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Research Article

Eco-Friendly Synthesis of Pyrazoline Derivatives

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ABSTRACT

Pyrazoline class of compounds serve as better moieties for an array of treatments, they have antibacterial, antifungal, anti-inflammatory, antipyretic, diuretic, cardiovascular activities. Apart from these they also have anticancer activities. So, pertaining to its importance, many attempts are made to synthesize pyrazolines. Since conventional methods of organic synthesis are energy and time consuming. There are elaborate pathways for green and eco-friendly synthesis of pyrazoline derivatives including microwave irradiation, ultrasonic irradiation, grinding and use of ionic liquids which assures the synthesis of the same within much lesser time and by use of minimal energy.

Keywords: Green synthesis, Chalcone, Pyrazoline, Microwave Irradiation, Ultrasonic Irradiation, Grinding Method, Ionic Liquids.

INTRODUCTION

The Pyrazolines[1] (figure 1) are basic in nature, having two adjucent nitrogen atoms within the five membered heterocyclic ring molecules and has only one endocyclic double bond[1, 2]. Chalcones, α, β-unsaturated carbonyls, play a crucial role in many biological processes as well as are well-known intermediates for synthesizing various heterocycles[2] and bear a very good synthon so that variety of novel heterocycles with good pharmaceutical profile can be designed[3]. Presence of enone functionality in chalcone shows the antibiotic activity.

Pyrazoline which is derivative of chalcone has also been reported to show a broad spectrum of potential pharmacological activities[4] including antibacterial[5], antifungal[6], anti-inflammatory[7], analgesic[8], antipyretic[9], insecticidal[10], diuretic[11], cardiovascular[12] and antidepressant[13] and present in a number of pharmacologically active molecules such as phenazone/ amidopyrene/ methampyrone (analgesic and antipyretic), azolid/ tandearil (anti-inflammatory), indoxacarb (insecticide) and anturane (uricosuric). Changes in its substitutents have offered a high degree of diversity that has proven useful for the development of new therapeutic agents having improved potency and lesser toxicity[14]. Various researchers have synthesized and evaluated the pyrazoline derivatives. A popular conventional synthetic route for pyrazoline synthesis is based upon use of corrosive reagents which are harmful for nature.

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[15]. Numerous solvent assisted and solvent-free methods have been reported for the preparation of pyrazoline derivatives. The present article elaborates on various green techniques reported previously for synthesis of pyrazoline derivatives, which will be useful for researchers for synthesizing pyrazoline derivatives in less time, yield effective and safely.

Green Synthesis of Pyrazoline Derivatives

"The design of chemical products and processes that are more environmentally benign and reduce negative impacts to human health and the environment"[16]. There are various green techniques available in the literature for synthesis of pyrazoline derivatives.

Some green methods for organic synthesis of pyrazolines[1-33] :

Microwave Irradiation
Ultrasonic Irradiation
Grinding Technique
Ionic liquids

Microwave Irradiation

Microwave, which consists of electric and magnetic field, acts as a non-ionising reaction that causes ionic motions and rotations, but there is no change in molecular structure. Atleast one liquid polar is required in microwave synthesis[17]. Polar mechanism shows the microwave effect that when polarity is increased from ground state towards the transition state during the reaction[18]. Reaction

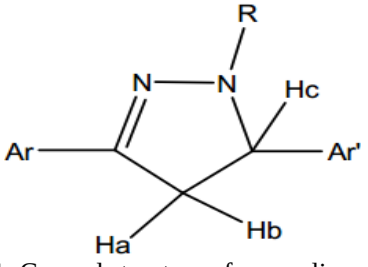

Figure 1: General structure of pyrazolines

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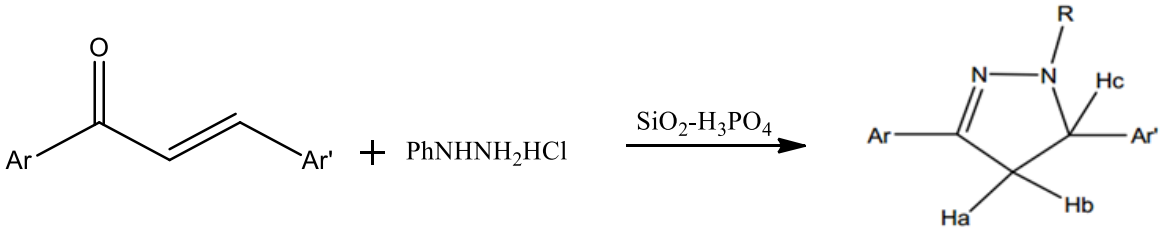

Figure 2: Synthesis of pyrazolines by microwave irradiation.

