LEMON JUICE: EFFICIENT AND ECO-FRIENDLY NATURAL CATALYST FOR ONE POT MULTICOMPONENT SYNTHESIS

Submitted in partial fulfilment of the requirements for the degree of

Bachelor of Pharmacy

BY

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CERTIFICATE

This is to certify that the project entitled **LEMON JUICE: EFFICIENT AND ECO-FRIENDLY NATURAL CATALYST FOR ONE POT MULTICOMPONENT SYNTHESIS** is a bonafide work of SHAIKH ZARRIN BANU MOHAMMED ARIF (17PH57), KHAN HANA TABASSUM ABUL WAFA (17PH21), KHAN MUSHAHIDUL ISLAM (16PH34), AND SHAIKH MOHD ZISHAN NASIR (17PH48) submitted for the appreciation of the degree of Bachelor of Pharmacy in Department of Pharmaceutical Chemistry.

Dean **Director**

APPROVAL FOR BACHELOR OF PHARMACY

This project entitled **LEMON JUICE: EFFICIENT AND ECO-FRIENDLY NATURAL CATALYST FOR ONE POT MULTICOMPONENT SYNTHESIS** by SHAIKH ZARRIN BANU MOHAMMED ARIF (17PH57), KHAN HANA TABASSUM (17PH21), KHAN MUSHAHIDUL ISLAM (16PH34), SHAIKH MOHD ZISHAN NASIR (17PH48) is approved for the degree of Bachelor of Pharmacy in Department of PHARMACEUTICAL CHEMISTRY.

Examiners:

Supervisors:

DECLARATION

I declare that this written submission represents my ideas in my own words and where others ideas or words have been included, I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falcified any idea /data/fact/source in my submission. I understand that any violation of the above will be cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed

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ABSTRACT

Citric acid present in lemon juice is used as natural acid catalyst for one pot synthesis of various heterocyclic compounds with formation of products in high yield.Among other fruit extract lemon juice is given top priority for one pot multicomponent synthesis due to feature such as non toxic inexpensive, easily available, biodegradable.The catalyst is many organic reaction reflectors the importance and High expectation in kofield of research.Citric acid plays an important role as biocatalyst in the synthesis of key intermediate for the pharmaceutical and chemical industry.

A multicomponent reaction (MCR) is a convergent reaction in which three or more starting material react to form a single product , where essentially all or modt of the aton contribute to the newly formed product.In recent years multicomponent reaction had gain much importance in organic synthesis, since they produced the desired product in single operation without isolating the intermediate.The advantages of MCRs are one pot reactions consume very less amount of solvent or no solvent, superior atom economy, generally takes less time compared to divergent reaction,lower cost, simple procedure and environment friendly.

KEYWORDS

One pot synthesis; lemon juice; biocatalyst; citric acid.

INTRODUCTION

The chemical industry is vitally important to world economy; however, the success of industry has led to some environmental dmage and low public perception of industry. In order to prevent further environmental damage and to encourage more young people in to the industry the public acceptability needs to be raised by adoption of greener and cleaner processes bd green product design [1-3].

Organic solvent and metal catalyst used in organic synthesis are hazardous, toxic and often costly. Biocatalyst in various organic reaction, the aqueous extract of fruit juices has gain sustainable attention from synthetic organic chemist, beside their harmless and eco-friendly behaviour, these fruit juices are also safe, cheap, can be accessed effortlessly [4].

