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SILICA-SUPPORTED METHANESULFONIC ACID: AN EFFICIENT, HETEROGENEOUS CATALYST FOR BENZOXAZOLE SYNTHESIS

Sujit S. Mathakari*

Department of Chemistry, Shri Madhavrao Patil Mahavidyalaya, Murum-413605, Dist: Osmanabad, Affiliated to Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, India.

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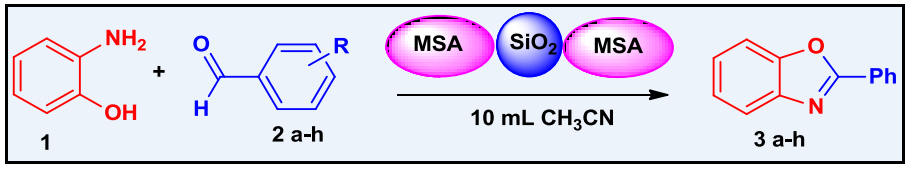
***Corresponding Author**
Sujit S. Mathakari
Department of Chemistry, Shri Madhavrao Patil Mahavidyalaya, Murum-413605, Dist: Osmanabad, Affiliated to Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, India.

ABSTRACT

In the present research work, we have described synthesis of a series of benzoxazoles through the cyclisation of 2-aminothiophenol with aryl and heteroaryl aldehydes. The reported protocol is very much efficient in attendance of 10 mol % silica supported methane sulfonic acid as a heterogeneous catalyst in 10 mL CH_3CN solvent at 60 ^oC. 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; Cyclization; Benzoxazoles; Heterogeneous catalyst; Efficient protocol.

Graphical Abstract



INTRODUCTION

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

Five membered heterocycles comprehending a C=N bond such as benzimidazole, benzoxazole and benzothiazole are important structural scaffold in natural products as well as pharmaceutical and agrochemical compounds.[11-13] Benzoxazoles are an important class of heterocyclic compounds that have many applications in the field of medicinal chemistry such as melatonin receptor agonists[14], amyloido genesis inhibitors[15], Rho kinase inhibitors[16] and antitumor agents.[17] Additionally, UK-1,[18] AJI9561 and salvianen[19] are the cytotoxic natural products which contains the benzoxazole core structure.[20] Furthermore, benzoxazoles derivatives exhibits the cathepsin S inhibitor[21], selective peroxisome proliferator-activated receptor γ antagonist JTP-426467.[22]

In general, two methods were mostly used in literature for synthesizing 2-substituted benzoxazoles. One is the condensation of 2-aminophenols with carboxylic acid derivatives, which catalyzed by various strong acids[23] or requires microwave conditions.[24] Second important process is the oxidative cyclization of phenolic Schiff bases synthesized via the condensation of 2-aminophenols and aromatic aldehydes. Various oxidant catalysts were

reported for latter method such as DDQ[25], Mn-$(OAc)_3$[26], Zinc sulfamate[27], $Th^{+}.ClO^{4-}$[28], $BaMnO_4$[29], NiO_2[30] and $PhI(OAc)_2$.[31] However, all of these available methodologies comes with certain drawbacks, as requirement of excess amount of oxidants, tedious work up process, long reaction time, hazards environment and production of side products etc. Therefore, a more effective and simple protocol is required for the selective synthesis of benzoxazols with good yield under ambient circumstances.

Now a days, researchers and academicians are more attracted towards developing ecofriendly, efficient methods by the using green solvent, heterogeneous catalysts, solid supported catalysts, metal free catalysts, reactions at room temperature.[32-36]

Herein, we extend our interest towards the development of novel and cleaner methods for classical synthesis of benzoxazoles. Accordingly, we report proficient approach for the synthesis of benzoxazoles using Silica-supported methanesulfonic acid catalyst at ambient temperature. The reported methane sulphonic acid catalyst offered some advantages in comparison to reported catalysts such as solid catalyst, easy availability, non-metallic acidic character, effective and efficient even at ambient temperature, non-corrosive and non-toxic. The current approach was found be highly selective, effective and yielded the desired product with satisfactory yield within short reaction period.

2. Experimental

2.1. General

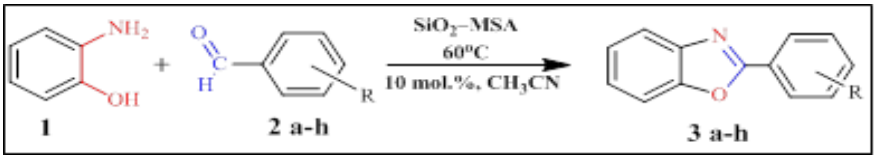
All the chemicals were obtained from commercial chemical supplier and used it with further purification. methanesulfonic acid (98%) was purchased from sigma Aldrich chemicals and do necessary purification before used it. All crucial preliminary materials for benzoxazole derivatives and necessary reagents were acquired from Sigma Aldrich and used without additional distillation. All solvents were purified and dried by typical methods earlier to use. All the melting points were determined in open capillary tubes and are uncorrected. 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.

