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Graphical Abstract

First report of multiple metal ions containing glass ceramic material as a heterogeneous ditopic catalyst for the chromatography free synthesis of 2-amino-

3, **5**-dicarbonitrile-6-arylthio-pyridines in water

Priyabrata Manna^a* and Prabir Kumar Maiti^a

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First report of multiple metal ions containing glass ceramic material as a heterogeneous ditopic catalyst for the chromatography free synthesis of 2-amino-3, 5-dicarbonitrile-6-arylthio-pyridines in water

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ABSTRACT

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1. Introduction

Alteration of synthetic methodologies to the need of combinatorial chemistry has always been a tremendous job to solve, since combinatorial chemistry is extensively useful to meet the growing demand of pharmaceutical industry towards drug discovery.^{1a-c} The current drug discovery research is facing great challenge towards lead finding and lead optimization, because of lack of easily accessible and functionalized small heterocycles.¹ One such most important "privileged structure" in drug discovery is the 2-amino-3,5-dicarbonitrile-6-arylthio-pyridine. It has engrossed much attention because various compounds with this structural motif display significant and diverse biological activities (Figure 1). 2 6-arylthio-pyridine can be used as anti-prion, anti-hepatitis B virus, anti-bacterial and anti-cancer agents.³ In addition, they can be used as potassium channel openers for the treatment of urinary incontinence; as potential targets for the development of new drugs for the treatment of Parkinson's disease, hypoxia, asthma, kidney disease, epilepsy, cancer and Creutzfeldt–Jacob disease.^{3a,3d,4}

Over the years, copious synthetic methods have been developed for the construction of this valuable "privileged structure". Literature survey demonstrates that the majority of the strategies rely on the three-component reaction of aldehydes, malononitrile, and thiophenols catalyzed by Lewis/Brønsted base catalysts which include Et₃N, DBU, piperidine, KF/alumina, $K_2CO_3/KMnO_4$, etc.⁵ In addition a few improved methods are reported by the use of basic ionic liquid [bmIm]OH, ZnCl₂, silica nanoparticle, boric acid, ZrOCl₂.8H₂O/NaNH₂ in [bmim]BF₄ under ultrasound irradiation, nano MgO and by Zn(II) and Cd(II) MOFs etc.^{2,6} Although all of these methods are quite useful,

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This is the first of use of multiple metal ions containing glass ceramic material as a reusable

heterogeneous catalyst for multicomponent organic synthesis. A new glass ceramic material was

prepared for this purpose and applied in the sustainable and ecofriendly synthesis of 2-amino-3, 5-dicarbonitrile-6-arylthio-pyridines in water. The catalyst can be recycled and reused for five

however most of them require the use of exotic reaction conditions such as microwave irradiation or an ionic liquid; toxic organic solvents; anhydrous condition; use of expensive catalysts. Moreover, the main disadvantage is that the catalysts are destroyed in the workup procedure and cannot be recovered or reused. Therefore, there is still need for versatile, simple and environmentally friendly process to synthesize highly substituted 6-arylthio-pyridines using a reusable heterogeneous catalyst.

Glass might be described as a transparent amorphous material possessing the properties of hardness, rigidity, and brittleness. Whereas glass-ceramics are polycrystalline material prepared by the controlled crystallization of parent glass article.⁷ The mica containing glass ceramics are unique because they can be machined to precision tolerances using conventional tools.⁸⁻¹¹ These mica glass-ceramics also exhibits good mechanical strength and impact resistance, excellent thermal shock resistance, superior dielectric properties.¹²⁻¹⁴ Glass-ceramic materials contain multiple metal ions and oxide anions in their framework structure. The metal ions can act as Lewis acid and the O²⁻ ion can act as Lewis base. The presence of both acidic and basic sites in the same material triggers their application as heterogeneous catalysts in organic synthesis. Remarkably, they have greater catalytic activity than the individual components because of their enhanced active acidic and basic sites along with increased surface area. Moreover, because of very good mechanical strength and robustness they are unaffected even under harsh reaction condition which gives them high recycling efficiency. However despite their enormous potential to act as a heterogeneous catalyst, to the best of our knowledge glassceramic material is not used as a catalyst in the one pot multicomponent synthesis. Therefore, enormous opportunities

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are still left to convert the raw potential of this material to highly active catalyst.



