Acollective laboratory studies on one pot multi-component synthesis of a few varieties of heterocyclic compounds following greener approach by rice husk based greener catalyst

Abstract

An efficient, straight forward and sustainable synthetic procedures for the synthesis of few important class of bioactive heterocyclic compounds like dihydro-dichromeno-pyridine-6,8-diones, tetrahydrotetrazolo[5,1-*b*]quinazolinones and2,4-diaryl hexahydroquinoline-5-ones have been designed using a novel bio-degradable heterogeneous catalyst-sulphonated rice-husk (SRH). The greener catalyst has high porosity and high density of acid groups along with bio-degradable characteristics which has made it different and advantageous material for catalysis as compared to other conventional homogenous solid acid catalyst. We report primarily a new protocol for the synthesis of a group of biologically active compounds such as dihydro-dichromeno-pyridine-6,8-dione, tetrahydrotetrazolo[5,1-*b*]quinazolinone and2,4-diaryl hexahydroquinoline-5-ones derivatives using sulphonated rice husk (SRH) under greener condition. Operational simplicity, easy recovery of the product, metal free technique and reusability of the catalyst with excellent yield are the important and promising features of this procedure. The prepared solid heterogeneous catalyst was subjected for characterization using different spectroscopic techniques like FTIR, SEM, EDX, Powder XRD before its application for desired reaction.

Keywords: Heterocyclic compounds,Sulphonated rice husk, Greener catalyst, One pot Multi-component reaction.

Introduction

Aromatic heterocyclic compounds always have a special importance over other class of organic compounds from the very fast age of its discovery. In this context, Coumarin derivatives, 1,4-dihydropyridines(DHPs), hexahydroqunolines, and tetrahydroterazoloqunazolinones,play an important role in medicinal chemistry due to their significant biological activity.An oxygen-containing bicyclic aromatic compound is coumarin,[1-2] they can be derived from natural resources and have been shown to have a variety of biological activities such as anti-fungal,[3] anti-inflammatory,[4] anti-tubercular activities,[5] antiviral,[6] anticancer,[7] etc. Dihydro-dichromeno-pyridine-6,8-dione derivatives also contain coumarin scaffolds which are considered as one of the important fused ring heterocyclic bioactive compounds and thusa verity of scientific research have been made towards the targeted synthesis of coumarin analogues to find their significant applications in the field of medicinal chemistry.

Another important class of heterocyclic compound,Tetrazoloquinazolinones, nitrogen-bridgehead fused heterocycles with a tetrazole and quinazoline ring, is typical structural moieties in pharmacological and biological applications. Tetrahydrotetrazolo[1,5-*a*] quinazolinones falls in the category of fused ring tetrazole derivatives and they are structurally analogous with tetrazolopyrimidines. Numerous pharmacological properties of these compounds have been reported including antimicrobial,[8]antituberculosis[9] and antidepressant,[10] activities.A fast developing area of medicinal chemistry is the investigation of favoured structures in drug discovery. Due to their extensive spectrum of pharmacological actions, quinolines are a very desirable target for combinatorial library synthesis as an important "privileged scaffold" of low molecular mass. Certain quinoline derivatives have been used for their anti-bacterial, anti-asthmatic, anti-malarial, anti-hypertensive, and anti-platelet properties and serving as tyrosine kinase inhibitors [11-15]. Substituted quinolines, quinolinones, tetrahydroquinolines, and

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hexahydroquinolines are chemotherapeutic agents also [16-18], and many heterocyclic [19] compounds containing the quinoline nucleus have anti-inflammatory activity and act as antagonist inhibitors [20]. Quinolines with 1,4-Dihydropyridine (DHP) nucleus have been found to be efficient in cardiovascular diseases as calcium channel blockers also [21-22].