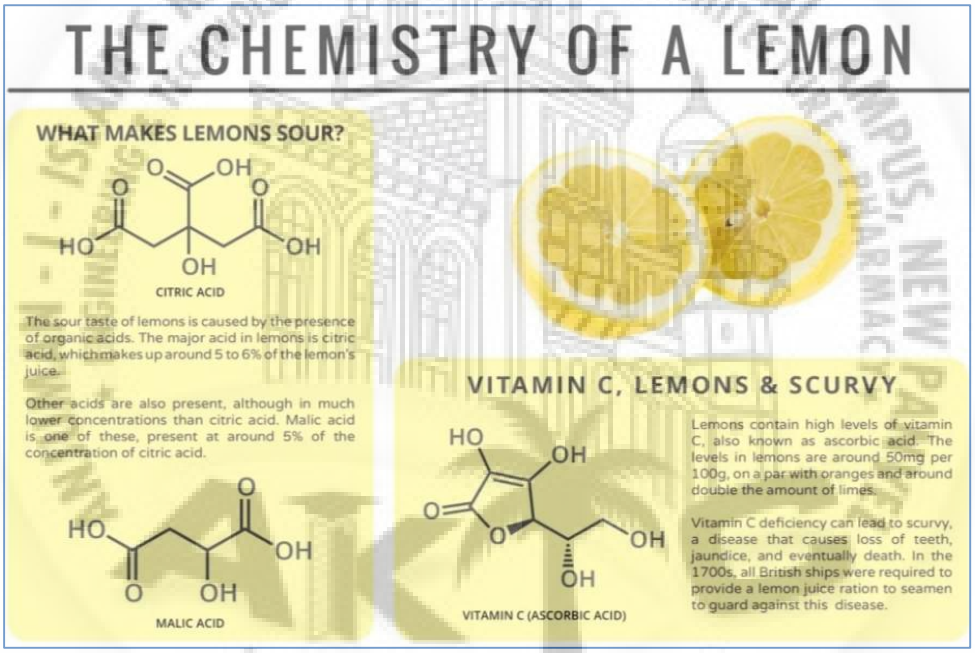


Figure 1: The Chemistry of a lemon.

Through many fruits juices application in chemical transformation have been documented until recently it is desirable to devote efforts to explore full potentials, utility and value of these class of biocatalyst "**Moreover the systemic study on the use of biocatalyst was lacking".**

While lemon juice has been used as a biocatalyst in synthesis of simple heterocyclic compounds earlier but its use in Synthesis of current series of compound under ultrasound irradiation was not known.

One pot rection have gained considerable importance due tontheir ability to generate, complex molecule from simple starting material in one step reaction, multicomponent reaction generates worthy complex structure by assembling atleast 3 adducts in one pot fashion.

The fruit juice is employed in to execute the multicomponent organic reaction due to it's catalytic properties. One of them is lemon juice which contain citric acid, ascorbic acid, having pH in acidic range.

Lemon juice is used in treatment of asthma and rheumatism, cancer prevention, high blood pressure, prevent kidney stones etc [5-8].

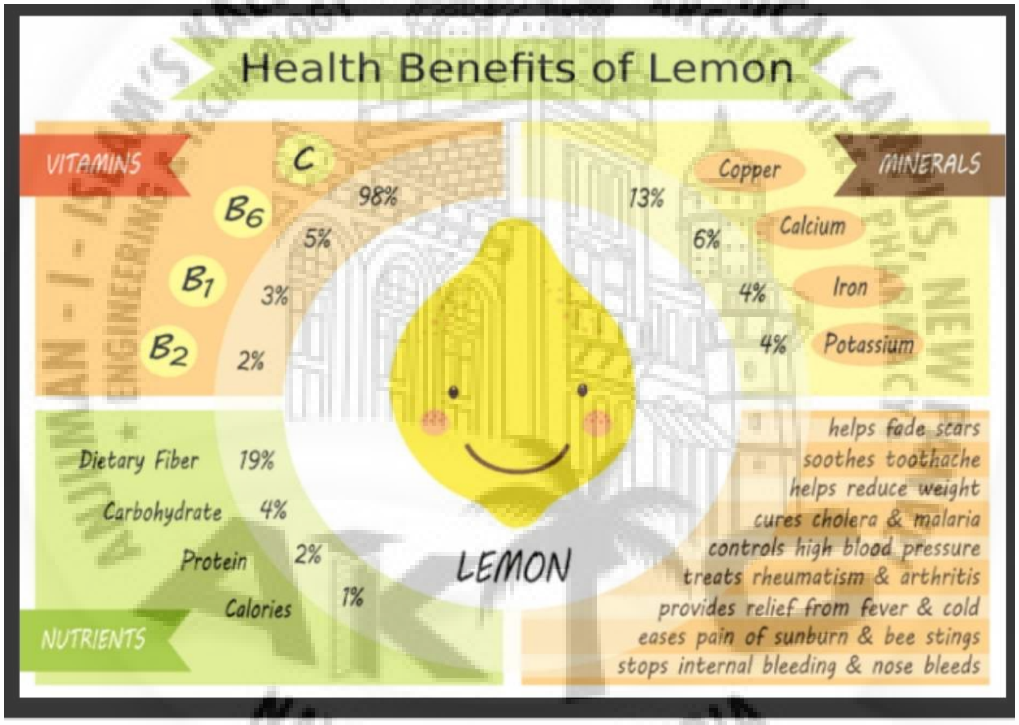


Figure 2: Health benefits of lemon.

