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Synthesis of 1, 3, 5-Triphenyl Pyrazoles Derivatives Using Polysaccharides Biopolymers as Catalyst

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ABSTRACT: Nitrogen-containing heterocyclic compounds and their derivatives have historically been invaluable as a source of therapeutic agents. Pyrazole, which has two nitrogen atoms and aromatic character, provides diverse functionality and stereochemical complexity in a five-membered ring structure. In the past decade, studies have reported a growing body of data on different pyrazole derivatives and their innumerable physiological and pharmacological activities. In part, such studies attempted to reveal the wide range of drug-like properties of pyrazole derivatives along with their structure–activity relationships in order to create opportunities to harness the full potentials of these compounds. Here, we summarize strategies to synthesize pyrazole derivatives and demonstrate that this class of compounds can be targeted for the discovery of new drugs and can be readily prepared owing to recent advances in synthetic medicinal chemistry.

KEYWORDS: pyrazole, heterocyclic, pharmacological, physiological, drugs, medicinal, rheumatoid

I. INTRODUCTION

Pyrazole derivatives have a wide range of biological activities. They can be used as anti-inflammatory , antipyretic , antidepressant , anti-rheumatoid arthritis , antibacterial , antitumor , antipsychotic , antimicrobial , antifungal , and anthelmintic activity.The synthesis of pyrazoles can be achieved by several different routes[1,2] . 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 ,and polystyrene sulfonic acid . 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.Its unique properties make it an attractive alternative to conventional organic or inorganic supports in catalytic applications.[3,4] 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 , aryl-14H-dibenzo[a.j]xanthenes , 1,4- dihydropyridines ,Pechmann condensation , thiadiazolo benzimidazoles , imidazoazines ,quinolines , and 3,4-dihydropyrimidine-2(1H)-ones [5,6].

II. 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, 1H NMR, and 13C NMR spectra. IR spectra were run on a Bruker, Eqinox 55 spectrometer. 1H NMR and 13C 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.[7,8]

III. 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. [9,10]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 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.[25,26] The progress of the reaction was monitored by TLC. [11,12]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. [13,14]

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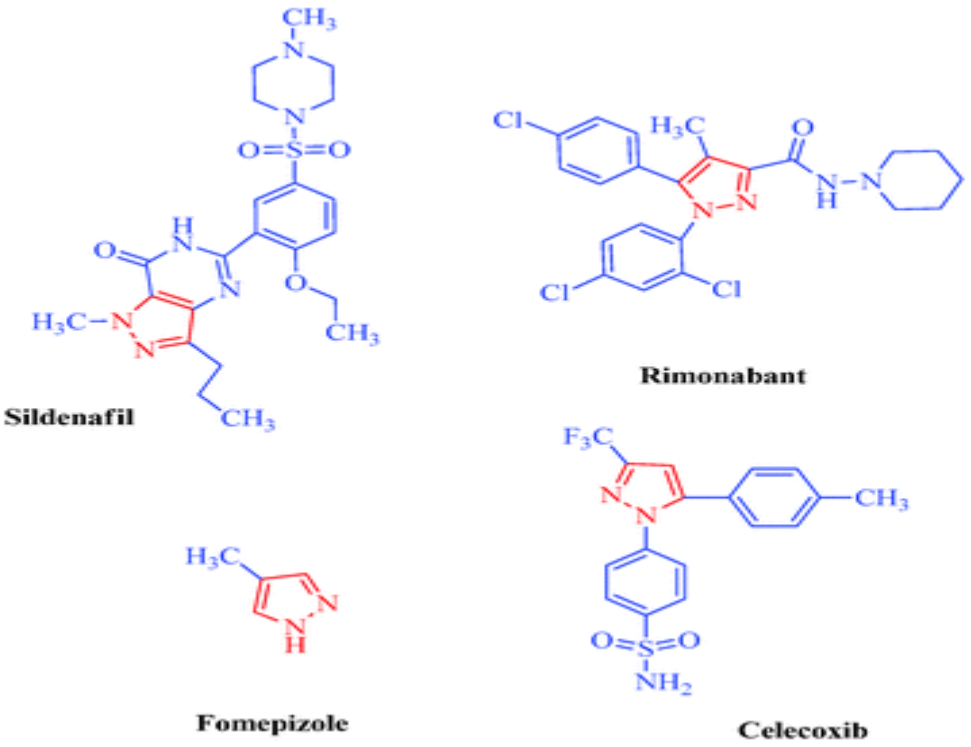

Scheme -1

IV. RESULTS AND DISCUSSION

Homogeneous acidic catalysts such as H2SO4, 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.[29,30] The optimum conditions of 25 °C (room temperature),[15,16,17] 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).[18]

