

One-Pot Multicomponent Synthesis Of 1H-Pyrazolo [3,4-B] Quinolines By Using Eco-Friendly Deep Eutectic Solvent

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Abstract

The multicomponent reactions of aniline, aldehydes and 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one in ecofriendly deep eutectic solvent were developed. The Choline chloride based deep eutectic solvent played a dual role as a solvent as well as catalyst and produced excellent yield of 1H-pyrazolo[3,4-b]quinolines under mild reaction conditions. It could be recycled for several runs without any loss of catalytic efficiency. This methodology offers several advantages like simple and straightforward synthesis, shorter reaction time, environmental sustainability and use of natural resources.

Keywords: Deep eutectic solvent, 1H-pyrazolo [3,4-b] quinolines, multicomponent reaction, green synthesis.

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I. Introduction

Multicomponent reactions (MCRs) have emerged as powerful tool in organic synthesis due to its high atom economy, sustainability, operational ease, high efficiency and capability to rapidly synthesize structurally diverse-molecules.^{1,2} These reactions are particularly useful in drug discovery and designing, agrochemistry, material science, natural products, aligning well with the principles of green chemistry.³⁻⁵ Heterocyclic derivatives such as pyridines, xanthenes, pyrimidines, indoles, imidazoles and fused systems like pyrazolo and pyrimido quinolines play a crucial role in pharmaceutical, medicinal and agrochemical fields because of their extensive biological and therapeutic activities.⁶⁻⁹

The multicomponent reactions involving aniline, aryl aldehydes and 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one serves as an effective strategy for synthesizing heterocyclic compounds particularly pyrazoloquinoline derivatives. These derivatives are known for their various biological applications, such as antimicrobial,¹⁰ antihyperglycemic,¹¹ antiviral,^{12,13} antitubercular,¹⁴ anticancer,¹⁵ antimalarial activities¹⁶ and blue luminescent properties.¹⁷ The synthesis of these 1H-pyrazolo[3,4-b]quinoline derivatives were accomplished by using different methods such as, ethanol,¹⁸ solvent free microwave assisted synthesis,¹⁰ water mediated microwave synthesis¹⁹ and L-proline catalysed novel synthesis²⁰ and water mediated Baker's yeast assisted synthesis.²¹

Earlier reported methodologies had certain limitations, including longer reaction times, complex procedures, use of hazardous chemicals and catalysts and non-compliance with the green chemistry approach. The researchers have made several efforts to develop sustainable organic transformations which follows green chemistry principles. As a part of this development, Abbott and coworkers discovered the new generation of liquids for various chemical processes and organic transformations called Deep Eutectic Solvents (DESs).^{22,23} DESs play a strategically important role in green and sustainable chemistry by offering economical, ecofriendly and efficient reaction media. These eutectic mixtures replace conventionally used solvents and catalysts while maintaining very high productivity makes them a better choice for synthesis, extraction, catalysis and various chemical processes. These DESs are considered as fourth generation of ionic liquids. These eutectic mixtures are successfully explored in several organic transformations such as Spirooxindole synthesis,²⁴ synthesis of imidazoheterocycles,²⁵ Knoevenagel condensation,²⁶ benzylation of phenol,²⁷ Perkin reaction,²⁸ Clauson-Kass reaction,²⁹ Pictet-Spengler reaction,³⁰ synthesis of thiazolopyridines,³¹ n-alkylation of amines,³² regioselective synthesis of imidazoheterocycles,²⁵ Paal-Knorr reactions³³ and synthesis of thiazolidinones.³⁴

Although several methodologies have been reported for the synthesis of 1*H*-pyrazolo[3,4-*b*]quinoline, however the use of DES in this context has not yet been explored. This gap encouraged us to develop one pot multicomponent approach for the synthesis of quinolines using environmentally benign DES as a catalyst as well as the reaction media.

II. Material And Methods

All starting materials were commercially available and purchased from Sigma Aldrich and Merck in high purity. All the reactions were monitored by TLC. IR spectra of the products were recorded on Bruker 870 FTIR (ATR, Alpha) spectrometer. ¹H NMR spectra of all derivatives were recorded on an AMX-300, 300 MHz spectrometer by using TMS as an internal standard. ¹³C spectra were recorded on a 100 MHz spectrometer using DMSO-*d*₆ as a solvent and chemical shift expressed in ppm. Melting points of synthesized products were determined using an open capillary method and are uncorrected.