2.2. Synthesis of Silica-supported methanesulfonic acid catalyst

Catalyst was prepared using procedure reported by *J. Joshi et al*.[37] 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.

2.3. General procedure for the synthesis of Benzoxazole Derivatives

To a mixture of o-amino phenol (0.01 mol) and aromatic aldehydes (0.01 mol), CH_3CN (10 mL) were added in 50 mL round bottom flask. To this solution, added a known amount of catalyst SiO_2–MSA (10 % mole). Resulting reaction mixture was heated at 60 ^oC reaction temperature with constant vigorous stirring. The progress of reaction was traced by TLC (CH_2Cl_2 and MeOH (90:10)), After completion of the reaction the mixture was cooled to room temperature and then poured into ice-water. The precipitated solid was filtered out washed with ice-water and further it was extracted with ethyl acetate. Catalyst was separated by simple filtration of ethyl extract and product was obtained after the evaporation of ethyl extract. Obtained product was purified by recrystallization with hot ethanol. Nevertheless, pure enough on TLC (90:10) was then passed through a short column of silica gel to afford pure benzoxazole products. The structures of final compounds are confirmed through spectral characterized.



Scheme: ***Synthesis of benzoxazoles from 2-amino phenol and aldehydes.***

2.4. Characterization of synthesized benzoxazole derivatives (3 a-h)

3-a) 2-Phenyl benzo[d]oxazole: **^{1}H NMR** ($CDCl_3$, in δ): 8.3- 8.2 (m, 2H), 7.8-7.7 (m, 1H), 7.6-7.5 (m, 1H), 7.5-7.4 (m, 3H), 7.3-7.2 (m, 2H; **IR** (KBr, cm-1): 3435, 2921, 1615, 1551, 1240, 743.); **Mass m/z**: 196.20 $[M+H]^+$

3-c) 2-p-Tolyl benzo[d]oxazole: **^{1}H NMR** ($CDCl_3$ in δ): 8.1 (d, 2H), 7.7- 7.6 (m, 1H), 7.5-7.4 (m, 1H), 7.3-7.2 (m, 4H), 2.5 (s, 3H); **IR** (KBr, cm^{-1}): 3460, 2955, 2842, 1650, 1604, 1455, 1240, 765, 640, 523; **Mass m/z:** 210.20 $[M+H]^+$

3-f) 2-(3-Methoxyphenyl) benzo[d]oxazole: **^{1}H NMR** ($CDCl_3$ in δ): 7.8-7.7 (m, 3H), 7.6-7.5 (m, 1H), 7.4 (t, 1H), 7.3-7.2 (m, 2H), 7.1-7.0 (m, 1H), 3.8 (s, 3H); **IR** (KBr, cm^{-1}): 3440, 3005, 2962, 2865, 1660, 1504, 1480, 1254, 1084, 780, 669, 630; **Mass m/z**: 226.23 $[M+H]^+$

3-i) 2-(2-Bromophenyl) benzo[d]oxazole: **^{1}H NMR** ($CDCl_3$ in δ): 8.0 (d, 1H), 7.8-7.7 (m, 1H), 7.6 (d, 1H), 7.6-7.5 (m, 1H), 7.4-7.3 (m, 4H); **IR** (KBr, cm^{-1}): 3453, 2920, 2840, 1635, 1442, 1220, 740, 653, 580; **Mass m/z**: 273.95, 275.90 $[M+H]^+$

3-j) 2-(furan-2-yl) benzo[d]oxazole: **^{1}H NMR** ($CDCl_3$ in δ): 7.7-7.6 (m, 1H), 7.6-7.5 (m, 1H), 7.5-7.4 (m, 1H), 7.3 (d, 2H), 7.2 (d, 1H), 6.6 (m, 1H); **IR** (KBr, cm^{-1}): 3482, 2950, 2812, 1650, 1600, 1402, 1354, 1240, 1062, 825, 726, 683; **Mass m/z**: 186.02 $[M+H]^+$

3. RESULT AND DISCUSSION

Numerous research articles were already published on the effective ways for the synthesis of benzoxazoles, herein, we gave a good alternative in the form of $SiO_2@CH_3SO_3H$ catalyzed protocol. Silica-supported methane sulfonic acid is easily prepared from commercially available methane sulfonic acid but still it is not been much explored. Recently, we successfully checked catalytic activity of methane sulfonic acid for synthesis of benzimidazole, benzoxazole and benzthiazole derivative.[8] Methane sulfonic acid is a omogeneous catalyst and it was not recovered after completion of reaction. Obtained results gave us inspiration to go ahead for to investigate catalytic efficiency of methane sulfonic acid and make it heterogeneous with supporting on silica. In the present work, we have exposed a clean and effective root for benzoxazole synthesis from 2-amino phenol and various substituted benzaldehydes in presence of catalytic amount of SiO_2–MSA catalyst in 10 mL of CH_3CN solvent, final product was obtained after stirring of reaction vessels at 60^{o}C for reported time. Current methodology gave respectable outcomes under ambient conditions with good and selective yield of target molecule.

