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An efficient practical chemo-enzymatic protocol for the synthesis of pyrazoles in aqueous medium at ambient temperature

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ABSTRACT

An expeditious oxidative cyclocondensation reaction of hydrazines/hydrazides with 1,3-dicarbonyl compound was efficiently developed in aqueous medium using *Saccharomyces cerevisae* (baker's yeast) as a whole cell biocatalyst at room temperature. The method has been assigned using green chemistry measures and found to give a range of N-substituted pyrazoles with moderate to excellent yields (70–92%). The reaction progress was monitored by gas chromatography.

1. Introduction

It is widely accredited that there is an increasing importance for more environmentally viable synthetic routes in organic synthesis. This progressive development known as 'Sustainable Technology' necessitates a change in scenario from traditional concepts of process efficiency to more economic and greener approaches [1]. In recent years, water as reaction medium has captured high priority as green media because it is safe to handle, environment-friendly, easily available, and enhances the reactivity and selectivity of reactions [2]. In this context, use of biocatalysts in aqueous media has emerged as a green synthetic strategy, to construct structurally diverse scaffolds from simple molecules. Biocatalysis highlights an effective and preferable alternative to the standard synthesis of potent chemicals as they can accept un-natural compounds as substrates. As whole-cell biocatalysts regenerate their own respective cofactors, they are frequently more advantages than isolated enzymes [3]. Among the various possible biocatalysts, baker's yeast (*Saccharomyces cerevisae*) is renowned catalyst, due to its low cost, easy handling, high bioavailability, and its growth does not require the assistance of a specialist in microbiology [4]. Baker's yeast projects better catalytic behaviour in aqueous medium [5] and has the ability to accelerate the transformations under mild reaction conditions such as temperature, light, stirring etc. [6] and is known to play vital role in various organic transformations [5,7]. Baker's yeast has been extensively used in the synthesis of library of heterocyclic compounds [8] such as, benzimidazoles, quinoxalines, polyhydroquinolines, 4H-pyranes, 1,4-dihydropyridines, 3,4-dihydro-pyrimidine-2-(1H)-ones, isoindolo[2,1-a]quinazolines, 1,4-benzothiazines etc. Recently Singh et al. [9] reported the synthesis of indolyl chromenes and bisindolyl alkanes in water using baker's yeast as the catalyst.

Pyrazole derivatives constitute the core structure of naturally occurring and biologically active heterocyclic compounds. Pyrazole nucleus containing compounds represent important building blocks for luminophores, dyes, insecto-acaricides, antibacterial, antidepressant, analgesic and antiphlogistic drugs [10]. Pyrazole derivatives are of great interest due to their pharmacological properties for instance, pyrazole diimide (Fig. 1, I) acts as anticancer drug [11]. Celecoxib {4-[5-(methylphenyl)-3-trifluoromethyl) pyrazol-1-yl] benzene sulphonamide} (Fig. 1, II) acts as inhibitor of cyclo-oxygenase-2 (COX-2) and reduces side effects in the gastrointestinal tract [12]. Methylthiopyrazole epothilone B (Fig. 1, III) shows strong antitumor activity through the stabilisation of microtubules by binding with tubulin [13]. Due to unique biological activities of pyrazole derivatives in medicinal chemistry, the development of elegant and efficient ways enabiling facile access to this heterocycle is desirable.

In recent years, a large number of protocols [14] for preparation of pyrazoles have been developed in different ways using polystyrene supported sulfonic acid (PSSA) [15], Al_2O_3/clay (montmorillonite K10) [16], Amberlyst-70 [17], polymer bound-*p*-toluene sulphonic acid (PTSA) [18], silica supported sulphuric acid (H_2SO_4·SiO_2) [19], $Sc(OTf)_3$ [20], Zn[(L)-proline]$_2$ [21], sulphamic

