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Synthesis of Nanostructured sawdust-BF_3: An efficient reagent for synthesis of 2,3,5-substituted-2*H*-pyrazole derivatives

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Abstract

Nanostructured sawdust-BF_3 has been prepared and shown to efficiently catalyse the one-pot reaction of 1,3-diketones and hydrazines under solvent-free conditions, to afford the corresponding 2,3,5-substituted-2H-pyrazole derivatives in excellent yields.

***Keywords**: sawdust-BF_3 NPs1,3-diketones, hydrazines2,3,5-substituted-2H-pyrazoles, solid acids.*

1 Introduction

Heterocycles are popularly known for displaying a wide range of the biological properties [1]. The recent success of pyrazole based COX-II inhibitors and their applications in medicinal chemistry have amplified the importance of pyrazoles to even a greater extent [2]. Several pharmaceutical drugs including celecoxib [2] and rimonabant [3] utilize the pyrazole as their core molecular entity [4,5], Pyrazoles are often synthesized by the 1,3-dipolar cycloaddition reaction of nitrilimines with alkynes [6], alkyne surrogates [7],or alkenes [5,6], pyrazoles also can be synthesized *via* 1,3-dipolar cycloadditions of diazo compounds[8], reaction of chalcones [9] and hydrazines, a four-component coupling of terminal alkynes, hydrazine, carbon monoxide, and aryl iodides [10], and the direct condensation of 1,3-diketones and hydrazines in the presence of an acidic catalyst [11]. The last one is the simplest and most straightforward procedure for the synthesis of pyrazoles. A variety of the catalysts such as H_2SO_4 [12], polystyrene supported sulfonic acid [13], layered zirconium sulfophenyl phosphonate [a-$Zr(CH_3PO_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$] [14], $Sc(OTf)_3$ [15], Y-zeolite [16] and magnesium perchlorat $Mg(ClO_4)_2$ [17] have been employed to affect this transformation.

Application of environmentally benign solvent-free conditions and solid acid catalyst represents powerful green procedure. In this work, the application of solid phase acidic green nano catalyst have investigated for synthesis of 2,3,5-substituted-2*H*-pyrazole derivatives (Scheme 1).

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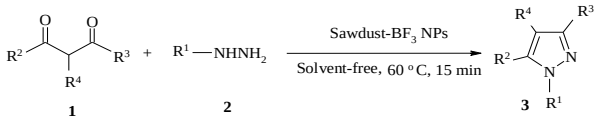


1 2 3

Scheme 1. Reaction between 1,3-diketones and hydrazines catalyzed by Nanostructured sawdust-BF_3 under solvent-free conditions

2. EXPERIMENTAL

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed at the analytical laboratory of Science and Researchs Unite of Islamic Azad University. The morphology of the catalyst were observed using a SEM model VEGA//TESCAN with an accelerating voltage of 15 kV. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

2.1. Synthesis of sawdust-BF_3 NPs

The nano-sawdust-BF_3 was prepared by combination of $BF_3.OEt_2$ (0.6 g, 4.2 mmol) drop by drop over 10 min via a syringe to sawdust powder (0.4 g) in a 50 ml flask include 5ml diethyl ether at room temperature. The reaction mixture was then stirred and then after 30 min, the ashy powder was separated and dried in an oven at 60°C for 4h and then pulverized at the mortar [18]. The morphology and size of sawdust-BF_3 NPs was observed by SEM images. As shown in Figure 1, the size of sawdust-BF_3 NPs is below 50 nm.

