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Natural Biopolymers is an Efficient Catalyst for the Synthesis of 1,3,5-Trisubstituted Pyrazoles

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Cellulose sulfuric acid is an efficient metal-free catalyst for the synthesis of 1,3,5-trisubstituted pyrazoles *via* the condensation of 1,3-diketones and hydrazines. The reaction was carried out in the solvent-free condition at room temperature and the products were isolated in good to excellent yields. Mild reaction conditions, as well as the ease of operation and workup are some advantages of the proposed protocol.

Keywords: Natural biopolymers, Cellulose sulfuric acid, Pyrazoles

INTRODUCTION

Pyrazole derivatives have a wide range of biological activities. They can be used as anti-inflammatory [1], antipyretic [2], antidepressant [3], anti-rheumatoid arthritis [4], antibacterial [5], antitumor [6], antipsychotic [7], antimicrobial [8], antifungal [9] and anthelmintic activity [10]. The synthesis of pyrazoles can be achieved by several different routes [11-15]. Pyrazoles can be synthesized *via* condensation of 1,3-diketones and hydrazines in the presence of inorganic supports, acidic catalyst such as silica-supported sulfuric acid [16], and polystyrene sulfonic acid [17]. Cellulose is one of the most abundant natural biopolymers in the world which has been in the center of attention over the past several decades owing to its biodegradablity and a renewable resource [18]. Its unique properties make it an attractive alternative to conventional organic or inorganic supports in catalytic applications. Recently, cellulose sulfuric acid (CSA) has emerged as a promising biopolymeric solid-support acid catalyst for acid-catalyzed reactions, such as the synthesis of α-amino nitriles [18], aryl-14*H*-dibenzo[*a,j*]xanthenes [19], 1,4-dihydropyridines [20], Pechmann condensation [21], thiadiazolo benzimidazoles [22], imidazoazines [23], quinolines [24] and 3,4-dihydropyrimidine-2(1*H*)-ones [25].

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EXPERIMENTAL

Materials and Methods

All chemicals used in this study were purchased from the chemical companies Fluka, Merck and Aldrich. The products were characterized by elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR spectra. IR spectra were run on a Bruker, Eqinox 55 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker Avans with 400 and 100 MHz (or 500 and 125 MHz), respectively. The elemental analyses were done by Costech ECS 4010 CHNS-O analyser. Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus.

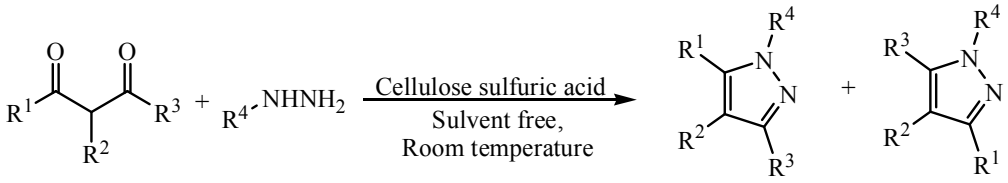
General Procedure

Catalyst preparation. Chlorosulfonic acid (1.00 g, 9 mmol) was added drop wise to a magnetically stirred mixture of cellulose (5.00 g, cellulose microcrystalline, Merck) at 0 °C during 2 h. After that, the mixture was stirred for 2 h until HCl was removed from the reaction vessel. Then, the mixture was washed with methanol (30 ml) and dried at room temperature to obtain cellulose sulfuric

Table 1. Synthesis of 1,3,5-Triphenyl-pyrazole in Various Conditions[a]

Entry	Catalyst (g)	Solvent	Conditions	Time (min)	Yield (%)[b]	Ref.
1	Cel.sul. acid[c] (0.10)	H_2O (25 ml)	r.t.	150	52	-
2	Cel.sul. acid (0.10)	H_2O (25 ml)	Reflux	120	74	-
3	Cel.sul. acid (0.10)	Chloroform (25 ml)	r.t.	150	33	-
4	Cel.sul. acid (0.10)	Chloroform (25 ml)	Reflux	120	57	-
5	Cel.sul. acid (0.10)	Ethanol (25 ml)	r.t.	150	67	-
6	Cel.sul. acid (0.10)	Ethanol (25 ml)	Reflux	120	80	-
7	Cel.sul. acid (0.10)	Solvent-free	r.t.	150	96	-
8	Cel.sul. acid (0.10)	Solvent-free	r.t.	120	95	-
9	Cel.sul. acid (0.05)	Solvent-free	r.t.	120	90	-
10	Cel.sul. acid (0.15)	Solvent-free	r.t.	120	96	-
11	Cel.sul. acid (0.15) 2nd run	Solvent-free	r.t.	120	94	-
12	Cel.sul. acid (0.15) 3nd run	Solvent-free	r.t.	120	94	-
13	Cel.sul. acid (0.15) 4nd run	Solvent-free	r.t.	120	93	-
14	Cellulose microcrystalline (0.10)	Solvent-free	r.t.	120	24	-
15	Cellulose microcrystalline (0.10)	Ethanol (25 ml)	Reflux	120	45	-
16	Without Catalyst	Ethanol (25 ml)	Reflux	120	45	-
17	SiO_2Cl	Solvent free	120 ºC	120	80	[29]
18	Zn[(L)proline]2	H_2O	r.t.	300	90	[30]
19	$H_{14}[NaP_5W_{30}O_{110}]$	Ethanol	Reflux	7.5	91.5	[31]
20	37% $P_2O_5{\cdot}SiO_2$	Solvent-free	120 ºC	120	86	[32]

[a]Phenylhydrazine (2 mmol) with 1,3-diphenyl-1,3-propanedione (2 mmol). [b]Cellulose sulfuric acid. [c]Isolated yield.