Table 1: Comparision Points between Conventional Method and Green Method [1-33]

Methods → / Parameters ↓	Conventional Method	Microwave Assisted Synthesis	Ultrasonic Technique Synthesis	Griding Technique	Synthesis by using Ionic Liquid
Temperature	The highest temperature (for a open vessels) that can be achieved is limited by boiling point of particular mixture	The temperature of mixture can be raised more than its boiling point i.e. superheating take place	Temperature is not required.	Temperature is not required.	The temperature of mixture is below 100ºC.
Reaction Rate	Reaction rate is less	Reaction rate is several fold high.	Reaction rate is lower than Microwave.	Reaction rate is lower than ultrasonic technique.	Reaction rate is slightly higher than conventional synthesis.
Reaction Time	Reaction time is much more about 5-20 h.	Reaction time is 5-10 min.	Reaction time is 2-5 h.	Reaction time is 5-30 h.	Reaction time is 5-12 h.
Source of energy	By thermal or electric source heating.	By electro-magnetic wave heating take place.	By sound energy (ultrasonic frequency >20 KHz)	By human energy.	By thermal or electric source heating.
Product Yield	50-60% yield	80-90% yield	Upto 90% yield	80-90% yield	80-90% yield

mechanism and medium is responsible for outcome. In case of stabilization dipole-dipole electrostatic interactions of transition state is more effective than that of ground state which enhances the reactivity by decrease in the activation energy[17]. Microwave irradiation technique is used for organic synthesis. This technique is accepted as a valuable tool for accelerating drug discovery and development processes[20].

SiO_2-H_3PO_4 as a catalyst

An appropriate equi-molar quantities of chalcones (2 mmol), phenyl hydrazine hydrochloride (2 mmol) and SiO_2-H_3PO_4 (0.5 g) is taken in borosil tube and tightly capped. The mixture is subjected to microwave irradiation for 6-8 min in a microwave oven and then cooled to room temperature. After separating the organic layer with dichloromethane the solid product is obtained on evaporation. The solid, on recrystallization from benzene-hexane mixture affords glittering product. The insoluble catalyst is recycled by washing with ethyl acetate (8 mL) followed by drying in an oven at 100°C for 1 h and reused for further reactions[1] (figure 2).

By various catalysts

Pyrazoline derivatives are synthesized by the reaction of thiosemicarbazide/ phenyl hydrazine/ hydrazine hydrate/ thiourea/ urea with 3-(3,4-dimethoxy-phenyl-1-(2,5-dimethyl-thiophen-3-yl)-propenone under microwave irradiation[2] (figure 3), which itself is derived from the reaction of 3-acetyl-2,5-dimethylthiophene with 3,4-dimethoxy benzaldehyde. The corresponding pyrazoline derivative is obtained in good to excellent yields[2].

By 1, 3-dipolar cycloaddition of N-crotonoyl- or N-cinnamoylsaccharin

Novel isoxazoline and pyrazoline derivatives of N-substituted saccharin are synthesized in good yields by 1,3-dipolar cycloaddition of N-crotonoyl- or N-cinnamoylsaccharin as dipolarophile to arylnitrile oxides or nitrile imines using p-hydroxyapatite 300 (p-HAP300) as catalyst under solvent-free microwave conditions. In this process, the yields are significantly improved compared to classical conditions without alteration of the selectivity[4].

