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Original Research Article

Sustainable Sulfonated Magnetic Natural Cellulose Fibers: A Robust and Reusable Catalyst for Efficient Synthesis of Bis(indolyl)methane and Imidazo[1,2-a]pyridine Derivatives

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Abstract: Novel heterogeneous catalysts development advances sustainable organic synthesis through performance enhancements and reduced environmental impact and recyclable catalyst systems. We developed biocompatible catalysts from natural and biodegradable materials for improving organic transformation capacities. Scientists developed sulfonated magnetic natural cellulose fibers for durable and eco-friendly usage as a solid acid catalyst before extensive characterization. The novel material showed its catalytic function in testing two multi-component reactions that generated biologically important heterocyclic scaffolds through bis(indolyl)methane formation as well as 3-aminoimidazo[1,2-a]pyridine derivative production. The reactions finished within short periods to yield products effectively under environmentally friendly conditions. The catalyst showed exceptional stability since an external magnet efficiently recovered it following multiple cycles where no activity decrease was observed allowing continuous usage for organic synthesis operations.

Keywords: Sulfonated magnetic natural cellulose fibers, bis(indolyl)methanes, imidazo[1,2-a]pyridines, reusable catalyst, solid acid catalyst.

INTRODUCTION

The chemical synthesis of fine products benefits from heterogeneous catalysts because they offer superior environmental and economic advantages. Solid acids provide superior benefits when compared to traditional mineral acids through their easy operability along with their environmentally friendly behavior and non-harmful characteristics along with their economic benefits and ability to be reused and simple separation methods [1-3]. Many different solid acids are extensively utilized in chemical applications such as zeolite frameworks [4], clay [5], montmorillonite [6] and modified silica-supported acids such as sodium bisulfate-silica, silica phosphoric acid, and silica sulfuric acid [7-9]. Biopolymers like chitosan and lignin and starch and cellulose have become promising materials for supporting catalysis which enlarges sustainable catalytic systems [10-14].

Cellulose fibers from plant sources demonstrate increasing popularity as versatile and eco-friendly materials for heterogeneous catalysis [15, 16]. Derived from agricultural residues like sugarcane bagasse, these fibers consist primarily of cellulose, hemicellulose, and lignin. The use of plant-based cellulose fibers stands out as an eco-friendly versatile material for heterogeneous applications in catalysis [17, 18]. The hydroxyl and carboxyl functional groups present in cellulose fibers enhance their catalytic activity by facilitating interactions with active sites and improving their performance in various reactions.

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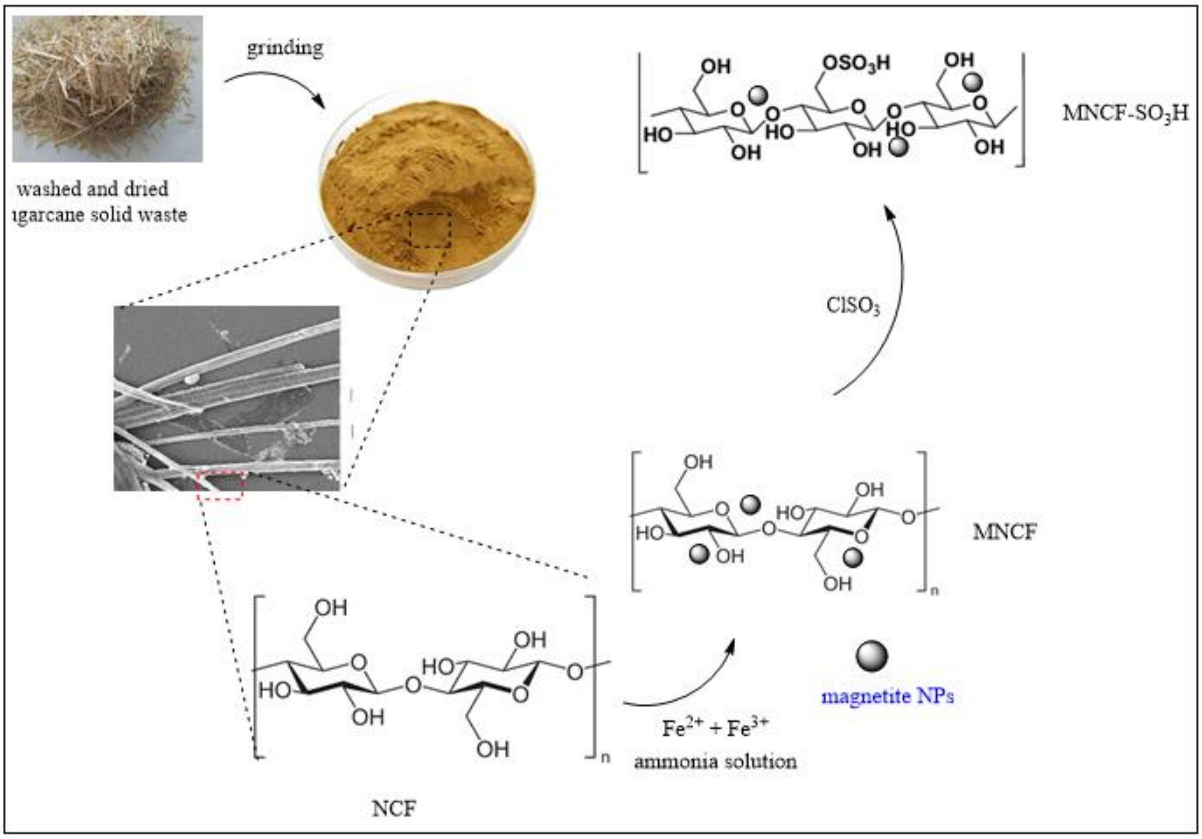
The combination of chemical adaptability and high surface area together with catalytic stability properties makes cellulose fibers useful across diverse applications. Cellulose fibers demonstrate successful application in biodiesel production because they perform transesterification of waste oils and the esterification of feedstocks with high free fatty acids [19, 20]. Additionally, they have been explored for adsorption-based heavy metal removal from wastewater, highlighting their multifunctional potential [20, 21]. As catalysts, cellulose fibers play a crucial role in sustainable biofuel synthesis, green chemical production, and other environmentally friendly transformations, contributing to the advancement of renewable catalytic systems [22, 23].

