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Development of New Method for the Synthesis of Pyrazole Derivative

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Abstract: *The pyrazole ring is a well-known structural originate in numerous pharmaceutically active compounds. Pyrazole framework plays a vital role in biologically active compounds and therefore represents an appealing pattern in medicinal chemistry [1-2]. likewise, pyrazole derivatives have showed important biological activities, such as anti-microbial [3], analgesic [4], anti-inflammatory [5] and anticancer [6] activities. This gave a great momentum to the search for probable pharmacologically active drugs carrying pyrazole substituents. In persistence of former work on the development of the suitable synthetic method for biologically active molecules [7–10] using some of the green pathway and considering the above urgent need here it was thought worthwhile to develop better synthetic protocol by carrying the cyclocondensation of multicomponents, aromatic aldehydes, ethylacetoacetate and phenyl hydrazine under neat condition or in organic medium.*

Keywords: Pyrazole Derivative.

I. INTRODUCTION

The pyrazole ring is a well-known structural originate in numerous pharmaceutically active compounds. Pyrazole framework plays a vital role in biologically active compounds and therefore represents an appealing pattern in medicinal chemistry [1-2]. likewise, pyrazole derivatives have showed important biological activities, such as anti-microbial [3], analgesic [4], anti-inflammatory [5] and anticancer [6] activities. This gave a great momentum to the search for probable pharmacologically active drugs carrying pyrazole substituents. In persistence of former work on the development of the suitable synthetic method for biologically active molecules [7–10] using some of the green pathway and considering the above urgent need here it was thought worthwhile to develop better synthetic protocol by carrying the cyclocondensation of multicomponents, aromatic aldehydes, ethylacetoacetate and phenyl hydrazine under neat condition or in organic medium.

a range of catalysts have been used for the preparation of these compounds via the condensation reaction. These catalysts comprise acetic acid or piperidine [11], sodium dodecyl sulfate [12], ETBA [13], silica-bonded S-sulfonic acid [14] and CAN [15]. Pyrazoles are the privileged scaffold and show capable biological activities. Pyrazole, a fortunate class of heterocyclic compounds, comprise an interesting template for medicinal chemistry and is represented by a number of commercial drugs like Sildenafil, Zometapin, Celebrex, and Rimonabant. The presence of two functionalities with different reactivity in pyrazole moiety may open new avenues for insertion of diversity in pyrazole frameworks which may be of high medicinal significance.

In conclusion a simple, convenient one-pot synthetic protocol has been developed for the synthesis of fully substituted pyrazoles. This new synthetic approach markedly advances the synthetic efficiency, decreases the production of toxic waste without using hazardous reagent.

II. EXPERIMENTAL

Melting points of the synthesized compounds were determined via Thiele's melting point apparatus and were found uncorrected. The IR spectra of the synthesized compounds were recorded using KBr pellets on a Fourier Transform IR Spectrophotometer (Model Shimadzu). The ^{1}H NMR spectra were recorded on Amx-400 liquid state PMR spectrometer with internal reference tetramethylsilane (TMS). Mass spectrum was recorded by LC-MS (model Shimadzu.). Purity of the compounds was checked by thin layer chromatography.

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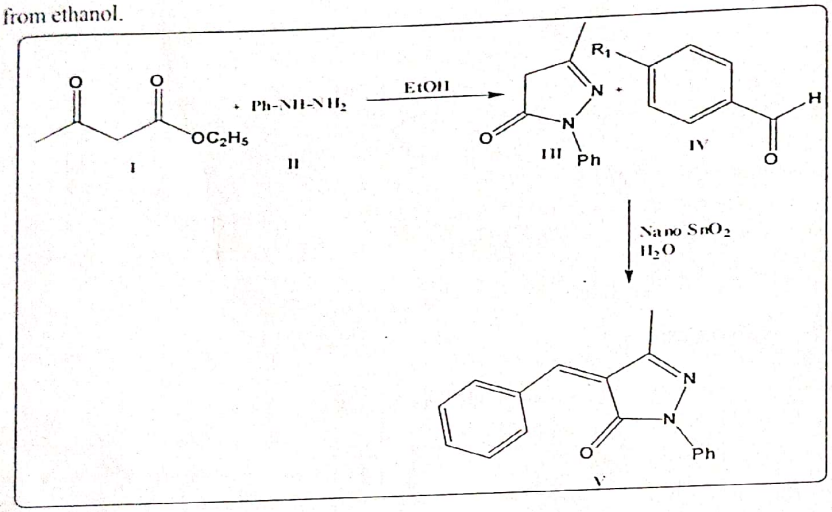
General Procedure for the Preparation of Pyrazolone Derivative:

Ethyl acetoacetate was taken in conical flask and Phenyl hydrazine in ethanol (15 mL) as a solvent with stirring. The temperature elevated during this addition and it was maintained at 60°C till crystalline solid separated. The reaction-mixture was further stirred till all reactant consumed in the reaction then it was allowed to cooled in an ice bath to complete the crystallization. Solid Separated was further washed, purified with ice cold ethanol.

General Procedure for the Preparation Pyrazole Dericvative:

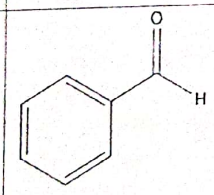
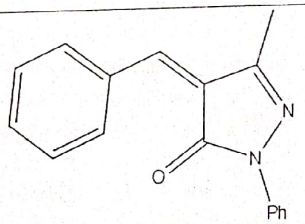
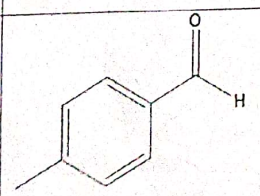
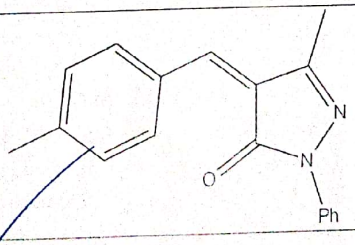
pyrazololone and substituted aromatic aldehyde were allowed to react in presence of catalytic amount of nano SnO_2 in ethanol as a solvent for specific period. The completion of reaction was constantly checked by TLC. After the confirmation of reaction the reaction-mixture was poured in crushed ice. The solid obtained was filtered, dried and recrystallized from ethanol.



III. RESULT AND DISCUSSION

Synthesis of pyrazole derivative via ethyl acetate, phenyl hydrazine and substituted benzaldehyde produces pyrazole in excellent yield. reaction proceed smoothly in aqueous medium. In first attempt benzaldehyde was allowed to react with pyrazolone formed from ethyl acetoacetate and phenyl hydrazine in presence of nano SnO_2 as a catalyst to produce 80% 4-(benzylidene)-3-Methyl-1-phenyl-1H-pyrazol-4-one in 4hr (Entry 1).

Table 1: Synthesis of pyrazole derivative using SnO_2 as a catalyst under optimized reaction condition.