Scheme 1. Synthetic route for 1,3,5-triphenyl-pyrazole

Table 2. Synthesis of 1,3,5-Trisubstituted Pyrazoles in the Presence of Cellulose Sulfuric Acid

Entry	R^1	R^2	R^3	R^4	Time	Yield (%)[a]	M.p. (°C)
1	C_6H_5	H	C_6H_5	2,4-$(NO_2)_2C_6H_3$	130	96	149-150
2	C_6H_5	H	CH_3	2,4-$(NO_2)_2C_6H_3$	120	93	128-130
3	CH_3	H	CH_3	2,4-$(NO_2)_2C_6H_3$	115	95	121-122
4	CH_3	Cl	CH_3	2,4-$(NO_2)_2C_6H_3$	110	90	167-168
5	C_6H_5	H	C_6H_5	C_6H_4	120	95	137-138
6	C_6H_5	H	CH_3	C_6H_4	120	90	55-57
7	CH_3	Cl	CH_3	C_6H_4	110	94	Oil
8	C_6H_5	H	C_6H_5	H	130	81	200-201
9	C_6H_5	H	CH_3	H	125	89	203-205
10	C_6H_5	H	C_6H_5	2-Cl-C_6H_4	130	94	126-127
11	CH_3	Cl	CH_3	4-Br-C_6H_4	110	90	87-88
12	C_6H_5	H	C_6H_5	4-Br-C_6H_4	110	93	117-119
13	C_6H_5	H	C_6H_5	4-Me-C_6H_4	100	92	104-105

[a]Isolated yield.

acid as white powder (5.28 g) [18].

General procedure for the synthesis of pyrazole derivatives. A mixture of 1,3-diketone (2 mmol), hydrazine derivatives (2 mmol) and cellulose sulfuric acid (0.10 g) was stirred magnetically at room temperature. The progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was washed with chloroform and filtered to recover the catalyst. The filtrate was evaporated and the crude product was recrystallized from iso-propanol to afford the pure pyrazoles derivatives.

RESULTS AND DISCUSSION

Homogeneous acidic catalysts such as H_2SO_4, etc, are commonly used for the synthesis of pyrazole derivatives [26]. However, the above-mentioned catalysts have several disadvantages because they are corrosive, toxic or volatile, and generate large amounts of waste [27]. Consequently, the

synthetized cellulose sulfuric acid was applied as a new catalyst for the synthesis of pyrazoles derivatives. This reagent is ideal for 'green chemistry', due to its non-toxicity and environmentally friendly feature. Also, these catalysts can be recovered and reused several times without a decrease in activity [28]. Initially, the synthesis of 1,3, 5-triphenyl-pyrazole using phenylhydrazine (2 mmol) with 1,3-diphenyl-1,3-propanedione (2 mmol) was investigated for optimization of the reaction under the various conditions (Table 1). The reaction was done at different temperatures and various molar ratios of substrates in the presence of cellulose sulfuric acid. The optimum conditions of 25 °C (room temperature), 120 min, a ratio of 1,3-diketone (mmol):hydrazine derivatives (mmol):cellulose sulfuric acid (g) equal to 2:2:0.10 were achieved, respectively for temperature, time, and the mole ratio of 1,3-diketone (mmol):hydrazine derivatives (mmol). Herein, we introduce cellulose sulfuric acid as an efficient catalyst for the synthesis of pyrazole derivatives which is comparable with some other catalysts (Table 1, entries 17-20). The reusability of the catalyst was also investigated. After each run, the mixture was washed with chloroform and filtered to recover the catalyst. Methanol was used to remove tars from the catalyst surface and the catalyst residue was washed with CH_2Cl_2 and reused (Table 1, entries 11-13). In order to investigate the catalytic activity of cellulose sulfuric acid, the reaction was catalyzed with cellulose and without catalyst (Table 1, entries 14-16).

The applicability of the present method to a large scale process was examined with 20 mmol of 2,4-dinitrophenylhydrazine and 20 mmol of 1,3-diphenyl-1,3-propanedione under thermal conditions which gave 1-(2,4-dinitrophenyl)-3,5-diphenyl-pyrazole in 94% yield. The current method is simple, efficient and fast for the synthesis of pyrazoles *via* the condensation of 1,3-diketones and hydrazines .Various hydrazines were used as substrates for the synthesis of pyrazoles under mild conditions, (Scheme 1 and Table 2). In all cases, the three-component reaction proceeded smoothly to give the corresponding pyrazoles in moderate to good yields. In summary, we have described that cellulose sulfuric acid is an efficient and natural biopolymer catalyst for the synthesis of pyrazoles derivatives.

CONCLUSIONS

In conclusion, cellulose sulfuric acid was applied for the preparation of pyrazoles in a simple and straightforward protocol. This reagent is ideal for 'green chemistry', due to its non-toxicity and environmentally friendly features. High yields, scale-up, simplicity of operation, easy work-up, and green conditions are the advantages of this protocol.

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