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EFFICIENT PROTOCOL FOR THE SYNTHESIS OF BENZODIAZOPINES IN ATTENDANCE OF SIO_2@MSA AS HETEROGENEOUS AND RECYCLABLE CATALYST

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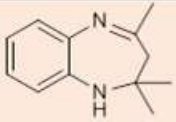
ABSTRACT

In the present research work, we have evaluated the catalytic efficiency of silica supported methane sulfonic acid for the synthesis of benzodiazepine derivatives through the cyclisation of 2-aminothiophenol with aliphatic/aryl and heteroaryl methyl ketones. The reported protocol is highly efficient in attendance of 0.5 g silica supported methane sulfonic acid as a heterogeneous catalyst in 10 mL CH_3CN solvent under reflux condition. Use of non-corrosive, non-toxic and efficient catalyst at ambient temperature are the key advantages of reported method and it comes with certain additional compensations like shorter reaction time, simple work-up technique, high yields, recyclability of catalyst and easy availability.

KEYWORDS: SiO_2@MSA; Benzodiazopines; Heterogeneous catalyst; Recyclable catalyst, Efficient protocol.

I. INTRODUCTION

A class of drug act as tranquilizers and commonly used in the treatment of anxiety is called as benzodiazepines. Benzodiazepines constitute an important class of biologically active compounds andtheir synthesis has been receiving much attention in the field of medicinal and pharmaceutical chemistry owing to their application as anticonvulsant, anti-inflammatory, analgesic, hypnotic, and sedative agents and to their hypnotic activity.[1–6]



2,2,4-trimethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine

The derivatives of 1,5-benzodiazepines are also used as dyes for acrylic fibres in photography.[7] In addition, benzodiazepines are the useful precursors for the synthesis of other fused ring compounds such as triazolo-, oxadiazolo, oxazino-, or furano-benzodiazepines.[8–11] Benzodiazepines are generally synthesized by the condensation of o-phenylenediamine (OPDA) with ∝, β unsaturated carbonyl compounds, b-haloketones, or with ketones[12] using acidic catalysts which are critical to enhance the condensation process. Different reagents such as BF_3-etherate, polyphosphoric acid, $NaBH_4$, $MgO/POCl_3$, $Yb(OTf)_3$, $Ga(OTf)_3$, lead nitrate, L-proline, acetic acid under microwave conditions, molecular iodine, and ionic liquids have also been used for the synthesis of benzodiazepines[13–20] Recently the synthesis of benzodiazepines has also been reported using different solid acid catalysts such as sulfated zirconia, Al_2O_3/P_2O_5, $Ag_3PW_{12}O_{40}$, PVP-$FeCl_3$, and zeolite catalysts.[21–25] Unfortunately, many of these catalysts suffer from one or more limitations, such as long reaction times, occurrence of several side reactions, drastic reaction conditions, low yields, and tedious workup procedure. In addition, the solid oxide catalyst used previously had poor textural parameters such as low surface area and pore volume which do not support a better performance in the synthesis of benzodiazepines. These factors stimulate the search for a better catalyst, which should offer a high activity for the synthesis of 1,5-benzodiazepines under mild reaction conditions. In recent years, mesoporous materials with different structure and tunable pore diameters have been receiving much attention.

Recently, methane sulfonic acid (CH_3SO_3H) is a strong organic acid that considered being a green solvent.[1] The combination of its favorable physical and chemical properties makes Methane sulfonic acid (MSA) a suitable solvent for development of sustainable processes. It has a very low vapor pressure and high boiling point, and no dangerous volatile compounds evolve from the liquid under normal operational conditions.[1,2] The toxicity of MSA is relatively low and has small affinity to oxidize organic compounds as well as less corrosive compared to many commercially available acids. It is readily biodegradable with a sulfate and carbon dioxide as the degradation products.[1] MSA is considered to be a natural product, and it is part of the natural sulfur cycle.[3] MSA is a strong acid with a p^{Ka} of -1.19 which is close to that of nitric acid ($p^{Ka} = -1.3$) and sulfuric acid ($p^{Ka1} = -3$) and higher than that of other organic acids such as formic acid (p^{Ka} = 3.82), acetic acid (p^{Ka} = 4.76) and citric acid (p^{Ka1} = 3.09).[4] The application of this strong acid as a commercial chemical is based on the fact that it is a non-oxidizing, non-volatile, highly conductive acid and that metal methane sulfonate salts are highly soluble in water.[1,5] Due to such compunctions, it attracts many chemists to use in organic synthesis.

