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Communication

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Study of Heterogeneous Catalysis by Iron-Squarate based 3D Metal Organic Framework for the Transformation of Tetrazines to Oxadiazole derivatives

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Supporting Information

ABSTRACT: We present here a simple, milder, and environmentally benign heterogeneous catalytic method for the transformation of tetrazines to oxadiazole derivatives at room temperature (25 °C) using our earlier synthesized iron-squarate based 3D metal organic framework, $[Fe_3(OH)_3(C_4O_4)(C_4O_4)_{0.5}]_n$ (FeSq-MOF).

Metal Organic frameworks (MOFs) or Porous Coordination Polymers (PCPs) are crystalline porous materials whose structures are defined by metal ions or clusters containing metals acting as lattice nodes and rigid bi- or multipodal organic linkers as spacers.[1,2] MOFs have many similarities with zeolites and related microporous solids from the structural point of view. Considering the fact that a large number of reactions in heterogeneous catalysis are based on zeolites and porous solids, there is interest in exploiting the potential of MOFs as heterogeneous catalysts.[3] MOFs constitute of large density of active metal sites with free or exchangeable coordination positions and show poor solubility in common solvents as well as tunable and uniform pore sizes, which make them smart heterogeneous catalysts. Thus, in a certain way, MOFs can complement zeolites as heterogeneous catalysts for the liquid-phase reactions. The main drawback of MOFs is that they mostly act as Lewis acid type catalysts, and for that the presence of coordination unsaturation at the metal site is essential. Unfortunately, in most of the structures, the nodal metal ions or clusters do not contain free coordination positions to interact with substrates and reagents.[4]

Synthesis of biologically important molecules by using MOFs as a catalyst is a very recent and challenging attempt.[5] Out of many molecules, substituted oxadiazoles are biologically important pharmacophores[6] because of their analgesic, anti-inflammatory, muscle relaxant, etc. activities.[6d] For this reason, a large number of marketed medicines bear a 1,3,4-oxadiazole core.[6e] In addition, pyridyl substituted oxadiazole derivatives are of great research interest because of their different coordination features and magnetic properties.[7]

Therefore, many synthetic strategies have been established over the years[8] to obtain oxadiazole derivatives. Among them, the syntheses of oxadiazoles from tetrazines using peracids and potassium hydroxide are very well-known.[9] However, most of the methods suffer a major drawback from the perspective of environmental apprehensions like toxicity, harsh reaction conditions, longer reaction time, cost effectiveness, difficulty in separation, recovery, and disposal of spent catalysts. In this regard, a challenging synthetic method using an easily synthesizable and reusable heterogeneous catalyst would be highly desirable.

In this work, we have explored the catalytic performance of our earlier synthesized iron-squarate based 3D MOF, $[Fe_3(OH)_3(C_4O_4)(C_4O_4)_{0.5}]_n$ (FeSq-MOF),[10] as a heterogeneous catalyst for the transformation of tetrazines (**2a**−**7a**) to oxadiazole derivatives (**2b**−**7b**; Figure 1), where **2a** = [3,6-bis(pyridin-2-yl)-1,2,4,5-tetrazine], **3a** = [3,6-bis(pyridin-3-yl)-1,2,4,5-tetrazine], **4a** = [3,6-bis(pyridin-4-yl)-1,2,4,5-tetrazine], **5a** = [3,6-diphenyl-1,2,4,5-tetrazine], **6a** = [3,6-di-p-tolyl-1,2,4,5-tetrazine], **7a** = [4,4′-(1,2,4,5-tetrazine-3,6-diyl)-diphenol], **2b** = [2,5-bis(2-pyridyl)-1,3,4-oxadiazole], **3b** = [2,5-bis(3-pyridyl)-1,3,4-oxadiazole], **4b** = [2,5-bis(4-pyridyl)-1,3,4-oxadiazole], **5b** = [2,5-bis(phenyl)-1,3,4-oxadiazole], **6b** = [2,5-bis(4-methylphenyl)-1,3,4-oxadiazole], and **7b** = [2,5-bis(4-hydroxyphenyl)-1,3,4-oxadiazole] (Table 1).

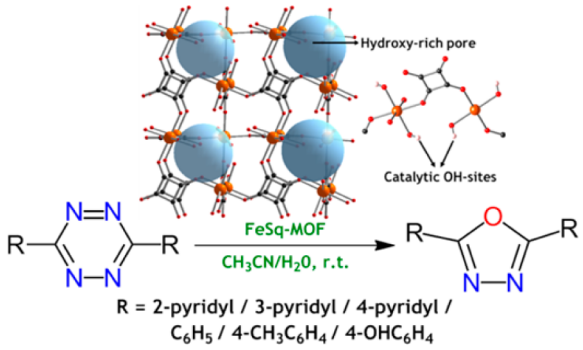

Figure 1. Schematic representation of the transformation of tetrazines (**2a**−**7a**) to oxadiazoles derivatives (**2b**−**7b**) at 25 °C using FeSq-MOF.

