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Copper and electrocatalytic synergy for the construction of fused quinazolinones with 2-aminobenzaldehydes and cyclic amines†

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A new copper and electrocatalytic synergy strategy for efficiently constructing fused quinazolinones has been developed. In the presence of cupric acetate and oxygen, aryl ketones and 1,2,3,4-tetrahydroisoquinoline can smoothly participate in this transformation, thus providing a variety of substituted quinazolinones in an undivided cell. The reaction shows good functional group tolerance and provides universal quinazolinones at a good yield under mild conditions.

Nitrogen heterocyclic compounds have played pivotal roles in malaria chemotherapy progressing from quinine to chloroquine, mefloquine, and amodiaquine in the last century.¹ Studies have shown that quinazolinone alkaloids and their analogs have good antimalarial activity.² At the same time, quinazolinones also demonstrate a series of pharmacological and biological activities among various nitrogen-containing heterocyclic compounds.³ These include anti-cancer,⁴ anti-inflammatory,⁵ anticonvulsant,⁶ and anti-allergy effects.⁷ Especially, due to their wide pharmacological activities, fused quinazolinones have been regarded as potential drug molecules against various types of diseases (Fig. 1).

In light of this utility, many methods for synthesizing quinazolinones have been developed over the last decade. Among them, traditional synthetic methods for fused quinazolinones involve the oxidative decarboxylation of isatin and tetrahydroisoquinoline catalyzed by Cu²⁺ or peroxide (Scheme 1a).⁸ In addition, 2-aminoarylmenthanol and isoquinoline can be converted to quinazolinone in the presence of MOF-derived cobalt nanoparticles (Scheme 1b).⁹ However, these methods require large amounts of oxidants and additives, high reaction temperatures, and pre-functionalized complex substrates, which limits their usefulness. Interestingly, Xie and their coworkers reported a visible-light-induced cyclization of 2-aminobenzaldehydes with tetrahydroisoquinoline for the synthesis of fused quinazolinones (Scheme 1c).¹⁰ Although this

reaction provided a green, simple, and oxidant-free strategy, further research for overcoming the limited substrate scope and ambiguous transformation process is still needed.

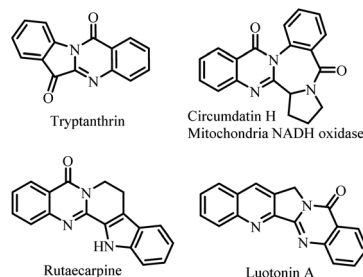
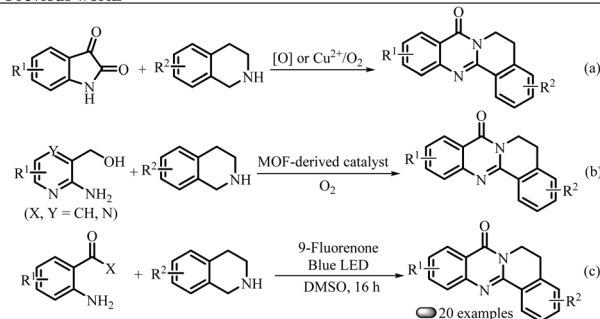
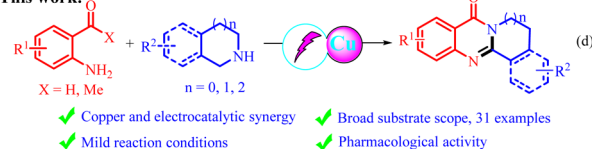


Fig. 1 Representative drugs and bioactive quinazolinones.

Previous works



This work:



Scheme 1 Strategies for the synthesis of quinazolinones.

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Organic mechatronic synthesis has attracted much attention in recent years due to its environmental friendliness, sustainability and mild reaction conditions.^{11,12} Organic conversion triggered by electricity is becoming a uniquely powerful tool for building new chemical bonds in organic synthesis.¹³ Recently, our research group have developed some organic electrochemical strategies for the efficient construction of N-containing heterocyclic compounds.¹⁴ Based on our previous works, in this work, we developed a new copper and electrocatalytic synergy strategy for the efficient construction of fused quinazolinones. The reaction shows good functional group tolerance and provides universal quinazolinones at a good yield at mild conditions (Scheme 1d).