The citrus lemon juice has properties such as antioxidant, antimicrobial, pharmacological, anti -inflammatory, anti-cancer, anti-allergic, cardiovascular protection, neuro protective and hepato protective.

Nowadays lemon juice is used extensively as a natural catalyst due to it's acidic nature still there is scope to exploit it's catalytic potential in synthesis of large number of medicinally important scaffold.[9]

PROPERTIES OF LEMON JUICE

Lemon juice is a weak organic acid, when heated the carbon compound breaks, which then produces black/brown color. The compound reacts with air undergoing oxidation. Another explanation is that the acid weakens the paper ,fibres,which causes the weak part to burn first [10].

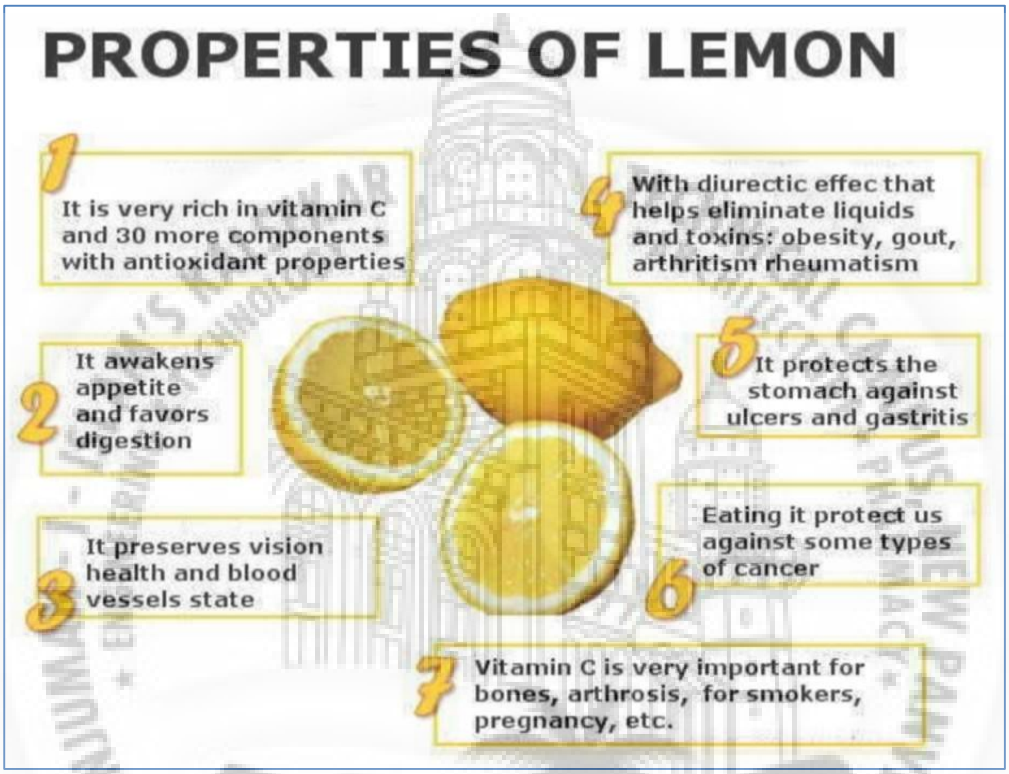


Figure 3: Properties of lemon.

PREPARATION OF CATALYST

Fresh lemon we taken and washed it thoroughly with water and cut by using a knife and then pieces where pressed manually. Then, the juice was filtered through muslin cloth to remove solid material and to get clear juice which was used as a catalyst [11].

Figure 4: Preparation of lemon juice as catalyst.

Citric acid and ascorbic acid work as an acid catalyst for organic transformation. A number of organic transformation have been carried out using lemon juices and this have proved to be useful for the preparation of heterocyclic compounds such as coumarins, dihydropyrimidinones, imidazoles, benzimidazole and isoxazoles [12-15].

OBJECTIVE

Green synthetic approach and development is one of the alternative to reduce the threat of climate change lies at doorstep of our planet.

Citrus limonium, citrus aurantum, citrus indica are important species of Citrus family locally known as 'limbu' or 'nimbu' in India, The lemon is a small evergreen tree and the tree's ellipsoidal yellow fruit. The lemon is indigenous to the north-west region of India. It is now widely grown in all tropical and subtropical countries. In India it is also cultivated in home garden. Lemon juice obtained from lemon is sour In taste. The use of lemon juice, pulp and zest in our day-to-day life can not be understand [16-17].

