© 2017 IJSRST | Volume 3 | Issue 9 | Print ISSN: 2395-6011 | Online ISSN: 2395-602X
National Conference on Green Approach towards Environment and Chemical Science

A simple, convenient Grape Juice Catalyzed Synthesis of Dihydropyrimidinone/thione by Grindstone Technique : A Green chemistry Approach

G. M. Nazeruddin[a]*, S. S. Mulani[b], Y. I. Shaikh[a], Samir S. Shaikh[c], Khursheed Ahmed[a]

[a]Department of Chemistry and Post Graduate Research Centre, Abeda Inamdar Senior College, Pune, Maharashtra, India
[b]Department of Chemistry and Post Graduate Research Centre Poona College of Arts, Science and Commerce, Pune, Maharashtra, India
[c]Department of Chemistry Post Graduate Centre, G.M. Arts, Commerce and Science College, Narayngaoan, Pune, Maharashtra, India

ABSTRACT

Multicomponent reactions (MCRs) are chemical reactions in which three or more compounds react to form a single product. In the present work Biginelli reaction was accomplished just by grinding equimolar quantities of ethyl acetoacetate, Urea/thiourea and aryl aldehyde with grape juice as a catalyst for 15 to 20 minutes at ambient condition. The crude product was recrystallized by ethanol. This protocol is a greener approach for organic transformations, thus facilitating efficient synthesis of bioactive compounds in environmentally benign way with shorter reaction time, mild reaction conditions, and easy workup with excellent yield of the product.

Keywords : Green Chemistry, Grape Juice, Multicomponent Reaction, Grindstone Technique.

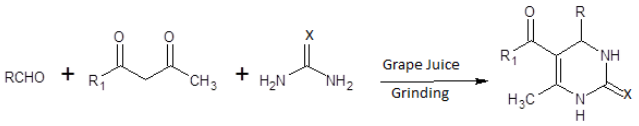
I. INTRODUCTION

The concept of "Green Chemistry"[1] has been widely adopted to meet the fundamental scientific challenges of protecting human health and environment while simultaneously achieving commercial viability. One of the thrust areas for achieving this target is to explore aqueous reaction medium for accomplishing the desired chemical transformation and eliminating the use of organic solvents.[2] Multicomponent reactions (MCRs) can provide products with diversity needed in the discovery of new compounds using simple and nonhazardous process[3-5]. Multicomponent reactions have been successfully adopted by the chemists for the synthesis of a large library of biologically active molecules. The multicomponent reactions (MCR's) are one of the most important protocols in organic synthesis and medicinal chemistry[6].These unique characteristics of the multicomponent reaction have attracted the attention of organic chemists. Moreover, higher selectivity is usually observed and the products can be easily isolated with good chemical purity by simple filtration avoiding more time consumption and tedious extractive workup. Recently great attention has been diverted towards cyclic and acyclic nitrogen containing heterocyclic compounds in pharmaceuticals as well as for medicinal purposes. Heterocyclic molecules are of biological interest due to their potential physical and chemical properties.[7] 3,4-Dihydropyrimidin-2(1H)-ones and thiones derivative have attracted increasing interest owing to their therapeutic and pharmaceutical properties, such as antiviral, antibacterial, anti-inflammatory and anti-tumour activities.[8-10]

Designing and development of non-hazardous synthetic methodologies for various organic transformations is one of the latest challenges to the organic chemists. Importance is now given for the development of environmental friendly and economic processes. Recent trends in organic synthesis utilize a non-conventional green techniques such as ultrasound (sonochemistry), microwave irradiation, grinding and by using ionic liquids which have also been proved to have many advantages[11]. Development of non- polluting, ecofriendly non-hazardous synthetic methodologies for organic reactions is one of the latest challenges to the

organic chemists. Even less hazardous byproducts are not desirable because of the growing concern for the environment. Lots of attempts are being made not only to quantify the greenness of a chemical process but also to consider factors such as product yield, the price of reaction components, safety in handling chemicals, hardware demands, energy consumptions and ease of product workup and purification. Grindstone technique has been considered as a clean and useful protocol in organic synthesis over the last few decades. In this technique, reaction occurs through generation of local heat by grinding the solid reactants using mortar and pestle. Reactions are initiated by grinding, with the small amount of energy through friction. The grinding reactions are simple to handle, reduce pollution, comparatively cheaper to operate and may be regarded as more economical and ecological [12-14].

The role of naturally available fruit juice in organic synthesis has attracted the interest of chemists, particularly from the view of green chemistry. In literature, a number of organic reactions using natural catalysts such as clay [15-16], natural phosphates [17-19], animal bone [20] and various fruit juices are reported. Due to acidic nature aqueous fruit juice like lemon [21-26], pineapple [27-28], coconut [29], *Acacia concinna*[30], *Sapindustrifolistus*[31] and *Tamarindusindica*[32] fruit has been found to be a suitable replacement for various homogeneous acid catalysts. In recent years, organic research is mainly focused on the development of greener and eco-friendly processes which involve in the use of alternative reaction media to replace toxic and expensive catalysts or volatile and hazardous solvents like benzene, toluene and methanol, commonly used in organic synthesis. Nowadays, many organic transformations have been carried out in water [33-35]. Water is unique solvent because it is readily available, inexpensive, nontoxic, safer and environmentally benign. The use of water as a reaction medium is not only inexpensive and environmentally benign but also provides completely different reactivity. [36] The applications of an aqueous extract of different fruit juice have witnessed a rapid development. This growing interest in fruit juice is mainly because of its biocatalysts, environmentally benign character, cost effectiveness. Fruit juice is also naturally occurring which was used as a biocatalysts in organic synthesis.In the present work Biginelli reaction was accomplished just by grinding equimolar quantities of ethyl acetoacetate, Urea/thiourea and aryl aldehyde with grape juice (pH 3.0 - 3.5)as a catalyst for 10 to 15 minutes at ambient condition. The crude product was recrystallized by ethanol. Tis protocol is a greener approach for organic transformations, thus facilitating efficient synthesis of bioactive compounds in environmentally benign way with shorter reaction time, mild reaction conditions, and easy workup with excellent yield of the product.



