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Research Paper

Water as a green solvent for fast and efficient synthesis of 1,5-benzodiazepines at room temperature by using Water-Tolerant Sulfonic Acid Nanoreactor Based on Tunable Ordered Porous Silica

Gholam Hossein Mahdavinia*, Soheila Ghassamipour
Department of Chemistry, Marvdasht Branch, Islamic Azad University, Marvdasht, Iran

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Abstract A rapid and new green synthesis of 1,5-Benzodiazepines is reported. The title compounds were prepared by the reaction of different 1,2-phenylenediamines and ketones in the presence of $ZrOCl_2.8H_2O$ on montmorillonite K10 and MCM-41-SO_3H as a nanocatalyst in water. These methods are simple, effective, better yield and environmentally friendly.

Keywords:
$ZrOCl_2.8H_2O$ on Montmorillonite K10; MCM-41-SO_3H ; Heterogeneous catalyst; 1,5-benzodiazepines

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***Corresponding author:** Gholam Hossein Mahdavinia
Address: Department of Chemistry, Marvdasht Branch, Islamic Azad University, Marvdasht, Iran
Tell: 09177317362
Email: hmahdavinia@gmail.com

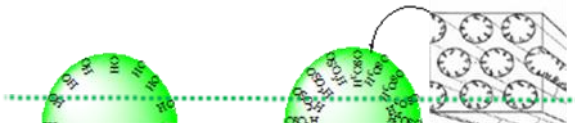
Introduction

With continually-growing green concerns, much attention has been directed toward the reduction or replacement of hazardous organic compounds from the reaction media in the green chemistry focus area [1], in which a variety of environmentally benign media such as water and supercritical fluids have been promoted as replacements [2] .

The synthesis of benzodiazepines is of interest, as they possess a large number of pharmacological properties [3]. They have shown anticonvulsant, anti-anxiety, analgesic, hypnotic, sedative, antidepressant and anti-inflamatory activity. The benzodiazepine derivatives have also been used as valuable precursors in the synthesis of various fused heterocyclic systems [4] such as triazolo-, oxazino-, oxadiazolo- and furano-benzodiazepines. In addition, they also find commercial use as dyes for acrylic fibers [5]. Despite their importance from the pharmacological, industrial and synthetic point of view, comparatively few methods for the preparation of benzodiazepines have been reported in the literature. These include the condensation reaction of o-phenylenediamine with a, β unsaturated carbonyl compounds in the presence of base [6], β-halo ketones [7] or compounds having a-hydrogen(s) next to carbonyl group in the presence of Lewis acid catalyst such as $Yb(OTf)_3$ [8], $InBr_3$ [9], BF_3-etherate [10], SiO_2 [11], MgO and $POCl_3$ [12], silica supported fluoroboric acid [13], I_2 [14], $Me_2S^+BrBr^-$ [15], $Sc(OTf)_3$ [16] and $AgNO_3$ [17]. These Lewis acids are highly oxophilic and forms strong but labile bonds with oxygen donor ligands. This feature often allows sub-stiochiometric amounts of the catalyst to be used to promote a verity of reactions. However, the use of either strongly acidic or basic conditions frequently lead to the formation of undesirable side products and competing with unwanted reactions, such as polymerization, self-condensation and rearrangements, which in turn decrease the purity and yields of the desired products. In view of current interest in catalytic processes, there is a merit in developing synthesis of benzodiazepines using inexpensive, mild and non-polluting reagents.

Generally, heterogeneous catalysts offer several advantages such as mild reaction conditions, high selectivity, high throughput and ease of work-up procedures. Among various solid supports, silica materials with ordered structure are usually preferred [18]. one of the best-known examples is MCM-41, which is a structurally well-ordered mesoporous material with a narrow pore size distribution between 1.5 and 10 nm, depending on the surfactant cation and a very high surface area up to 1500 $m^2\ g^{-1}$[19]. It has been proved that Si-MCM-41 lacks Brönsted acid sites and exhibits only weak hydrogen-bonded type sites [20-21]. Based on this idea, several types of sulfonic acid functionalized silica have been synthesized and applied as alternatives to traditional sulfonic resins in catalyzing chemical transformations [22]. An additional possibility to develop acidic solids is the modification of the surface of suitable support materials, as the chemical functionalities of these materials can be uniformly modified by covalent anchoring of different organic moieties [23]. Among the different types of silica-based sulfonic acids, Stein and co-workers prepared a novel sulfonic functionalized ordered microporous silicate, which shows a high loading and stability, and yet a uniform nanostructure [22]. Recently, MCM-41 functionalized sulfonic acid as heterogeneous solid acid catalyst has been used to catalyze a variety of reactions [24]. Also, $ZrOCl_2.8H_2O$ on montmorillonite K10 has attracted much attention recently because of its super-acidity, non-toxicity and low cost. $ZrOCl_2.8H_2O$ on montmorillonite K10 catalyzes reactions under very mild conditions. The use of zirconium (IV) salts as an efficient Lewis acid has been used for various transformations [25-29]. Many organic reactions have been devised in which the reagents are deposited on various inorganic solid supports. These reagents have

advantages over the conventional homogeneous solution techniques: easy set-up and work-up, mild experimental conditions, high yields and/or selectivity [26]. Montmorillonite K10 had a great



manufacturing industries [30].