The juice obtained from lemon have received more priority because of it's selectivity, reactivity and minimum waste.

Lemon juice is composed of following ingredients which is responsible it's catalytic activity [19-20]:

- Moisture (85%)
- Carbohydrates (11.2%)
- Citric acid (5-7%)
- Ascorbic acid (0.5%)
- And some other organic acid

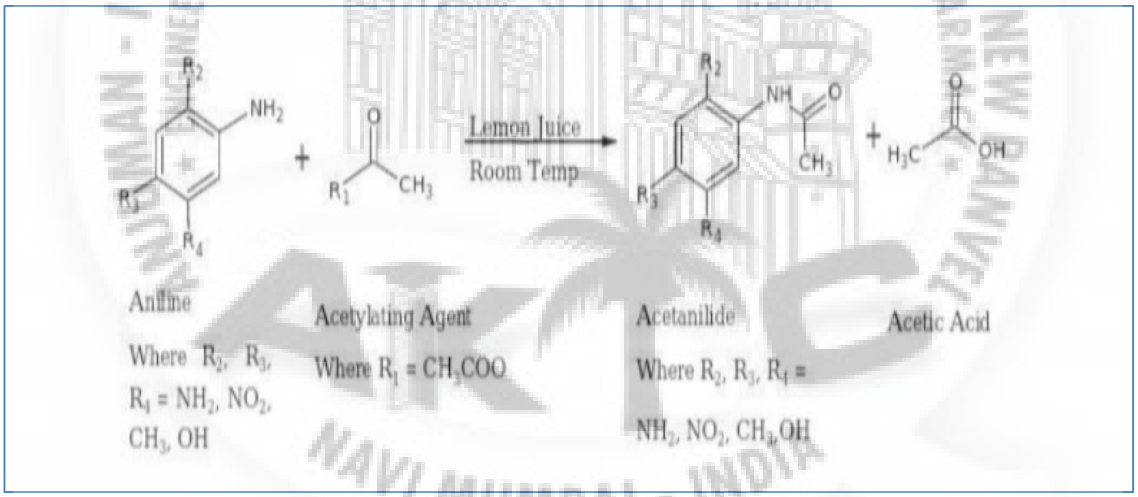
LITERATURE

In continuation of our research work for the development of sustainable methodologies for the synthesis of bioactive heterocyclic scaffolds. Herein, we report the synthesis of following compound by using lemon juice as natural, biodegradable catalyst under mild reaction condition.

a) Synthesis of phenyl acetamide

Aniline 1 mmol was added into 6 ml water containing 0.5ml lemon juice with constant stirring at room temperature. 2.5 ml of acetic anhydride was added dropwise to avoid the complete hydrolysis of acetic anhydride with constant stirring.

Citric cid present in lemon juice act as weak water-soluble catalyst when it comes in contact with amine and acetic anhydride, it leads to formation of acetanilide. Presence of electron donating group give product of high yield in less time [21,22].

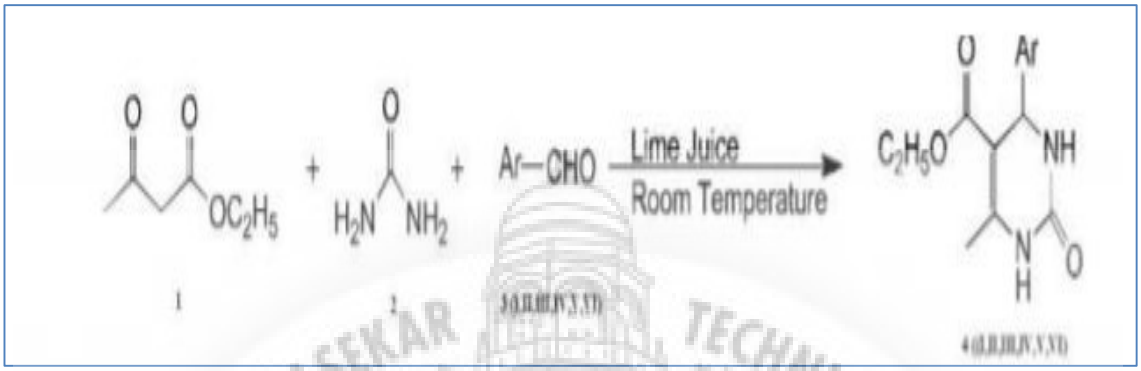


Reaction 1: One-Pot Synthesis of Phenyl acetamide.

