Review Article

Comparison of various synthesis methods and synthesis parameters of pyrazoline derivates

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J. Adv. Pharm. Technol. Res.

Abstract

Pyrazoline plays an important role in the development of heterocyclic chemistry theory and is widely used as a synthesis useful in organic synthesis. The structure of the pyrazoline derivative compound contains a 5-membered heterocyclic framework with two nitrogen atoms and one endocyclic double bond. The function of pyrazoline as a fragment was stable enough in the bioactive group to synthesize new compounds with various biological activities. Various methods that could be used for the synthesis of pyrazole derivatives were ultrasonic irradiation, microwave assistance, ionic liquids, grinding techniques, and conventional methods. However, the synthesis of pyrazoline derivatives using conventional methods had many problems, one of which is the product yield, which was <70%. Therefore, this article will discuss the importance of optimizing the synthesis reaction conditions by taking into account several synthesis parameters to get the best organic product results based on conventional methods. A literature search was conducted by employing PubChem, Chemspider Google Scholar, Research Gate, Science Direct, and Elsevier by selecting pyrazoline synthesis based on physicochemical profile, reaction mechanism, and synthesis method.

Key words: Parameter synthesis, pyrazoline derivates, synthesis methods

INTRODUCTION

Pyrazoline derivate synthesis is carried out in two stages. In Stage 1, Claisen-Schmidt condensation[1] was conducted between acetophenone and aromatic aldehyde analogs called the aldol condensation reaction[2] to get the desired enone. In Step 2, enones are reacted to give the desired pyrazoline by a regioselective synthesis of 1,3,5-triarylpyrazolines. Aryl hydrazine is used as a hydrochloride salt to reduce the reaction side of the product and improve the results of the cyclization reaction.[3] The reaction of aromatic ketones and aldehydes involving base catalysts will produce unsaturated ketones and αβ-unsaturated (chalcones) was reacted with hydrazine, which is a very popular reaction method for 2-pyrazoline synthesis[4] in reflux under certain reaction conditions.[5,6]

Pyrazoline is known as nitrogen in a five-membered ring of heterocyclic compounds.[7] Pyrazoline contains an acarbonyl aldehyde group that interacts with a series of substitution acetophenone to give an α-β unsaturated carbonyl compound called chalcones.[8] The existence of this structure is very important in pharmacological chemical drugs because the pyrazole ring structure has an active part that can provide many different biological activities. Pyrazoline derivatives have broad biological activity properties that are used effectively[9] as anti-inflammatory,[10] antimalarial,[1,11] antidepressant,[12] antimicrobial,[11,13]

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Submitted: 23-Mar-2021 **Revised:** 22-Apr-2021
Accepted: 06-Jul- 2021 **Published**: 20-Oct-2021

Access this article online

Quick Response Code:

Website: www.japtr.org

DOI: 10.4103/japtr.JAPTR_252_21

How to cite this article: Praceka MS, Megantara S, Maharani R, Muchtaridi M. Comparison of various synthesis methods and synthesis parameters of pyrazoline derivates. J Adv Pharm Technol Res 2021;12:321-6.

Table 1: Comparison of synthesis methods

Methods Parameter	Conventional	Microwave	Ultrasonic	Grinding	Ionic Liquid
Temperature	Reflux 110°C[30]	The vessels are done by heating from afar 20-150 °C[15,30]	25-50 °C[25]	Room temperature (RT)[33]	Mixed 100°C[32]
Reaction time	3-7h[25]	1-4 min[11,15,30]	10-20 min[25]	8-12 min[33]	2-6 h.[32]
Source of energy	electricity and heat[42]	Electromagnetic waves are fired[15,30]	Sound wavesz[25]	Human energy/ tools[33]	Heat/electricity[32]
Product yield	55-75%[6,42]	79-89%[25]	72-89%[25]	78-94%[33]	87-96%[32]