Multicomponent reactions (MCRs) are a powerful approach for synthesizing structurally diverse heterocyclic compounds, offering high atom economy, operational efficiency, and the ability to generate complex molecular architectures [24, 25]. They are useful in pharmaceutical research because their catalytic variants improve efficiency, selectivity, and reaction rates. Indole derivatives, which are found in many natural products, are very important in medicine [26, 27]. Bis(indolyl)methanes, which contain two indole units, exhibit diverse biological activities and pharmaceutical potential [28-30]. One typical way to make them is to use acid catalysts, either homogeneous or heterogeneous, to electrophilically replace indoles with ketones or aldehydes.

The Groebke-Blackburne-Bienaymé (GBB) reaction described in 1998 allows the synthesis of fused imidazole derivatives by using an aldehyde mixture with 2-aminoazines and isocyanides under acidic conditions. Imidazopyridines and their ring structure which fuses imidazole with pyridine show remarkable significance as biological compounds, especially 3-aminoimidazo[1,2-a]pyridines [31, 32].

The research examines the synthesis and characterization process of sulfonated magnetic natural cellulose fiber (MNCF-SO_3H) microparticles (MPs) for use as a new acid catalyst. Processing this natural cellulose fiber required grinding it into a homogeneous substance before treating it with basic solution to remove lignin and inorganic contamination. The researchers applied magnetite nanoparticles onto the MNCF followed by chlorosulfonic acid functionalization to produce MNCF-SO_3H MPs (Scheme 1).



Scheme 1: The synthesis procedure of MNCF-SO_3H

MATERIALS AND METHODS

Different analysis techniques were used for assessing the catalyst's structural and physicochemical properties. X-ray diffraction (XRD) analysis was conducted using STOE & CIE STADI P equipment with scintillation detection and secondary monochromator technology under Cu Kα radiation condition (λ = 0.1540 nm). Surface morphology analysis happened through use of a Philips XL30 ESEM environmental scanning electron microscope (SEM). Testing thermal stability involved the use of TGA upon Scinco STA 1500 simultaneous thermal analyzer under an air environment with a 10 °C min^{-1} heat ramp. Samples were measured for their melting points by an Electrothermal IA9100 melting point apparatus through an uncorrected method. The laboratory implemented Shimadzu IR470 spectrometer to obtain Fourier-transform infrared (FT-IR) spectra.

Synthesis of Natural Cellulose Fiber Microparticles (NCF):

A blender initiated the fragmentation process of sugarcane bagasse which led to obtaining cellulose fiber microparticles through grinding. A (4.0 g) weight of microparticles got suspended in (100 mL) of 0.1 M NaOH solution when mixing occurred at room temperature for (6) hours. After the treatment stage the particles underwent filtration to obtain separation and further cleaning with water until dried under pressured conditions at (70 °C).

