

Serendipitous synthesis of 2,3-dihydroquinazolin-4(1H)-ones in ZnCl₂/urea deep eutectic solvent

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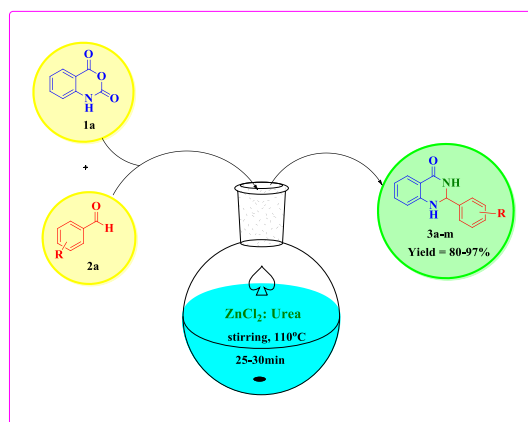
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Abstract

A green, sustainable, and efficient one-pot, synthetic strategy for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones (DHQs) was developed. The ZnCl₂/urea used as a deep eutectic solvent (DES) not only efficiently promoted the condensation between isatoic anhydride and benzaldehyde but unexpectedly acted as a nitrogen source (like ammonia) *in situ* to afford DHQs in excellent yields. This approach offers remarkable advantages, involving the triple role of DES in the synthesis of DHQs, atom-economical, green organocatalysts, metal-free conditions, cost-effectiveness, and tolerance to a range of functional groups.



Keywords: Deep eutectic solvent, 2,3-dihydroquinazolinone, green chemistry, heterocyclic compounds, solvent-free

Introduction

Among the major limitations of organic solvents are their flammability, volatility, toxicity, high cost, and environmental impact.¹ Nowadays, the most demanding and active area of research is developing atom-economic, environment-friendly, and green methods for organic transformations.²⁻⁵ In the past decade, ionic liquids (ILs) have attracted much attention due to their promising properties: non-flammability, stability, eco-friendliness, low volatility, and recyclability.⁶ Unfortunately, ILs have some impediments like a lack of biocompatibility, difficult purification, high air/moisture sensitivity, and expensive and complicated synthetic process.⁷

To overcome the aforementioned issues, recently researchers worldwide have paid substantial attention to deep eutectic solvents (DESs). These DESs combine hydrogen bond donors such as urea, and ammonium acetate, and hydrogen bond acceptors such as choline chloride or zinc chloride in precise molar ratios to generate relatively low boiling solvents.⁸⁻¹⁰ DESs are greener and more sustainable alternatives to ILs¹¹ and serve as excellent solvents in organic synthesis owing to their tremendous properties such as excellent catalytic action, cost-effectiveness, biodegradability, use without additional purification, non-toxicity, and non-volatility.¹²⁻¹⁴ As a result, DESs find a lot of applications in many organic conversions like Paal-Knorr reaction,¹⁵ Perkin reaction,¹⁶ Hantzsch reaction,¹⁷ Biginelli reaction,¹⁸ Diels-Alder reaction¹⁹, etc.

Heterocyclic compounds have displayed incredible applications in the chemical and pharmaceutical industries.²⁰⁻²² Among various nitrogen heterocycles, 2,3-dihydroquinazolin-4(1*H*)-ones (DHQs) have shown immense potential in various sectors, particularly in the medicinal field. The heterocycles bearing DHQ as a core of their structure or a structural unit have been reported to exhibit various biological activities such as anticancer,²³ antimalarial,²⁴ antiviral,²⁵ antitubercular,²⁶ antibacterial,²⁷ etc. For instance, quinethazone and fenquizone are DHQ-based antihypertensive drugs²⁸ (Figure 1).