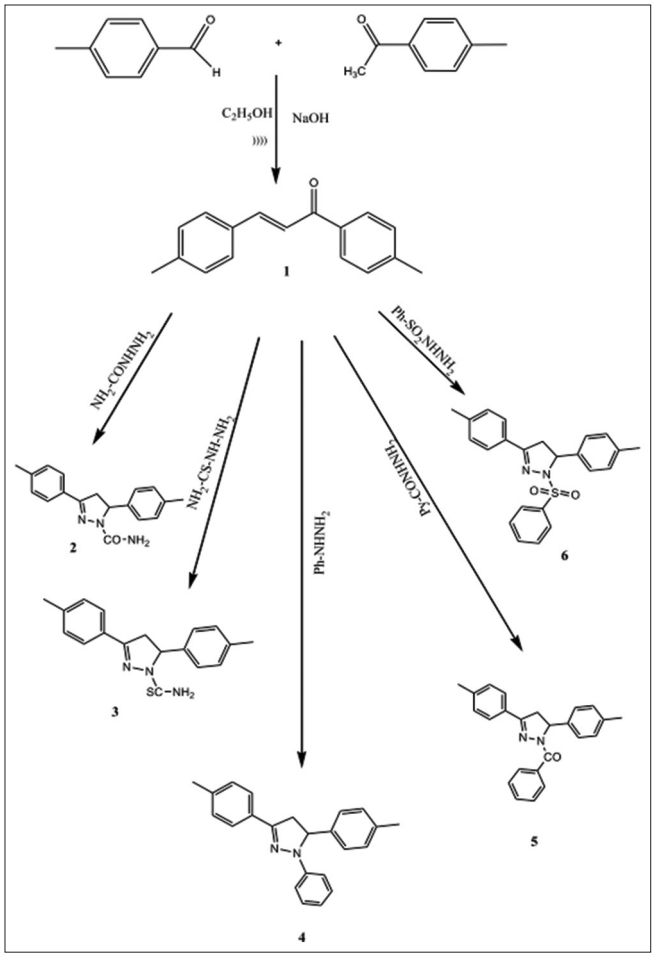

Figure 1: Synthesis of pyrazoline derivatives using ultrasonic irradiation[27]

antileukemic,[14] antioxidant,[15] analgesic,[16] anticancer,[2,17,18] immunosuppressant,[19] antidiabetic,[20] cytotoxic,[21,22] antihepatotoxic,[23] and antitumor agents.[19]

The process of standardization and optimization of reaction conditions is done by comparing the literature used for the synthesis of pyrazoline derivatives related to catalysts, solvents, reaction times, temperatures, etc.[24] Based on organic reactions, a compound must be synthesized easily and quickly, and the product must be easily separated and pure.[25] However, there are some disadvantages to this

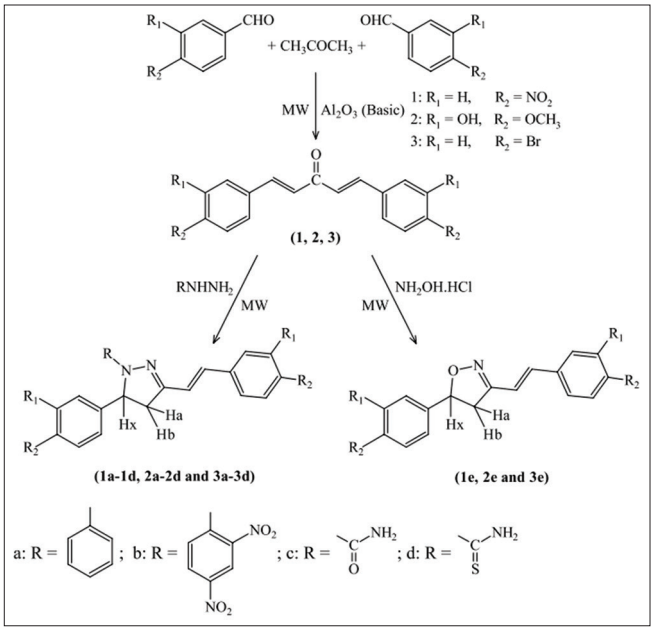

Figure 2: Synthesis of pyrazoline derivatives using microwave irradiation[30]

conventional method, for example, higher temperatures, longer reaction times, general inspection procedures, the formation of by-products, and environmental influences.[6] The development strategy for synthesis methods is carried out by selecting various synthesis methods and taking into account various synthesis parameters that can affect the results of the synthesis product [Table 1].