III. General Procedure

Synthesis of DES

Choline chloride (100 mmol) and urea (200 mmol) were combined in a flask and stirred while heating at 60 °C until a homogeneous liquid formed. The resulting eutectic mixture, which remains liquid at room temperature, was used directly in subsequent reactions without further purification.²³

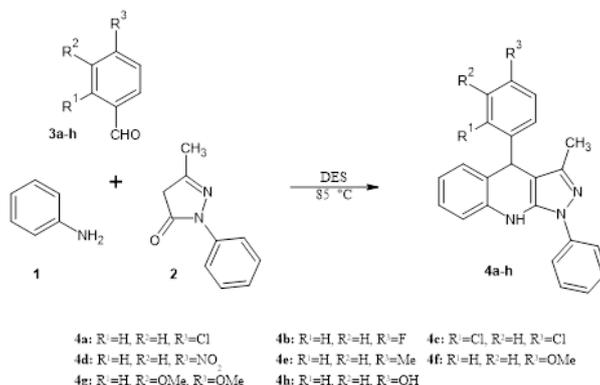
Synthesis of 1*H*-pyrazolo [3,4-*b*] quinolines (4a-h)

To a mixture of aniline **1** (1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **2** (1 mmol) and 2 cm³ of deep eutectic solvent (ChCl: Urea, 1:2) was added, followed by the in-situ addition of an aryl aldehyde **3a-h** (1 mmol). The reaction mixture was then refluxed for 100-110 minutes, and the progress of the reaction was monitored by TLC using a hexane-ethyl acetate solvent system. Upon completion, the reaction mixture was poured into ice-cold water. The resulting solid was filtered, washed with ethanol, and recrystallized from ethyl acetate.

IV. Results And Discussion

As part of our ongoing research on environment friendly and economical solvents in organic transformations, we have successfully employed deep eutectic solvents as a green reaction media as well as catalyst for various chemical reactions.^{25,31,34} In this current study, we report a sustainable and efficient multicomponent reaction (MCR) involving aldehydes, aniline and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one in urea and choline chloride-based DES (*Scheme 1*). This DES facilitates the synthesis of 1*H*-pyrazolo [3,4-*b*] quinolines, affording the desired products in good to excellent yields.

To optimise the reaction conditions, the reaction of aniline **1** (1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **2** (1 mmol) and 4-chlorobenzaldehyde **3a** (1 mmol) was selected as the model reaction. Initially, the reaction mixture was stirred at 65 °C without the use of a deep eutectic mixture; however, desired product was not observed even after 600 minutes of refluxing (*Table 1, Entry 1*). A series of deep eutectic mixtures were prepared and further used without any purification. (*Table 1*). Different choline chloride based eutectic mixtures were tested at 65 °C for the model reaction, yielding the desired product in low to moderate yield. The findings are summarized in *Table 1*. To our delight, remarkable improvement was observed when the deep eutectic mixture of choline chloride and urea (ChCl:Urea) in the ratio 1:2 was used. This eutectic solvent found to be a competent catalyst and produced high yield of product (*Table 1, Entry 15*). The strong hydrogen bonding among choline chloride and urea develops a synergistic effect, which likely plays a decisive role in improving the reaction's efficiency and activity.



Scheme 1: Synthesis of 1*H*-pyrazolo [3,4-*b*] quinolines

Further study into the effect of temperature on the model reaction was conducted by gradually increasing the temperature from 65 °C to 105 °C in 5 °C increments. The optimal reaction temperature was found to be 85 °C. (Table 1, Entry 19). To optimize the quantity of DES, the model reaction was carried out using different amounts of DES (1.0 g, 1.5 g, 2.0 g, 2.5 g and 3.0 g) at 85 °C. The respective yields of products were 60%, 80%, 90%, 90%, and 90%.