Experimental Method

In order to produce complex structures by the simultaneous formation of two or more bonds, multi-component reactions (MCRs) enable the combination of more than two building blocks in a practical, time-saving one-pot process. Additionally, MCRs are flexible, convergent, and atom-economy processes that are highly chemoselective. Numerous studies on the development of multicomponent reactions have been published over the years and have examined the pharmaceutical industry, academia, and combinatorial chemistry. One pot multi-component reactions (MCRs) can also provide strong support for the synthesis of the three types of heterocycles mentioned above by adhering to the basic principles of "Green Chemistry. There have been reports of MCRs using a variety of homogeneous and heterogeneous catalysts. The advantages of using heterogeneous catalysts would undoubtedly reinforce the environmental advantages of the reactions.[23]Heterogeneous catalysts made of solid acid materials, which are also sustainable and reusable, are preferred over homogeneous acid catalysts. Solid acid catalysts have a number of benefits over conventional liquid acids, including efficiency, operational simplicity, easy recycling and recoverability, non-corrosiveness, and environmental friendliness all of which are crucial in the industrial world. There are so many reported heterogeneous catalysts developed for the successful synthesis of various multi-component reactions butthe use of natural resources as heterogeneous catalyst have attracted us very much and we

Comment [mg3]: reactions[23].

consideredrice huskas prominent greener solid support for catalysis. Rice husk is very common agricultural by-product highly abundant in south asian countries.It contains cellulose, hemicellulose, lignocellulosic material along with high silica content.[24-25] It is an agricultural waste material and has utility in commercial purpose such as production of cattle food, rice-bran oil etc. A few characteristics like light weight, high external surface area and porosity,economic advantage, non-toxicity, high abundance, and bio-degradability haveattracted us to use it as a good bio-derived heterogeneous catalyst for the synthesis of heterocyclic compounds in a suitable convenient manner.[26]Here in this work, we used up the rice husk based heterogeneous catalyst and report the synthesis of dihydro-dichromeno-pyridine-6,8-dione, tetrahydrotetrazolo[5,1-b]quinazolinoneand 2,4-diaryl hexahydroquinoline-5-one derivatives using aromatic aldehydes as primary reactant.

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Figure1. Some examples of biologically active drugs containing coumarine, tetrazole and quinoline skeletons

Results and discussion

In conjunction with our ongoing work on the synthesis of solid heterogeneous catalysts and organic compounds,[27-29] herein, we describe the one pot synthesis of dihydro-dichromeno-pyridine-6,8-dione, tetrahydrotetrazolo[5,1-*b*]quinazolinoneand 2,4-diaryl hexahydroquinoline-5-one derivatives (Scheme 1, Scheme 2 and Scheme 3) in the presence of newly developed sulphonated rice husk (SRH) as our promising greener catalyst. After the preparation of the catalyst, it was characterized through different spectroscopic methods such as FTIR, SEM-EDX, Powder-XRD to confirm the formation of SRH catalyst. The comparison of FTIR, SEM image and XRD pattern of RH and SRH strongly supports the synthesis of sulphonated catalyst using previously reported method of our group.[27-29]The new broad band around 3400 cm^{-1}in FTIR spectra along (Figure 2a) with the band around 1100cm^{-1} indicating the incorporation of $–SO_3H$ groups into RH surface after sulphonationand the presence of band at 1100$cm^{-1}$is attributed to the symmetric and asymmetric stretching of S=O bonds of $–SO_3H$ groups.[27-29]The XRD study shows three typical peaks at 2θ =20.82°, 22.28°, and 26.67°, with a broad peak at roughly 20° being formed by the carbon-composed aromatic sheets that are aligned randomly (Figure 2b). The XRD analysis after sulphonation demonstrates a significant decrease in peak height and broadening of the significant XRD peak situated at around 20^0. Thus the powder XRD analysis of both RH and SRH shows characteristic changes in the nature of both RH and SRH which clearly indicates the formation of SRH from RH due to sulphonation[27-29] (Figure 2b).In SRH, a molecular aggregation occurs as a result of the addition of the $-SO_3H$ functional group to the skeleton of rice husk material, as demonstrated by a comparison of the SEM images of RH and

Comment [mg6]: compounds [27-29],

Comment [mg7]: group[27-29].

SRH.[27-29]An EDX study of rice husk and sulphonated rice husk revealed discernible changes in the weight percentage of the elements, particularly carbon, sulphur, oxygen, and silicon. The literature review and the aforementioned promising data analysis have provided us with solid evidence that the heterogeneous catalyst (SRH) has unquestionably created.

