7	90	195-196[66]
5k	2-Thionyl	10	90	264-266[1]
5l	4-Br-2-OHC_6H_3	7	96	278-280[c]

[a]Reaction condition: aldehyde (1 mmol), *o*-phenylenediamine (1 mmol), dimedone (1 mmol) and catalyst **1** (0.002 g) at 80 °C. [b]Isolated yields. [c]Novel compound.

In determining optimal conditions, some of the 4-substituted-1,5-benzodiazepine derivatives were prepared in the presence of different aldehydes, having both types of substituent electron-donating and electron-withdrawing. According to the proposed mechanism, the results demonstrate electron-withdrawing functional groups various positions, especially in para-substituted aromatic aldehydes, have shorter reaction times and higher efficiency. But in general, in all substituted aromatic, the reaction time is short, and the efficiency is excellent, as stated in the references[1,4,19], which shows the best and effective performance of Fe_3O_4@TiO_2-H_5IO_6 as a catalyst in preparing 1,5-benzodiazepines (Table-2).

According to the reported mechanisms in the literature [4], we proposed a probable mechanism for the preparation of 4-substituted-1,5-benzodiazepines **5** by using the acidic catalyst **1** (Scheme 3). Initially, the NH_2 group of *o*-phenylenediamine attacks/ the activated carbonyl group of dimedone to give intermediate **6**. In the following, imine **6** performs a 1,3-hydrogen shift to produce enamine **7**. The amino group of **7** reacts with the carbonyl group of aldehyde to form intermediate **8**. Finally, the seven-membered ring benzodiazepine is obtained by the intramolecular cyclization of adduct **8**.

As exhibited in Table-3, the most important benefits of the current protocol over the presented methods can be understandable just by comparison of our outcomes with those of lately published pathways.



Scheme-3. The suggested mechanism for synthesizing of **5** by $Fe_3O_4@TiO_2$-H_5IO_6.

Table-3: Comparison of the results for the preparation of compound **5b** with various used catalysts.

Catalyst	Conditions	Time (min)	Yield[a] (%)
Sulfated polyborate (10 mol%)	**solvent-free, 100 °C**	**10**	**98**[1]
ZnS Nanoparticles (0.01 g)	**EtOH, reflux**	**8**	**94**[19]
La_2O_3 (1 mol%)	**solvent-free, 60 °C**	**210**	**83**[67]
$La(OH)_3$ (1 mol%)	**solvent-free, 60 °C**	**180**	**85**[68]
$Fe_3O_4@TiO_2$-H_5IO_6 (0.002 g)	**solvent-free, 80 °C**	**7**	**95**

[a]Isolated yields.

To investigate any leaching of H_5IO_6 from the $Fe_3O_4@TiO_2$-H_5IO_6 solid acid catalyst, we have performed an in situ filtration technique. When the reaction progress reached 50%, warm acetonitrile (5 mL) was added, and the catalyst isolation was carried out by simple filtration. After removing the solvent, the catalyst-free residue continued the process under the conditions which before were optimized. As we expected, the progress of the reaction stopped, which confirms that no leaching of the supported catalytic

centers has happened under optimized conditions. Furthermore, the reusability of Fe_3O_4@TiO_2-H_5IO_6 was investigated in the model reaction. After completion of the reaction, acetonitrile (5 mL) was added to the mixture, and the catalyst was filtered, washed with EtOH (10 mL), and deionized water (10 mL), followed by drying at 100 °C. Applying the recovered catalyst for six successive runs in the model reaction generated the product, having a negligible reduction in yield (Fig. 6). As seen, establishing the fact that the Fe_3O_4@TiO_2-H_5IO_6 catalyst possesses recycling ability with no significant decrease in its activity.

Fig. 6: Reusability of Fe_3O_4@TiO_2-H_5IO_6 in the reaction of benzaldehyde, *o*-phenylenediamine, and dimedone.

Conclusions

In this work, for the first time, TiO_2 coated Fe_3O_4 was functionalized by periodic acid, and it was utilized as a new, efficient and reusable magnetic nanocatalyst for the synthesis of benzodiazepine derivatives. This new catalytic system demonstrated the advantages of environmentally benign character, quickly separation, non-toxicity, mild reaction conditions, short reaction times, and good reusability.

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