Scheme 1:Synthesis of dihydropyrimidone/ thioneWhere, X= S,O.

II. MATERIALS AND METHODS

All melting points were measured in open capillary and are uncorrected. The products were characterized by IR spectra, 1H NMR. IR spectra were recorded on Perkin–Elmer FT-IR-1710 Instrument. 1H NMR was recorded onBrukerMSL-300 instrument using TMS as an internal standard. All reagents were purchased from Merck and Loba and used without further purification.

Experimental:

Preparation of aqueous extract of grape juice (Vitisamurensis):The seed less grapes were purchased from the local market and the (10 g) was crushed in water (50 mL) by grinder, and it was centrifuged using micro centrifuge (REMI RM-12C). The clear portion of the aqueous extract of the grapes was used as catalyst for thereaction.

General method for series of dihydropyrimidinone / thiones (DHPMs) derivatives:

The mixture of 10 mmol of aldehyde, 10 mmol of ethyl acetoacetate, 10 mmol of urea / thiourea and 5 ml grapejuice was grinded using mortar pestle at room temperature with monitoring by TLC. Then the reaction mixture washed with water and was filtered, the crystalline solid recovered by crystallization with ethanol. Its identity was confirmed by IR and NMR and its melting point. This procedure is followed for the synthesis of all the dihydropyrimidinones / thiones.

III. RESULTS AND DISCUSSION

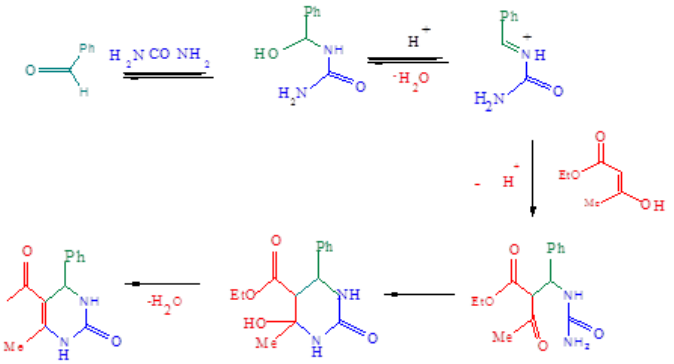
The synthesis of dihydropyrimidinones/thiones (DHPMs) derivatives which was accomplished by Biginelli reaction between substituted aryl aldehydes, ethyl acetoacetate and urea/thiourea (Scheme1) using natural and biocatalyst, which is an efficient and environmentally friendly catalyst. The results are presented in table1.The probable mechanism of the reaction is depicted in scheme 2. The reaction was accompanied having green chemistry approach, shorter reaction time, mild reaction conditions and easy workup procedure along with excellent yield. As compared to other catalyst reported in the literature[37 -39]this is a mild and highly selective transformation and synthesis in a facile and environmentally friendly manner. Moreover, fruits are inexpensive and easily available in the market, the extracted juice can be easily used as catalyst in the organic transformations.

Table 1: Grape juice catalyzed synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones and thiones just by grinding at ambient condition

Sr.No	R	R_1	X	Yield (%)	M.P (^{o} C) Observed	M.P (^{o} C) Reported
1.	H	OEt	O	96	202-203	(201-203)[40]
2.	4-OMe	OEt	O	93	201-203	(199-201)[40]
3.	3-NO_2	OEt	O	92	228-230	(230) [41]
4.	2-OH	OEt	O	85	200-202	(200-202) [42]
5.	4-OH	OEt	O	92	225-226	(226-228)[43]
6.	H	OEt	S	90	208-210	(210-212)[44]
7.	4-OMe	OEt	S	85	136-138	(137-139)[45]
8.	4-Cl	OEt	S	86	182-184	(180-182)[46]
9.	2-OH	OEt	S	81	188-190	(183-185)[47]
10.	2-Cl	OEt	S	90	202-204	(205-206)[48]

The structures of the products were confirmed by comparing their M.P. /B.P. and spectral data with authentic samples.

The mechanism of the reaction is depicted in scheme 2grape juice plays a complex role in accelerating the coupling reaction and thus promotes the formation of products (Scheme 2).



Scheme 2: A probable mechanism for the reaction\

IV. CONCLUSION

This is a convenient and facile one pot synthesis ofdihydropyrimidinone and thioneswith a greener approach for organic transformations, thus facilitating efficient synthesis of bioactive compounds in environmentally benign way with shorter reaction time, mild reaction conditions, easy workup,less expensive with excellent yield of the product.

V. ACKNOWLEDGEMENTS

Authors are thankful to MCE Society Pune-411001 for financial assistance.

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