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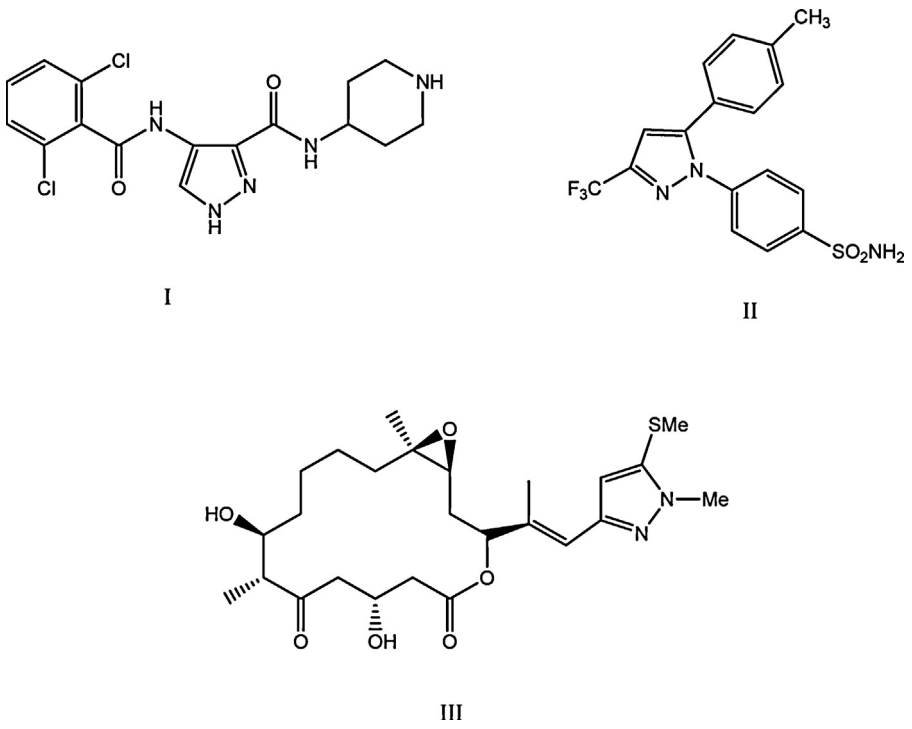

Fig. 1. Biologically active compounds containing pyrazole as a core structure.

acid [22] as catalysts. These reported methodologies produced good results in many instances. However most of the methods reported suffer from certain limitations such as use of expensive reagents, tedious procedure for preparation of catalysts, low selectivity, generation of acidic and metallic waste and tedious workup conditions. Hence, the development of an efficient, simple, easy workup and environmentally benign protocol using green solvent for the construction of pyrazole derivatives is of significant interest. In view of the above valid points, we disclose herein an environmentally benign and effective protocol for the synthesis of pyrazole derivatives employing baker's yeast (*S. cerevisae*) in fermenting medium at an ambient temperature. To the best of our knowledge, the role of baker's yeast in the cyclocondensation of hydrazines/hydrazides and 1, 3-diketones has not been previously reported.

2. Experimental

2.1. Materials and instruments

Solvents and reagents involved in the synthesis were sourced from commercial suppliers and used as such. Progress of all reactions and purity of dicarbonyl compound, hydrazines and hydrazides were monitored by thin layer chromatography (TLC) carried out on silica gel G 60 F_{254}plates (Merck). Chromatograms were developed using petroleum ether: ethyl acetate (7:3) as solvent system. The melting points of products were measured in open capillary tubes and are uncorrected. GC analysis was performed using a 25 m HP-5 column (crosslinked 5% PH ME Siloxane) with an inner diameter of 0.25 mm and a film thickness of 0.25 m. GC was operated using a temperature profile with a starting temperature of 40 °C, then increased by 15 °C/min to an end temperature of 300 °C Infrared spectra were recorded on Perkin Elmer FT-IR spectrometer. The ^{1}H and ^{13}CNMR spectra were recorded on a Brucker-Avance 300 MHz spectrometer using TMS as an internal standard and $CDCl_3$ as a solvent. Mass spectra were recorded on Shimadzu QP 2010 GCMS. Baker's yeast was purchased from local market.

2.2. Experimental procedure

2.2.1. Fermentation of baker's yeast

In a round bottom flask containing 5 mL of 0.01 M phosphate buffer (pH 7.0), bakers' yeast (400 mg) and D-glucose (750 mg) were added and resulting solution was stirred for 12 h at 32 °C for fermentation.

2.2.2. Synthesis of pyrazoles

To the fermented baker's yeast 1,3-dicarbonyl compound (1 mmol) and hydrazine/hydrazide (1.2 mmol) were added and the reaction mixture was stirred at room temperature for indicated time (Table 1). The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, it was extracted with dichloromethane and finally dried over anhydrous sodium sulphate. The organic layer was concentrated in vacuo. The resulting crude product was purified by column chromatography using petroleum ether:ethyl acetate (7:3) as eluent.

Table 1
Effect of amount of catalyst on the reaction of acetyl acetone and phenyl hydrazine.[a]

Entry	Amount of catalyst (mg)	Reaction time[b] (h)	Yield (%)[c]
1	100	00:15	78
2	200	00:15	83
3	300	00:15	85
4	**400**	**00:15**	**92**
5	500	00:15	89

Bold values mean that at 400 mg of catalyst yield of product is maximum.

[a] Reaction conditions: acetyl acetone (1 mmol), phenyl hydrazine (1.2 mmol), D-glucose, phosphate buffer (pH 7.0, 5 mL) at room temperature.

[b] Reaction progress monitored by TLC.

[c] Isolated yield.