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VERY IMPORTANT PUBLICATION

Electrochemical Dehydrogenative Cross-Coupling of Quinoxalin-2(1*H*)-ones with Amines for the Synthesis of 3-Aminoquinoxalinones

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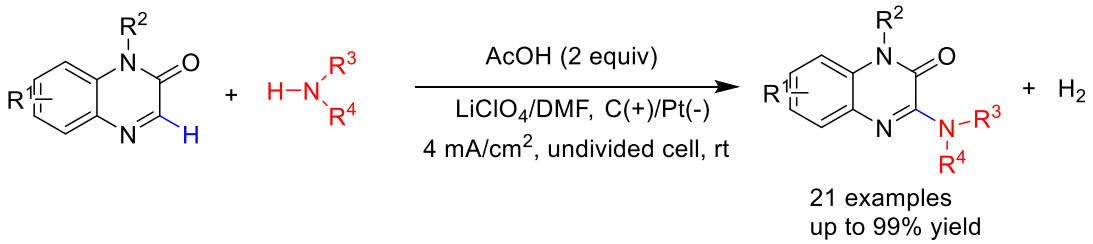
Abstract:

An efficient protocol for the synthesis of 3-aminoquinoxalinones via the electrochemical dehydrogenative C-3 amination of quinoxalin-2(1*H*)-ones was developed. With aliphatic amines and azoles as the nitrogen sources, a series of 3-aminoquinoxalinones was obtained in up to 99% yield. This direct electrolytic method avoids the use of transition metals and external oxidants, and represents an appealing alternative for the synthesis of 3-aminoquinoxalinones.

Key words: quinoxalinone, direct electrolysis, dehydrogenative cross coupling, oxidative amination

Graphic Abstract:



Introduction

Efficient synthesis of quinoxaline-2(1*H*)-ones has attracted much attention due to their diverse biological properties and pharmacological properties.[1] In particular, the

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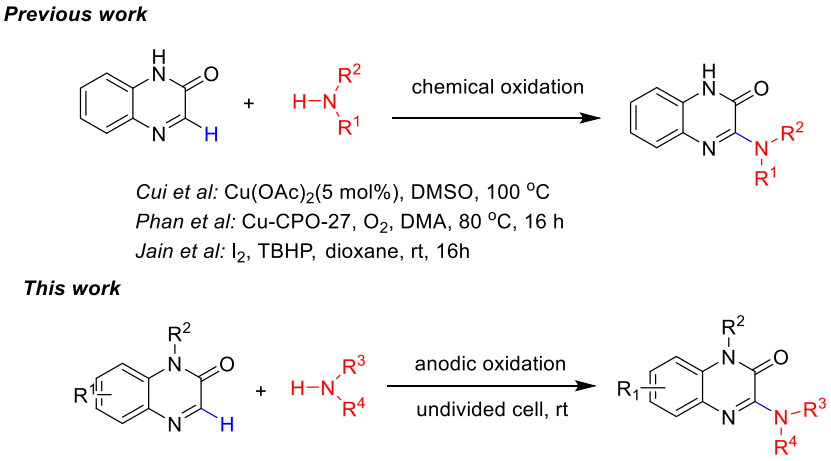
3-aminoquinoxalinone motif is found widely in bioactive compounds, such as antibacterial, antiviral, anticancer, anti-diabetic, and anti-inflammatory agents.[2] Consequently, many synthetic strategies have been developed for the synthesis of 3-aminoquinoxalinones, the most conventional approaches involving either the construction of the quinoxalin-2(1*H*)-one heterocycle or the nucleophilic substitution of quinoxalin-2(1*H*)-one derivatives bearing a halo or other leaving group.[3] The oxidative functionalization of C-H bonds has emerged as an appealing method in organic chemistry, since the prefunctionalization of C-H bonds is avoided. In this regard, Gulevskaya et al. reported the first direct oxidative C-H amination of quinoxalin-2(1*H*)-ones without the prefunctionalized steps.[4] This protocol is highly significant due to the atom- and step-economy character, whereas an excess of strong oxidants, such as $KMnO_4$ or $AgPy_2MnO_4$, is required. Recently, Cui[5] and Phan[6] independently reported the copper-catalyzed C-H amination of quinoxalin-2(1*H*)-ones for the synthesis of 3-aminoquinoxalinones (Scheme 1). Despite the significant progress, only limited examples for the synthesis of 3-aminoquinoxalinones via direct C-H amination under metal-free conditions have been reported. More recently, Jain et al. successfully developed an iodine-catalyzed synthesis of 3-aminoquinoxalinones (Scheme 1),[7] wherein, 2 equiv of TBHP as the oxidant was necessary for this transformation. In view of the pharmaceutical significance of 3-aminoquinoxalinones, a green method for the synthesis of 3-aminoquinoxalinones is still highly desirable.