Preparation of Magnetic Cellulose Fiber Microparticles (MNCF):

The synthesis of magnetic cellulose fiber microparticles happened through a co-precipitation method which occurred in water. The solution contained (4.0 g) natural cellulose fiber microparticles and (0.2 g) iron(II) chloride tetrahydrate and (0.54 g) iron(III) chloride hexahydrate in (50 mL) distilled water while stirring (1) hour. The system received gradual addition of (11) pH-adjusting 25% ammonium hydroxide solution at (60 °C) while maintaining stirring for one additional hour. The procedure finished with magnetic cellulose fiber microparticles which was separated through external magnet use before using distilled water and ethanol washes followed by drying at (80 °C).

Preparation of Sulfonated Magnetic Cellulose Fibers (MNCF-SO_3H):

Stirring (1.0 g of magnetic NCF microparticles with (20 mL chloroform solution at (0 °C) marked the first step in preparing sulfonated magnetic cellulose fiber microparticles. Chlorosulfonic acid (0.5 mL) received dropwise addition to the mixture while it returned to reach room temperature after (30) minutes. An additional (1) hour of stirring enabled the reaction process to finish. After adding chlorosulfonic acid dropwise to magnetic NCF in chloroform (0 °C) the mixture reached room temperature as MNCF-SO_3H microparticles formed next. The microparticles received an external magnetic separation followed by triple methanol washing before drying at room temperature.

Synthesis of Bis(indolyl)methanes:

The reaction to make bis(indolyl)methanes proceeded through the simultaneous mixing of 4-(Benzyloxy)benzaldehyde (0.10 g, 0.50 mmol), 2-Methylindole (0.13 g, 1.00 mmol) with the catalyst (0.01 g, 1.25 mol%) at room temperature under solvent-free conditions for 10 to 15 minutes. The reaction's advancement was checked through TLC by running it on a solution of ethyl acetate and n-hexane eluent. The reaction mixture received chloroform addition (2 × 5 mL) following completion and the catalyst was extracted through external magnetic force. The authors used reduced pressure to evaporate the chloroform phase until they obtained pure crude product. Death of the product required purification through recrystallization from ethanol mixed with water.

Synthesis of 3-Aminoimidazo[1,2-a]pyridines:

A 2-Amino-6-methylpyridine (0.10 g, 1.00 mmol) and benzaldehyde (0.10 g, 1.00 mmol) with cyclohexyl isocyanide (0.10 g, 1.00 mmol) solution was prepared in (5 mL) of water. The following reaction mixture contained MNCF-SO_3H (0.03 g, 7.50 mol%) as an addition. The reaction mixture stirred at (60 °C) for a period between 40 to 60 minutes. The reaction progress evaluation used thin-layer chromatography with ethyl acetate and n-hexane as the elution mixture. The mixture required cooling to reach room temperature after obtaining proper TLC results for complete reaction. Separating the catalyst became possible with an external magnet while extracting the product worked through ethyl acetate. The product resulted from concentrated crude material after organic phase separation through vacuum pressure-evaporation before purification by ethyl acetate as well as ethanol recrystallization.

RESULTS AND DISCUSSION

Sulfonated magnetic cellulose fibers (MNCF-SO_3H) structural characterization

FTIR Analysis of NCF and MNCF-SO_3H Microparticles:

The FTIR spectra of both NCF and MNCF-SO_3H microparticles are shown in Fig. 1. The bands observed at 1279, 1360, and 1442 cm^{-1} correspond to C–H bending, CH wagging, and O–H bending, respectively. The glucose ring vibrations appear between 1000 and 1100 cm^{-1}, while the C–O bond stretching in the C–O–C and C–OH groups is detected between 1014 and 1070 cm^{-1}. A broad band around 3465 cm^{-1} is observed, corresponding to the O–H stretching vibration.

For MNCF-SO_3H, the FTIR spectrum shows the presence of new absorption peaks, indicating successful sulfonation and the incorporation of Fe_3O_4 nanoparticles. The bands observed at 645, 591, and 445 cm^{-1} are attributed to the stretching vibrations of Fe–O bonds. The peaks at 1175 and 1028 cm^{-1} correspond to the stretching vibrations of SO_3H groups, and the band at 620 cm^{-1} is associated with the stretching of C–S bonds. An absorption peak at 3253 cm^{-1} is related to the O–H stretching vibration, confirming the presence of ferric hydroxide in Fe_3O_4.