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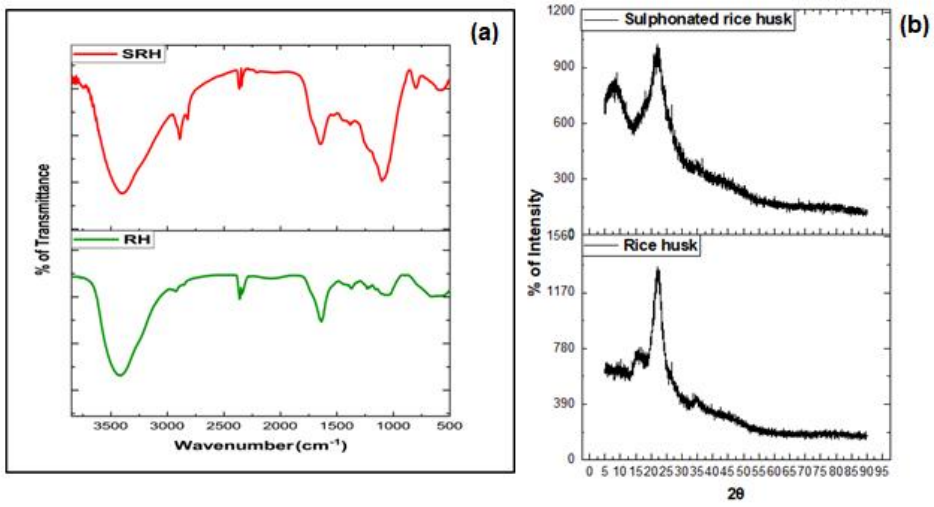


Figure 2. (a) FTIR spectra of RH and SRH. (b) Powder XRD spectra of RH and RH

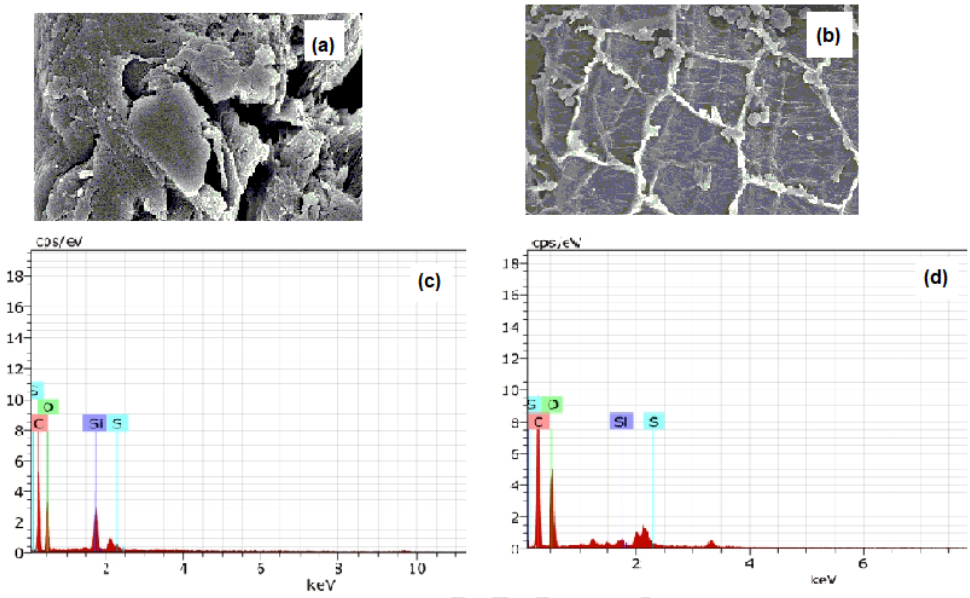
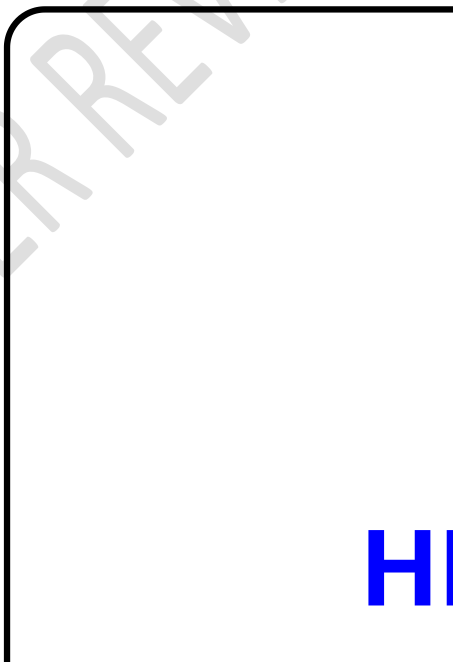