Furthermore, MSA has many potential applications in catalysis[1,6-8], and as solvent for polymer synthesis and depolymerization.[9,10] With its beneficial physical and chemical properties, MSA is also a valuable candidate as reagent in extractive metallurgy, but it has been very little explored to date. Now days, we are working on developing ecofriendly and efficient protocols for organic transformations[36-38] and recently reported catalytic application of SiO_2@MSA for the synthesis of benzoxazoles.[39]

However, supported MSA, which could be a cost-effective and eco-friendly solid acid catalyst, and an attractive alternative to supported acid catalyst for 1,5-benzodiazepines synthesis, has not been reported in the literature. The present work was aimed at developing silica-supported MSA (SiO_2@MSA) as a cost-effective, eco-friendly, and reusable solid acid catalyst for 1,5-benzodiazepines heterocycles.

In the present study, we have synthesis of benzodiazepines using silica-supported MSA catalyst. Benzodiazepines derivatives were synthesize from o-phenelynediamine reacts with various methyl ketones taken in acetonitrile solvent. Appropriate conditions were confirmed through the optimization of various reaction parameters. Here in, we reported SiO_2@MSA catalyst showed efficient catalytic activity for benzodiazepines synthesis under ambient conditions. Additionally prepared catalyst is recyclable and showed good activity up to 4th cycle.

2. Experimental Work

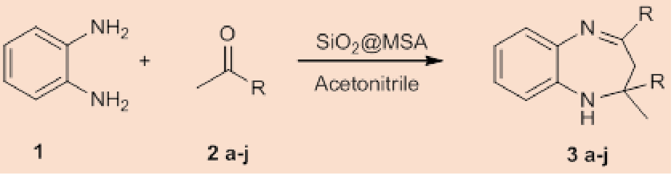
All the chemicals used for synthesis were of LR (laboratory reagent) grade. methanesulfonic acid (98%) was purchased from sigma Aldrich chemicals and do necessary purification before used it. TLC (thin layer chromatography) was performed on microscopic glass slides coated with silica gel-G using, petroleum ether:ethyl acetate (8:2) as a solvent system and the spot were visualized by exposure to iodine vapours. The IR spectrum of synthesized compounds were recorded on FT-IR spectrophotometer using potassium bromide. ^1H NMR was required on The IR spectra (in cm^{-1}) were recorded on a perkin-Elmer spectrophotometer in KBr pellets. ^{1}HMR spectra were recorded on Varian Gemini (200 MHz) spectrometer using DMSO as solvent and TMS as an internal standard. ^{13}C-NMR spectra recorded on 50 MHz in DMSO solvent, in δ ppm. All chemical shifts values are reported in δ scale downfield from TMS. Homogeneity of the compound was checked by TLC on silica gel plates.

2.1. Synthesis of Silica-supported methanesulfonic acid catalyst

Catalyst was prepared using procedure reported by *J. Joshi et al*.[40] 10 g of dried silica gel was treated with MSA solution (5 mL of MSA in 50 mL of carbon tetrachloride) at room temperature with stirring for 24 h. The gel was filtered and washed with ethanol and then with petroleum ether to remove free MSA. The gel was dried at room temperature for 24 h and later at 120 °C for 6 h.