Ultrasound Irradiation

Ultrasound waves are known for their wide applications in various fields like life sciences, medical, cleaning, sonar,

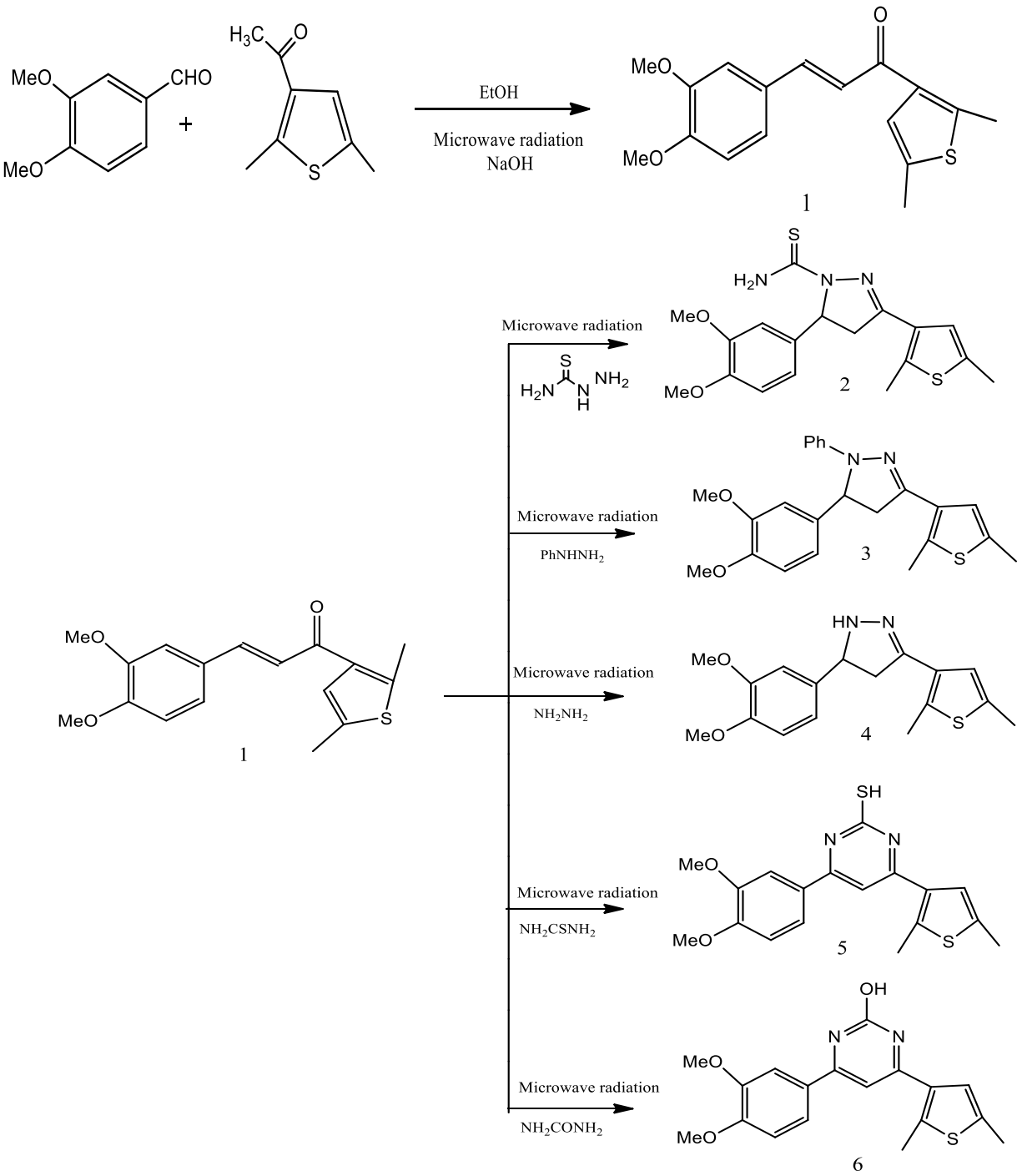

Figure 3: Various pyrazoline derivatives synthesized by microwave irradiation.

1. 3-(3,4-Dimethoxyphenyl)-1-(2,5-dimethylthiophen-3-yl)-prop-2-en-1-one
2. 5-(3,4-Dimethoxy-phenyl)-3-(2,5-dimethyl-thiophen-3-yl),-4,5-dihydro-pyrazole-1-carbothioicacid amide
3. 5-(3,4-dimethoxyphenyl)-3-(2,5-dimethylthiophen-3-yl)-1-phenyl-4,5-dihydro-1H-pyrazole
4. 5-(3,4-Dimethoxy-phenyl)-3-(2,5-dimethyl-thiophen-3-yl)-4,5-dihydro-1H-pyrazole
5. 4-(3,4-Dimethoxyphenyl)-6-(2,5-dimethylthiophen-3-yl)-pyrimidine-2-thiol
6. 4-(3,4-dimethoxyphenyl)-6-(2,5-dimethylthiophen-3-yl)pyrimidin-2-ol

electronics, agriculture, oceanography, material science etc.