Figure 1. Biologically active 2-amino-6-(arylthio)pyridine-3,5dicarbonitriles.

2. Results and Discussion

Inspired by the foregoing discussion, we have synthesized the glass ceramic material having the compositions as given in Table1. It was applied in the synthesis of 2-amino-3,5-dicarbonitrile-6-arylthio-pyridine (4) in water (Scheme 1). Synthesis using water as a solvent is said to be sustainable and green process.

Table 1. Composition of prepared glass in wt%.

Chemical Composition (in Wt %)	SrCO ₃	K ₂ CO ₃	SiO ₂	MgO	Al ₂ O ₃	MgF ₂	B_2O_3
	3.59	13.36	43.13	18.70	12.56	16.57	3.96



Scheme 1. Glass ceramic material catalyzed synthesis of pyridines (4).

In order to ascertain the feasibility of this transformation 4methoxybenzaldehyde, 4-bromothiophenol, and malononitrile were selected as model substrates, and conversion to its arylthioipyridine analogue was studied under a variety of conditions. Different solvents like DCE, DCM, toluene, THF, EtOH, MeOH, and water were tested (Table 2). Among them, water afforded the best yield of pyridine (4). The observed rate increase in water was explained by the hydrophobic effect, i.e., the propensity of hydrophobic organic molecules to associate in order to minimize their contact surface with water. Similarly, temperature played a determining role because there was only 25% pyridine formation after stirring the reaction mixture at 30– 35 °C (Table 2, entry 10) in water instead of 92% yield at 100 °C (Table 1, entry 9).

Table 2. Optimization of reaction conditions for the one-pot synthesis of pyridines.^a



on Lou				
1	DCM	30-35	15	
2	THF	60-65	26	
3	Acetone	50-55	40	
4	EtOAc	70-75	44	
5	MeOH	60-65	80	
6	EtOH	75-80	80	
7	Toluene	100-110	84	
8	DMF	120-130	79	
9	H_2O	100	92	
10	H_2O	30-35	25	
-				

^aReaction conditions: 4-methoxybenzaldehyde (1 mmol), thiophenol (1 mmol), malononitrile (2 mmol), glass ceramic material (20 mg), reaction in different solvents for 2h.

^bIsolated yields.

Having obtained the optimized reaction conditions, the scope of the reaction was subsequently investigated, and the representative results are summarized in Table 3. Regardless of the electronic nature and the position of substitution on the aromatic ring of precursors 1 and 2, the reaction afforded the corresponding pyridines (4) in excellent yields. It was pleasing to find that acid-sensitive heteroaryl aldehydes and methoxysubstituted aryl aldehydes were well tolerated under the present condition. Sterically bulky naphthalene-2-thiol reacted very efficiently under this condition. Therefore, the present glass ceramic material catalyzed protocol has a broad substance tolerance.

Table 3. Structure of the synthesized 2-Amino-3,5-dicarbonitrile-6-thio-pyridine (**4**).^a