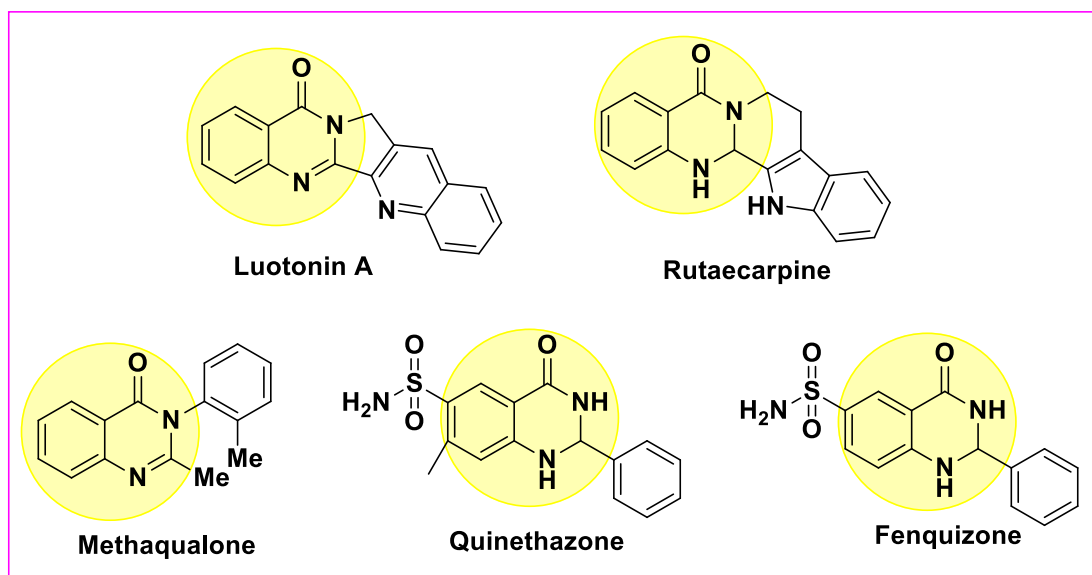


Figure 1. DHQ core structure in some important drugs.

Accordingly, various reaction methods targeting the synthesis of diversely substituted DHQs have been reported in the literature. One of the commonly used methods involves a three-component reaction between isatoic anhydride, ammonium acetate (a nitrogen source), and aldehyde^{29, 30} that has been carried out using

different Brønsted/Lewis acids catalysts such as citric acid,³¹ β -CD-SO₃H,³²⁻³⁴ cellulose-H₃BO₃, Sc (OTf)₃,³⁵ *p*-TSA,³⁶ and acetic acid³⁷, etc. However, all of these reactions suffer from different limitations including acidic environment, prolonged reaction times, use of sophisticated catalysts prepared in multiple steps, moderate yields, and cumbersome work-up/purification procedures.^{38,39} In 2019, Solorzano and coworkers⁴⁰ also employed the same three-component reaction protocol between isatoic anhydride, benzaldehyde, and ammonium acetate or different aromatic amines (as a nitrogen source) for the synthesis of DHQs, using ZnCl₂/urea as a DES at 110 °C (Figure 2).

In continuation with our research interests in the synthesis of nitrogen heterocycles coupled with the incredible medicinal significance of DHQs, we explored the reaction between isatoic anhydride and different benzaldehydes in ZnCl₂/urea DES that serendipitously led to the formation of DHQs disclosing an unprecedented role of DES in synthesizing this class of heterocyclic compounds. The present demonstrates a triple role of DES as a green solvent, an eco-friendly catalyst that promotes condensation, and a substrate that can donate nitrogen to the product making it a relatively easier and cost-effective protocol for the synthesis of DHQs. A plausible mechanism showing the generation of ammonia from DES that eventually acts as a nitrogen source in the formation of DHQs in these reactions is also proposed. To the best of our knowledge, this is the first report in which the urea in DES has been proposed to release ammonia that subsequently acts as a nitrogen source in this reaction. Also, our reaction procedure demonstrated that the reaction can proceed without ammonium acetate as opposed to the previously published work³⁷. However, the reaction remains a three-component reaction based on the components contributed by the reactants.