Figure 3. (a) SEM image of SRH. (b) SEM image of RH. (c) EDX-image of SRH. (d) EDX-image of RH

And finally the prepared catalyst was used up for the synthesis of a group of important heterocyclic compounds through one pot multi-component reaction (Scheme 1, Scheme 2 and Scheme 3) with preferable regents under suitable reaction condition.

Scheme 1. Synthesis of substituted dihydro-dichromeno-pyridine-6,8-dione derivatives using sulphonated rice husk[a]



[a] Reaction of aromatic aldehyde (1 mmol), 4-hydroxycoumarine (2 mmol), and ammonium acetate(1.2 mmol)

[b]Isolated yield after purification through recrystalisation.

Initially the reaction was started with taking anisaldehyde (1 mmol), 4-hydroxycoumarine (2 mmol), ammonium acetate (1.2 mmol) at a time in a 25 mL glass made sealed reaction tube

vessel. In absence of catalyst, it was observed that the formation of the corresponding product had a low yield, which could be attributed to solvent-induced catalysis (Table 1, entry 11, 12) but excellent yield was observed in presence of arbitrary amount of 100 mg of SRH catalyst in ethanol solvent at 70^0 C temperature (Table 1, entry 2). The role of catalytic efficiency was observed by decreasing the amount of catalyst through sequence wise experiment and the yield of the product was observed with amount of catalyst. From the optimized condition, it is clear that SRH catalyst is suitable as a greener catalyst for the conversion of dihydro-dichromeno-pyridine-6,8-dione with excellent yield in short reaction time. The amount of catalyst used and the duration of the reaction were also investigated in order to determine the optimal reaction condition. It was observed that the best result was obtained at 70^0 C temperature using 60 mg of catalyst SRH in ethanol (Table 1, entry 7).The generality of the reaction was observed with a variety of aromatic and heterocyclic aldehydes (Scheme 1) having electron donating and electron withdrawing substituents of the aromatic aldehydes. The targeted compounds (4a-4j) are successively synthesized using SRH as an efficient catalyst under greener reaction condition and the progress of the reaction was monitored by thin layer chromatography (TLC) and the pure product was separated by recrystallization of the crude product in petroleum ether/ethyl acetate (v/v ratio70/30) mixture.

Table 1. Optimisation of the reaction condition for the synthesis of dihydro-dichromeneo-pyridine-6,8-dione.[(a)]

Entry	Catalyst (mg)	Solvent	Temperature (^{o} C)	Time (min)	Yield (%)[b]
1	110	Ethanol	80	360	98
2	100	Ethanol	70	318	98
3	90	Ethanol	70	300	98

4	80	Ethanol	70	258	98
5.	70	Ethanol	70	240	98
6.	70	Ethanol	70	198	98
7.	**60**	**Ethanol**	**70**	**180**	**98**
8.	50	Ethanol	70	180	94
9.	50	Ethanol	60	180	90
10.	50	Ethanol	60	150	90
11.	None	Ethanol	70	190	60
12.	None	Methanol	70	190	50
13.	60	Methanol	70	200	95
14.	80	Ethanol/H_2O (4:1)	70	200	90
15.	80	Ethanol/H_2O (1:1)	70	200	84

[a]Reaction of anisaldehyde (1 mmol), 4-hydroxycoumarine (2 mmol), [b] Isolated yield after purification through recrystalisation.