CHO R ¹ F		$\begin{array}{c} 20 \text{ mg} \\ \hline \textbf{Glass Ceramic} \\ \hline \textbf{H}_2 \textbf{O}, \\ 2h \text{ Reflux} \end{array} $		N R ²
1 (1 mmol) (1	2 3 mmol) (2 mmol	H ₂ I I)	N' N' `S 4	
Entry	\mathbb{R}^1	\mathbb{R}^2	Yield ^b (%)	Ref.
4a	4-OMe	4-Br	92	_
4 b	3-Br	3-C1	91	_
4c	4- Br	4-Br	92	_
4d	2-Br	SH	86	_
4 e	3-Br	SH	88	-
4 f	4-Me	3-C1	95	_
4 g	4-OMe	Н	92	2
4h	4-C1	Н	91	2
4i	3,4-(OMe) ₂	Н	89	6b
4j	4- Br	Н	90	15
4k	м−сно	$\mathbf{R}^4 = \mathbf{R}^5 = \mathbf{R}^6 = \mathbf{H}$	76	5g

^aReaction conditions: Aldehydes (1) (1 mmol), thiophenol derivatives (2) (1 mmol), malononitrile (3) (2 mmol), glass ceramic material (20 mg), refluxing in H_2O (2 mL) for 2h.

^bIsolated yield.

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All compounds were synthesized and characterized by IR, 1 H and 13 C NMR and CHN analysis. The spectral and analytical data of all the compounds are given in the supporting information.

A plausible synthetic mechanistic route, underpinning the formation of pyridine (4) is depicted in Scheme 2. Here, oxides (O^{2}) of the glass ceramic material act as a base to carry out this present reaction.¹⁵ The multiple metal ions (Mⁿ⁺) having Lewis acidic character participate in the reaction by coordinating with the substrate, intermediates and transition states as shown in the scheme 2 and thereby facilitates the reaction.^{15a} This approach comprises the relay processes of the following domino sequences.¹⁶ Condensation of an aldehyde with malononitrile leads to the corresponding Knoevenagel product (5). The thiophenol (2) is deprotonated by the oxides (O^{2}) to form thiolate anion. Next, the second molecule of malononitrile undergoes Michael addition followed by simultaneous thiolate addition to CN^{-} of the adduct and cyclization leads to dihydropyridine (6), which undergoes oxidative aromatization to provide highly substituted pyridine. Therefore, here both acidic and basis character of the catalyst is responsible for its high catalytic activity.



Scheme 2. Probable mechanism for the synthesis of pyridine.

2.1. Characterization of the catalyst

2.1.1. SEM image analysis

Sample heated at 800°C for 5h, exhibits phase separation within the glass matrix forming fine submicron microstructure consist of some blocky crystal (Figure 2, panel a). Increase in the heat treatment temperature from 800°C to 900°C results in slightly bigger blocky crystals (panel b). At 1000°C, those blocky crystals become dense and closely placed. Sample heated at 1000°C for 5h, exhibits the development of large sized crystals with acicular morphology and forms "house of cards" microstructure (Panel c). The appearance of blocky crystals might be due to the formation of mica booklets with low aspect ratio. With increase in heat treatment temperature, number of mica crystal per unit volume decreases and compactness of crystals structure increases. At the same time aspect ratio of crystal increases towards higher heat treatment temperature at 1100°C. From less stable fine submicron blocky crystal to more stable large size crystal, this energetically unfavorable configuration might therefore be the driving force for crystals at higher temperature 1000°C and 1100°C compare to lower temperature.

2.1.2. XRD analysis

In the XRD pattern a broad crystal peak for prepared glass sample indicates amorphous nature of glassy phase. This glass sample was nucleated at 720°C and crystallized at different temperature (800, 900, 1000 and 1100°C) for sufficient crystal growth for about 5h. At 800°C, formation of potassium fluorophlogopite and strontium fluorophlogopite were in same ratio and intensity. At higher temperature 900°C three additional peaks of potassium fluorophlogopite and two additional peaks of



Figure 2. SEM picture of the catalyst heated at different temperatures.