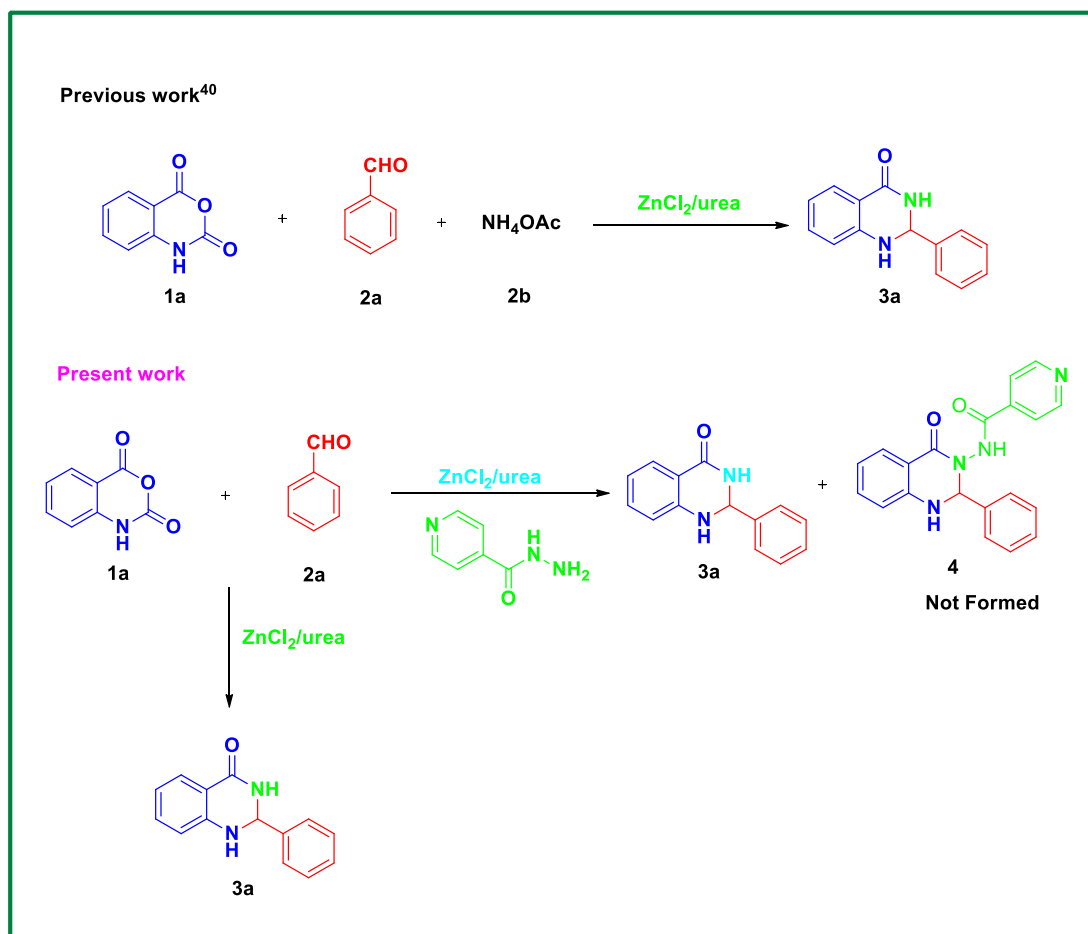
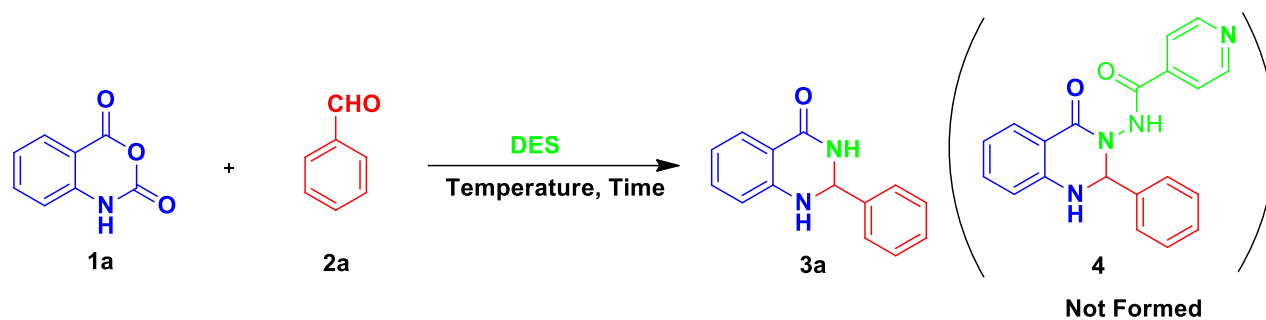


Figure 2. Present and past reactions towards DHQs synthesis.