b) Synthesis of dihydropyridines

An equimolar mixture of urea and ethyl acetoacetate was employed to react individually with benzaldehyde to synthesize dihydropyridines. The citric acid present in lemon juice act as

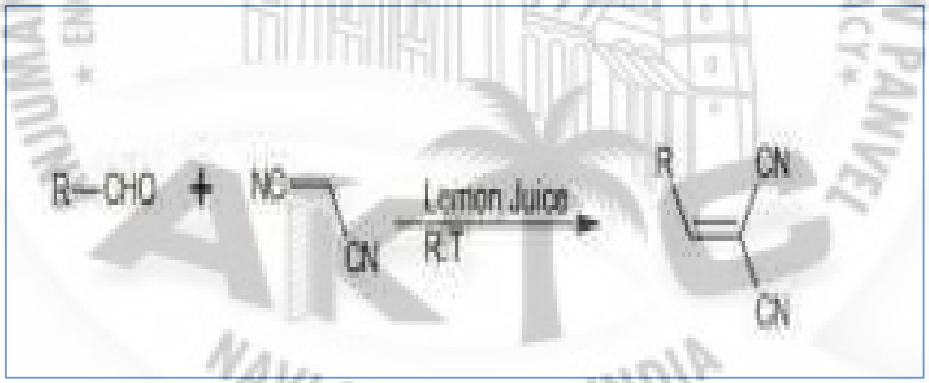
solvent cum acid catalyst for our Biginelli reaction. It took about 12 hours to complete the reaction at Room temperature.Electron rich aromatic aldehyde needs longer time for completion as compared to electron deficient aromatic aldehyde in fruit juice at R.T [23,24].



Reaction 2: One-Pot Synthesis of Dihydropyridines.

c) Knoevenagel condensation of aromatic aldehyde and malanonitrile

The reaction of aromatic aldehyde and malanonitrile using lemon juice as natural catalyst gave product with high yield. Here lemon juice act as environmentally benign acid catalyst for the reaction between aldehyde and malanonitrile [25, 26].



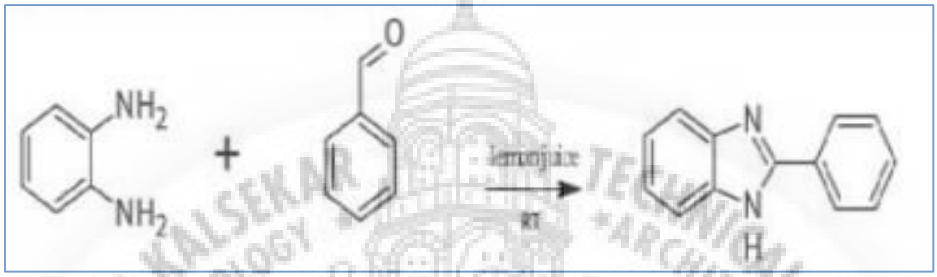
Reaction 3: Knoevenagel condensation of aromatic aldehyde and malanonitrile.

d) Synthesis of benzimidazole

A mixture of o- phenylenediamine (1mmol), araldehyde(1mmol) and lemon juice (1-2ml) were stirred and grind in mortor and pestle which was followed by TLC.Water (20ml) was added

after the completion of reaction. The product so obtained was filtered, washed with hot water and then recrystallised.

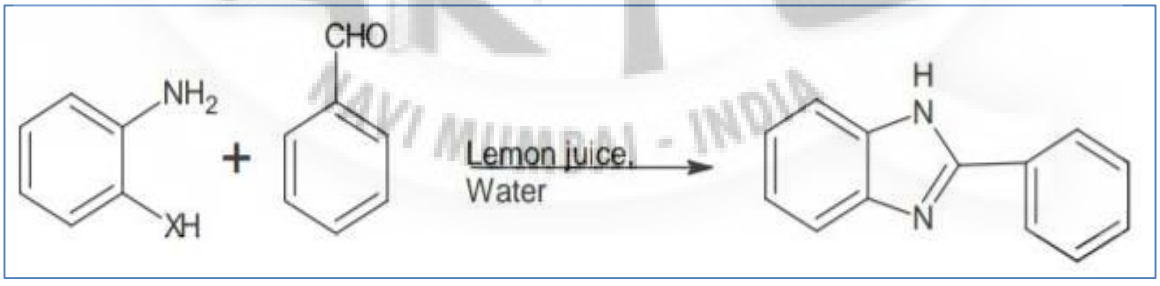
Here lemon juice is employed as mild, efficient catalyst and antioxidant for the preparation of benzimidazole in excellent yield [27, 28].