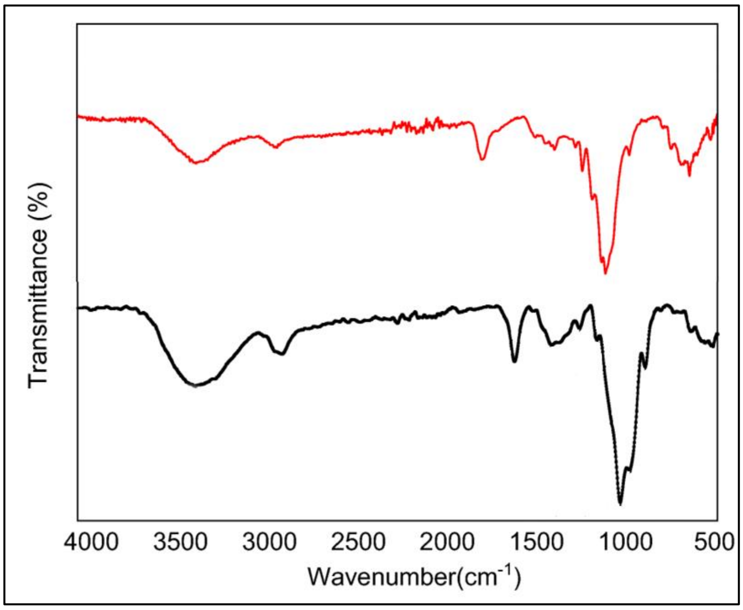


Figure 1: The FTIR spectra of the NCF (red) and MNCF-SO$_3$H MPs (black)

Fig 2 presents the XRD patterns of NCF microparticles and MNCF-SO$_3$H. As observed, strong peaks at 2θ = 21.16° and 16.27° are attributed to the crystalline structure of cellulose. In the MNCF-SO$_3$H pattern, additional diffraction peaks at 2θ = 30°, 35.5°, 43°, 53.8°, and 62.5° correspond to the characteristic planes of cubic spinel Fe$_3$O$_4$. These results confirm the successful formation of Fe$_3$O$_4$ nanoparticles within the MNCF-SO$_3$H structure while preserving the cellulose framework throughout the magnetization and sulfonation processes.

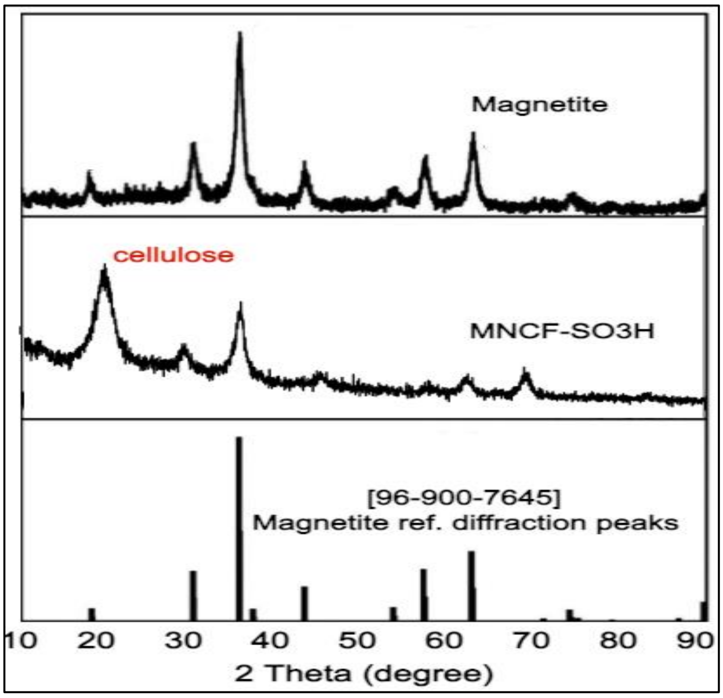


Figure 2: The [XRD] pattern of the NCF MPs and MNCF-SO$_3$H

The structural features become apparent in Fig 3 through SEM images of NCF and MNCF-SO$_3$H microparticles. The NCF microparticles maintain a fibrous shape that measures approximately 5 micrometers in diameter. The fibers show an exclusive combination of thin walls and smooth outer layer. The Fe$_3$O$_4$ nanoparticles successfully embed onto the tubular surfaces of MNCF-SO$_3$H microparticles. The TEM investigations show hollow microfiber structures having an inner diameter size close to 500 nm. Magnetite nanoparticles of less than 100 nm size disperse well on these fibers to achieve adsorption.