Results and Discussion

We initiated our study by heating an equimolar mixture of isatoic anhydride, isonicotinic acid hydrazide (isoniazid), and benzaldehyde in $\text{ZnCl}_2/\text{urea}$ DES at 110 °C for 35 min (Table 1, entry 1) with the aim to synthesising a new molecular hybrid of DHQ and isoniazid (**4**). The monitoring of the reaction by thin-layer chromatography (TLC) indicated the formation of a UV-fluorescent spot which was separated using column chromatography. Surprisingly, the initial proton NMR analysis of the isolated compound ruled out the formation of the expected product (**4**) based on the absence of proton resonances of isoniazid and prompted us to characterize the structure of this unknown compound. The subsequent detailed NMR analysis of the compound interestingly indicated the serendipitous obtention of 2-phenyl DHQ (**3a**) as reported previously,⁴¹⁻⁴³ and prompted us to explore the scope of this reaction further in the synthesis of DHQ derivatives. We were subsequently curious to know which substrate acts as a nitrogen source in the reaction. To accomplish this, we refluxed the same starting materials in ethanol which again offered the same product **3a** as confirmed by TLC and NMR spectroscopy, however, extended the reaction time led to a decrease in the yield (Table 1, entry 2). To confirm whether isoniazid or DES played the role of the nitrogen source, further reaction optimization was conducted without isoniazid (Table 1, entry 3). Delightfully, the reaction proceeded in 25 minutes with an improved yield (95%) of **3a**. Hence, these studies confirmed that the isoniazid did not play any role in the reaction but somehow negatively impacted the reaction outcome in terms of reaction time and product yield (Table 1, entries 1–3). The reaction was also performed using only urea in different moles of urea (3.5 mmol and 1 mmol) and afforded the unreacted starting materials without any traces of the product (TLC-based) (Table 1, entries 4 and 5). The same reaction outcome was observed when this reaction was carried out in refluxing ethanol for 2.5 h (Table 1, entry 6). These results led us to believe that urea alone is ineffective in catalyzing this reaction. Similarly, the reaction carried out using Lewis acid catalyst, ZnCl_2 (1 mmol) in ethanol, or under solvent-free conditions also did not produce the desired product (Table 1, entries 7 and 8) ruling out their individual role in the conversion to a product.

The use of another DES system choline chloride (ChCl) and urea (ChCl/urea) in catalyzing the reaction of **1a** and **2a** was unsuccessful (Table 1, entry 9). Finally, the Lewis acid capacity of ChCl and AlCl_3 to catalyze this reaction also did not lead to the product **3a** (Table 1, entries 10 and 11). Based on these optimization studies, the reaction conditions employing $\text{ZnCl}_2/\text{urea}$ DES (Table 1 entry 3) were proven to be the best choice and were subsequently used for further derivatization of **3a**. The results are depicted in Table 2.

Table 1. Optimization of protocols for the synthesis of DHQ

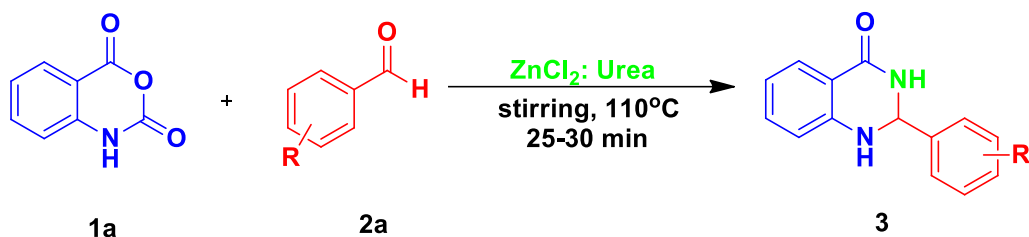
Entry	DES (molar ratio)	Solvent (mL)	Temperature (°C)	Time (min)	Yield (%) ^a
1	ZnCl ₂ /Urea (1:3.5)	-	110	35	88 ^b
2	ZnCl ₂ /Urea (1:3.5)	EtOH	80	60	72 ^c
3	ZnCl ₂ /Urea (1:3.5)	-	110	25	95
4	Urea (3.5mmol)	-	110	25	0
5	Urea (1mmol)	-	110	25	0
6	Urea (1mmol)	EtOH	80	150	0
7	ZnCl ₂ (1mmol)	EtOH	80	150	0 ^d
8	ZnCl ₂ (1mmol)	-	110	25	0 ^d
9	Choline chloride/Urea (1:2)	-	110	25	0
10	Choline chloride (1mmol)	-	110	25	0 ^d
11	AlCl ₃ (1mmol)	-	110	25	0 ^d

^aIsolated yield.

^bReaction protocols: **1a** (1mmol), **2a** (1mmol), isoniazid (1mmol), 8 g of DES (ZnCl₂/Urea (1:3.5) at 110 °C.

^cReaction protocols: **1a** (1mmol), **2a** (1mmol), isoniazid (1mmol), 8 g of DES (ZnCl₂/Urea (1:3.5) and ethanol at 80 °C.

^dReaction protocols: **1a** (1mmol), **2a** (1mmol), urea (1mmol), ZnCl₂ (1mmol), ethanol, reflux.

