Green One-Pot Synthesis of 5-Amino-1-Aryl-3-Phenyl-4-Carbonitrile Derivatives using Chloride-lactic acid DES

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Abstract

In this study, an efficient and environmentally friendly method was developed for the synthesis of a series of 5-amino-1-aryl-3-phenyl-1H-pyrazole-4-carbonitrile derivatives via a one-pot multicomponent reaction. The synthetic approach involves the reaction of substituted aromatic aldehydes, malononitrile, and phenylhydrazine under mild conditions. The different reaction media namely a conventional ethanol–water system and a choline chloride–lactic acid (ChCl:LA) deep eutectic solvent (DES). The results demonstrated that both methods successfully afforded the desired pyrazole derivatives; however, the deep eutectic solvent system showed superior performance in terms of reaction rate, product formation, and ease of isolation. The ChCl:LA DES acted as a green, eco-friendly

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solvent and catalytic medium, enhancing the overall efficiency of the multicomponent reaction. The developed method provides a simple, cost-effective, and green approach for the synthesis of biologically privileged pyrazole derivatives.

1. Introduction

Heterocyclic compounds represent one of the most important classes of organic molecules due to their extensive presence in natural products, pharmaceuticals, agrochemicals, and functional materials. Among these pyrazole derivatives have attracted significant attention because of their remarkable biological and pharmacological activities, such as anti-inflammatory, antimicrobial, antiviral, antitumor, and analgesic effects. In addition, several clinically important drugs contain the pyrazole scaffold as a key structural component, highlighting the importance of developing efficient and sustainable synthetic methods for pyrazole derivatives. Representative examples of pyrazole-containing drugs are depicted in **Figure 1** [1].

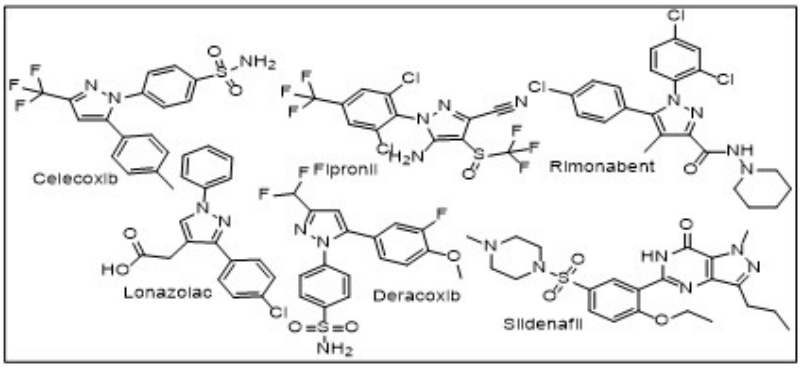


Figure 1: Diverse pharmacological active Drug molecules containing pyrazole motif.

Amino-substituted pyrazoles have gained considerable interest due to their role as valuable intermediates in medicinal chemistry and pharmaceutical research. These compounds serve as versatile building blocks for the synthesis of various biologically active heterocyclic systems. Among them, 5-aminopyrazole derivatives have emerged as highly important synthetic precursors because their multifunctional nature enables further transformations leading to fused heterocycles and pharmacologically relevant molecules [2]. Several studies have reported the design and synthesis of pyrazole-based heterocycles for pharmaceutical applications.

For example, pyrazolo[1,5-a]pyrimidine derivatives have been investigated as dual inhibitors of cyclin-dependent kinase 2 (CDK2) and tropomyosin receptor kinase A (TRKA), demonstrating promising antiproliferative activity against cancer cell lines. These findings further emphasize the pharmaceutical relevance of pyrazole-based scaffolds and stimulate continuous efforts toward the development of improved synthetic strategies for these compounds, biologically active pyrazole derivatives as illustrated in **Figure 2** [3].