Mechanism

A plausible mechanism forthe synthesis of dihydro-dichromeno-pyridine-6,8-dione is established by considering the acidic behaviour of the catalyst (Figure.4). The reaction starts with a protonation which occurs at the aldehyde oxygen of aromatic aldehyde and thena successive condensation reaction occurs between 2 molecules of 4-hydroxy coumarine with 1 molecule of aldehyde to give a bis-coumarol intermediate and the bis-coumarol intermediate undergoes tautomerization followed by a cyclocondensation reaction with NH_4OAc to give the final product dihydro-dichromeno-pyridine-6,8-dione.[30]

Figure 4. The plausible mechanism for the synthesis of dihydro-dichromeno-pyridine-6,8-dione

Scheme 2. Synthesis of substituted tetrahydrotetrazolo[5,1-*b*]quinazolinonederivatives using sulphonated rice husk[a]

[a] [a]Reaction of aromatic aldehydes (1 mmol), 5-amino-1H-tetrazole (1 mmol) and 5,5-dimethylecyclohex-1,3-dione (1 mmol) . [b]The yields are isolated through recrystalisation.

One pot synthesis of tetrahydrotetrazolo[5,1-b]quinazolinones, initially carried out with taking anisaldehyde (1 mmol), 5-amino-1*H*-tetrazole (1 mmol) and 5,5-dimethylecyclohex-1,3-dione (1 mmol) taken in a 25 mL RB. Maximum yield was observed in the presence of 120 mg of the catalyst (Table 2, entry 3) in ethanol solvent at 80^{o} C temperature in 8 hours. To get the optimized condition the reaction was carried out in presence of varying amount of catalyst. In absence of catalyst the formation of the expected product was retarded (Table 2, entry 13).The amount of the catalyst and time of the reaction was checked thoroughly to find out the optimized reaction condition and it was observed that the best result was obtained at 70^{0}C temperature using minimum amount of catalyst SRH (90 mg) in presence of ethanol solvent (Table 2, entry 7). In addition, the reaction was carried out in presence of different solvent

(Table 2, entries 9-12) to observe the solvent-effect in this reaction and ethanol was proved to be effective in this case. The generality of the reaction was observed with a variety of aromatic and heterocyclic aldehydes (Scheme 2) containing electron donating and electron withdrawing substituents and the targeted compounds (4a-4i) are successively synthesized using SRH as an efficient greener catalyst under greener reaction condition. The progress of the reaction was monitored continuously by thin layer chromatography (TLC) and the crude product was separated from ethylacetate extract by addition of petroleum ether followed by purification through washing with ethylacetate and petroleum ether mixture {petroleum ether/ethyl acetate (v/v ratio70/20) mixture}.

Table 2. Optimisation of the reaction condition for the synthesis of tetrahydrotetrazolo[5,1-*b*]quinazolinonederivatives [(a)]

Entry	Catalyst (mg)	Solvent	Temperature (^{o} C)	Time	Yield (%)[b]
1	120	H_2O	100	8 h	86
2	120	H_2O	90	8 h	78
3	120	Ethanol	80	8 h	88
4	120	Ethanol	80	6 h	86
5.	100	Ethanol	80	6 h	86
6.	90	Ethanol	80	6 h	86
7.	**90**	**Ethanol**	**70**	**6 h**	**86**
8.	80	Ethanol	60	6 h	80
9.	90	DMF	70	6 h	65

10.	90	CH_3CN	70	6 h	<50
11.	90	DMSO	70	6 h	<50
12.	90	Toluene	70	6 h	<40
13.	None	Ethanol	70	6 h	Trace
14.	90	Solvent-free	70	6 h	73
15.	80	Ethanol/ H_2O(4:1)	70	8 h	50
16.	80	Ethanol/ H_2O(1:1)	70	8 h	55
17.	90	Methanol	60	8 h	80

[a]Reaction of anisaldehyde (1 mmol), 5-amino-1H-tetrazole (1 mmol) and 5,5-dimethylecyclohex-1,3-dione (1 mmol) .

[b]The yields are isolated through recrystalisation.