Reaction 4: Synthesis of benzimidazole.

e) Synthesis of benzazoles

Patil et al reported the multicomponent synthesis of substituted benzothiazole and benzazoles derivatives using lemon juice in water by the reaction of 2-aminothiophenol or 2-aminophenol aryl aldehyde and lemon water mixture (1:1) was added in reaction vessel. They found that lemon juice plays a role of biocatalyst which provides non hazardous and mild conditions which are basic principle of green chemistry [29, 30].

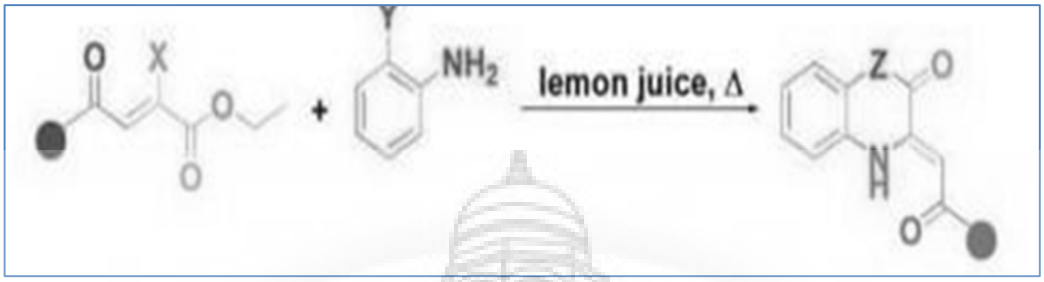


Reaction 5: Synthesis of benzazoles.

f) Synthesis of quinoxalines

Petronijevic et al (2017) reported eco-friendly and clean one pot synthesis of 3,4-dihydro-2(1H)-quinoxalinones and 3,4-dihydro-1,4-benzoxazine-2-ones.Lemin juice (citrus limonium)

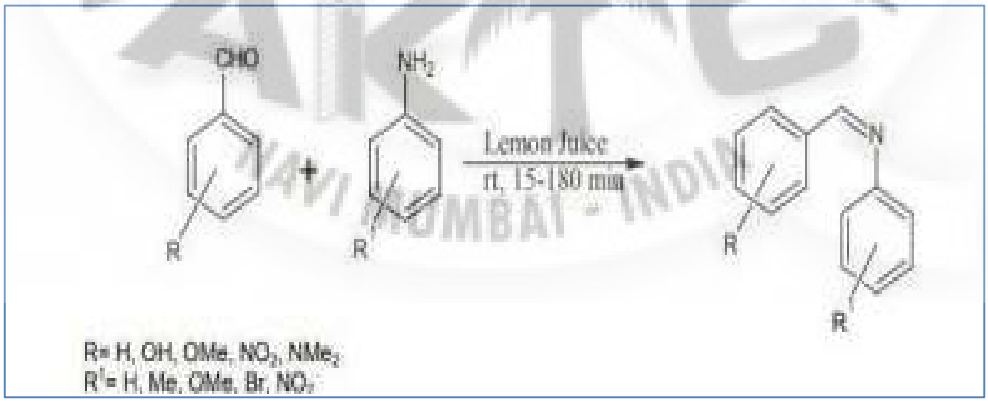
acts as an alternative to toxic solvents and catalyst.The reaction proceeds by substituted ester keto ester and substituted amines with lemon juice and reflux for 24h.After simple work up the newly synthesized products were isolated [31-33].



Reaction 6: Synthesis of quinoxalines.

g) Synthesis of Schiff base

Schiff base plays an important role in synthesis of large number of industrial and biologically active compound.Synthesis of Schiff base is often carried out with acid catalyst and generally by refluxing the mixture of aldehyde or ketone and amine in organic medium.It was observed that the incorporation of more than one heterocyclic moeity into a single framework may result in the production of novel heterocycles with enhanced bioactivity.Schiff base was synthesized by incorporating these moeties and the synthesized product was found to have anti fungal,anti bacterial and cytotoxic property.This method proves to be cost effective since there is elimination of acidic waste [34-37].



