



REVIEW OF RESEARCH

ISSN: 2249-894X

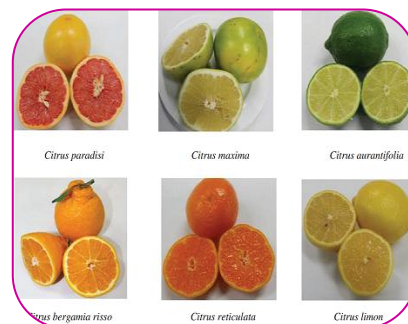
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A SIMPLE, EFFICIENT AND GREEN PROTOCOL FOR KNOEVENAGEL CONDENSATION REACTION BY USING CITRUS MAXIMA (POMELO) FRUIT JUICE

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ABSTRACT:-

A simple, mild and environment-friendly procedure has been developed for Knoevenagel condensation between aromatic aldehydes and malononitrile in the presence of environmentally benign catalyst Citrus Maxima (Pomelo) Fruit Juice at room temperature with stirring. The products are obtained in excellent yields and are in a state of high purity.

KEY WORDS: Green Protocol for Knoevenagel condensation reaction, fruit juice

INTRODUCTION:

The condensation of aldehydes or ketones, usually possessing α -hydrogen, with compounds of the form $Z-CH_2-Z'$ or $Z-CH_2-Z$ where Z and Z' are electron withdrawing groups is called the Knoevenagel reaction [1]. Knoevenagel condensation is a classic reaction in organic synthesis [2], for its significant synthetic utility in C-C bond formation reactions, which is pivotal in organic chemistry [3]. Knoevenagel condensation has numerous applications in the elegant synthesis of the fine chemicals, speciality chemicals, drugs, dyes etc. [4].

Knoevenagel condensation is base catalyzed reaction and sometimes reported in acid catalysis. In literature, the most of the synthetic protocols are being described in basic catalysts and organic/ aqueous medium. Various catalysts are known to effect the Knoevenagel condensation reactions using NaOH, KOH, $AlPO_4-Al_2O_3$ [5], $BiCl_3$ [6], $ZnCl_2$ [7] etc. Several other methods include P_2O_5 -piperidine [8-9], modified hydrotalcite [10], $KF-Al_2O_3$ [11], graphite [12], IR irradiation [13] and solvent free reactions using mechanochemical grinding, ball milling, MWI and ultrasound sonication irradiation.

One of the important catalyst in Knoevenagel condensation is 1, 8 Diazabicyclo (5, 4, 0) undecene-7 or DBU. DBU is a bicyclic amine which is a clear light yellow liquid of relatively low volatility. DBU has been widely used as a catalyst in many reactions such as Michael addition reaction of β -ketoesters to acrylates and enones [14], conjugate addition of acylsilanes to unsaturated esters and ketones [15], for intramolecular aldehyde-ketone benzoin reactions [16] and in combination with other catalysts for oxidation of aldehydes to methyl esters [17]. Mechanochemical grinding and ball milling are useful tools in organic synthesis that allows a highly efficient mixing of reagents under solvent free conditions [18, 19]. In organic chemistry it found numerous applications including C-C bond formations [20], amine condensations, in syntheses of

heterocycles [21] and fullerene modifications [22]. In grinding, efficient mixing is particularly important in solid-solid reactions which continuously develop fresh contacts between the reacting components. Grinding and ball milling, in particular, milling generates new contact sites between the solids more efficiently. Due to high reagent concentrations and the efficient mixing, the reactions between solids with intermediate local melting and those with at least one liquid reagent gets benefited from such techniques.

In chemical synthesis, these tools modify the reaction conditions and enhance the reactivity of the reagents (mechanical activation). This is due to induced mechanical breaking of molecular bonds (mechanochemistry) and efficient mixing and the enormous increase of the reagent surfaces which both lead to a close contact between starting components on an almost molecular scale. Besides this, the factors like temperature and pressure have a significant role for such change in reactivities of the components. For example, during the milling, extreme conditions occur on the surfaces of two colliding bodies for times in the order of microseconds. According to a model developed by Urakaev and Boldyrev, local temperatures of 400-1500 K and pressures of thousand atmospheres can be part of typical conditions in the ball mill [23].