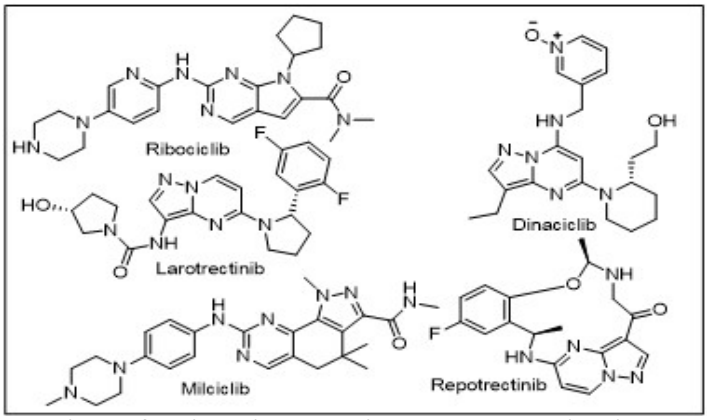
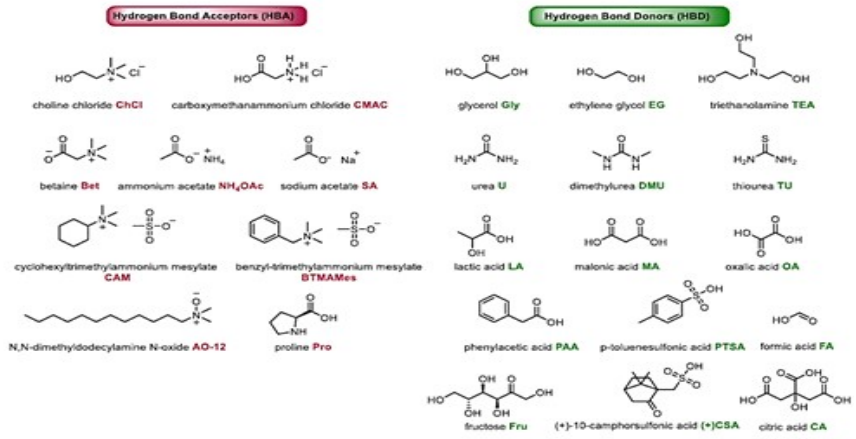


Figure 2: Biologically active pyrazole derivatives

The different subclass of pyrazoles, 5-aminopyrazole-carbonitrile derivatives exhibits potential biological applications. The construction of condensed heterocyclic systems has functional versatility in modern organic synthesis [4]. Numerous synthetic approaches have been developed for the preparation of aminopyrazole derivatives. Like the condensation of hydrazine with activated nitrile-containing substrates, followed by cyclization processes yielding to the formation of the pyrazole ring. However, many of these methods suffer from several drawbacks such as the use of hazardous solvents, harsh reaction conditions, long reaction times, and the requirement for expensive or toxic catalysts. Therefore, the development of greener and more efficient synthetic methodologies remains an important objective in contemporary organic chemistry [5].

Recent advances in catalytic methodologies have introduced various catalytic systems for the synthesis of aminopyrazole derivatives. For instance, calcined Mg–Fe hydrotalcite, Modified layered hydroxide (LDH), Magnetic nanoparticle $CoFe_2O_4@SiO_2$-, iron nanoparticle, catalysts have been

employed for the one-pot synthesis of 5-amino-1H-pyrazole-4-carbonitrile derivatives. This heterogeneous catalytic system offers certain advantages such as recyclability and improved reaction efficiency. Nevertheless, the preparation of such catalysts often involves multiple steps and may require additional energy input, which can limit their practical applicability in large-scale synthesis [6]. Green chemistry have significantly influenced the development of sustainable synthetic methodologies by emphasizes on reduction of hazardous substances, the use of renewable resources, and the development of environmentally benign reaction conditions. In which, one-pot multicomponent reactions (MCRs) have emerged as powerful synthetic strategies because they allow the formation of complex molecules from simple starting materials in a single reaction vessel without the isolation of intermediates [7-10]. One-pot multicomponent reactions offer several advantages such as operational simplicity, high atom economy, reduced waste generation, and improved efficiency [11]. Various green solvents that have been developed in recent years, deep eutectic solvents (DESs) have attracted considerable attention as environmentally friendly alternatives to conventional organic solvents. Deep eutectic solvents are typically formed through hydrogen-bond interactions between a hydrogen bond donor and a hydrogen bond acceptor, resulting in a eutectic mixture with a melting point significantly lower than that of its individual components [12].



JRE 4 | DES components used in microwave-assisted reactions.

Figure 3: Hydrogen-bond interactions and the formation of deep eutectic solvents

Deep eutectic solvents possess several advantageous properties including low toxicity, biodegradability, low volatility, easy preparation, and tunable physicochemical characteristics, green reaction media for numerous organic transformations. Due to Hydrogen-bond interactions DESs have been widely investigated as both solvent and catalyst. Thereby simplifying reaction procedures and improving the sustainability of chemical processes [**Figure 3]** [13]. The classification and key functional properties of different types of DES systems are illustrated in **Figure 4** highlighting their versatility and applicability in modern organic synthesis.