Materials and Methods

General

Chemicals were obtained from Merck and Sigma-Aldrich and used without further purification**.** Melting points were recorded on a Büchi B-540 apparatus and are uncorrected. IR spectra were recorded on an ABB Bomem Model FTLA 200-100 instrument. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer at 300 and 75 MHz using TMS as an internal standard. Chemical shifts are reported (δ) relative to TMS, and coupling constants (J) are reported in Hertz (Hz). Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer with 70eV ionization potential.

Synthesis and functionalization of MCM-41

In the present work MCM-41 was modified to covalently anchor sulfonic groups on the inside surface of channels and provide the silica supported material with Brönsted acid properties (Scheme 1).

The MCM-41 was synthesised according to the previously described method using cetyltrimethylammoniumbromide ($C_{16}H_{33}(CH_3)_3N^+Br$), as the templating agent [31]. The surfactant template was then removed from the synthesized material by calcination at 540 ºC for 6 h.

MCM-41 was modified using a 100 ml suction flask equipped with a constant-pressure dropping funnel containing chlorosulfonic acid (0.466 g, 0.004 mol) and a gas inlet tube for conducting HCl gas over an adsorbing solution. Into it was charged 1.20 g of MCM-41and chlorosulfonic acid was then added dropwise over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately (Scheme 1). After completion of addition the mixture was shaken for 30 min. and the white solid (MCM-41-SO_3H) was obtained (1.52 g).

Scheme 1. Schematic representation for the preparation of MCM-41-SO_3H

Characterization

XRD analysis was performed from 1.5° (2θ) to 10.0° (2θ) at a scan rate of 0.02° (2θ)/sec. The XRD patterns after the calcinations of synthesized cerium (IV) silicate samples are presented in Fig. 1.

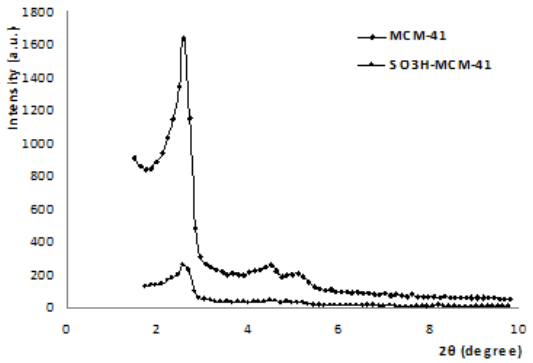


Fig. 1. XRD patterns of MCM-41 and MCM-41-SO3H

The sample of MCM-41-SO_3H produced relatively well-defined XRD patterns, with one major peak along with three small peaks identical to those of MCM-41 materials [32]. The SEM image of mesoporous MCM-41-SO_3H was taken using 2 minutes gold coat for high magnification and is shown in Fig. 2.

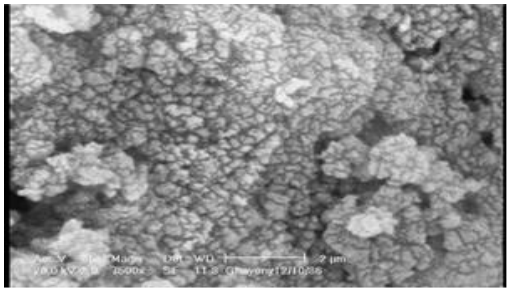


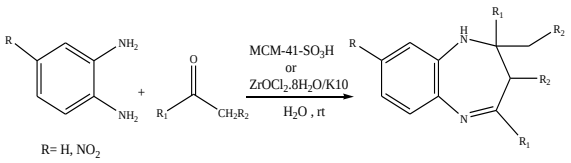
Fig. 2. SEM image of MCM-41-SO_3H

Typical Experimental Procedure for the Synthesis of 1,5-Benzodiazepine

A mixture of 1,2-diamine (1.0 mmol), ketone (2.0 mmol), and MCM-41-SO_3H (0.15g) or $ZrOCl_2.8H_2O$ on montmorillonite K10 (0.1g) in water (5 ml) was stirred at room temperature for 10-40 min (with first catalyst) or 10-25 min (with second catalyst). The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, the product was extracted with ethyl acetate (15 ml ×2). The combined ethyl acetate layers dried over anhydrous sodium sulfate and were concentrated under reduced pressure to give the crude product. Upon crystallization using a mixture of hexane and ethyl acetate the pure products were obtained.