strontium fluorophlogopite appeared. Two new peaks of strontium aluminum oxide appeared at 31.95° (20) and 41.47° (20) at 900°C. It was also found that strontium aluminum oxide phase was one of the major phases at that temperature. At 1000°C, one additional strontium fluorophlogopite peak appeared at 41.59° (20) along with peaks at 900°C and 800°C. Some new peaks of enstatite were found at 35.47° (20) and 67.21° (20) at 1000°C. At 1100°C the sharpness of the peaks of both strontium fluorophlogopite and potassium fluorophlogopite decreased. At 1100°C two additional peaks of potassium fluorophlogopite and strontium aluminum oxide appeared. Formation of strontium aluminum oxide and enstatite might be the indication that at higher temperature a partial decomposition of strontium fluorophlogopite took place at ceramised products that increased the strength of this glass-ceramics material. After all these observation, it is needless to mention that strontium fluorophlogopite, potassium fluorophlogopite and strontium aluminum silicate phases are major phases formed in all glassceramics sample crystallized at higher temperature.



Figure 3. XRD patterns for glass and glass-ceramics sample at different crystallization temperatures [SF-strontium fluorophlogopite (JCPDS ref. File-00-019-0117), KF-Potassium fluorophlogopite (JCPDS ref. File-01-076-

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0816), E-enstatite (JCPDS ref. file-00-002-0546), SO- Strontium aluminum oxide(JCPDS ref. file-00-024-1187)].

2.1.3. Differential thermal analysis (DTA)

Two well defined exothermic peaks were visible for DTA thermo-grams when the glass sample was analyzed at a heating rate of 5/min, first peak appeared (Tp^1) at 786°C and second crystal peak (Tp^2) appeared at 856°C. By X-Ray analysis, it was confirmed that 1st crystal peak was for potassium fluorophlogopite and second crystal peak for strontium fluorophlogopite. From DTA analysis we also obtained glass transition temperature (Tg) at around 675°C and nucleation temperature (Tn) at around 720°C.



Figure 4. Differential thermal analysis plots of glass samples of heating rate $5^{\circ}C$ /min.

2.2. Optimization of catalyst loading

The reactions were carried out using different amounts of the catalyst and the optimum amount (20 mg) has been determined. Figure 5 shows a remarkable increase in output according to the increase in the quantity of the catalyst upto 20 mg (Figure 5). With higher amount of catalyst no significance increase in the yield was observed. In order to use the minimum amount of the catalyst, we have been limited to 20 mg for the continuation of the study. The reaction forming **4a** was chosen as a model for this purpose.



Figure 5. Amount effect of the catalyst in the synthesis of pyridines.

2.3. Recycling experiment

The reusability of the catalyst in the 6-arylthio-pyridine formation reaction was examined taking the reaction forming **4a** as model reaction. Nearly quantitative catalyst (up to 95 %) could be recovered from each run. In a test of four cycles, the catalyst could be reused without significant loss of catalytic activity. The kinetics of the fresh catalyst was evaluated as shown in Figure 6. The yield did not increase substantially after 2 h. Also we had performed the kinetic study with the recycled catalyst for the next consecutive three runs. The results of kinetic plots suggested that the catalyst retained good efficiency after recycling.

To confirm the heterogeneous nature of catalyst and catalytic activity bound to the solid phase, a hot-filtration test was performed. 4-Methoxybenzaldehyde, 4-bromothiophenol, malononitrile, and the glass ceramic material catalyst mixed together in water on an oil bath under reflux. The catalyst was filtered off (from the hot reaction mixture) after 15 min. The filtered reaction mixture was then refluxed without the catalyst for the next 2 h; no further formation of the corresponding product was observed, indicating that no homogeneous catalyst was involved.



Figure 6. Kinetics plot demonstrating the recycling efficiency of the glass ceramic material catalyst or the reaction forming **4a**.

3. Conclusion

In conclusion, a glass ceramic material has been synthesized and successfully used for the first time for one pot multicomponent synthesis in water. The present method shows very high atom economic with very high yields of the products. The catalyst is highly stable, environmentally benign and renewable. Because of simplicity of the procedure associated with environmentally benign features, it is hoped that this methodology will be embraced by the synthetic organic community at large.

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