2.2. General Procedure for the Synthesis of 1,5 -Benzodiazepines

A mixture of OPDA (1mmol), ketones (2.5mmol), SiO_2@MSA (0.5 g) was reflux in acetonitrile (10ml) until thin layer chromatography indicated the reaction was completed. Ethyl acetate (10%) in hexane was used as the mobile phase and both the reactant and the final products were spotted on the TLC plate. After completion of the reaction vessels poor in 50ml H_2O and extracted with ethyl acetate (10 ml X 3), catalyst was filter out and separated from the above solution. The collected organic layer was concentrated and the crude product was obtained and it was purified by recrystallization.



Scheme: Synthesis of 1, 5 -Benzodiazepines using SiO_2@MSA catalyst.

3. RESULT AND DISCUSSION

The effect of different solvents have been studied under the same reaction conditions, as shown in table. The yield of the product varied with the nature of the solvents; better conversion and easy isolation of product was found with acetonitrile. Acetonitrile dissolves a wide range of ionic and non-polar compounds. In a similar manner, the reaction with o-phenylenediamine and methyl ketones.

Same reaction was carried out without any solvents. The observation shown that the reaction was not brought into completion, even after starting for a period 8 hrs, and the reaction mixture showed a number of spot in thin layer chromatography (TLC). After the screening of solvents and reaction temperature we have finalized, acetonitrile as solvents and reaction carried out at 60 °C. Additionally, the effect of treatment of catalyst on present reaction also studied and we have found (0.5 g) of SiO_2@MSA catalyst showed remarkable efficiency for the studied protocol. Under the optimised protocol. We have synthesis series of benzodiazepines derivatives. The yield and melting point of synthesized compounds are given in table.

We have also study the reusability of used catalyst to the course of benzodiazepine from acetone and o-phenylenediamine in 10 mL acetonitrile solvent. Result showed that prepared catalyst were give remarkable yield of target molecule up to 4th cycle. Recyclability of SiO_2@MSA shown in figure 1.

Table 1: Influence of Various Reaction Parameters on Reaction Out Comes.

Sr. No.	Catalyst SiO_2@MSA(in gm)	Solvent	Temp. (inC°)	Reaction Time(in hr)	Yield (In %)
1	0.5	Solvent free	R.T	8	30
2	0.5	ETOH	R.T	8	56
3	0.5	ETOH	60	8	70
4	0.5	CH_3-CN	60	4	92
5	0.5	Toluene	60	12	50
6	0.5	DMF	60	14	62
7	0.7	CH_3-CN	60	4	92
8	0.4	CH_3-CN	60	5	88