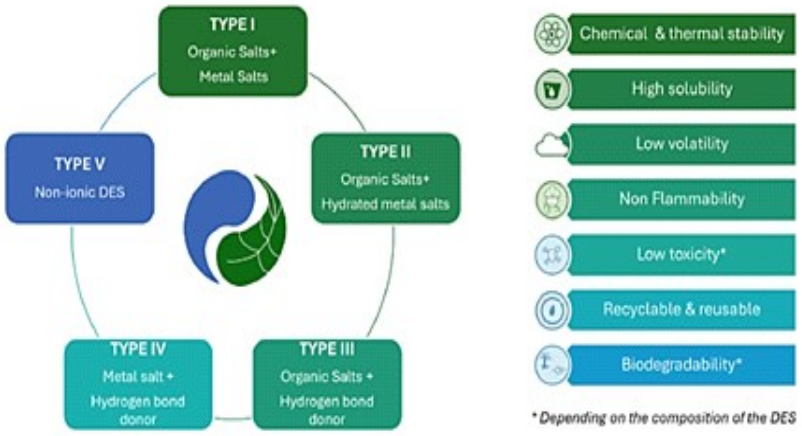


Figure 4: Classification of deep eutectic solvents

A wide variety of DES particularly choline chloride act as the hydrogen bond acceptor. Choline chloride-based DESs are inexpensive, biodegradable, and readily available. When combined with hydrogen bond donors such as organic acids, alcohols, or amides, choline chloride forms stable eutectic mixtures with excellent solvent properties [14]. DES system provides a highly polar and hydrogen-bonding environment that can facilitate MCRs and heterocycle formation. Furthermore, the components of this solvent system are derived from renewable resources, which further enhance its environmental compatibility [15-16]. Choline chloride–lactic acid deep eutectic system and its role in promoting organic transformations is presented in **Figure 5**, highlighting the hydrogen-bonding network responsible for its catalytic efficiency [17].

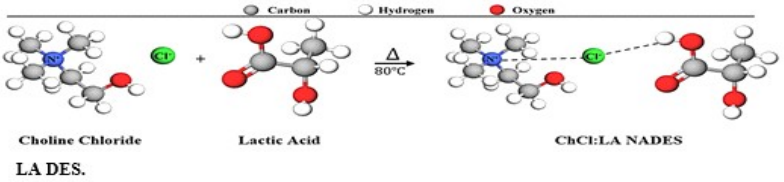


Figure 5: Hydrogen-bonding network and its catalytic efficiency

Despite the significant progress achieved in the use of deep eutectic solvents for organic synthesis, the application of DES systems in the synthesis of aminopyrazole derivatives remains relatively limited. Therefore, the exploration of DES-based methodologies for the efficient and environmentally friendly synthesis of these important heterocycles continues to be an active area of research [18]. In light of these considerations, the development of green and efficient synthetic approaches for the preparation of 5-aminopyrazole-carbonitriles using deep eutectic solvents represents a valuable contribution to sustainable heterocyclic chemistry. The present study describes a green one-pot synthesis of 5-amino-1-aryl-3-phenyl-1H-pyrazole-4-carbonitrile derivatives using a choline chloride–lactic acid deep eutectic solvent as an environmentally benign reaction medium. This methodology provides simple, efficient, and sustainable alternative to previously reported synthetic procedures while avoiding the use of hazardous solvents and metal catalysts.

2. Experimental

2.1 Materials and Methods

Substituted aromatic aldehydes, malononitrile, phenylhydrazine, ethanol, lactic acid, choline chloride, and other reagents were obtained from the laboratory stock of the Department of Chemistry and were used without further purification. Distilled water was used throughout all experimental procedures. Thin layer chromatography plates coated with silica gel were used to monitor the progress of the reactions.

2.2 Preparation of Choline Chloride–Lactic Acid (ChCl:LA) DES

The deep eutectic solvent composed of choline chloride and lactic acid was prepared according to a reported procedure with slight modification. Choline chloride and lactic acid were mixed in a molar ratio of 1:9 in a round-bottom flask. The mixture was heated at 80 °C with continuous stirring until a clear homogeneous liquid was obtained. After

complete dissolution, the resulting deep eutectic solvent (ChCl:LA DES) was allowed to cool to room temperature and was stored in a sealed container for further use in the synthesis reactions [19].