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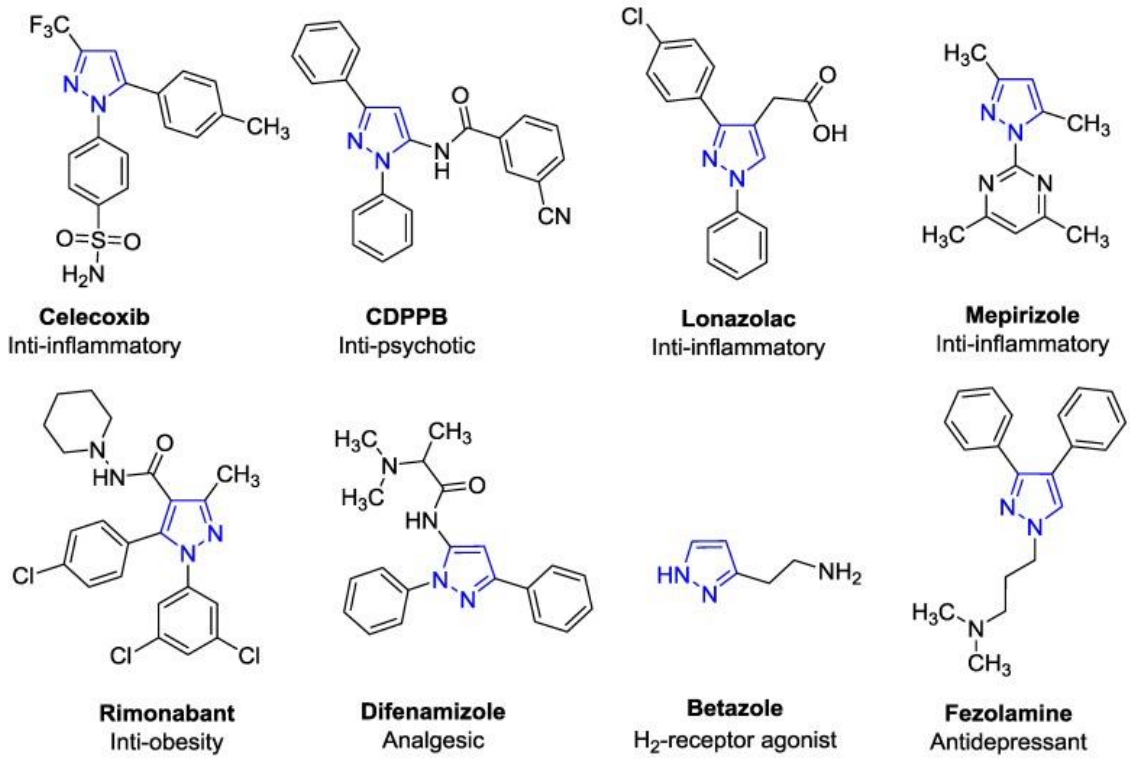

Herein, we introduce cellulose sulfuric acid as an efficient catalyst for the synthesis of pyrazole derivatives which is comparable with some other catalysts (Table 1). The reusability of the catalyst was also investigated.[19,20] After each run, the mixture was washed with chloroform and filtered to recover the catalyst. Methanol was used to remove tars from the catalyst surface and the catalyst residue was washed with CH2Cl2 and reused (Table 1). In order to investigate the catalytic activity of cellulose sulfuric acid, the reaction was catalyzed with cellulose and without catalyst (Table 1). 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-diphenyl1,3-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[21,22] .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.[23,24]

Table 1 Natural products containing pyrazole moieties

Name	Isolated from	Structure	Applications
L-α-Amino-β (pyrazolyl-N)-propanoic acid – First natural product containing pyrazole	*Citrullus vulgaris*		– Antidiabetic
Withasomnine 4′-Hydroxywithasomnine 4′-Methoxywithasomnine	*Withania somnifera* Dun		– Analgesic – Anti-inflammatory Depressant to – CNS (Central

Name	Isolated from	Structure Applications
		Nervous System) – Circulatory system
Pyrazofurin	*Streptomyces candidus*	– Antitumor
Pyrazofurin B		– Antiviral
Formycin	*Streptomyces candidus, Streptomyces lavendulae &Nocardia interforma*	– Antiviral – Antitumor
Formycin B	*Streptomyces lavendulae & Nocardia interforma*	– Antiviral – Antitumor
Oxoformycin B – A metabolite of Formycin and Formycin B	*Streptomyces lavendulae &Nocardia interforma*	– Antiviral – Antitumor
Nostacine A	*Nostoc spongiaeformae*	– Cytotoxic
Fluviols (A–E)	*Pseudomonas fluoresences*	– Antimicrobial

V. CONCLUSIONS

In conclusion, cellulose sulfuric acid was applied for the preparation of pyrazoles in a simple and straightforward protocol.[31,32] 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[27,28]

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