Reaction 7: Synthesis of Schiff base.

h) Synthesis of triazole derivatives

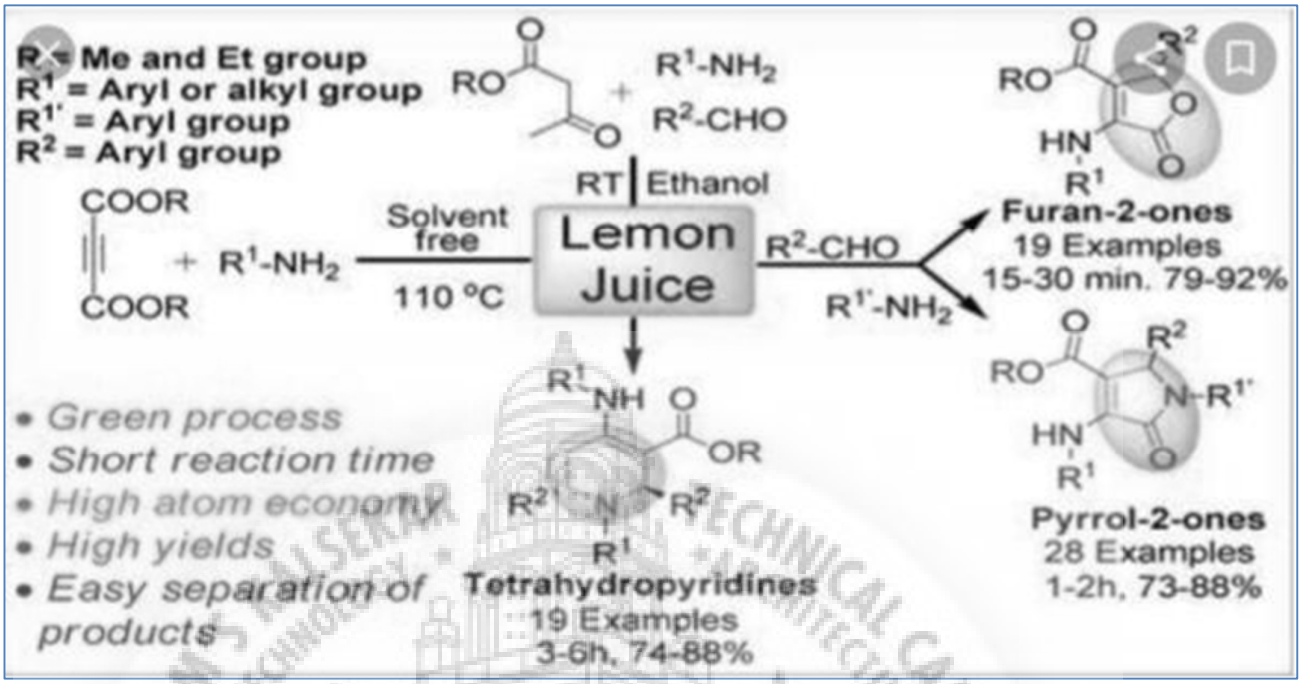
Three component one pot clean biocyclocondensation reaction was reported by reacting 4-chloro-2-nitroaniline and aromatic aldehyde with thiosemicarbazide [38].

Reaction 8: Synthesis of triazole derivatives.

Here the citric acid present in lemon juice acts as acid catalyst for the synthesis of triazole derivatives. The use of water as green solvent and lemon juice as natural catalyst provided convenient approach for the synthesis.The formed product was found to have anti fungal property.

i) Synthesis of furan-2-ones, pyrrol-2-ones and tetrahydrpyridines

New and facile one pot approach for the synthesis of polysubstituted pyrrol2-one, furan-2-one and tetrahydrpyridines from easily available starting material using lemon juice as green catalyst is presented. The synthesis of furan-2-ones and pyrrol-2-ones derivatives were achieved from dialkyl acetylene carboxylate, different aldehyde and amine in high yield and short reaction times by employing 0.25 ml of lemon juice at 110 degree Celsius under solvent free condition [39].



Reaction 9: Synthesis of furan-2-ones, pyrrol-2-ones and tetrahydropyridines.