2.3 General Procedure for the Synthesis of Pyrazole Derivatives Using Ethanol–Water System

A mixture of ethanol (10 mL) and distilled water (10 mL) was placed in a round-bottom flask. Malononitrile (4 mmol) was added to the solvent mixture and stirred until completely dissolved. Subsequently, the appropriate substituted benzaldehydes (4 mmol) was added to the reaction mixture with continuous stirring. After that, phenylhydrazine (4 mmol) was added slowly to the reaction mixture under constant stirring. The reaction proceeded at room temperature, and the formation of a solid precipitate was observed shortly after the addition of phenylhydrazine.The progress of the reaction was monitored by thin layer chromatography (TLC) until complete consumption of the starting materials was observed.

2.4 General Procedure for the Synthesis of Pyrazole Derivatives Using ChCl:LA DES

In a typical procedure, substituted aromatic aldehyde (4 mmol), malononitrile (4 mmol), and phenylhydrazine (4 mmol) were added to a reaction flask containing the prepared ChCl:LA deep eutectic solvent (2-4 mL).The reaction mixture was stirred and heated at approximately 60 °C for the required reaction time. The progress of the reaction was monitored by TLC until disappearance of the starting materials was observed. After completion of the reaction, the mixture was allowed to cool to room temperature. Distilled water was then added to the reaction mixture to precipitate the product. The resulting solid was collected by filtration, washed with cold water to remove residual solvent, and dried. The crude product was further purified by recrystallization from ethanol to afford the desired 5-amino-1-aryl-3-phenyl-1H-pyrazole-4-carbonitrile derivatives. After completion of the reaction, the precipitated solid product was separated by filtration using Whatman filter paper. The crude product was washed several times with cold distilled water to remove impurities and traces of the solvent. The obtained solid products were purified by recrystallization from hot ethanol; affording pure crystalline pyrazole derivatives. The progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel plates. The developing solvent system used was hexane: ethyl acetate (3:1).

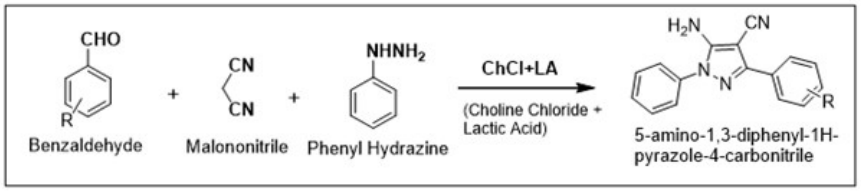
2.5 Melting Point Determination

The melting points of the synthesized compounds were determined using the capillary tube method. A small amount of the dried solid sample was packed into a melting point capillary tube. The capillary tube was placed in a paraffin oil bath, and the temperature was gradually increased. The temperature was monitored using a calibrated thermometer, and the melting point was recorded as the temperature range between the onset of melting and complete liquefaction of the sample.

3. Results and Discussion

The synthesis of pyrazole derivatives was achieved through a one-pot multicomponent reaction between substituted aromatic aldehydes, malononitrile, and phenylhydrazine. The reaction proceeds through condensation followed by cyclization to afford the corresponding pyrazole derivatives [**Scheme 1].** Particular attention was given to the influence of the reaction medium, including conventional solvents and deep eutectic solvent (DES), on the efficiency of the transformation. The obtained products were isolated and characterized based on their physical properties and melting point measurements. The experimental results are discussed in terms of reaction efficiency, product formation, and comparison with literature data.

General Scheme:



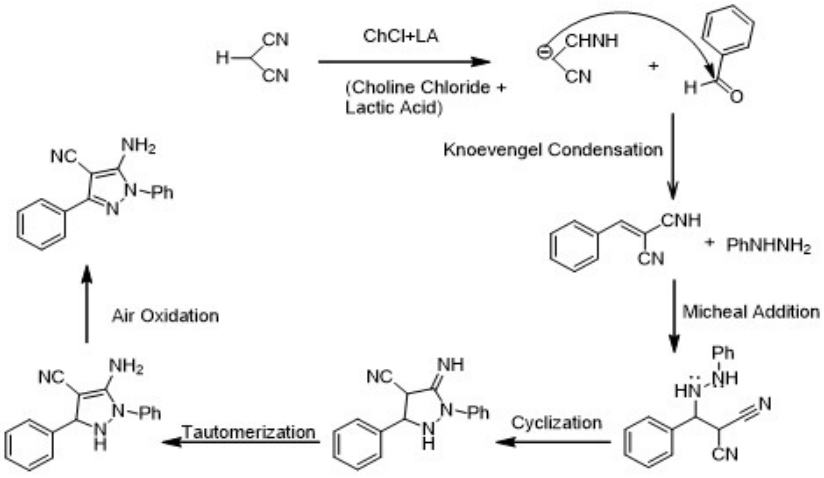
Scheme 1: General synthetic route for the preparation of substituted pyrazole derivatives.