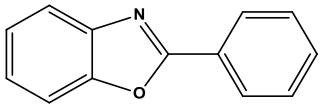
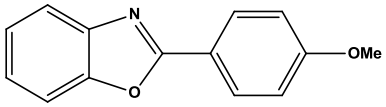
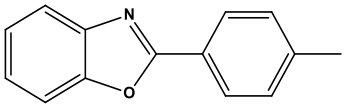
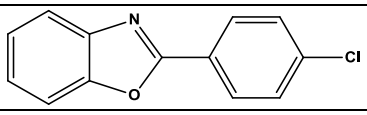
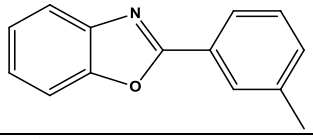
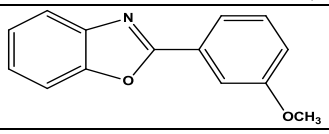
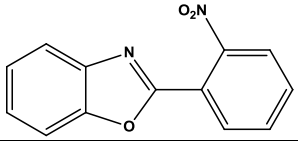
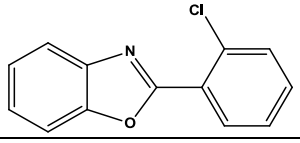
The appropriate reaction conditions were investigated via examining various reaction parameters. Additionally, effect of amount of loading of catalyst and effect of solvent and temperature were studied. To finalize optimized conditions, 2-amino phenol (1 mmol) and benzaldehyde (1 mmol) taken as model reaction. After the optimization of all parameters, we have finalized the reaction condition as 2-amino phenol (1 mmol) and benzaldehyde (1 mmol) reacted well at 60 ^{o}C in 10 mL CH_3CN in the presence of 10 mol% catalyst.

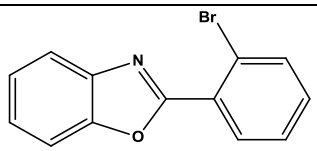
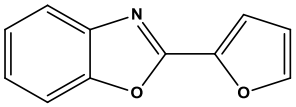
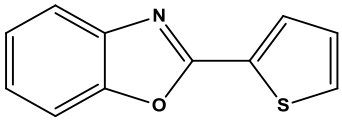
With this optimized reaction condition, we have proceeded to investigate the scope and generality of this protocol using collection of various substituted aromatic aldehydes and 2-

amino phenol in CH_3CN as solvent. Consequently, a diversity of commercially accessible different structurally substituted aldehydes were treated in the optimized reaction conditions to obtained benzoxazole derivatives and obtained results are summarized in Table I. As shown in Table I, all substituted aldehydes participated well in this cyclization reaction and afforded the desired products of benzoxazole in good to efficient yields using catalytic amount of SiO_2–MSA.

However, from these results, it can conclude that SiO_2–MSA is highly suitable catalyst for the synthesis of benzoxazoles with different functional substituent on the aldehyde rings. In addition, these substituted functionalities were preserved throughout the course of reaction in presence of prepared catalyst under optimized reaction conditions. Moreover, result reveals that, aromatic aldehydes with different substituent at ortho, meta or para positions showed comparable results towards the formation of respective derivative.

Table I: Synthesis of series of benzoxazole derivatives under optimized conditions.[(a)]

Entry	Product	Time (in h)[b]	Yield (in %)[c]	M.P. (in ^oC)
1		2.30	94	104-105
2		2.00	95	97-98
3		2.25	92	114-115
4		3.40	90	120-121
5		4.00	88	108-109
6		3.25	90	73-74
7		4.20	85	90-92
8		3.40	88	74-76

9		4.30	82	52-54
10		2.20	92	86-88
11		2.40	91	105-107
Reaction conditions: (a) 2-amino phenol (0.01 mol), aldehyde (0.01mol). (**b**) Reaction time was monitored by TLC. **(c)** isolated yield				

4. CONCLUSION

Present protocol gave a better alternative for the synthesis of benzoxazoles under ambient conditions. 10 mol. % of SiO_2–MSA catalyst showed efficient activity for the transformation of 2-amino phenol and aromatic aldehydes. Presented methodology gave remarkable yield of final product in short time. The advantages of the present technique are the operational simplicity, high efficiency, no side products formation, easy of workup procedure and catalyst was recovered after the completion of reaction.

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