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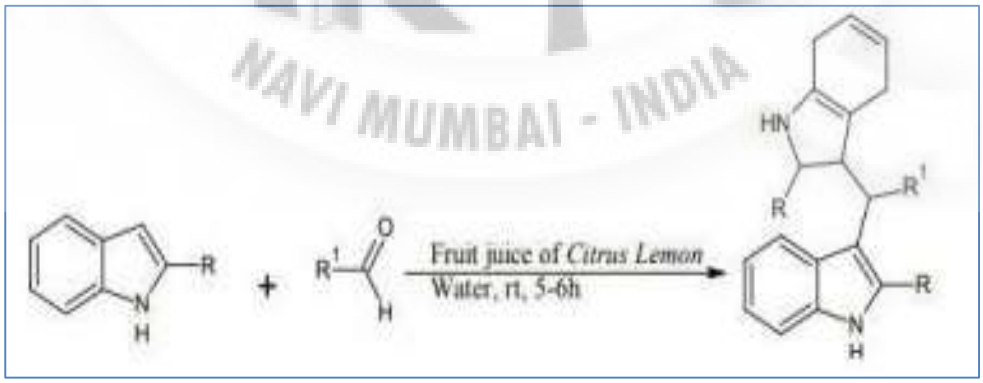
j) Synthesis of bis, tris indoyl methane

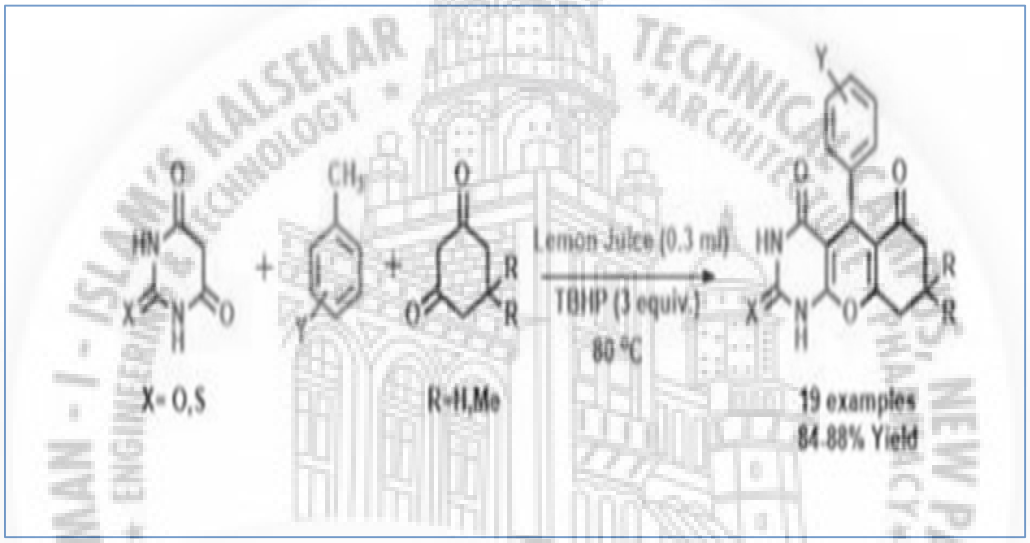
Pal et al reported the biocondensation of indoles and aldehyde for the synthesis of bis, tris(indoyl) methane. This reaction proceeds indoles and aldehyde were treated in lemon juice (citrus limonium) mixture at pH 3 in stirring at room temperature for 5-6 hours.This method is suitable in term of short reaction time, reaction procedure is very simple and better yeild was obtained [40].



Reaction 9: Synthesis of bis, tris indoyl methane.

k) Synthesis of chromenopyrimidine derivatives

Chromenes are very important structural moeity found in a variety of natural products like anthocyanins,tocopherols, alkaloids flavonoids and biologically active molecules.Previously, chromenopyrimidine have been produced by multicomponent reaction of barbituric acid ,1,3 cyclohexane Dione and aromatic aldehyde using various catalyst.This was found to be expensive.Now chromenopyrimidine is synthesized using lemon juice as catalyst via C-H activation of methylarenes by using tert- butyl hydroperoxide (TBHP,70%in H_2O)as an oxidant [41].



Reaction 10: Synthesis of chromenopyrimidine derivatives.

CONCLUSION

The lemon juice was found to be safe, effective, biodegradable natural catalyst for synthesis of various heterocyclic compounds with several advantages such as mild reaction condition, product with high yield in less time, simple experimental setup. The reaction catalyzed by lemon juice avoid risk of hazardous metals. Therefore, there is immense expectancy for the application of lemon juice as efficient catalyst for one pot synthesis

FUTURE PROSPECTS

Use of environmentally friendly catalyst for synthetic methodology is very essential.Lemon juice is easily available and environmentally friendly catalyst.Recently many reactions have been reported showing good utility of lemon juice as greener and eco friendly catalyst.Various biologically important heterocyclic compounds can be synthesized using lemon juice as catalyst and solvent.Therefore ,there is an immense prospect for future sustainable application of lemon juice in the field of catalysis and synthetic organic chemistry.

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