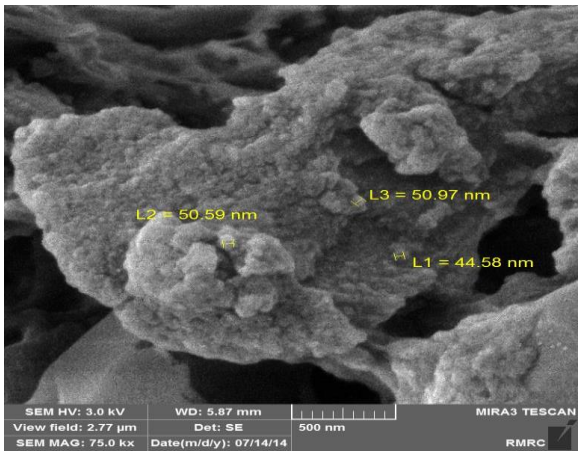


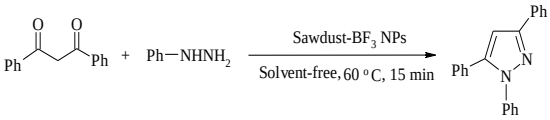
Fig. 1. The SEM image of Nanostructured sawdust-BF_3

2.2. General procedure for preparation of compounds 3a-p

A mixture of 1,3-diketones (2 mmol), hydrazines (2 mmol) and sawdust-BF3 NPs (0.001 g) were placed in a round bottom flask. The materials were mixed and heated in 60 ºC for 15 min. The progress of the reaction was followed by TLC (n-hexane:ethylacetate). After the completion of the reaction, the mixture was filtered to separate the catalyst. After evaporation of the solvent, the crude product was recrystallized from hot ethanol to obtain the pure compound.

3. RESULTS AND DISCUSSION

In continuation of previous research on the use of solid acids in organic synthesis [19-21], the synthesis of 2,3,5-substituted-2H-pyrazole derivatives have investigated by condensation of 1,3-diketones and hydrazines in the presence of sawdust-BF3 NPs as a inorganic solid acid. To optimize the reaction conditions, the reaction of 1,3-diphenylpropane-1,3-dione and phenylhydrazine was used as a model reaction to pyrazoles synthesis. According to the obtained data, using the sawdust-BF3 NPs (0.001 g) under solvent-free conditions for the pyrazoles formation is the best reaction conditions (Scheme 2).



Scheme2 Reaction between 1,3diphenylpropane-1,3-dione and phenylhydrazine catalyzed by Nanostructured sawdust-BF_3

The stable catalyst is easily prepared and used for preparation of 2,3,5-substituted-2*H*-pyrazole derivatives. To prove the better catalytic activity of sawdust-BF_3 NPs, Initially, the reaction has studied with other catalysts under solvent-free conditions at 15 min, and the results are listed in Table 1.

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Entry	Catalyst	Time (min)	Yield[a] (%)
1	H_2SO_4	15	35
2	Y-Zeolite	15	45
3	$Sc(OTf)_3$	15	83
4	$Zr(CH_3PO_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$	15	70
5	$Mg(ClO_4)_2$	15	80
6	sawdust-BF_3 NPs	15	96
7	PSSA*	15	95
			-

Table 1. Reaction between 1,3-diphenylpropane-1,3-dione and phenylhydrazine in different catalytic and under solvent-free conditions
[a]Isolated yield *Polystyrene supported sulfonic acid

Table 1 clearly demonstrates that sawdust-BF_3 NPs is an effective catalyst in term of yield of obtained product.

To find out the optimum quantity of sawdust-BF_3 NPs, the model reaction was carried out at 60 °C using different quantities of sawdust-BF_3 NPs (Table 2). According to the obtained data, 0.001 g of sawdust-BF_3 NPs gave excellent yield in 15 min (Table 2, entry 1).

Entry	Solvent	Time /min	Yield[a] /%
1	$CHCl_3$	15	57
2	EtOH	15	85
3	EtOAC		22
4	n-exan	15	Trace
5	Solvent-free	15	96

Table 2. Optimization amount of sawdust-BF_3 NPs on the reaction of 1,3-diketones and hydrazines at 60 °C

The above reaction was also examined in various solvents (Table 3).

The results indicated that different solvents affected the efficiency of the reaction. Most of these solvents required a longer time and gave moderate yields, and the best results were obtained when solvent-free conditions was used (Table 3, entry 5).