The reaction involves the initial condensation of the aldehyde with malononitrile to generate an activated intermediate, which subsequently reacts with phenylhydrazine leading to cyclization and formation of the pyrazole ring. To evaluate the influence of the reaction medium, the synthesis was performed using different solvents, including ethanol–water and deep eutectic solvent (DES). The use of DES provided a greener and more sustainable reaction medium due to its low toxicity, biodegradability, and ability to enhance reaction efficiency, exhibited improved product formation and easier work-up compared with conventional solvents, hence

highlights the potential of DES as an environmentally friendly alternative solvent in heterocyclic synthesis.

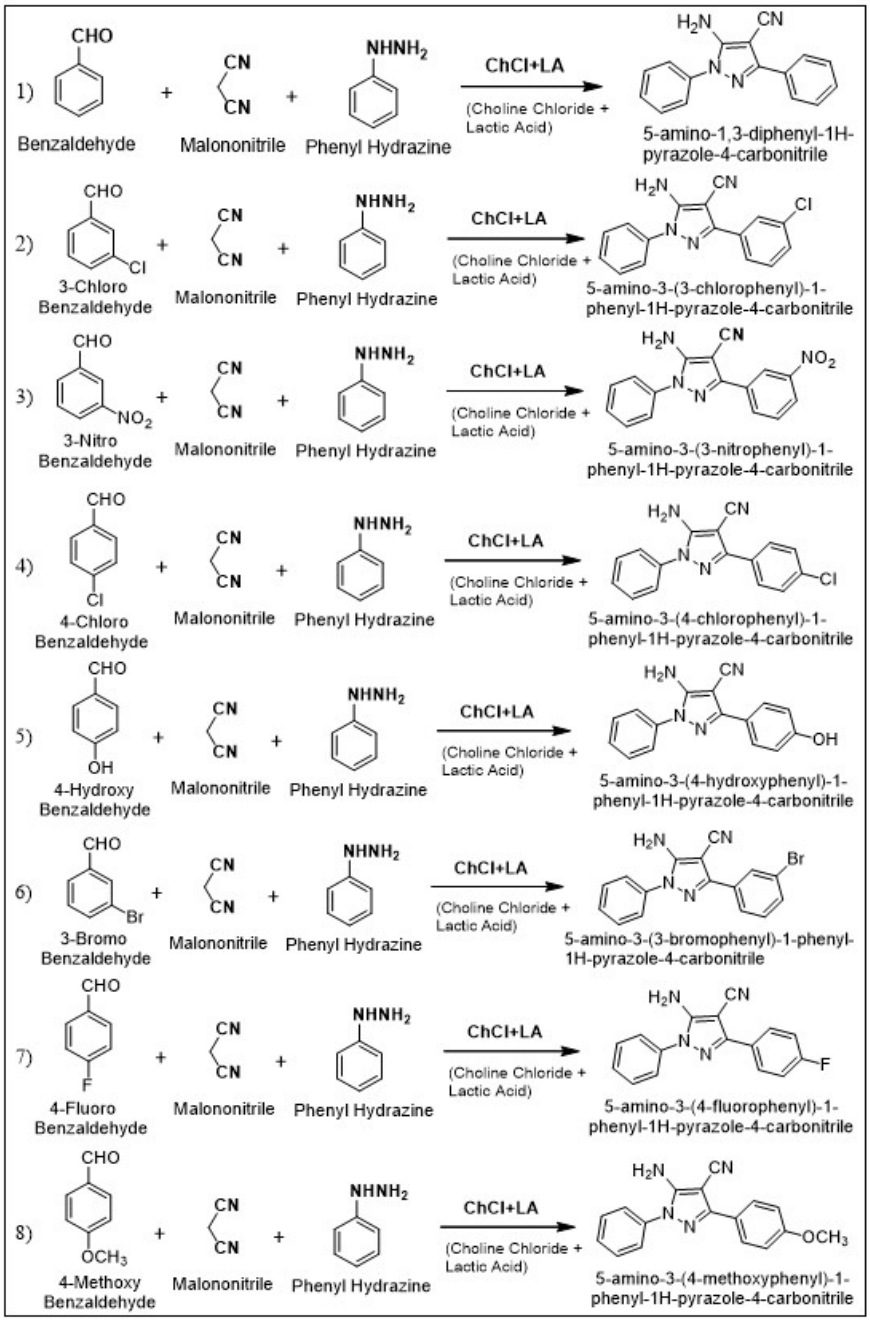
The formation of pyrazole derivatives can be explained by a sequence of condensation and cyclization steps. Initially, the aldehyde reacts with malononitrile via a Knoevenagel condensation to form an adduct. This intermediate subsequently undergoes nucleophilic addition with phenylhydrazine to yield Micheal adduct, followed by intramolecular cyclization to generate the pyrazole ring system. Plausible Mechanism is depicted in **Scheme 2.** The efficiency of the reaction is influenced by the electronic nature of the substituents on the aromatic aldehyde. Electron-withdrawing groups generally facilitate the condensation step, while electron-donating groups may slightly reduce the reaction rate. Initially, a Knoevenagel condensation occurs between the aromatic aldehyde and malononitrile to form a benzylidene malononitrile intermediate. Subsequently, phenylhydrazine undergoes nucleophilic addition to the activated double bond of the intermediate.This step is followed by intramolecular cyclization and rearrangement leading to the formation of the pyrazole ring system. The reaction medium, particularly the ChCl:LA deep eutectic solvent, facilitates these transformations by providing a hydrogen-bonding environment that enhances the reactivity of the starting materials.