We began our study by choosing 2-aminobenzaldehyde **1a** and tetrahydroisoquinoline **3a** as template substrates to screen the optimal reaction conditions. The reaction was carried out in an undivided three-necked flask with an aluminum rod cathode and a carbon rod anode, ⁿBu₄NBF₄ as the supporting electrolyte, and a mixture of Cu(AcO)₂ with these compounds in 10 mL MeOH solution at room temperature (Table 1). To our delight, the reaction performed very well under the original electrized conditions, leading to obtaining the product **4a** with a 94% yield in 13 hours (entry 1). A shorter or longer reaction time was insufficient to effectively form the product (entry 2 and 3). Changing the electrolyte from ⁿBu₄NBF₄ to ⁿBu₄LiClO₄ or

ⁿBu₄NPF₆ resulted in a reduced product yield (entries 4 and 5). Both increasing or decreasing the current afforded the final product in lower yield (entries 6 and 7). As for the reaction solvent, DMSO, DMA, DMF and CH₃CN exhibited lower product yields when compared with CH₃OH (entries 8–11). Further increase the polar of solvent by adding 0.5 mL H₂O, the reaction will be suppressed (entry 12). When using KI or NaI instead of NH₄I, the reaction proceeded with poor reactivity (entries 13 and 14). Using N₂ or air instead of O₂, the reactivity will be affected (entry 15 and 16). This result indicated that O₂ are significant for this transformation. Using the Pt plate as electrode led to poor reaction efficiency (entry 17 and 18). When there is no Cu(CH₃COO)₂, the yield drops to 57% (entry 19). Finally, the electrolyte or electricity are necessary for this transformation (entry 21).

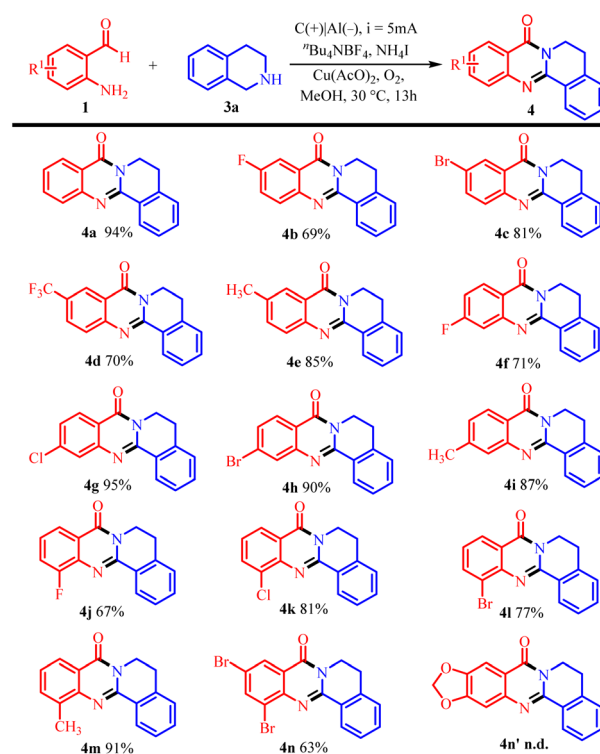
Under optimal conditions, the application range of substrates for electrolytic synthesis of quinazolinones was studied. Firstly, the conversion of various substituted 2-aminobenzaldehyde was investigated. Of particular note, functional groups such as Me, MeO, F, Cl and Br were well tolerated in the reaction (Table 2, **4b–m**). When the functional group is located in C-5 position, the yield of the electron-donating group is higher than that of the electron-withdrawing group. When the functional group is located at the C-4 position, the yield of the reaction is higher than that at the C-3 and C-5 positions. When