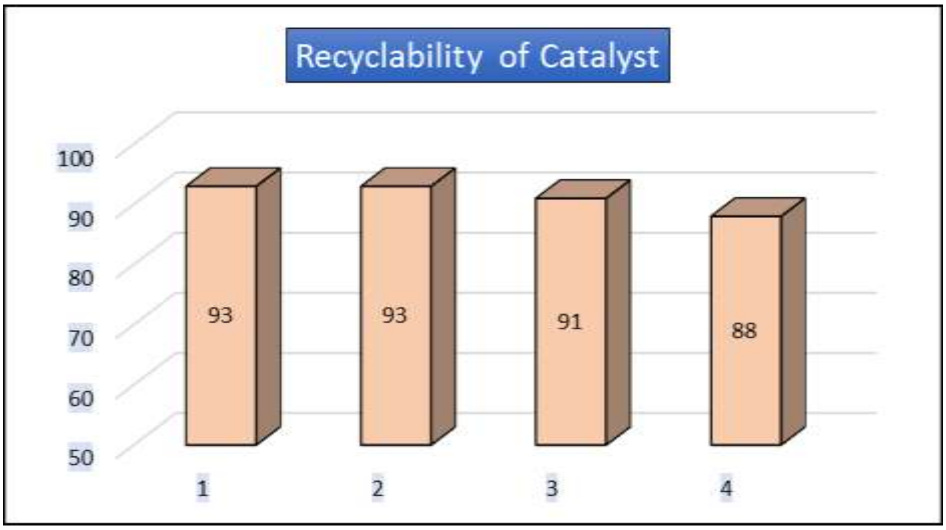
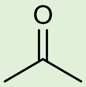
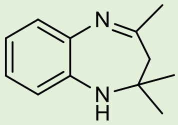
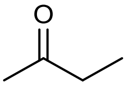
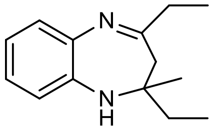
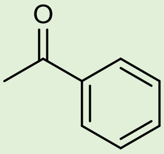
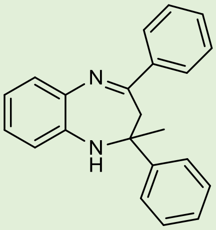
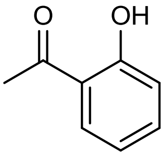
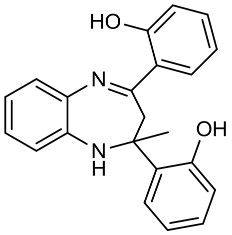
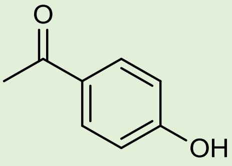
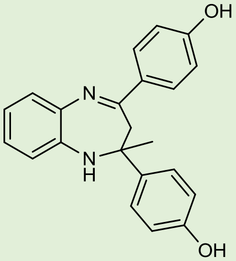
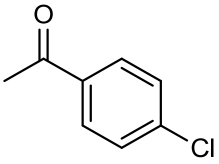
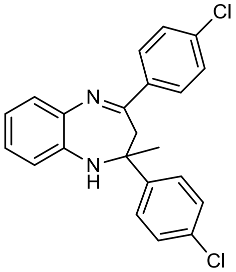
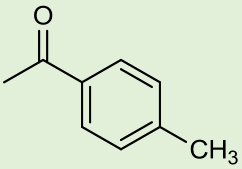
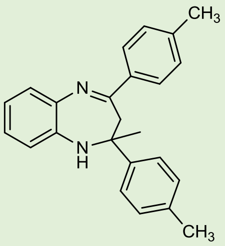
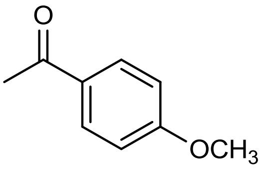
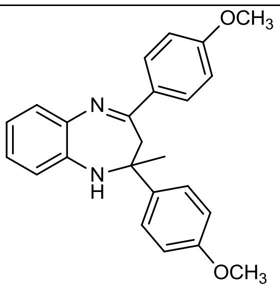
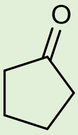
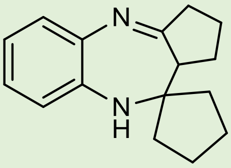
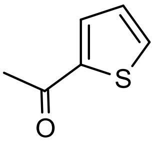
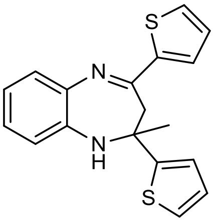


Figure 1: Recyclability of SiO_2@MSA Catalyst.

Table 2: Analytical Data of Synthesised Final Compounds.

Sr. No.	Ketone	Product	Reaction time(in hr)	Yield (in %)	M.P In (c°)
1			5	93	137
2			8	90	139
3			6	92	151
4			8	88	165
5			6	90	172
6			5	93	144
7			6	92	211

8			7	89	240
9			7.5	90	139
10			6.2	88	93

CONCLUSIONS

In SiO_2@MSA has been employed as efficient catalysts for the benzodiazepines synthesis under ambient conditions. Benzodiazepines obtained in good yield from o-phenylenediamine and variety of ketones. All the reactions were carried out at 60 °C temperature while using the catalyst SiO_2@MSA in (0.5g). The reaction conditions were mild, and the isolation of products and separation of catalyst were also very easy. The key point of the present work is the recyclability of SiO_2@MSA showed remarkable to good efficiency up to 4th cycle. In addition, it was easily separated from reaction vessels and reuse after just washing with water, heated at 100 °C for 2 hr.

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