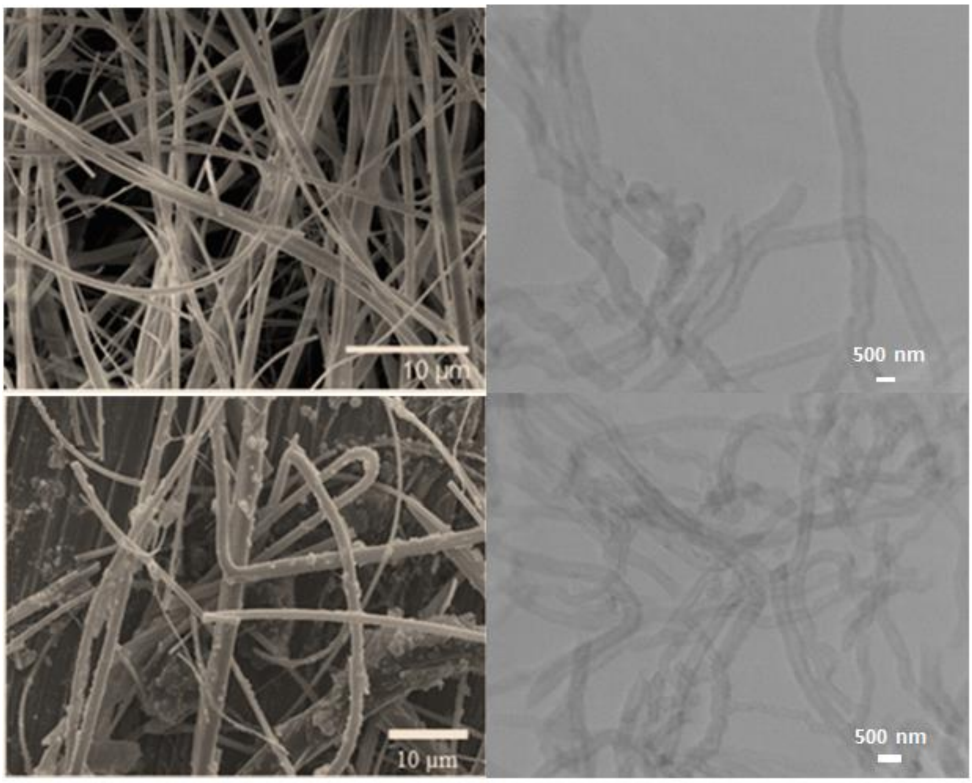


Figure 3: The SEM and TEM images of the NCF (top) and MNCF-SO_3H MPs (down)

The study used TGA analysis to confirm the microstructure of the produced microparticles. Fig. 4 shows the TGA profiles of NCF together with sulfonated NCF (NCF-SO_3H) microparticles along with MNCF-SO_3H microparticles. The weight reduction starting at room temperature reaches 120 °C because moisture together with volatile compounds evaporates. The decomposition of functional groups combined with the breaking up of the cellulose polymer matrix leads to an extra weight loss in NCF at 320 °C. The thermal decomposition profiles for NCF-SO_3H and MNCF-SO_3H match each other.

Following sulfonation, an extra weight loss step appears below 200 °C in the TGA curve, suggesting the incorporation of SO_3H groups within the structure. By the end of the analysis at 800 °C, the residual mass varies among samples due to differences in Fe_3O_4 and SO_3H content. The TGA findings indicate that the final catalyst composition consists of approximately 47% Fe_3O_4 nanoparticles and 7% SO_3H relative to the total weight.

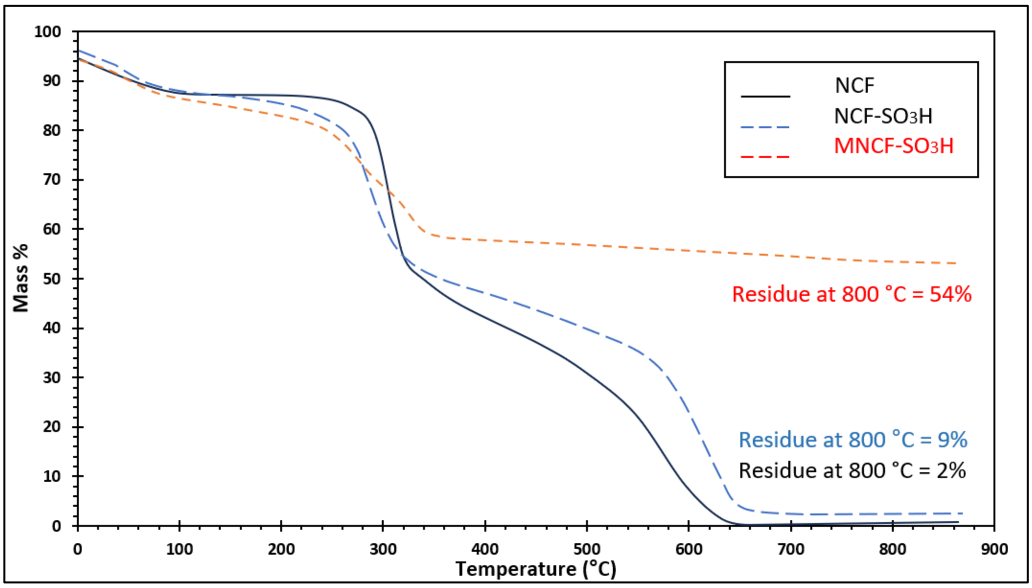
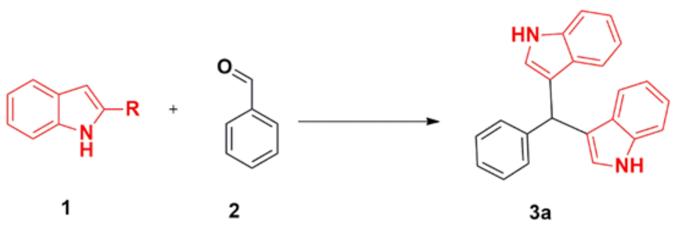