Table 2. Synthesis of DHQ & its derivatives

Entry	R	Product	Yield (%) ^a	Measured mp (°C)	Reported ^{Ref} mp (°C)
1	Ph		95	214-216	216-218 ^{43,50}
2	4-(Cl)-C ₆ H ₄		92	204-206	205-206 ^{43,44}
3	4-(F)-C ₆ H ₄		96	200-201	203-204 ⁴³
4	4-(NO ₂)-C ₆ H ₄		90	>300	>300 ^{45,46}
5	4-(Br)-C ₆ H ₄		94	195-196	196-198 ⁴⁷

Table 2. Continued

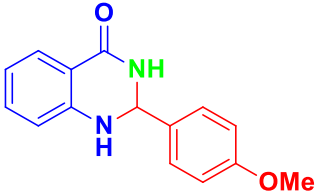
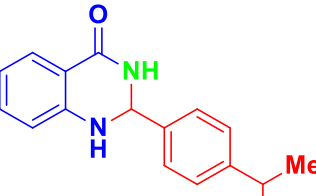
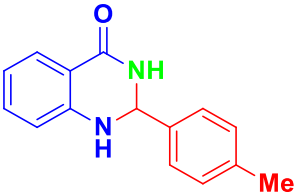
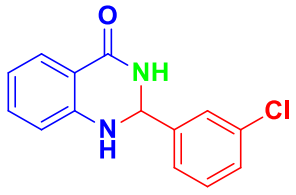
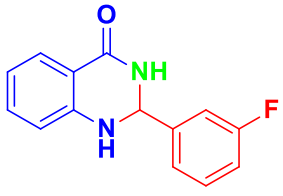
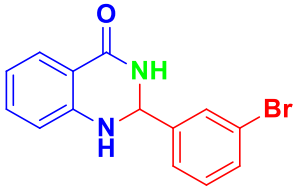
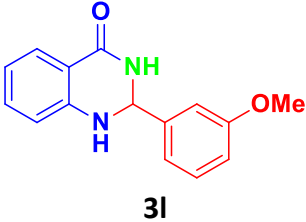
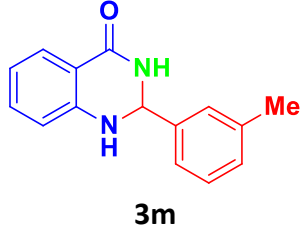
Entry	R	Product	Yield (%) ^a	Measured mp (°C)	Reported ^{Ref} mp (°C)
6	4-(OMe)-C ₆ H ₄	 3f	91	183-185	181-183 ⁴³
7	4-(<i>iso</i> -Propyl)-C ₆ H ₄	 3g	96	161-164	162-163 ⁴⁷
8	4-(Me)-C ₆ H ₄	 3h	80	221-222	224-225 ^{47,48,50}
9	3-(Cl)-C ₆ H ₄	 3i	94	184-186	185-187 ^{43,44}
10	3-(F)-C ₆ H ₄	 3j	97	263-266	264-266 ⁴³
11	3-(Br)-C ₆ H ₄	 3k	92	228-230	227-228 ⁴⁸

Table 2. Continued

Entry	R	Product	Yield (%) ^a	Measured mp (°C)	Reported ^{Ref} mp (°C)
12	3-(OMe)-C ₆ H ₄	 3l	88	147-149	148-150 ⁴⁴
13	3-(Me)-C ₆ H ₄	 3m	94	206-207	206-207 ⁴⁸

^aIsolated yield.^RReference.

Different aldehydes bearing electron-withdrawing or electron-donating groups were coupled with isatoic anhydride to get deeper insights into their reactivity. Worth of note, the electronic factors did not play much role as both aldehydes bearing electron-donating and electron-withdrawing groups reacted smoothly with isatoic anhydride under the optimized conditions offering the corresponding DHQs in good to high yield (80-97%). The mechanistic pathway depicting the significance of DES in the synthesis of DHQs is outlined in Figure 3.^{40, 49}

The reaction is initiated by in-situ-generated ammonia from urea in a deep eutectic solvent (Figure 3). The generation of ammonia vapors in the reaction was confirmed by using litmus paper test (color changes from red to blue). The ZnCl₂ component facilitates the nucleophilic addition of ammonia to carbonyl carbon at the C-4 position of isatoic anhydride **1a**, followed by decarboxylation to yield anthranilamide **A** as an intermediate. The Schiff base **B** is subsequently formed when the amino group of **A** attack the carbonyl carbon of the aldehyde, which has been activated by the eutectic mixture. In the final step, the activated azomethinic group is attacked by the nitrogen of the amide, resulting in the desired DHQ derivative.