Mechanism

A plausible SRH catalyzed synthesis oftetrahydrotetrazolo[5,1-*b*]quinazolinonederivatives are established considering the acidic behaviour of the catalyst (Figure. 5). At very first step of the reaction, protonation occurs at aldehyde oxygen of aromatic aldehyde followed by Hantzsch condensation of aldehydes with *β*-diketones and ammonium acetate. In situ intermediates are rapidly produced, which undergo cyclization and extert the desired producttetrahydrotetrazolo[5,1-*b*]quinazolinonederivatives product.

Figure 5. The plausible mechanism for the synthesis of tetrahydrotetrazolo[5,1-b]quinazolin-8(4H)-one

Scheme 3. Synthesis of 2,4-diarylhexahydroquinolinone derivatives using sulphonated rice husk[a]

[a] Reaction of aromatic aldehyde (1mmol), 5,5-dimethyl-cyclohexane-1,3-dione (1 mmol), acetophenone (1 mmol) and ammonium acetate (1 mmol) and SRH (50 mg). The yields are isolated through column chromatography.

One pot synthesis of 2,4-diaryl hexahydroquinoline-5-one derivatives was initially carried out with taking aromatic aldehyde (1 mmol) along with acetophenone (1 mmol) and 5,5-dimethylecyclohex-1,3-dione (1 mmol) and ammonium acetate (1 mmol) taken in a 25 mL glassed sealed reaction tube. It was observed that when all the reactants were taken together at a time in a vessel to react randomly in presence of 120 mg arbitrary amount of catalyst, it produced 9-arylhexahydroacridine as a major product. Literature studies along with a few controlled experiment suggested that formation of in situ chalcone derivative is important for the synthesis of 2,4-diaryl hexahydroquinoline-5-one as major productand after observing the science behind it, the reaction was started first with condensation reaction between the participated aromatic aldehyde (1 mmol) and acetophenone (1 mmol) in presence of SRH catalyst only for 1 hour followed by addition of 5,5-dimethylecyclohex-1,3-dione (1 mmol) and ammonium acetate (1

mmol) at a time into the reaction mixture. After addition of 5,5-dimethylecyclohex-1,3-dione (1 mmol) and ammonium acetate (1 mmol) the progress of the reaction was monitored continuously by thin layer chromatography (TLC) until the reaction was adequately completed. For determining the optimized reaction condition, p-tolualdehyde (1 mmol) was taken as the participating aromatic aldehyde along with other substituents. The variation of the amount of catalyst along with temperature was made to determine the precise optimized condition for the reaction (Table 3, entry 9). The optimized reaction condition was followed for the synthesis of other compounds under scheme 3 (5a-5h). The generality of the reaction was observed for the aromatic aldehydes having electron withdrawing, electron donating substituents. All the products were isolated from ethyl acetate extract of the reaction mixture by column chromatographyusing petroleum ether/ethyl acetate(v/v 70:30) and the generality of the reaction was observed with a variety of aromatic and heterocyclic aldehydes (Scheme 3) having electron donating and electron withdrawing substituents at *ortho, meta* and *para* position of the aromatic aldehyde. The targeted compounds (4a-4h) are successively synthesized using SRH as an efficient catalyst under greener reaction condition and the progress of the reaction was monitored continuously by thin layer chromatography (TLC).

Comment [mg9]: chromatography

Table 3. Optimization of the reaction condition for the synthesis of 2,4-diarylhexahydroquinolinone derivatives

Entry	Catalyst (mg)	Solvent	Temperature (^{o} C)	Time	Yield (%)[b]
1	100	H_2O	100	8 h	92
2	120	H_2O	100	8 h	92
3	120	Ethanol	80	8 h	98
4	110	Ethanol	80	8 h	98

5.	100	Ethanol	80	7 h	98
6.	90	Ethanol	80	7 h	96
7.	80	Ethanol	80	8 h	96
8.	70	Ethanol	80	8 h	96
9.	**70**	**Ethanol**	**80**	**6 h**	**96**
10.	60	Ethanol	70	6 h	87
11	70	Neat	70	8 h	82
12.	70	DMF	70	8 h	69
13.	70	CH_3CN	70	8 h	trace
14	70	Ethanol/H_2O	70	8 h	81
15	70	Methanol	80	8 h	70

[a] Reaction of p-tolualdehyde(1mmol), acetophenone (1mmol), 5,5-dimethyl-cyclohexane-1,3-dione (1mmol), ammonium acetate (1.2 mmol) and SRH (60 mg). The yields are isolated through column chromatography.