Figure 4: The TGA curves of the NCF, NCF-SO_3H and MNCF-SO_3H MPs

Application of Sulfonated Magnetic Cellulose Fibers (MNCF-SO_3H) in Multi-Component Reactions

To begin, we investigated the catalytic efficiency of this material in the synthesis of bis(indolyl)methanes through a pseudo three-component reaction. Optimization of the reaction parameters involved evaluating the influence of different solvents, catalyst dosages, and reaction durations on the formation of bis(indolyl)methane 3a, using indole 1 and benzaldehyde 2 as representative substrates. As outlined in Table 1, the highest yield was obtained when MNCF-SO_3H microparticles (0.01 g) were used under solvent-free conditions at ambient temperature (Table 1, entry 8). The reaction also proceeded effectively in water; however, a longer reaction time was required to achieve completion (Table 1, entry 6).

Table 1. Optimization of reaction conditions for the synthesis (**3a**) [a]

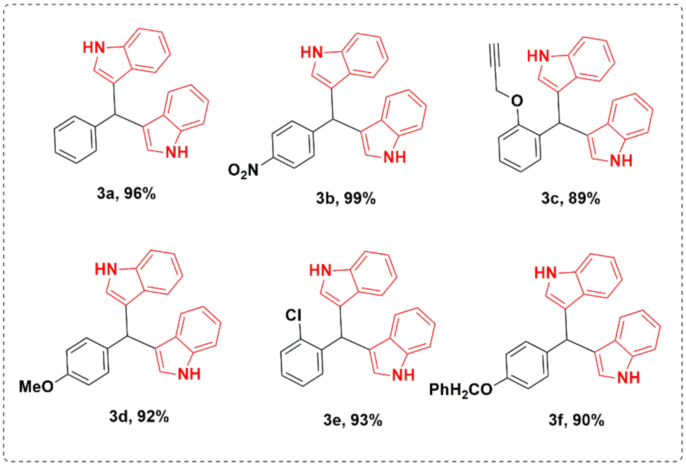


Entry	Solvent	Catalyst (gram)	Time (min)	Yields (%) [b]
1	Dichloromethane	MNCF-SO_3H (0.01)	10	46
2	Chloroform	MNCF-SO_3H (0.01)	10	35
3	Methanol	MNCF-SO_3H (0.01)	10	70
4	Ethanol	MNCF-SO_3H (0.01)	10	60
5	H_2O	MNCF-SO_3H (0.01)	10	75
6	H_2O	MNCF-SO_3H (0.01)	45	92
7	Solvent Free	MNCF-SO_3H (0.005)	10	84
8	Solvent Free	MNCF-SO_3H (0.01)	10	96
9	Solvent Free	NCF-SO_3H (0.01)	10	80
10	Solvent Free	MNCF MPs (0.01)	10	48

[a] Reaction conditions: indole **1** (1.0 mmol), a benzaldehyde **2** (0.5 mmol), and catalyst in ambient temperature. [b] Isolated yields

To evaluate the catalytic performance of MNCF-SO_3H, its activity was compared with NCF-SO_3H and MNCF microparticles. The remarkable efficiency of MNCF-SO_3H is primarily due to the cooperative interaction between Fe_3O_4 nanoparticles and sulfonic acid groups, which significantly enhances catalytic effectiveness. Additionally, the versatility of this reaction was investigated by utilizing various indole derivatives and aromatic aldehydes. These substrates included compounds with both electron-donating and electron-withdrawing substituents on the phenyl ring. The reaction proceeded efficiently, yielding bis(indolyl)methanes in high yields, as summarized in Table 2.