SYNTHESIS METHODS OF PYRAZOLINE DERIVATE

Various methods that could be used for the synthesis of pyrazole derivatives are.[26]

Ultrasonic irradiation

Green chemistry from ultrasonic irradiation had been applied to the fields of green chemistry and pharmacy. Sonication provided an advantage in the synthesis of pyrazoline derivate because of the cavitation effect created under local conditions in the media as shown in Figure 1. Therefore, the reaction could be resolved in a short time

and the number of products that could be obtained was very high. This method could promote the synthesis of pyrazoline derivate with a short reaction time and good results.[27-29]

Microwave irradiation

Green chemistry used benign synthetic procedures that were very efficient and environment friendly to synthesize a variety of bioactive heterocyclic frameworks that were useful for the synthesis of drugs, plastics, petrochemicals, agricultural chemicals, cosmetics, and many more. Hence, green chemistry was a daily necessity. In this methodology, pyrazolines were synthesized under microwave irradiation as shown in Figure 2.[30] The structure of this compound was established by elemental analysis and spectral data. This method had several advantages compared to conventional synthesis including clean reaction procedures, easy inspection, and short reaction times, giving excellent results for the product.[31] The development of a sensitive and fast method was carried out for these samples. Thus, a pyrazoline derivative was obtained as the one giving better results than conventional methods. The current use of microwave energy was very broad because it was more environment friendly, was safer, had a better selectivity and no need for catalysts, and was faster, cleaner, and able to provide more products than conventional methods.[15,31] It was often used as an alternative in more efficient synthesis due to the ease of operation and mild reaction conditions when mixed with free solvents. Previous studies had shown that microwave irradiation was a reaction condition in dry media that was energetically beneficial and saved more reaction time.[11,30]

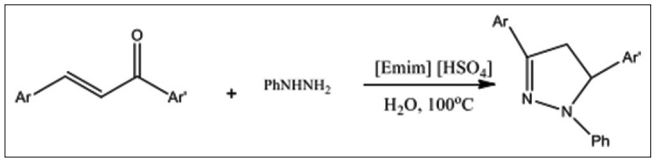

Figure 3: Synthesis of pyrazoline derivatives using ionic liquid[24]

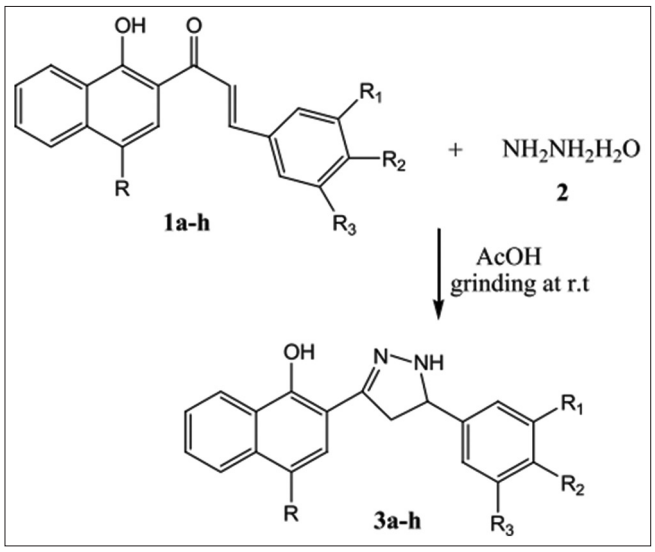

Figure 4: Synthesis of pyrazoline derivatives using grinding technique under solvent-free conditions[33]

Ionic liquid

Ionic liquid is salt in 100°C liquid state. Liquid salt is certainly different from liquid because it requires a higher temperature to melt salt. In 1948, the first ionic liquid and chloroaluminate were discovered, and since then many studies had found various ionic liquids that could be implemented in the synthesis. 1-n-butyl-3-methylimidazolium and 1-ethyl3-methylimidazolium (EMIM) had developed green route to compounds 1,3,5-pyrazoline derivatives substituted in liquid media EMIM hydrogen ionic sulfate liquid, which was useful as a catalyst in reflux conditions as shown in Figure 3.[24] In addition, 1,3,5-tri-substitute-2-pyrazoline compounds used one-pot cyclocondensation between arylhydrazines and chalcones to obtain better results. The catalyst was recycled without losing much of its catalytic activity.[32] The used catalyst could be used without losing its catalytic activity.[24]

Grinding technique

Milling was an effective instrument for mixing substrates very efficiently under solvent-free reaction conditions. The method applied to the simple apparatus was suitable for use in mechanochemical reactions with pestles and mortars, through mixing and triturating mills as shown in Figure 4.[33,34] The grinding technique was developed as a new method in the synthesis of organic heterocycles using mechanical techniques from ball milling. Mechanical engineering was needed to grind the powder into finer particles. The reactants were broken down with solvent molecules in the classical