Table 1 Optimisation of reaction conditions^a

Entry	Variation from the standard conditions	Yield ^b (%)
1	None	94%
2	10 h instead of 13 h	60%
3	18 h instead of 13 h	90%
4	ⁿ Bu ₄ LiClO ₄ instead of ⁿ Bu ₄ NBF ₄	N.R.
5	ⁿ Bu ₄ NPF ₆ instead of ⁿ Bu ₄ NBF ₄	63%
6	3 mA instead of 5 mA	79%
7	9 mA instead of 5 mA	85%
8	DMSO as solvent	N.R.
9	DMA as solvent	31%
10	DMF as solvent	22%
11	CH ₃ CN as solvent	45%
12	9.5 mL CH ₃ OH + 0.5 mL H ₂ O as solvent	N.R.
13	KI instead of NH ₄ I	32%
14	NaI instead of NH ₄ I	41%
15	N ₂ instead of O ₂	N.R.
16	Air instead of O ₂	22%
17	C(+) Pt(−) instead of C(+) Al(−)	30%
18	Pt(+) Pt(−) instead of C(+) Al(−)	26%
19	Without Cu(AcO) ₂	57%
20	Without electrolytes or electricity	N.R.

^a Reaction conditions: aluminum rod cathode, carbon rod anode, constant current = 5 mA, **1a** (0.2 mmol), **3a** (0.3 mmol), ⁿBu₄NBF₄ (0.5 mmol), NH₄I (0.5 mmol), Cu(AcO)₂ (1% mmol), MeOH (10 mL), O₂, 30 °C, undivided cell. ^b Isolated yield.

Table 2 Substrate scope of 2-aminobenzaldehyde **1**^a



^a Reaction conditions: aluminum rod cathode, carbon rod anode, constant current = 5 mA, **1** (0.2 mmol), **3a** (0.3 mmol), ⁿBu₄NBF₄ (0.5 mmol), NH₄I (0.5 mmol), Cu(AcO)₂ (1% mmol), MeOH (10 mL), O₂, 30 °C, undivided cell.

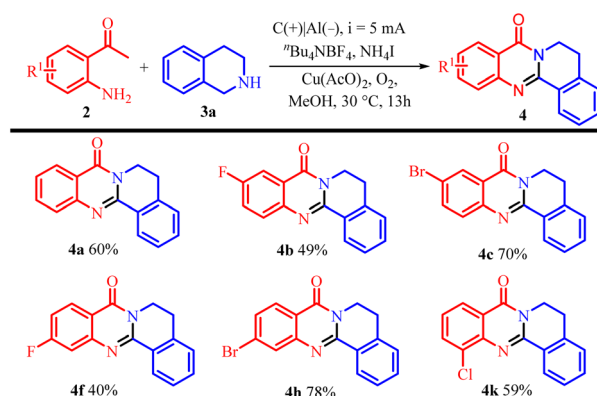


substituent group is located in C-3 position, the corresponding electron-withdrawing group substitution products **4j**, **4k** and **4l** are obtained with yields of 67%, 81% and 77%, respectively (Table 2, **4j–l**). The electron donor substitution product **4m** with 91% yield was also obtained. The yield of di-substituted quinazolinone **4n** was 63% (Table 2, **4n**). It is a pity that 6-amino-benzo[*d*][1,3]dioxole-5-carbaldehyde couldn't participate in this transformation (Table 2, **4n'**).

Then, we continued to investigate the substrate range of tetrahydroisoquinoline (Table 3). When C-7 is linked to Br substituent, the reactivity is very well, and gave the yield 86% (Table 3, **4t**). While other tetrahydroisoquinolines with electron-attracting or electron-donating groups reduced the reactivity (Table 3, **4o–s**, **4u**). The yield of di-substituted quinazolinone **4v** was 43% (Table 3, **4v**). It is noteworthy that other cyclic amine substrates tetrahydropyrrole and hexamimide were also compatible with the reaction (Table 3, **4w** and **4x**). Interestingly, the natural active alkaloid red pine was obtained in this reaction (Table 3, **4y**).