Table 2: bis(indolyl) methanes synthesis catalyzed MNCF-SO_3H



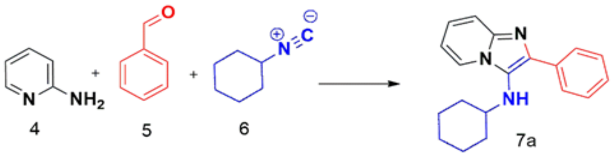
To further analyze the catalytic performance, MNCF-SO$_3$H was evaluated against previously reported catalysts [33-36], with a comparative summary presented in Table 3. The results highlight MNCF-SO$_3$H as a highly efficient catalyst for bis(indolyl)methane synthesis, delivering excellent product yields within significantly shorter reaction times (Table 3, entries 1–4). Although certain other catalysts also achieve high yields, they generally require extended reaction durations (Table 3, entry 3), making MNCF-SO$_3$H a more time-efficient alternative.

Table 3. Comparative Analysis of Catalytic Efficiency of Various Reported Catalysts for Bis(indolyl)methane 3a Synthesis

Entry	Catalyst	Solvent	Time (min)	T(°C)	Yield (%)
1	Heteropoly acid	H_2O	120	r.t.	84
2	Silica sulfuric acid	S.F.	45	r.t.	92
3	TCAOS	H_2O	60	r.t.	95
4	Cellulose sulfuric acid	S.F.	8	r.t.	92
5	**MNCF-SO$_3$H**	**S.F.**	**10**	**r.t.**	**96**

We investigated the catalytic synthesis of 3-aminoimidazo[1,2-a]pyridines by using MNCF-SO$_3$H due to both 3-aminoimidazo-fused heterocyclic compounds' significance in research and our ongoing methods development. The evaluation of optimal reaction conditions started by designing a model reaction which combined benzaldehyde (0.20 mmol) with 2-aminopyridine (0.20 mmol) and cyclohexyl isocyanide (0.20 mmol). The researchers tested different reaction parameters such as solvent selection and catalyst consumption as well as reaction temperature to maximize efficiency (Table 4).

Table 4. Optimization of Reaction Parameters for the Synthesis of 3-Aminoimidazo[1,2-a] pyridine (**7a**)[a]

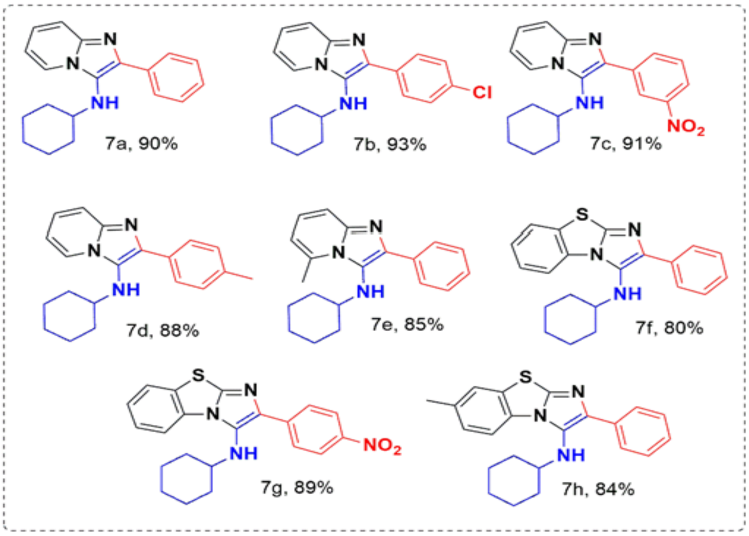


Entry	Solvent	Catalyst (gram)	T(°C)	Yields (%)[b]
1	Methanol	MNCF-SO$_3$H (0.03)	r.t.	15
2	Methanol	MNCF-SO$_3$H (0.03)	Reflux	76
3	Ethanol	MNCF-SO$_3$H (0.03)	60	45
4	Dichloromethane	MNCF-SO$_3$H (0.03)	Reflux	36
5	Solvent Free	MNCF-SO$_3$H (0.03)	60	25
6	H_2O	MNCF-SO$_3$H (0.01)	60	79
7	H_2O	MNCF-SO$_3$H (0.02)	60	83
8	H_2O	MNCF-SO$_3$H MPs (0.03)	60	90
9	H_2O	MNCF-SO$_3$H MPs (0.03)	r.t.	35
10	H_2O	NCF-SO$_3$H (0.03)	60	70
11	H_2O	MNCF MPs (0.03)	60	54

[a] Reaction conditions: 2-Amino pyridine 4 (1.00 mmol), benzaldehyde 5 (1.00 mmol), and cyclohexyl isocyanide 6 (1.00 mmol) with catalyst in water at 60 °C. [b] Isolated yields

As detailed in Table 4, the optimal reaction conditions were established by employing (0.03 g) of MNCF-SO$_3$H in water at 60°C, which resulted in the highest yield and the shortest reaction time (Table 4, entry 8). To assess the reaction's scope, a diverse set of 2-amino heterocycles (4), substituted benzaldehydes (5), and cyclohexyl isocyanide (6) were examined, as summarized in Table 5. Various 2-amino heterocyclic compounds, including 2-aminopyridine, 2-amino-6-methylpyridine, 2-aminobenzothiazole, and 2-amino-5-methylbenzothiazole were effectively utilized, leading to the successful synthesis of 3-aminoimidazo[1,2-a]pyridines with yields ranging from good to excellent.