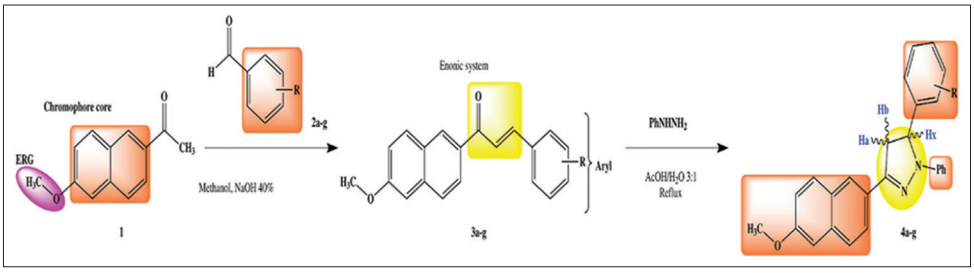

Figure 5: Synthesis of pyrazoline derivatives using conventional methods[36]

method. In addition, the reactants were broken down by mechanical forces in ball milling which led to an amorphous mixture approach of all reagents and the reaction took place on a larger surface. The implementation of solvent-free ball milling was very rare in organic synthesis. However, this technique was attracting attention because of its low cost, simplicity, and good results in pure form without the need for further purification. This technique was also environment friendly. Therefore, this ball grinding technique was superior to conventional methods.[33,35]

This procedure had many advantages including high selectivity, efficiency, purification, easy separation, and mild reaction conditions. Apart from being safe for the surrounding environment, economically, toxic waste could be eliminated or minimized so that the waste treatment costs were not too large.[34]

Conventional methods

One of the simplest methods was the conventional method which was carried out with conventional equipment such as reflux with the reaction shown in Figure 5.[36] The heating reaction was slow but also caused hot surfaces at certain reaction sites, which led to the decomposition of the substrate, reagents, and products over time of synthesis.[11] In contrast to this, green chemistry techniques assisted by microwave energy allowed the heating of vessels over a long distance to be more uniform, resulting in relatively smaller decomposition products. The heating reaction with conventional equipment was not only slow but also created a hot surface at the reaction site which led to the breakdown of products, substrates, and reagents over time.[37]

Conventional heating used an oil well that is heated first, then the solvent. The decomposed product results in an uneven distribution due to temperature differences in the solvent and bath wall.[38,39]

PYRAZOLINE DERIVATE SYNTHESIS PARAMETERS

In the synthesis of pyrazoline derivate, various factors affected the parameters that needed to be considered when synthesis took place to get better product results, one of which was: [40]

Based on the above parameters, a comparison can be made between the green synthesis method and the conventional method.

The temperature used in conventional methods with reflux was the highest temperature achieved with restrictions on boiling certain points of the mixture. The temperature in conventional methods was higher than in other methods. The decrease in reaction rate was caused by an increase in the number of perfect collisions with higher kinetic energy.[6] Temperatures that were too high could lead to product decomposition and poor results on the synthesis of pyrazoline derivate.[11]

The constant in the reaction rate used an exponential function as the temperature increases. The high reduction in total at the time of synthesis was due to the benefits of exposure to microwave-assisted heat in chemical pyrazole synthesis. The decrease in the rate of reaction at the time of synthesis was due to the increase in the perfect collision of the number of collisions, which resulted in higher kinetic energy.[6]

Reaction time in conventional methods was longer than in other methods.[15,25,30] A decrease in reaction time was carried out in line with the increase in the resulting product.[41] The reaction time required for the microwave and ultrasonic methods tended to decrease from a few hours to a few minutes.[25] A decrease in reaction time was carried out in line with the increase in the resulting product.[41]

The energy source needed for microwave irradiation-assisted synthesis by applying green synthesis was very beneficial in terms of energy saving and to make it easier to control than conventional methods.[15]

The results of products in conventional methods tended to be less good compared to other methods due to high heating, a longer time, and more solvent consumption.[25] Therefore, it is recommended that the synthesis of pyrazoline derivate in conventional methods uses green chemistry.[42]

CONCLUSION

In the synthesis of pyrazoline derivatives, various synthesis methods could be used. One of the simplest synthetic methods was the conventional method. However, the conventional method was not as superior as the green synthesis method because it produced a product yield of <70%. This became a challenge in the world of synthetic chemistry to optimize reaction conditions by considering various parameters to obtain good-resulting products. Parameters that needed to be considered were temperature, reaction time, energy source, and product yield. One of the efforts to optimize the reaction conditions was to modify the variation in the concentration of solvent, temperature, and catalyst used during the reaction.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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