Background Of The Work:

Condensation reactions of aldehydes with active methylene compounds in organic chemistry are well explored and thoroughly studied but in pyrazole chemistry the reaction is not exploited as such. In case of pyrazole, 4-formyl pyrazole was condensed with few active methylene compounds. Hangargeet *al.* [24] have carried out the reaction of 4-formyl pyrazoles with 3-methyl-1-phenyl pyrazolin-5-(4*H*)-one in Dioxane by using basic hydrotalcite at room temperature. Shindalkar and co-workers [25] reported the same reaction using heterogeneous borate-zirconia catalyst. (Scheme 3.25) Shingareet *al.* [26] have reported the Knoevenagel condensation of 4-formyl pyrazoles with 1, 2-dihydro-3-methyl-1-phenylpyrazol-5-one. (Scheme 3.26) DBU catalyzed Knoevenagel condensation has been described by Ware and coworkers [27] by reacting aromatic aldehydes and active methylene compounds like cyanoethylacetate, cyanoacetamide and malononitrile. A range of novel pyrazole derivatives has been prepared in moderate to good yield from substituted formyl pyrazole by Knoevenagel condensation with acylglycine, benzamidine hydrochloride, malononitrile and giving different products. [28]

Many chemical processes employ large amounts of hazardous and toxic solvents. The choice of pursuing aqueous reactions is becoming more important and urgent than ever before, due to its environmental impact and cost of chemical processes. Organic reactions under solvent-free [29,30] and aqueous [31-33] conditions have increasingly attracted chemists' interests, particularly from the view point of green chemistry. [34] Knoevenagel condensation of malonic acid and carbonyl compounds is an important route for substituted α , β -unsaturated acids and the method of choice particularly for cinnamic acids is through Doebner modification. [35,36] This involves heating of aromatic aldehydes and malonic acid in the presence of excess of basic solvents like pyridine and piperidine to facilitate easy decarboxylation of initially generated α , β -unsaturated malonic acids which afford cinnamic acids. There has been a number of reports [37] on the condensation of carbonyl substrates with a variety of active methylene compounds using inorganic catalysts, traditional bases both under conventional as well as microwave heating conditions. Very few Knoevenagel condensations using water as solvent have been reported. [38,39] However, no reaction utilizing water as solvent has been reported for the synthesis of cinnamic acids.

GREEN CHEMISTRY:

Among the challenges for chemists include discovery and development of novel and simple environmentally safe chemical processes for selective synthesis by identifying alternative reaction conditions and solvents for much improved selectivity, energy conservation and less or no toxic waste generation and inherently safer chemical products. Therefore, to address depletion of natural resources and preservation of ecosystem it is just urgent to adopt so called "greener technologies" to make chemical agents for wellbeing of human health. Schiff's bases are reported to show characteristic biological activities including

antibacterial, antifungal, anticancer and herbicidal properties [40-45]. Other application of Schiff's bases includes industrial synthesis of high value lifesaving beta lactam [46] antibiotics from class of penicillins and cephalosporins. In recent years, environmentally benign synthetic methods have received considerable attention. Vermaet *al.*[47] reported synthesis of enamines and imines under microwave irradiation accompanied with solvent less conditions. Kaupet *a.*[48] reported the synthesis of Schiff bases using water as a solvent. In continuation of our ongoing program [49,50] towards ecofriendly green synthesis, it was thought worthwhile to synthesize Schiff bases utilizing greener methodologies.

Green chemistry, also called sustainable chemistry, is a philosophy of chemical research and engineering that encourages the design of products and processes that minimize the use and generation of hazardous substances [51], green chemistry seeks to reduce and prevent pollution at its source. In 1990 the Pollution Prevention Act was passed in the United States. This act helped create a *modus operandi* for dealing with pollution in an original and innovative way. It aims to avoid problems before they happen. As a chemical philosophy, green chemistry applies to [organic chemistry](#), [inorganic chemistry](#), [biochemistry](#), [analytical chemistry](#), and even [physical chemistry](#). While green chemistry seems to focus on industrial applications, it does apply to any chemistry choice. In 2005 [Ryōji Noyori](#) identified three key developments in green chemistry: use of [supercritical carbon dioxide](#) as green solvent, [aqueous hydrogen peroxide](#) for clean [oxidations](#) and the use of hydrogen in [asymmetric synthesis](#). [52].