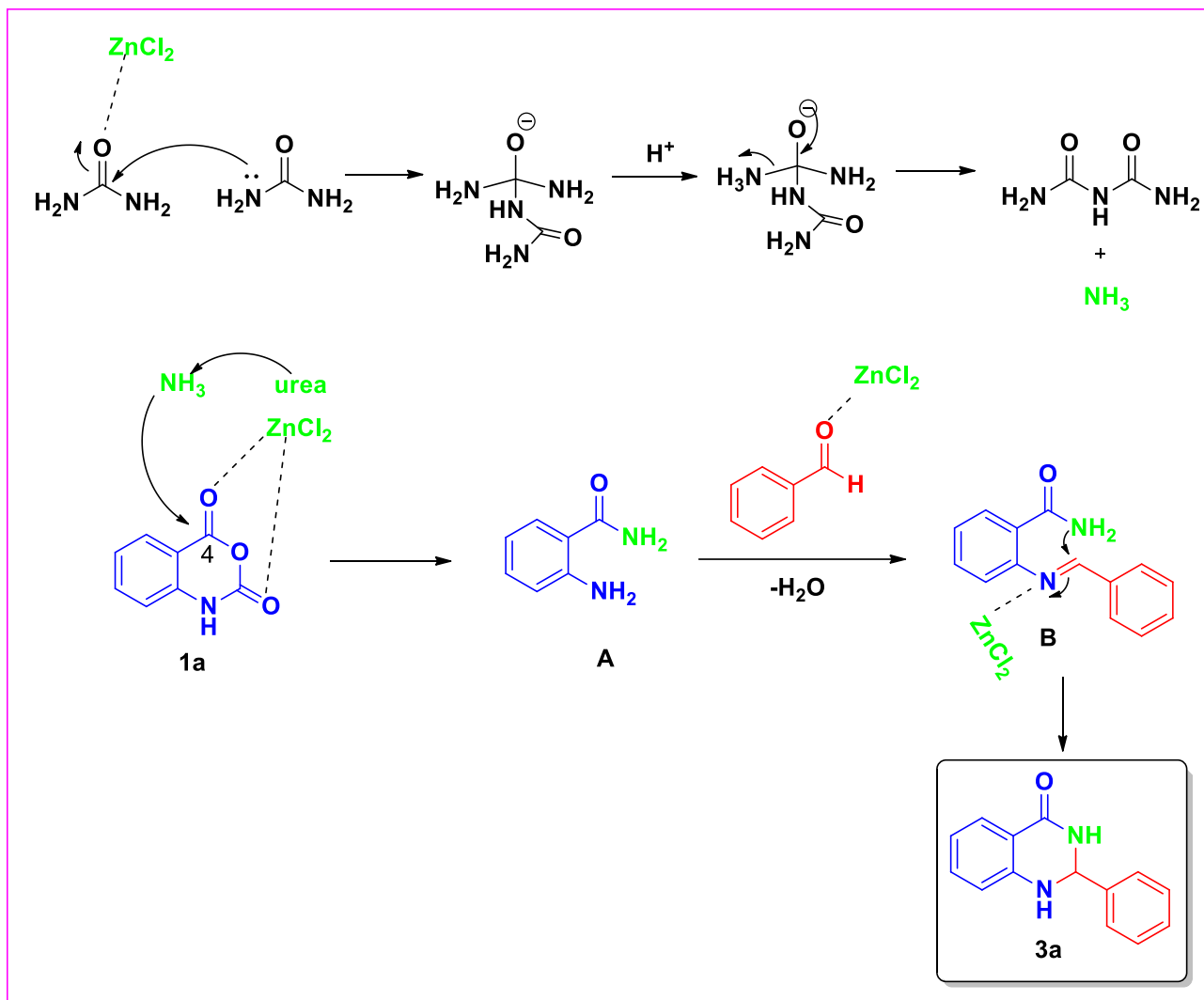


Figure 3. A proposed mechanism for the synthesis of DHQ.

Conclusions

An accidental three-component reaction in DES offered 2,3-dihydroquinazolines in excellent yields. The method employed was found to be atom-economical, cost-effective, green, and eco-friendly. Moreover, DES in this method played a triple role as a nitrogen source, catalyst, and solvent. The reaction conditions showed a wide range of tolerance abilities to varying substituted aldehydes bearing both electron-donating and electron-withdrawing groups.

Experimental Section

General. All chemicals were purchased from commercial sources (Acros, Spectrochem, Merck, and Aldrich). ^1H and ^{13}C NMR spectra were recorded on Bruker spectrometer using a 600 MHz spectrometer. TLCs Kieselgel-60 F-254 used to monitor the reaction were procured from Merck. Melting points were recorded using the

melting point apparatus. Prominence-i (LC-2030C 3D) and PerkinElmer FT-IR Spectrometer were used to perform the LC-MS and IR spectral analysis of the compounds, respectively.