Mechanism

The mechanism of the reaction starts with the protonation of the aldehyde and the condensation of aldehyde and acetophenone to give chalcone derivative as intermediate (Figure 6). After that successive cyclocondensation of chalcone, dimedone and ammonium acetate (NH_4OAc) takes place in presence of SRH catalyst which leads to the formation of 2,4-diarylhexahydroquinoline.

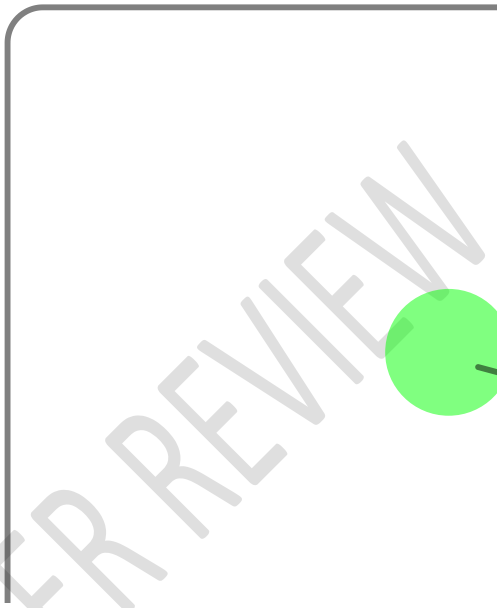


Figure 6. The plausible mechanism for the synthesis of tetrahydrotetrazolo[5,1-b]quinazolin-8(4H)-one

Catalyst Recyclability Experiment

To check the recyclability of the catalyst, a model reaction between anisaldehyde (2 mmol), 4-hydroxycoumarine (4 mmol), ammonium acetate (2 mmol) in presence of 120 mg of sulphonated rice husk was carried out under optimised reaction condition. After successful completion of the each reaction step, ethyl acetate (10 ml) was added to the reaction mixture. Then the supernatant liquid (ethyl acetate extract) was decanted off and this process was repeated until the catalyst was free from reaction mixture. Then the recovered catalyst was washed with acetone repeatedly and dried under vacuum and its weight was measured after every recovery step and the next reaction was repeated. The temperature and time of the reaction were kept constant following optimized reaction condition. The amount of catalyst, reactant (aldehyde),

reaction time,temperature and yield percentage of the product have been shown in table 4 (entry 1-6).The catalyst was easily separated from the reaction mixture and successfully reused upto 6th run (Figure 8). The FTIR spectra of recovered SRH catalyst after successive reactions were shown in figure 7 which further support the efficiency of the prepared catalyst.

Table 4. Table for the amount of recovered catatyst with isolated product yield[a]

Comment [mg10]: catalyst

Entry	Catalyst (mg)	Aldehyde (x mmol)	Temperature (^{o} C)	Time (min)	Yield (%)[b]
1	120	2.00 mmol	70	180	98
2	110	1.83 mmol	70	180	94
3	100	1.66 mmol	70	180	87
4	90	1.50 mmol	70	180	80
5.	80	1.33 mmol	70	180	75
6.	70	1.16 mmol	70	180	70

[a]Reaction of anisaldehyde(x mmol), 4-hydroxycoumarine (x mmol), ammonium acetate (x mmol), [b] Isolated yield after purification through recrystalisation.