Table 5. Synthesis of 3-Aminoimidazo-Fused Heterocycles Catalyzed by MNCF-SO_3H

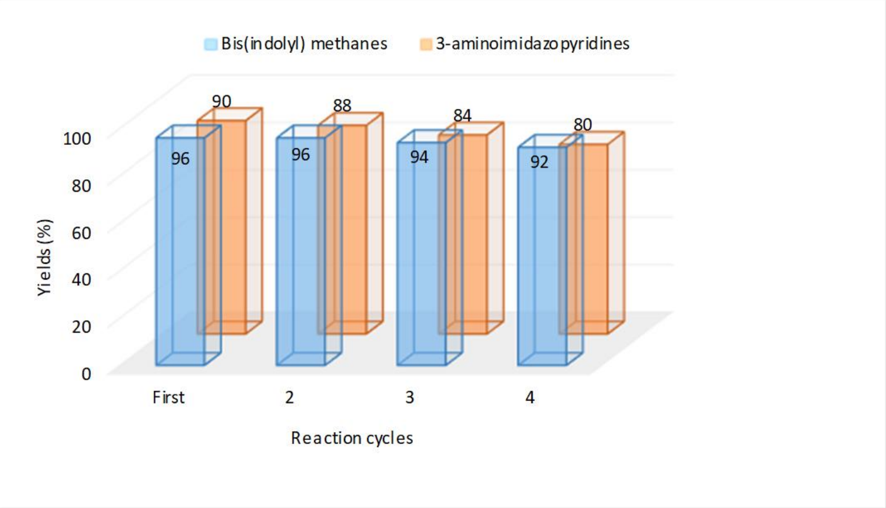


The catalytic performance of MNCF-SO_3H was evaluated against previously reported methods [37-39] for the synthesis of 3-aminoimidazo-fused heterocycles, focusing on yield, solvent choice, and reaction time. As illustrated in Table 6, MNCF-SO_3H demonstrated exceptional efficiency, delivering high yields within significantly shorter reaction times while utilizing water as an environmentally friendly solvent.

Table 6: Comparative Analysis of MNCF-SO_3H with Reported Catalysts Under Various Reaction Conditions

Entry	Catalyst	Solvent	Time (min)	T(ºC)	Yield (%)	Ref
1	MWCNTs-OSO_3H	MeOH	40	r.t.	91	
2	Silica sulfuric acid	MeOH	180	r.t.	95	
3	Cellulose sulfuric acid	MeOH	180	r.t.	94	
4	Fe_3O_4@SiO_2~FLU NPs	S.F.	60	60 ˚C	98	
5 [40]	**MNCF-SO_3H**	**Water**	**40**	**r.t.**	**90**	

The investigation of MNCF-SO_3H recyclability occurred throughout every reaction to evaluate its operational stability while measuring its efficiency. The optimized reactions used model systems under these conditions until the catalyst was separated through magnetic intervention from reaction mixtures. The catalyst received two rounds of acetone (5 mL each) wash followed by drying at 60°C before its use in subsequent runs. The catalyst showed steady productivity throughout multiple cycles as it kept its initial high efficiency level even after using it four times consistently (Scheme 2).



Scheme 2: Reusability of the catalyst in the multicomponent reactions

CONCLUSION

In conclusion, we have developed and characterized sulfonated magnetic natural cellulose fibers as a durable and eco-friendly biopolymer-based solid acid catalyst. The catalytic performance of this novel material was demonstrated in two multi-component reactions, facilitating the efficient synthesis of bis(indolyl)methane and 3-aminoimidazo[1,2-a]pyridine derivatives. These reactions proceeded with excellent yields in minimal time while utilizing sustainable and green reaction conditions. This catalyst system stands out for its cost-effectiveness, recyclability, and reusability across multiple cycles without any significant loss of activity. Additionally, it offers a straightforward and practical approach, featuring simple product isolation, mild reaction conditions, and the use of non-toxic solvents, making it a promising tool for green chemistry applications.

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