Recently, ultrasound is utilized to accelerate a wide number of synthetically useful organic reactions. Further, these waves prove to be important in synthetic organic chemistry by lowering the reaction temperature and reaction time[14].

(E)-1,3-di(p-tolyl)prop-2-en-1-one is prepared by reaction of 4-methylacetophenone with 4-methylbenzaldehyde in dilute ethanolic sodium hydroxide solution under

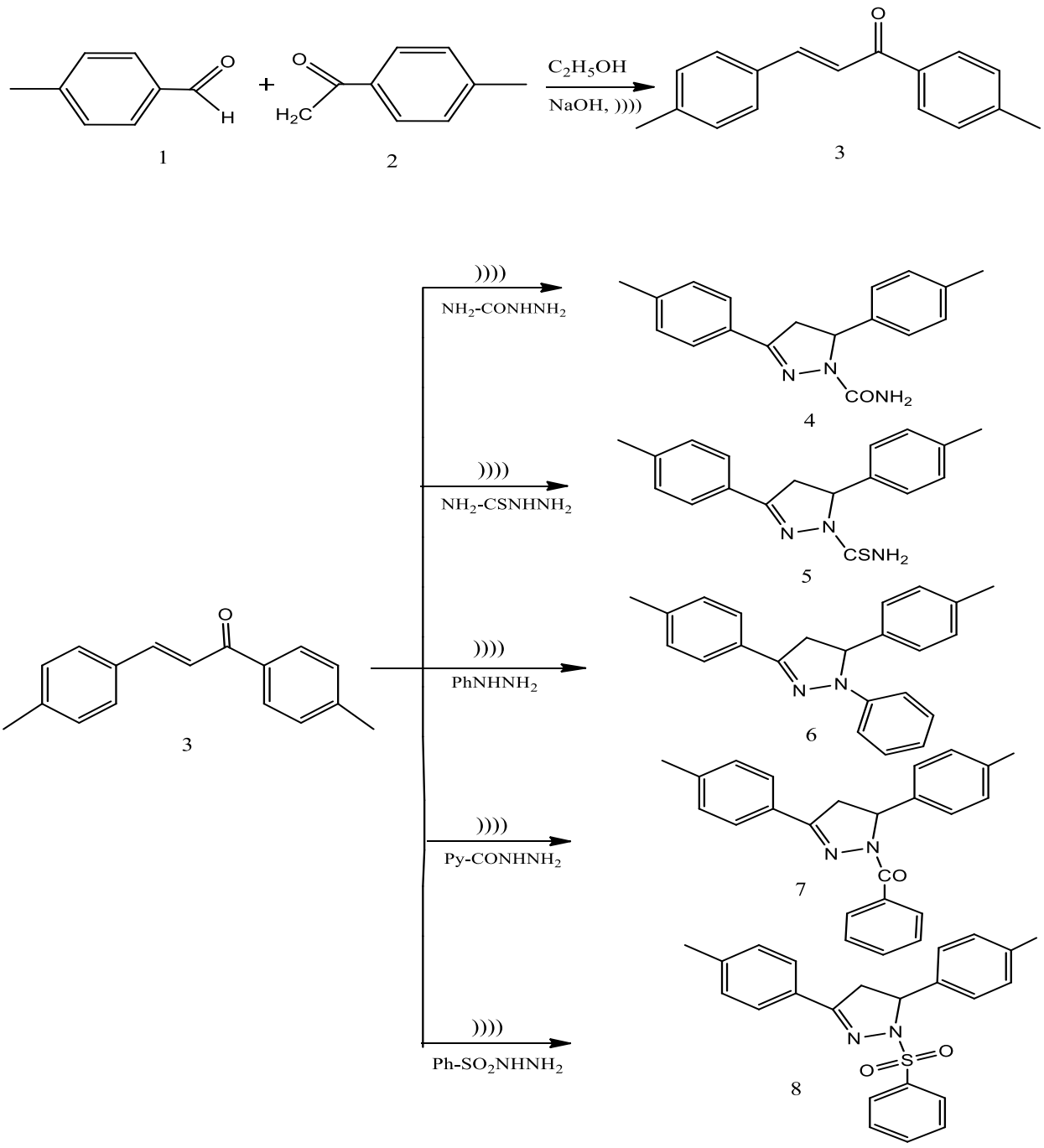

Figure 4: Synthesis of chalcone and pyrazoline derivatives 4-8 by ultrasonic irradiation