The synthesis, structural description, and magnetic properties of the FeSq-MOF have been reported by us previously.[10] It has been found that the 3D FeSq-MOF contains two types of voids. The larger ones are composed of aromatic squarate ligands and hence are hydrophobic in nature. On the other hand, the smaller ones are hydrophilic as they have coordinated hydroxyl groups on the surface of the voids. The morphology of FeSq-MOF has also been characterized by SEM technique. The SEM micrograph showed well-shaped, high quality cubic crystals with

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Table 1. FeSq-MOF Mediated Transformation of 2a−7a to 2b−7b

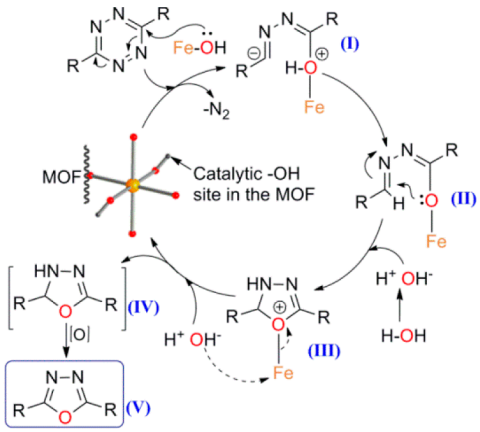
Sl. no.	S[a]	P[a]	FeSq-MOF (5 mol %)	
			T (h)	% yield[b]
1	**2a**	**2b**	1	97
2	**3a**	**3b**	2	95
3	**4a**	**4b**	1.5	96
4	**5a**	**5b**	24	64
5	**6a**	**6b**	18	55
6	**7a**	**7b**	20	53

[a]S = Substrate; P = Product. [b]Isolated yields of the products.

crystal sizes ranging between approximately 200 and 250 μm (Figure S1).

An earlier report for the transformation of oxadiazoles from tetrazines using OH^- ions[9a] has given us a hint that the hydroxyl richness of the framework probably makes the FeSq-MOF a potential heterogeneous catalyst. In order to observe the catalytic efficiency of the FeSq-MOF as a heterogeneous catalyst, substrate **2a** was allowed to stir in the presence of the FeSq-MOF in CH_3CN and H_2O mixture (1:1) at 25 °C. After stirring the heterogeneous reaction mixture for 1 h, the conversion of **2a** to **2b** was noticed. Later, the same reaction was extended for other substrates, **3a−7a**. The results are summarized in Table 1. The transformations of **2b−4b** from **2a−4a** were completed within 1−2 h at 25 °C in excellent yields, whereas transformation of **5b −7b** from **5a−7a** showed moderate yields and needed ∼24 h for completion at 25 °C. The above catalytic transformations were performed in a wide range of solvents, including a mixture of solvents, but the best results (optimum time and significant yield) were obtained in only a CH_3CN-H_2O (1:1) mixture. CH_3CN was used for dissolving the reactant/substrate, and H_2O probably assisted the catalytic transformation (Scheme 1). Although other polar

Scheme 1. Proposed Mechanism for Transformation of Tetrazines (2a−7a) to Oxadiazole (2b−7b) Derivatives



solvents like MeOH, EtOH, etc. could also dissolve the substrates, a greater amount of solvent was needed. Additionally, it has been tested that all of the above catalytic reactions display excellent to moderate yields using 5 mol % of the catalyst. To ascertain the role of FeSq-MOF as a heterogeneous catalyst, the MOF was filtered off after the completion of reactions, and the filtrates were collected. The filtrates were evaporated to dryness and kept at 4 °C overnight, which resulted in solid products. The ESI-MS spectra of the solids reveal the presence of the products **2b−7b** (Figures S4−S9). Further, the solids were used for the ^1H as well as ^{13}C NMR analysis, which matches well with the reported σ values in ppm (Figures S10−S21).[6a,8b]

Analyzing the diameter of the hydroxyl rich pores (4.7 Å) of the FeSq-MOF and the length of the reactant (∼11−15 Å), it can be speculated that the above heterogeneous catalytic transformation is occurring only on the surface of the smaller hydroxyl rich voids. However, understanding the exact mechanism of such a transformation is a difficult task. It can be proposed that the tetrazine is first attacked by the OH group coordinated to the iron center to form species I, which is transformed to the species II via H-shift (Scheme 1). Thereafter, ring closure occurs with the formation of the Fe(II)-coordinated 2,3-dihydro-oxadiazolium cation (III).