Surprisingly, when 2-aminophenone **2a** was used instead of the substrate 2-aminobenzaldehyde **1a** in this reaction, the corresponding fused quinazolinones have been obtained (Table 4). With -F, -Cl and -Br substituents, it effectively provides the required quinazolines under given conditions, with moderate to good yield (Table 4, **4b**, **4c**, **4f**, **4h** and **4k**).

To further emphasize the practical application of the above method, we first carried out gram preparation and obtained the

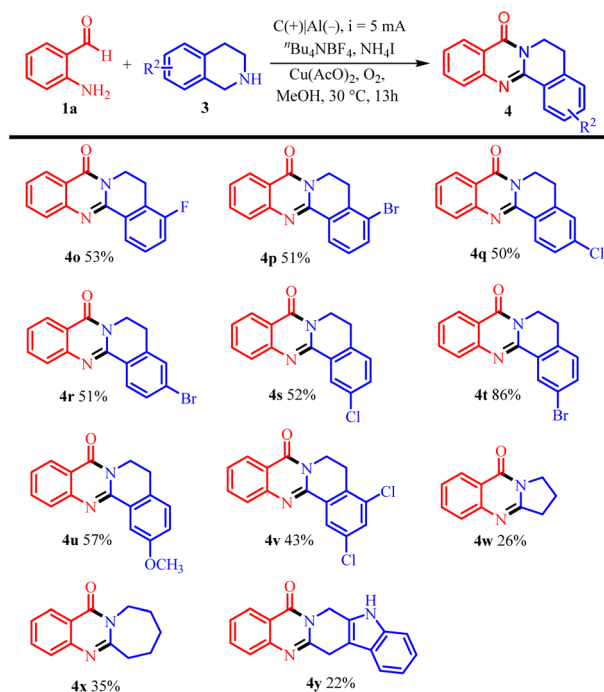
Table 4 Substrate scope of ketone **2**^a

^a Reaction conditions: aluminum rod cathode, carbon rod anode, constant current = 5 mA, **2** (0.2 mmol), **3a** (0.3 mmol), ⁿBu₄NBF₄ (0.5 mmol), NH₄I (0.5 mmol), Cu(AcO)₂ (1% mmol), MeOH (10 mL), O₂, 30 °C, undivided cell.

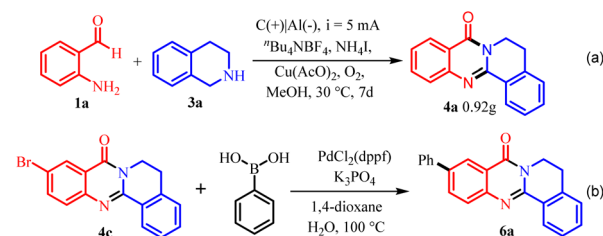
corresponding product **4a** with a 45% (0.92 g) yield (Scheme 2a). The phenylation of product **4c** could be smoothly carried out in the meantime, resulting in the corresponding product **6a** (Scheme 2b).

Due to their good biological activity of quinazolinones, we have performed the antibacterial activity research of the synthetic products in this work. Among the synthetic quinazolinones compounds, 19 compounds show good effect of anti-resistant strains of *Candida albicans*, and had the synergistic antibacterial effect when combined with fluconazole (Table S1†). This method provides a new tool for the development of antifungal drugs and the overcoming of drug resistance.

To further understand the reaction mechanism, we conducted several control reactions (Scheme 3). Firstly, the free radical inhibitor 2,2,6,6-tetramethylpiperidine (TEMPO) and dibutylhydroxytoluene (BHT) can suppressed this reaction in part. This suggests that the reaction could be carried out *via* a radical pathway (Scheme 3a and b). Secondly, when the compound **5** was used as an intermediate, the product **4a** was obtained in good yield, which further indicated that compound **5** was the required intermediate (Scheme 3c). Thirdly, when O₂ is replaced by air, the yield is reduced to 22%; and using N₂ atmosphere, no desired product can be obtained (Scheme 3d). The results revealed that O₂ is very essential for this transformation. Finally, cyclic voltammetry experiment result