Entry	Aromatic Aldehyde	Product	Time (hr)	Yield (%)
1			4	80
2			5	76

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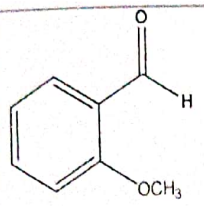
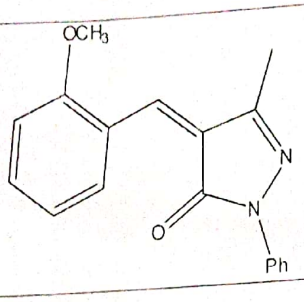
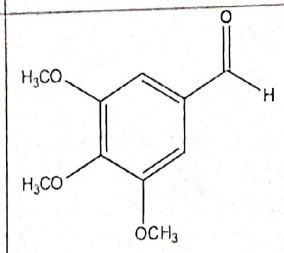
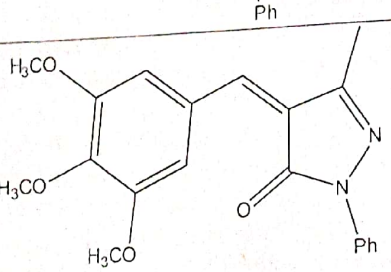
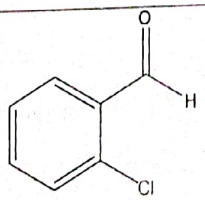
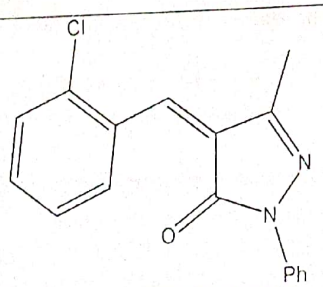
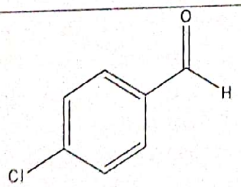
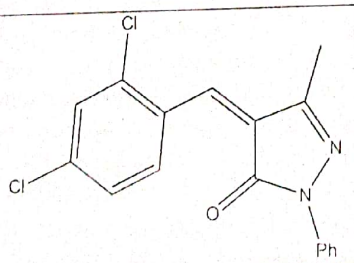
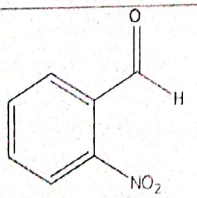
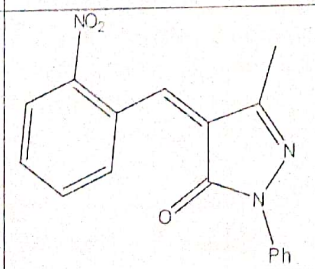
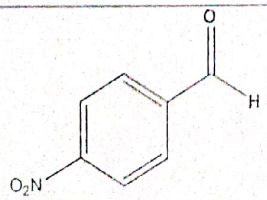
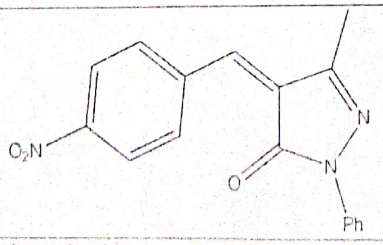
3			5.5	72
4			6	74
5			3	85
6			3	82
7			2.5	90
8			3	87

All reactant are taken in equimolar amount. X indicates isolated product

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Inorder to study the effect of electron releasing group on reaction mechanism 4-methyl benzaldehyde was taken for the synthesis of pyrazole derivative and it was seen that the declined product yield of around 76% (Entry 2). Further study for the preparation of pyrazole derivative from ethyl acetoacetate, phenyl hydrazine 2-methoxy benzaldehyde and 3,4,5 trimethioxy benzaldehyde in a separate set of reaction in presence of ethanol as a solvent and nano SnO_2 as a catalyst produces yield 72 and 74% respectively (Entry 3,4). So it was concluded that the electron donating group on aromatic aldehyde was not able to generate satisfactory yield. considering the fact electron withdrawing group were taken for further study.

In next attempt 2-chloro benzaldehyde and 4-chloro benzaldehyde were used in different set of reaction ion ethanol as a medium of reaction displayed an astonishing result with yield of 82 and 84% respectively. This increased yield with electron withdrawing substituent on aromatic aldehyde show positive effect. Taking into account the fact the research was continued with 2-nitro and 4-nitro benzaldehyde and interesting thing to note down for pyrazole derivative was excellent yield of 90 and 87% was recorded with very short reaction time 2.5 hr and 3 hr respectively.

IV. CONCLUSION

Synthesis of pyrazole derivative from ethyl acetate, phenyl hydrazine and substituted aromatic aldehyde in presence of catalytic amount of SnO_2 and water as a solvent which is a efficient technique to form product from good to excellent yield. This protocol follows the principle of green chemistry. The recyclability of catalyst was checked and it was found that effectiveness of catalyst remains up to sixth cycle. The heterogeneous catalyst nano SnO_2 was easily saperated from the reaction mixture at the end of reaction and can be reused further.

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