Entry	Catalyst (g)	Time (min)	Yield[a] (%)
1	0.001	15	96
2	0.0005	15	49
3	0.0007	15	73
4	0.0015	15	96

[a]Isolated yield

Table 3. Solvent effect on the reaction between 1,3-diketones and hydrazines catalyzed by sawdust-BF_3 NPs

To study the scope of the reaction, a series of 1,3-diketones and hydrazines catalyzed by sawdust-BF_3 NPs were applied. The results are shown in Table 4. In all cases, hydrazines

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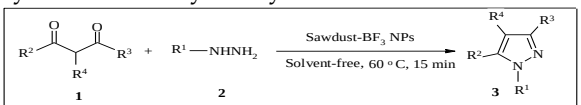
substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in excellent yields.

Table 4. Reaction between 1,3-diketones and hydrazines catalyzed by sawdust-BF_3 NPs



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Entry	R^1	R^2	R^3	R^4	Product	Yield% [a]	m.p. (°C) found	m.p. (°C) reported (Ref.)
1	2,4-$NO_2C_6H_4$	C_6H_5	C_6H_5	H	**3a**	95	148-149	149-150[17]
2	2,4-$NO_2C_6H_4$	C_6H_5	CH_3	H	**3b**	67	129-131	128-130[14]
3	2,4-$NO_2C_6H_4$	CH_3	CH_3	H	**3c**	93	122-124	122-123[15]
4	2,4-$NO_2C_6H_4$	CH_3	CH_3	Cl	**3d**	94	166-167	167-168[17]
5	C_6H_5	C_6H_5	C_6H_5	H	**3e**	96	134-136	137-138[16]
6	C_6H_5	C_6H_5	CH_3	H	**3f**	91	56-58	55-57[15]
7	C_6H_5	CH_3	CH_3	H	**3g**	91	oil	oil [15]
8	C_6H_5	CH_3	CH_3	Cl	**3h**	87	oil	oil [13]
9	H	C_6H_5	CH_3	H	**3i**	80	203-205	203-205 [12]
10	4-BrC_6H_4	CH_3	CH_3	Cl	**3j**	93	88-90	87-88 [17]
11	4-BrC_6H_4	C_6H_5	C_6H_5	H	**3k**	90	118-120	117-119 [17]
12	4-BrC_6H_4	C_6H_5	CH_3	H	**3l**	89	178-179	178-180 [17]
13	4-MeC_6H_4	C_6H_5	C_6H_5	H	**3m**	92	104-106	104-105[17]
14	4-MeC_6H_4	C_6H_5	CH_3	H	**3n**	85	84-86	82-84[17]
15	4-$MeOC_6H_4$	C_6H_5	C_6H_5	H	**3o**	82	oil	oil [17]
16	4-$MeOC_6H_4$	C_6H_5	CH_3	H	**3p**	86	oil	oil [17]

[a] Yields refer to the pure isolated products.

All products were known and were identified by comparing their physical or spectral data with other literature [12-17].

To examine the reusability of sawdust-BF_3 NPs under solvent free condition, after each run, the product was dissolved to $CHCl_3$ and filtered to separate the catalyst and then dry the solid residue. This process repeated for three cycles and the yield of product **3e** did not change significantly (Table 5).

Table 5. Recycling studies of reaction between 1,3-diphenylpropane-1,3-dione and phenylhydrazine in the presence of sawdust-BF_3 NPs to give product **3e**

Entry	Catalyst	Time (min)	Yield %[a]
1	fresh	15	92
2	1	15	90
3	2	15	89
4	3	15	85

[a] Yields refer to isolated products.

4. CONCLUSIONS

In summary, sawdust-BF_3 NPs has synthesised and shown that it has advantages in the preparation of 2,3,5-substituted-2*H*-pyrazoles such as shorter reaction times, simple work-up, and affords excellent yield. The solid phase acidic catalyst was re-usable for a number of times without appreciable loss of activity. The present method does not involve any hazardous organic solvent. Therefore, this procedure could be classified as green chemistry.

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