1. 4-methylbenzaldehyde
2. 4-methylacetophenone
3. (E)-1, 3-di-4-tolylprop-2-en-1-one
4. 4, 5-dihydro-3, 5-di-4-tolylpyrazole-1-carboxamide
5. 4, 5-dihydro-3, 5-di-4-tolylpyrazole-1-carbothioamide
6. 4, 5-dihydro-1-phenyl-3, 5-di-4-tolyl-1H-pyrazole
7. (4, 5-dihydro-3, 5-dip-tolylpyrazol-1-yl) (phenyl) methanone
8. 3, 5-bis (4-methylphenyl)-1-(phenylsulfonyl)-4, 5-dihydro-1H-pyrazole

ultrasonic irradiation in the water bath of an ultra-sonic cleaner at room temperature[21].

The synthetic route of compound **3, 4, 5, 6, 7, 8** is outlined in Scheme below[14] (figure 4)

Ultrasound is found to have beneficial effect on the synthesis of chalcone and pyrazoline derivatives as decrease in time from 8 to 10 h in conventional procedure to less than 1 h, and noticeable improvement in yields of reactions[14, 22].

Grinding

Griding technique is used nowdays over conventional methods, most of the reaction are carried at room

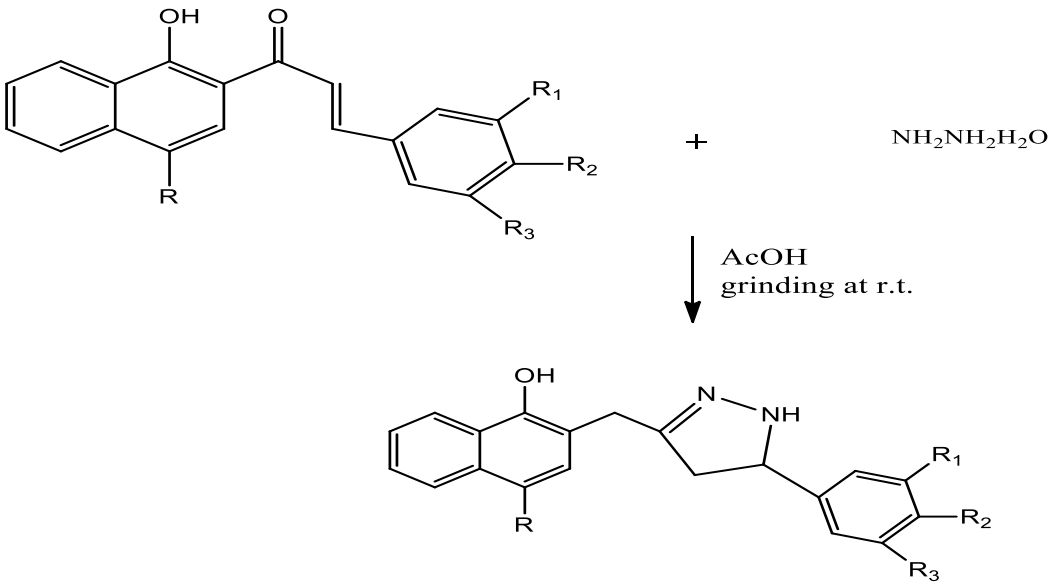

Figure 5: 2'-hydroxychalcones, 2-pyrazolines synthesized by solvent free grinding technique.