A variety of aromatic aldehydes containing different substituents were used to investigate the scope of the reaction see **table 1**. The corresponding pyrazole derivatives were successfully synthesized and isolated as crystalline solids



Scheme 2: Plausible mechanism for the synthesis of pyrazole derivatives

Table 1: Synthesis of substituted pyrazole derivatives.



The synthesized compounds were characterized by their physical appearance and melting points. The melting points were determined using the capillary tube method and compared with the reported literature values.

Table 2: Physical data of synthesized pyrazole derivatives

Sr No	Derivatives	Melting Point (°C) Found	Literature (°C)	Yield (%)
1	Benzaldehyde	160	158 -162	83
2	3-Chlorobenzaldehyde	128	—	85
3	3-Nitrobenzaldehyde	119	128 -130	91
4	4-Chlorobenzaldehyde	125	128 -131	89
5	4-Methoxybenzaldehyde	110	107 -110	90
6	4-Hydroxybenzaldehyde	207	206 - 208	92
7	3-Bromobenzaldehyde	143	—	93
8	4-Fluorobenzaldehyde	160	163 -165	85

The experimentally determined melting points were generally in good agreement with reported

4. Conclusion

This study successfully demonstrated the synthesis of a series of 5-amino-1-aryl-3-phenyl-1H-pyrazole-4-carbonitrile derivatives through a one-pot multicomponent reaction involving substituted aromatic aldehydes, malononitrile, and phenylhydrazine.Two different reaction systems were investigated, namely a conventional ethanol–water solvent system and a choline chloride–lactic acid (ChCl:LA) deep eutectic solvent (DES). The comparative evaluation of these methods revealed that both systems are capable of promoting the formation of the desired pyrazole derivatives under mild conditions. However, significant differences in efficiency, reaction time, and product isolation were observed.The ethanol–water system provided a simple and accessible reaction medium, allowing the formation of the target compounds with efficiency. Nevertheless, the reactions generally required longer reaction times and, in some cases, afforded moderate yields.In contrast, the use of the ChCl:LA deep eutectic solvent proved to be a more efficient and environmentally friendly alternative. The DES system facilitated faster reactions, improved product formation, and easier isolation of the synthesized compounds. The enhanced performance of this system can be attributed to its dual role as both solvent and catalyst, providing a hydrogen-bonding environment that promotes

the reaction pathway.A series of substituted pyrazole derivatives was successfully synthesized using different aromatic aldehydes bearing electron-donating and electron-withdrawing groups. The results demonstrated that the reaction is generally applicable to a variety of substrates, although the nature of the substituents influenced the reaction efficiency and yield.The synthesized compounds were obtained as crystalline solids and characterized using melting point determination and thin-layer chromatography (TLC). The experimentally observed melting points were found to be in reasonable agreement with reported literature values, confirming the successful formation and acceptable purity of the target compounds.Overall, this work highlights the effectiveness of multicomponent reactions for the rapid construction of heterocyclic compounds and emphasizes the advantages of deep eutectic solvents as green and sustainable reaction media. The use of ChCl:LA DES offers a simple, cost-effective, and environmentally benign approach for the synthesis of biologically relevant pyrazole derivatives

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