CITRUS MAXIMA (POMELO)

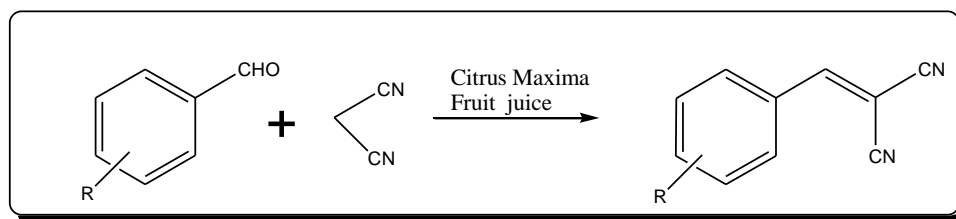
The *Citrus maxima* (pomelo) is the largest citrus fruit from the Rutaceae family. It is a natural (non-hybrid) citrus fruit, similar in appearance to a large grapefruit & it is commonly found in region.



Raw juice of this fruit is used as catalyst in the present reaction as it is found to be acidic in pH (pH = 3.3 Fresh Juice). It substituted the conventionally used hazardous chemical catalysts.

EXPERIMENTAL:

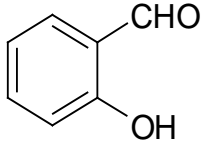
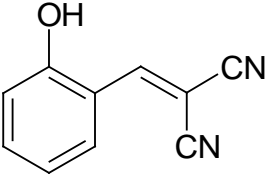
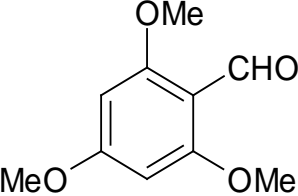
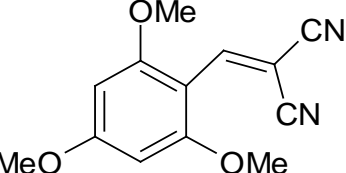
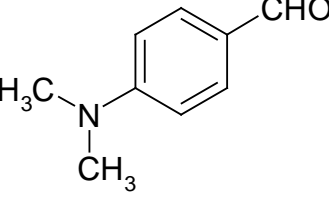
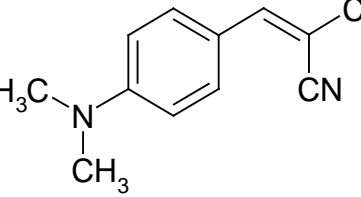
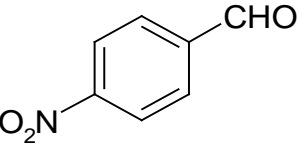
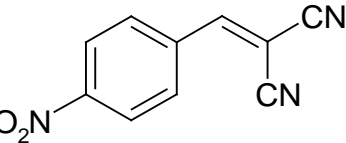
For the present work, we used the extract of *Citrus maxima* (pomelo) as a natural catalyst. As citrus maxoma fruit juice is acidic in nature (pH about 3–4), it will be worked as acid catalyst for condensation. After completion of reaction all the products obtained were characterized by matching physical and spectral data with those of reported in the literature. The progresses of reactions were monitored by Thin Layer Chromatography (TLC plates) purchased from Merck in which a layer of 0.2mm silica gel was coated on Aluminum foil. The melting points of the synthesized products were recorded in an open capillary and are uncorrected.

General Procedure for the Synthesis of Substituted phenyl methylene malononitrile:**Scheme 1**

Equimolar mixture of substituted aromatic aldehydes and malononitrile was thoroughly mixed with 1 ml of citrus maxima fruit juice formerly drawn out from the fresh citrus maxima fruits available in konkan region. The reaction mixture further stirred at room temperature for an appropriate time period for the completion of reaction. After the complete conversion of reactants to products as confirmed by Thin Layer Chromatography, the reaction mixture was then suspended in cold water and stirred for a while. Thus, obtained solid product was filtered on suction and washed with distilled water, dried under IR lamp and then recrystallized from absolute alcohol.