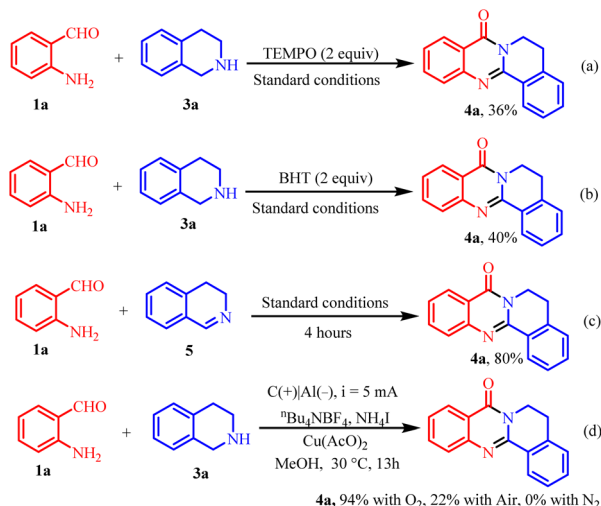
Table 3 Substrate scope of tetrahydroisoquinolines **3**^a

^a Reaction conditions: aluminum rod cathode, carbon rod anode, constant current = 5 mA, **1a** (0.2 mmol), **3** (0.3 mmol), ⁿBu₄NBF₄ (0.5 mmol), NH₄I (0.5 mmol), Cu(AcO)₂ (1% mmol), MeOH (10 mL), O₂, 30 °C, undivided cell.



Scheme 2 Synthetic applications.





Scheme 3 The control experiments.

suggested that the oxidation of I^- initiates this reaction (Scheme S3†).

Based on the above observations and the precious literature,^{8b,10} a plausible reaction mechanism was proposed (Scheme 4). Initially, the iodine anion is oxidized to an iodine radical, which reacts with **3a** to form the radical intermediate **A**. **A** undergoes anodization and deprotonation to give the imide intermediate **5**. Subsequently, a formal [4 + 2] cycloaddition of **5** and 2-aminophenylacetaldehyde would produce intermediate **D**, which was further hydrolyzed to give intermediate **E** which undergoes multiple oxidations to furnish the product **4a**. Finally, H^+ is reduced to hydrogen gas on the cathode. Cu could be stripped from the cathode to regenerate the catalyst.¹⁵

Additionally, 2-aminophenone would be firstly oxidized to give 2-aminobenzaldehyde **1a** catalyzed by the Cu and molecular oxygen in this reaction.¹⁶ Subsequently, 2-aminobenzaldehyde reacts with intermediate **5**, thus giving the final product **4a**.

In summary, we have successfully developed an efficient copper and electrocatalytic synergy strategy for the synthesis of

quinazolinones *via* the intermolecular oxidation cyclization reaction. It is worth noting that the reaction is characterized by broad substrate scope and mild reaction conditions. At the same time, the synthesized products have good antifungal activity.

Data availability

All relevant data are within the manuscript and its additional files.

Conflicts of interest

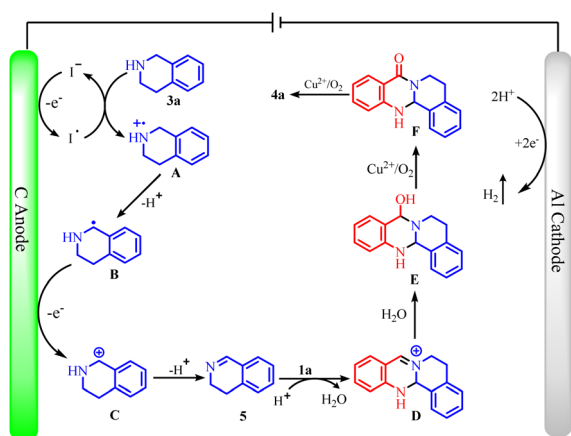
There are no conflicts to declare.

Acknowledgements

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Scheme 4 Plausible mechanism for the reaction.



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