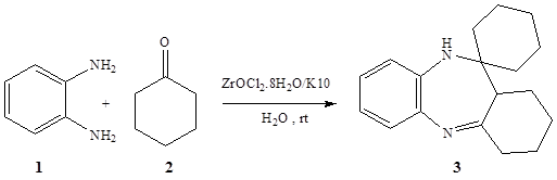
Results & Discussion

We report herein an efficient synthesis of 1,5-Benzodiazepines in water in the presence of MCM-41-SO_3H and $ZrOCl_2.8H_2O$ on montmorillonite K10 as a catalyst. (Scheme 2). The reaction of 1,2 phenylenediamines and ketones afforded the 1,5-Benzodiazepines in excellent yields (Table 1). Several functionalized 1,5-Benzodiazepines were prepared from various 1,2 phenylenediamines and ketones (Table 1). $ZrOCl_2.8H_2O$/K10 and MCM-41-SO_3H work under heterogeneous conditions. The first catalyst could conveniently be prepared [33] from the readily available ingredients, $ZrOCl_2.8H_2O$ and montmorillonite K10 while the second catalyst was synthesized and modified for the first time by our group. The conversion required 10-25 min to get the products in maximum yields using $ZrOCl_2.8H_2O$/K10 and 5-8 min using MCM-41-SO_3H. However, the yields of the products were almost similar with both of these two catalysts.



Scheme 2. Main synthetic pathway for the formation of 1,5-Benzodiazepines in presence of MCM-41-SO_3H and $ZrOCl_2.8H_2O$ on montmorillonite K10

As a starting point of our exploration, the reaction of ophenylenediamine and the cyclohexanone was carried out in water at room temperature for 20 min by taking a 1:2.1 mol ratio mixture of *o*-phenylenediamine and cyclohexanone in the presence of 0.1 g $ZrOCl_2.8H_2O$ on montmorillonite K10 to give the desired products in excellent yield (Scheme 3). To find out if water provides a kinetic advantage over the other solvents, the progress of the model reaction in various solvents at room temperature was monitored (TLC) (Scheme 3).



Scheme 3. Formation of **3b** catalyzed by $ZrOCl_2.8H_2O$ on montmorillonite K10

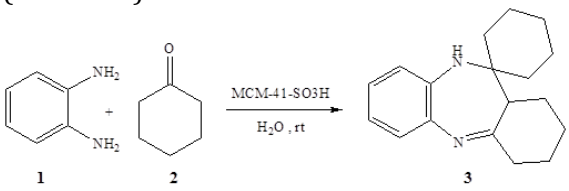
Complete consumption (TLC) of 1,2 phenylenediamines took place after 20, 60, 30 and 60 min in water, CH_3CN, EtOH/H_2O, DMF, respectively (Table 2) .

Table 2. The effect of amount of by $ZrOCl_2.8H_2O$/K10, solvent for synthesis of **3b**

Entry	Amount of catalyst(g)	Solvent	Time (min.)	Yield (%)
1	0.1	H_2O/ C_2H_5OH	30	60
2	0.1	DMF	60	40
3	0.1	CH_3CN	60	---
4	0	H_2O	300	0
5	0.05	H_2O	25	70
6	0.1	H_2O	20	92
7	0.15	H_2O	20	92

The major thrust of this work is to provide an environmentally friendly approach for the synthesis of 1,5-Benzodiazepines using a heterogeneous catalysis . The second important point which could be elicited evidently form these results is that when

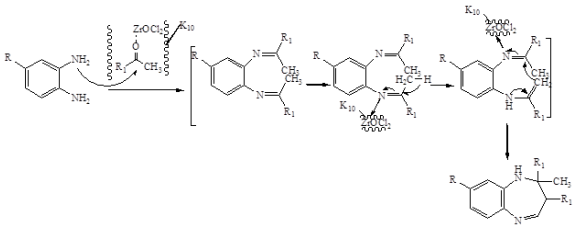
similar reactions were conducted in different amounts of $ZrOCl_2.8H_2O$/K10 as catalyst for the model reaction in water (10 ml) in the presence of 0, 50, 100 and 150 mg of $ZrOCl_2.8H_2O$/K10 separately. The best results were obtained using 100 mg of catalyst (yield=87 %). Using lower amounts of catalyst resulted in lower yields, while higher amounts of catalyst did not affect the reaction times and yields and in the absence of catalyst, the product was not formed (Table 2). Based on above observations, as $ZrOCl_2.8H_2O$ on montmorillonite K10 was found to be an efficient catalyst for performing this reaction. Also due to good catalytic activity of MCM-41-SO_3H, in an initial study for optimizing condition, this Brönsted acid nanoreactor showed good catalytic activity in water in comparison with some conventional organic solvents including methanol, ethanol, and ethyl acetate. Then when we studied the role of the amount of catalyst on the above model reaction (ophenylenediamine with cyclohexanone) in the presence of 100, 150 and 200 mg of MCM-41-SO_3H. According to this data, the optimum amount of catalyst is 150 mg. Increasing the amount of catalyst did not improve the yield and the reaction time, while by decreasing it the reaction time increased and the yield was lower. (Scheme 4).