Table 1: Optimization of reaction conditions^(a)

Entry	Solvent / Catalyst	Temperature (°C)	Time (min)	Yield (%) ^(b)
1.	-	65	600	-
2.	ChCl ₄ (+) Tartaric Acid (2:1)	65	95	22
3.	ChCl:FeCl ₃ (1:2)	65	100	11
4.	ChCl:Malonic Acid(1:1)	65	90	33
5.	ChCl:Fumaric Acid (1:1)	65	95	15
6.	ChCl:Succinic Acid(1:1)	65	100	20
7.	ChCl:Citric Acid (2:1)	65	95	35
8.	ChCl:Glycerol (1:3)	65	95	45
9.	ChCl:Malic Acid (1:1)	65	85	28
10.	ChCl:Adipic Acid (1:1)	65	105	19
11.	ChCl:Penyl Acetic Acid (1:1)	65	100	13
12.	ChCl:ZnCl ₂ (1:2)	65	80	10
13.	ChCl:LaCl ₃ (2:1)	65	80	10
14.	ChCl:Thiourea(1:2)	65	115	67
15.	ChCl:Urea(1:2)	65	120	75
16.	ChCl:Urea(1:2)	70	110	80
17.	ChCl:Urea(1:2)	75	110	85
18.	ChCl:Urea(1:2)	80	105	87
19.	ChCl:Urea(1:2)	85	105	90
20.	ChCl:Urea(1:2)	90	105	90
21.	ChCl:Urea(1:2)	95	105	90
22.	ChCl:Urea(1:2)	105	105	90
23.	Urea	85	105	trace
24.	ChCl	85	105	10

^(a) Reaction conditions: Aniline **1** (1mmol), 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **2** (1 mmol), 4-chlorobenzaldehyde **3a** (1 mmol) in 2.0 g DES.
^(b) Isolated yields.

These observations indicate that 2.0 g of DES is adequate to drive the reaction effectively. Furthermore, without the deep eutectic mixture, no product formation was seen. When the model reaction was studied using only urea or choline chloride instead of DES, the product yield was found to be minimal (Table 1, Entry 23 & 24). This indicates that the improved reaction efficiency is due to the ChCl:Urea eutectic mixture rather than from its individual components, urea and choline chloride. This effect is attributed to the strong hydrogen bonding between the urea and choline chloride. When urea is mixed with choline chloride in different ratio, the resulting eutectic mixture exhibits slightly higher polarity than individual components, along with an increased hydrogen bond donor capability and improved dipolarity-polarizability.³⁵ To synthesize structurally diverse 1*H*-pyrazolo[3,4-*b*]quinoline derivatives, DES ChCl:Urea (1:2) emerged as an excellent catalyst as well as solvents, ensuring good yields of product.

Thus, the optimal reaction parameters for this methodology were determined as aniline **1** (1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **2** (1 mmol) and aldehydes **3a-h** (1 mmol), in 2.0 g DES at 85°C for 100-110 minutes (Table 1, Entry 19). After optimization of required reaction conditions, this protocol was further evaluated to the synthesis of 1*H*-pyrazolo[3,4-*b*]quinoline derivatives. The results indicates that DES ChCl:urea (1:2) outperforms other deep eutectic mixtures in terms of utilised reaction time and yield of the products (Table 2). The co-existence of urea and choline chloride through extensively strong H-bonding exhibits strong synergistic effect on the reaction, which is likely a key factor behind its exceptional catalytic performance.

Table 2: Synthesis of 1*H*-pyrazolo [3,4-*b*] quinolines (4a-j)^(a)

Entry	Compound	Time (min)	Yield (%) ^(b)	Melting point (°C)
1.	4a	105	90	196-198
2.	4b	105	85	202-204
3.	4c	100	90	206-208
4.	4d	105	90	211- 213
5.	4e	110	85	200-202
6.	4f	110	85	203-205
7.	4g	105	85	205-207
8.	4h	110	82	208-209

(a) **Reaction conditions:** Aniline **1** (1mmol), 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **2** (1 mmol), aldehyde **3a-h** (1 mmol) at 85 °C in 2.0 g DES.
 (b) **Isolated yields.**

Recyclability

The recyclability of ChCl:Urea based DES was investigated using the model reaction of aniline **1** (1mmol), 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **2** (1 mmol), 4-chlorobenzaldehyde **3a** (1 mmol) and DES (2.0 g) under optimized conditions. The progress of the reaction was tracked by TLC. After the completion of the reaction, the reaction mixture was poured into the ice-cold water. The solid product was filtered, washed with ethanol and recrystallised by using ethyl acetate. To recover the DES, the aqueous phase was concentrated under reduced pressure to remove water. The recovered solvent was then reused in subsequent reactions. The DES ChCl:Urea could be reused up to five times (Figure 1). Moreover, the model reaction was successfully scaled up to a 10 g batch under the same optimized conditions, demonstrating the method's scalability.