Preparation of DES. The DES was prepared as per the reported method.⁴⁰ The ZnCl₂ and urea (1:3.5) were taken in a test tube and heated at 80 °C until the solid phase converted into a transparent liquid and used further without any purification.

General procedure for the synthesis of DHQ. A mixture of isatoic anhydride (**1a**) and benzaldehyde (**2a**) was dissolved in ZnCl₂/urea deep eutectic solvent for 25 min, and the reaction progress was monitored using TLC. After completion of the reaction, water was added to the reaction mixture. Solid precipitate obtained filtered out and purified by using recrystallization in ethanol. Compounds **3a**, **3c**, **3f**, **3g**, **3j**, and **3m** were characterized with NMR spectroscopy, remaining derivatives were confirmed with IR spectra, LCMS and melting points also verified with literature.

2-Phenyl-2,3-dihydroquinazolin-4(1H)-one (3a).¹¹ (CAS Registry Number: 954-91-6) IR (ATR): 1608, 1653, 3067, 3166, 3299 cm⁻¹. ¹HNMR (600 MHz, DMSO-*d*₆): 5.75 (s, 1H), 6.66-6.69 (t, *J* 15.03 Hz, *J* 7.42 Hz, 1H), 6.74-6.75 (d, *J* 8.02 Hz, 1H), 7.11 (s, 1H), 7.23-7.26 (dd, *J* 7.15 Hz, *J* 1.02 Hz, 1H), 7.33-7.40 (m, 3H), 7.49-7.50 (d, *J* 7.30 Hz, 2H), 7.61-7.62 (d, *J* 7.30 Hz, 1H), 8.29 (s, 1H); ¹³C NMR (APT) (150 MHz, DMSO-*d*₆): 67.0, 114.8, 115.4, 117.5, 127.3, 127.8, 128.7, 128.8, 133.7, 142.1, 148.3, and 164.3. MS *m/z* 225 (M+1).

2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (3b).¹¹ (CAS Registry Number:13165-11-2) IR (ATR): 1609, 1651, 3058, 3190, 3311 cm⁻¹. MS *m/z* 258.05 (M+1); Anal. Calc. for C₁₄H₁₁ClN₂O: 258.05; found: 259.

2-(4-Fluorophenyl)-2,3-dihydroquinazolin-4(1H)-one (3c).¹¹ (CAS Registry Number:359605-44-0) IR (ATR): 1603, 1648, 3040, 3175, 3302 cm⁻¹. ¹HNMR (600 MHz, DMSO-*d*₆): 5.78 (s, 1H), 6.67-6.70 (t, *J* 14.77 Hz, *J* 7.50 Hz, 1H), 6.74-6.75 (d, *J* 7.94 Hz, 1H), 7.10 (s, 1H), 7.21-7.26 (m, 3H), 7.53-7.55 (dd, *J* 14.11 Hz, *J* 3.39 Hz, 2H), 7.61-7.62 (d, *J* 7.80 Hz, 1H), 8.29 (s, 1H); ¹³C NMR (APT) (150 MHz, DMSO-*d*₆): 66.4, 114.9, 115.4, 115.6, 117.7, 127.8, 129.4, 129.5, 133.8, 138.3, 148.2, 161.7, 163.3, and 164.0. MS *m/z* 243 (M+1).

2-(4-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (3d).¹¹ (CAS Registry Number:26029-31-2) IR (ATR): 1604, 1640, 3030, 3162, 3290 cm⁻¹. MS *m/z* 270 (M+1).

2-(4-Bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (3e).¹¹ (CAS Registry Number:358386-50-2) IR (ATR): 1603, 1644, 3012, 3191, 3290 cm⁻¹. MS *m/z* 303 (M+1).

2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (3f).¹¹ (CAS Registry Number:61195-16-2) IR (ATR): 1611, 1648, 2991, 3177, 3304 cm⁻¹. ¹HNMR (600 MHz, DMSO-*d*₆): 3.75 (s, 3H), 5.71 (s, 1H), 6.66-6.69 (t, *J* 14.79 Hz, *J* 7.39 Hz, 1H), 6.73-6.75 (d, *J* 8.08 Hz, 1H), 6.94-6.95 (d, *J* 8.62 Hz, 2H), 7.01 (s, 1H), 7.23-7.25 (t, *J* 7.60 Hz, *J* 7.26 Hz, 1H), 7.41-7.43 (d, *J* 8.62 Hz, 2H), 7.60-7.62 (d, *J* 7.67 Hz, 1H), 8.19 (s, 1H); ¹³C NMR (APT) (150 MHz, DMSO-*d*₆): 55.6, 66.7, 114.1, 114.9, 115.4, 115.5, 127.8, 128.6, 134.2, 134.8, 148.4, 159.9, 164.1. MS *m/z* 255 (M+1).