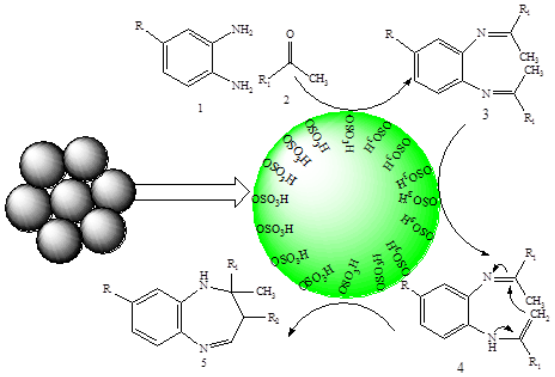
Scheme 4. Formation of 3b catalyzed by MCM-41-SO_3H

A proposed mechanism for this transformation using $ZrOCl_2.8H_2O$/K10 is depicted in Scheme **5** As shown, $ZrOCl_2.8H_2O$/K10 activates the carbonyl oxygen, forming the intermediate diimine. A 1,3-shift of the hydrogen attached to the methyl group then occurs to form an isomeric enamine, which cyclizes to afford the seven membered ring.

Also in a purposed mechanistic pathway for MCM-41-SO_3H, as shown in Scheme **6** the carbonyl oxygen is activated by the acidic sites of the inner mesochannels, to give the intermediate diimine which was then converted to isomeric enamine. Finally subsequent cyclization occurred in the sufficiently spaced channel of nanoreactor, nanocatalyst yielding the desired product.



Scheme 5. Proposed mechanism



Scheme 6. Proposed mechanism for the formation of benzodiazepines

Conclusion

In conclusion, we have developed a new and efficient method for the region-selective synthesis of 1,5-benzodiazepines utilizing two heterogeneous catalysts, $ZrOCl_2.8H_2O$ on montmorillonite K10 and MCM-41-SO_3H. The simple experimental work-up, high yields and application of inexpensive catalysts is the advantages of the present procedures.

Compliance with ethical guidelines

All subjects fulfill the informed consent.

Acknowledgments

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Authors' contributions

Design and conceptualization, methodology, data analysis and final writing: Gholam Hossein Mahdavinia

The author declared no conflict of interest.

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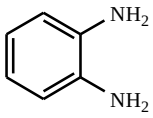
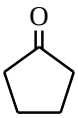
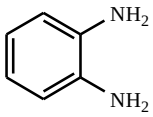
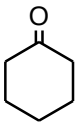
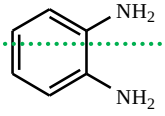
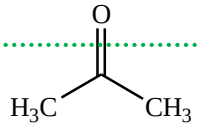
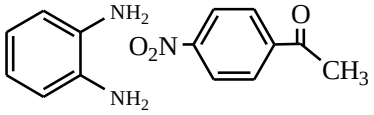
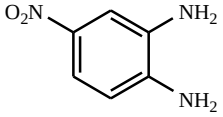
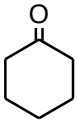
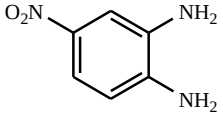
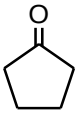
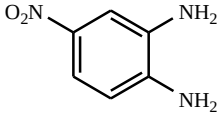
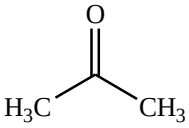
Table 1. Preparation of 1,5-Benzodiazepines using $ZrOCl_2.8H_2O$ on montmorillonite K10 and MCM-41-SO_3H[1,2]

Entry	R	Ketone	Product	Catalyst[3]	Time (min.)	Yield (%)	Mp
1			3a	i ii	20 6	84 85	136-137(139)
2			3b	i ii	25 6	87 88	135-137(139)
3			3c	i ii	10 5	96 95	145-147(141)
4			3d	i ii	15 6	93 ---	158-160
5			3e	i ii	20 8	90 96	151-152
6			3f	i ii	10 8	80 87	149-151
7			3g	i ii	10 8	94 95	148-150