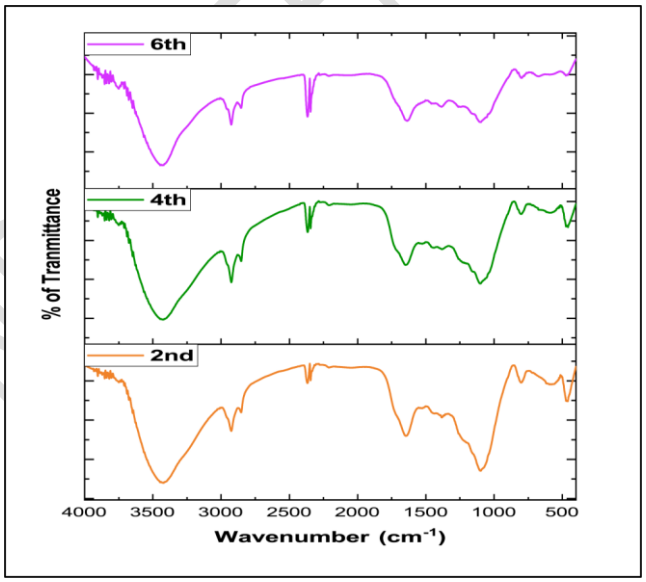


Figure 7. FTIR spectra of reused catalysts after 2nd, 4th and 6th run.

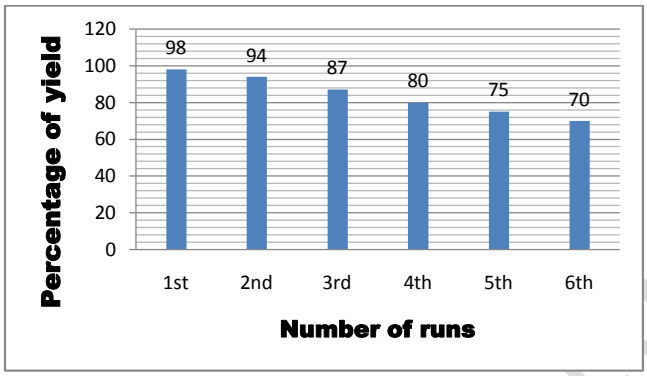


Figure 8. Recyclability experiment of catalyst

Conclusion

In conclusion, the novelty of this work goes on a simple and greener methodology for the synthesis of variety of substituted dihydro-dichromeno-pyridine-6,8-diones,tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-onesand 2,4-diarylhexahydroquinolinone derivatives with a good yield. This heterogeneous catalyst is found to be sufficiently efficient for the synthesis of dihydro-dichromeno-pyridine-6,8-diones, tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-ones and 2,4-diarylhexahydroquinolinone derivativesin a greener way. The greener catalyst is highly recyclable upto 6^{th} run and has the ability to catalyse a wide range of acid-catalysed reactions or cyclocondensation reactions.

Suplimentary data

Supplementary data include experimental details of ^{1}H NMR, ^{13}C NMR spectra of all the synthesized compounds under Scheme 1, Scheme 2 and scheme 3 and EDX data of rice husk(RH) and the prepared rice husk based catalyst (SRH).

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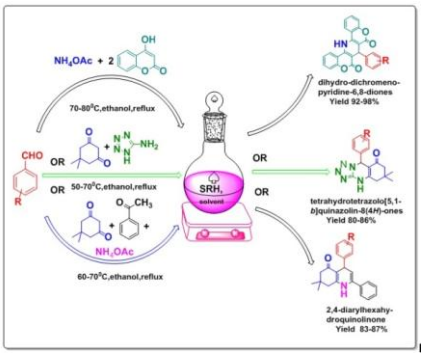
Appendix

Table of Content



An environmental friendly route for synthesis of dihydro-dichromeno-pyridine-6,8-diones, tetrahydrotetrazolo[5,1-*b*]quinazolinones and 2,4-diaryl hexahydroquinoline-5-ones derivatives using sulphonated rice husk

An eco-friendly procedure have been applied for the the synthesis of biologically active dihydro-dichromeno-pyridine-6,8-diones, tetrahydrotetrazolo[5,1-*b*]quinazolinones and 2,4-diaryl hexahydroquinoline-5-ones derivatives using a novel bio-degradable heterogeneous catalyst, sulphonated rice-husk (SRH). SRH provide a high density of acid groups along with heterogeneity making it quite different from conventional solid acids containing single acid groups. It is emerging as an efficient greener catalyst which can be a substitution of the previous methods containing toxic materials. Moreover, the catalyst is reusable upto 6th run with slow decrease in its catalytic activity.

Comment [mg11]: extra the