2-(4-Isopropylphenyl)-2,3-dihydroquinazolin-4(1H)-one (3g).¹¹ (CAS Registry Number:83800-96-8) IR (ATR): 1607, 1654, 2948, 3196, 3298 cm⁻¹. ¹HNMR (600 MHz, DMSO-*d*₆): 1.18 (d, *J* 6.99 Hz, 6H), 2.85 (septet, 7H), 5.7 (s, 1H), 6.66-6.68 (t, *J* 15.02 Hz, *J* 7.36 Hz, 1H), 6.73-6.74 (d, *J* 7.66 Hz, 1H), 7.07 (s, 1H), 7.22-7.27 (m, 3H), 7.41-7.43 (d, *J* 7.95 Hz, 2H), 7.61-7.62 (d, *J* 7.82 Hz, 1H), 8.24 (s, 1H); ¹³C NMR (APT) (150 MHz, DMSO-*d*₆): 24.3, 33.7, 67.0, 114.8, 115.4, 117.5, 126.7, 127.4, 127.8, 133.7, 139.5, 148.4, 149.2, and 164.1. MS *m/z* 267 (M+1).

2-(p-tolyl)-2,3-dihydroquinazolin-4(1H)-one (3h).¹¹ (CAS Registry Number:13324-79-3) IR (ATR): 1600, 1654, 3045, 3198, 3302 cm⁻¹. MS *m/z* 239 (M+1).

2-(3-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (3i).¹¹ (CAS Registry Number:83800-92-4) IR (ATR): 1612, 1643, 3028, 3181, 3290 cm⁻¹. MS *m/z* 243 (M+1).

2-(3-Fluorophenyl)-2,3-dihydroquinazolin-4(1H)-one (3j).¹¹ (CAS Registry Number:386242-54-2) IR (ATR): 1609, 1648, 3178, 3284, 3345 cm⁻¹. ¹HNMR (600 MHz, DMSO-*d*₆): 5.79 (s, 1H), 6.67-6.70 (t, *J* 14.85 Hz, *J* 7.68 Hz, 1H), 6.76-6.77 (d, *J* 8.30 Hz, 1H), 7.16-7.34 (m, 5H), 7.41-7.45 (dd, *J* 7.81 Hz, 1H), 7.60 (d, *J* 7.46 Hz, 1H), 8.42 (s, 1H); ¹³C NMR (APT) (150 MHz, DMSO-*d*₆): 66.1, 113.9, 114.1, 11.9, 115.5, 115.6, 117.7, 123.2, 127.8, 130.8, 130.84, 133.8, 145.3, 147.9, 161.7, 163.3, and 163.88\$. MS *m/z* 243 (M+1).

2-(3-Bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (3k).¹¹ (CAS Registry Number:304451-29-4) IR (ATR): 1609, 1646, 3033, 3199, 3281 cm⁻¹. MS *m/z* 303 (M+1).

2-(3-Methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (3l).¹¹ (CAS Registry Number:198068-91-6) IR (ATR): 1606, 1643, 2911, 3060, 3200 cm⁻¹ MS *m/z* 255 (M+1).

2-(*m*-tolyl)-2,3-dihydroquinazolin-4(1H)-one (3m).¹¹ (CAS Registry Number:83800-93-5) IR (ATR): 1612, 1645, 3030, 3183, 3299 cm⁻¹. ¹HNMR (600 MHz, DMSO-*d*₆): 2.31 (s, 3H), 5.71 (s, 1H), 6.66-6.68 (t, *J* 14.84 Hz, *J* 7.42 Hz, 1H), 6.73-6.75 (d, *J* 7.81 Hz, 1H), 7.07 (s, 1H), 7.16 (d, *J* 4.15 Hz, 1H), 7.22-7.28 (m, 3H), 7.60 (d, *J* 8.04 Hz, 1H), 8.24 (s, 1H); ¹³C NMR (APT) (150 MHz, DMSO-*d*₆): 21.5, 67.1, 114.8, 117.5, 124.4, 127.8, 127.95, 128.7, 129.5, 133.7, 137.8, 141.9, 148.3, and 164.0. MS *m/z* 239 (M+1).

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Supplementary Material

Provided as a separate file.

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