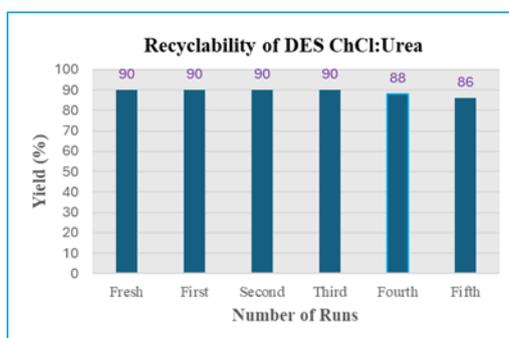


Figure 1: Recyclability of DES ChCl: Urea

V. Conclusions

To summarize, a practical and environmentally conscious strategy has been established for the synthesis of a variety of 1*H*-pyrazolo [3,4-*b*] quinoline derivatives through a multicomponent reaction facilitated by a deep eutectic solvent (DES). This approach stands out due to its high efficiency, broad compatibility with different substrates, cost-effectiveness, and minimal environmental impact. The reaction conditions are mild, the work-up is straightforward, and the DES used is not only reusable but also suitable for larger-scale applications, making this method a promising option for green and scalable synthesis.

VI. Representative Spectral Analysis

4-(4-Chlorophenyl)-3-methyl-1-phenyl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinoline (4a): Colour : White solid, Melting Point: 196-198 °C (Lit²⁰ 196-198 °C). ¹H NMR (300 MHz, DMSO-*d*₆, δ ppm): 2.28 (3H, s); 4.92 (1H, s); 7.12-7.68 (13H, m); 13.72 (1H, s); ¹³C NMR (100 MHz, DMSO-*d*₆) : 15.0, 31.0, 120.5, 123.0, 128.2, 128.8, 129.0, 129.2, 129.3, 129.6, 129.8, 129.9, 130.3, 131.4, 132.1, 134.3, 142.6, 147.1, 160.3; IR (Stretching frequency ν, cm⁻¹) : 740 (Cl-Ph), 1610, 1651(C=N), 3213 (N-H); Mass *m/z* (M+H)⁺ : 372.1222

3-Methyl-4-(4-nitrophenyl)-1-phenyl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinoline (4d): Colour: Orange solid; Melting point: 211-213 °C (Lit²⁰ 210-212 °C). ¹H NMR (300 MHz, DMSO-*d*₆, δ ppm): 2.46 (3H, s); 4.89 (1H, s); 7.14-7.81 (13H, m); 13.22 (1H,s); ¹³C -NMR (100 MHz, DMSO-*d*₆) : 12.8, 33.9, 121.1, 121.9, 126.7, 127.1, 128.0, 129.4, 129.5, 129.7, 129.8, 129.9, 130.2, 131.9, 132.4, 134.3, 141.8, 148.3, 160.3; IR (Stretching frequency ν, cm⁻¹): 810, 1348, 1563 (NO₂), 1510, 1580 (C=N), 3325 (N-H); Mass *m/z* (M+H)⁺ : 383.1498.

4-(4-Methoxyphenyl)-3-methyl-1-phenyl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinoline (4f): Colour: Yellow solid, Melting point: 203-205 °C(Lit²⁰ 204-206 °C). ¹H NMR (300 MHz, DMSO-*d*₆, δ ppm): 2.22 (3H, s), 3.88 (3H, s), 4.87 (1H, s), 7.17-7.81 (13H, m), 13.34 (1H, s); ¹³C NMR (100 MHz, DMSO-*d*₆) : 14.1, 34.2, 48.1, 120.0, 121.3, 121.6, 125.7, 126.8, 127.7, 128.8, 129.1, 129.5, 129.6, 130.3, 132.1, 132.9, 136.3, 142.7, 148.7, 160.0; IR (Stretching frequency ν, cm⁻¹): 1560, 1588 (C=N), 3244 (N-H); Mass *m/z* (M+H)⁺ : 368.1787.

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