Physico-chemical data of the synthesized compounds:

Sr. No	Aldehyde (R=)	Structure of the product	Melting Point	Colour of Product	% Yield
1			84	Light brown Crystals	91
2			158	Colourless Solid	72
3			118	Yellow Crystals	61
4			128	Yellow Crystals	55
5				White Crystals	95
6			188	Yellow Crystals	79

7			160	Yellow Crystals	89
8				Yellow Crystals	76
9			180	Orange Crystals	65
10				Yellow Crystals	86

RESULTS AND DISCUSSION:-

We herein report a Knoevenagel condensation of aromatic aldehydes with malononitrile using a catalytic amount of citrus maxima (pomelo) fruit juice under solvent-free conditions. In addition to its simplicity, this catalyst resulted in better yields for the products (Table 1) in the Knoevenagel condensation. A stoichiometric amount of catalyst was sufficient to obtain good yields.

The synthesis of p-methoxyphenylmethylenemalononitrile (3) is described as a representative example: A mixture of 10 mmol (1.36 g) of p-methoxybenzaldehyde, 10 mmol (0.66 g) of malononitrile, and 1 ml citrus maxima fruit juice was stirred at room temperature. Reaction is monitored by thin-layer chromatography (TLC). Then the reaction mixture was filtered, and the pure yellow crystalline product was recovered by crystallization with ethanol. Its identity was confirmed by infrared (IR) spectrum (Fig. 1), NMR spectrum (Fig. 2),

Figure-1

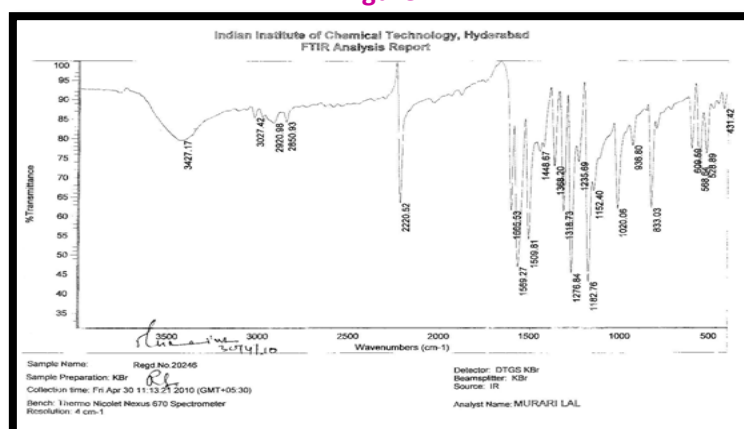
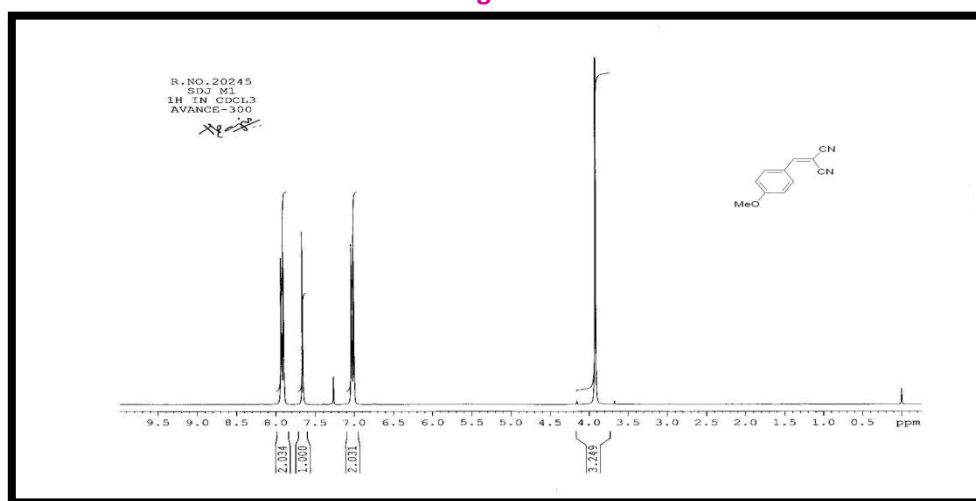


Figure-2



CONCLUSIONS:

In conclusion, we have developed a rapid, economic and environment-friendly method for the synthesis of Substituted phenyl methylene malanonitrile by Knoevenagel condensation between substituted aromatic aldehydes and malononitrile in the presence of citrus maxima (pomelo) fruit juice. The main advantage of our method is that it is general and also no organic solvent or reagent was used throughout the reaction.

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