In a water medium, due to the attack of the OH^- ion at the Fe(II) center, a highly unstable 2,3-dihydro-oxadiazole (IV) is formed which subsequently oxidizes in the air to the aromatic oxadiazole derivative (V).

In order to find whether Fe(II) is leaching out or not, after 30 min of the reaction, FeSq-MOF was filtered off through a Gooch-type sintered glass crucible (pore size = 15−90 μm) and the reaction was allowed to further stir for 1.5 h. As illustrated in Figure 2a, there was no substantial increase in yield after

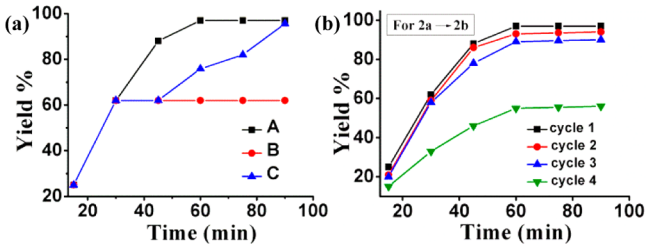


Figure 2. (a) Leaching test indicating no contribution from homogeneous catalysis of active species (A) in the presence of FeSq-MOF, (B) after 30 min of catalyst filtration, (C) readdition of catalyst (after 45 min). (b) Kinetic profiles in four consecutive reaction cycles for conversion of **2b** from **2a** using FeSq-MOF as a catalyst.

filtering off the catalyst. Again, after 45 min, FeSq-MOF was added to the reaction mixture, and it was found that there is a sudden increase in the yield of product. In overall, the stepped reaction profile in Figure 2a showed that, on removing the FeSq-MOF, the reaction practically stops, and re-adding the filtered FeSq-MOF to the reaction mixture restarts it. This simple test showed that the catalytic behavior of FeSq-MOF is heterogeneous in nature. To draw a definitive conclusion that iron is not leaching from the MOF, Inductively Coupled Plasma Optical Emission Spectrometric (ICP-OES) analysis was performed, which revealed that no metal leaching occurred in solution.

Finally, for a more comprehensive study of the catalytic activity of FeSq-MOF in the above reactions, a recycling test with three consecutive runs was performed (Figure 2b). As mentioned before, in the first cycle, 97% yield of the transformed product (**2b**) was achieved after 1 h of reaction (yield was determined from NMR analysis). Similarly, for the other two transformed oxadiazoles (**3b** and **4b**), yields up to 95% and 96% were achieved after 2 and 1.5 h, respectively (Figure S22a). However, for the other transformed oxadiazoles (**5b−7b**), yields of 64%, 55%, and 53% were achieved after 24,

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18, and 20 h, respectively. For the transformation of **2b**, in second and third runs, no substantial changes in the yields (94% and 90%) were observed for the same reaction time. However, after three runs, an appreciable fall in the yield of **2b** has been observed down to 56% (Figure 2b). In order to reveal any structural changes in the catalyst FeSq-MOF after four cycles of reactions, FTIR and powder X-ray diffraction (PXRD) analysis of recovered FeSq-MOF were performed after each cycle of reaction, and the results are discussed in the Supporting Information (Figures S2, S3).

To check whether Fe(II) salts are also able to convert tetrazines to oxadiazole derivatives, the substrate tetrazines (**2a**−**4a**) were allowed to react with Fe(II) salts (synthesis details in Supporting Information and Table S1). Solution state ESI-MS analysis reveals the formation of $[Fe(\mathbf{2b}/\mathbf{3b}/\mathbf{4b})]^{2+}$complexes (**1**−**9**) along with the respective transformed products (**2b**−**4b**; Figures S26−S28). However, the reaction of substrates (**5a**−**7a**) with Fe(II) salt indicates the stability of only transformed products (**5b**−**7b**) in solution, which is confirmed by ESI-MS analysis (Figure S29). Besides, complex **1** was structurally (Table S2) and magnetically characterized and described in detail in the Supporting Information (Figure S30−S33).

In conclusion, we present here a simple and efficient synthetic method for the transformation of tetrazines to oxadiazole derivatives using FeSq-MOF as a heterogeneous catalyst at 25 °C. Compared to Fe(II) salts, FeSq-MOF exhibits superiority in terms of product isolation, reusability, and easy-handling. Therefore, besides being simple, milder, and environmentally benign, this catalytic method gives easy access to the synthesis of the chemically and biologically important oxadiazole derivatives.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Includes experimental details, a scheme, ESI-MS, ^{1}H and ^{13}C NMR, PXRD, structural and magnetic study detail, and crystallographic tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Abraham Clearfield on the occasion of his 86th birthday.

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