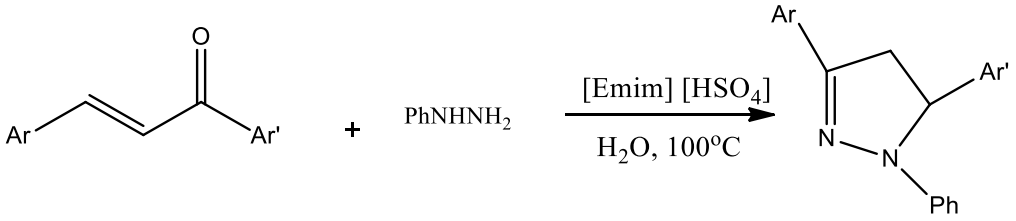

Figure 6: Synthesis of pyrazoline derivatives using ionic liquid.

temperature in absence of solvent free reaction. Local heat generated by grinding of crystals of substrate and reagent is used as a driving force of the reaction. Simple, rapid, efficient and environmentally benign procedures for synthesis of 2-pyrazoline derivatives are achieved by Zangade *et al.* reacting 2'-hydroxychalcones with hydrazine hydrate under solvent-free grinding technique. The short reaction time, cleaner reaction, easy workup, higher yields and mild reactions conditions make are the main adventage of this method which makes it attractive in comparison with the classical reaction[22] (figure 5).

The grinding mode for solid-state reactions are reported for some well-known reactions such as Grignard reactions[23], Reformatsky reactions[24], Aldol condensations[25], Dieckmann condensations [26], Knoevenagel condensations [27], Reductions[28] and others[29, 30]. Most of these reactions are carried out at room temperature in absence of solvent-free environment, using a mortar and pestle. In grindstone technique, reaction occurs through generation of local heat by grinding of crystals of substrate and reagent. Reaction is initiated by grinding, with the transfer of very small amount of energy through friction. In some cases, a mixture and reagent turn to a glassy material. Such reactions are simple to handle, reduce pollution, comparatively cheaper to operate and may regarded as more economical and ecologically favorable procedure in chemistry[22].

Ionic Liquids

Ionic liquids are the liquids consistency of ions. They are the salts whicha re present in liquid state below 100° C. The liquids differ from molten salts, in which the higher temperature is required to melt the salts. The first ionic liquid was invented in 1948 and was Chloroaluminate. Since then lot of work has been done ionic liquids. The various ionic liquids used in synthesis are EMIM (1-ethyl-3-methylimidazolium), BMIM (1-n-butyl-3-methylimidazolium)[31]. A novel and green route is developed by Dhanmane *et al.* for the synthesis of 1,3,5-trisubstituted pyrazoline derivatives from phenyl hydrazine and substituted chalcones in an aqueous media by using 1-ethyl-3 methylimidazolium (Emim) hydrogen sulphate (HSO_4) ionic liquid as a catalyst at reflux condition.

The reaction protocol gave 1,3,5-trisubstituted-2-pyrazolines in good to high yields via a one-pot addition–cyclocondensation between chalcones and arylhydrazines[32] (figure 6). The catalyst can be reused without much loss in the catalytic activity[32].

Comparison Between Conventional Method And Green Method For Synthesis Of Pyrazoline

Certain parameter such as energy input, time required and cost of manufacturing are important in industrial manufacturing of either raw material or active drug ingredient. Activity of any novel molecule is as important as its total manufacturing cost. Considering this we hereby put some points which describe the cost effectiveness of green methods over conventional method (table 1).

The table 1 describes various comparative parameter for various synthesis techniques. One of the most important factors of microwave synthesis in that the reaction

temperature can be increased approximately 40K above the boiling point of the solvent[33], which cannot happen in conventional method. Whereas, in ultrasound and grinding techniques, energy is obtained from ultrasonic waves and grinding friction respectively. Thus increase in temperature is not required in ultrasonic and griding techniques. In contrast to this the reaction temperature remains below 100^{o} C when ionic liquid technique is used and hence not useful for the reactions which take place above 100^{o} C. When compared for rate of reaction, it is found that highest rate of reaction is obtained by microwave techniques. Whereas reaction rate is higher in ionic liquid technique than conventional methods. Yield obtained is also higher for all green methods over conventional methods.

CONCLUSION

The present article describes various synthetic routes for synthesis of pyrazoline scaffolds by using green methods. As can be seen, the green methods have many advantages over the conventional methods in terms of time required, yield of the product and cost of manufacturing. All these methods are simple and can be carried out at normal laboratory conditions. Considering the use of pyrazoline scaffolds in various active molecules, we mainly discussed the synthetic routes of pyrazoline scaffold which would be helpful to the researchers in development of cost effective novel molecule.

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