Organic electrosynthesis is regarded as a green and environmentally friendly way to achieve C-H bonds functionalization, and it is revolutionizing the way of organic synthesis.[8,9] In this context, electrochemical oxidative amination of C-H bonds has been well documented by Xu,[10] Wang,[11] Ackermann,[12] Lei[13] and our group,[14] and has even been reviewed recently by Kärkäs.[15] Nevertheless, the electrochemical C-H amination of electron-deficient heterocyclic compounds is less well established.

In continuation of our interest in the electrochemical formation and cleavage of chemical bonds,[14,16] herein, we report an intermolecular electrochemical cross-coupling of quinoxalin-2(1*H*)-ones with aliphatic amines or azoles for the synthesis of 3-aminoquinoxalinones (Scheme 1). To the best of our knowledge, this is the first

example of C-H amination of quinoxalin-2(1*H*)-ones under electrolytic conditions. This protocol features mild reaction conditions and wide range of substrates, avoiding the utilization of transition metal catalysts and external oxidants. Moreover, owing to constant current electrolysis (CCE) in undivided cell, the protocol is easy to scale up for industrial setting.



Scheme 1. Oxidative amination of quinoxalin-2(1*H*)-ones

Results and discussion

We initiated our studies by using quinoxalinone, **1a,** and morpholine, **2a,** as model substrates to identify the optimal reaction conditions. As shown in Table 1, when constant current electrolysis of **1a** and **2a** was performed in an undivided cell equipped with graphite electrodes using NaI as a mediator at room temperature, the desired product **3a** was isolated in 27% yield (entry 1). Encouraged by this result, different solvents were screened. The results showed that DMF was the optimal solvent, while other solvents such as MeOH, CH_3CN, and aqueous 1,4-dioxane only led to trace amount of product (entries 1 *vs* 2-5). Subsequent optimization revealed that NaBr as the mediator could give the best yield of 26%, while other iodides and bromide as the mediators gave lower yields (entries 7 *vs* 1, 6 and 8). Next, we turned our attention to optimize the acid additives. When acetic acid was used as the acid additive, the yield of **3a** improved to 32% (entry 9). However, only trace amounts of **3a** were detected when using TsOH or solid acid Amberlyst-15(H)® as the additives, and most of the starting material **1a** was recovered (entries 10-11). Further studies showed that the

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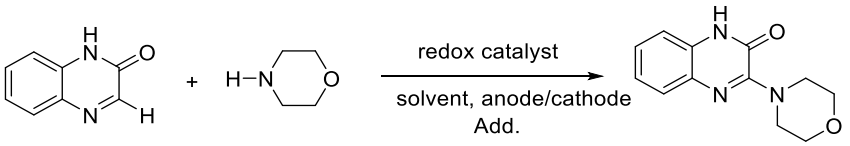
isolated yield of **3a** was improved to 68% when the ratio of **1a** and **2a** was increased to 1:5 with a longer reaction time (10 h) (entry 13). Control experiment demonstrated that the yield of **3a** could be obtained in 73% yield in the absence of NaBr. Therefore, the following optimization experiments were carried out under the direct electrolytic conditions. It was observed that when the cathode material was changed from graphite to platinum, not only did the yield of **3a** increase to 81%, but the reaction time also shortened to 7 hours (entry 15). This result is in accord with the low over-potential of the Pt cathode for hydrogen evolution. In contrast, when Pt wire, glass carbon (GC) or RVC were used as the cathode, the desired product **3a** was obtained in trace amounts and the starting material **1a** was recovered completely (entries 15 *vs* 16, 17 and 18). In addition, it was observed that an almost identical yield of **3a** was produced at a current density of 2 mA/cm^2 (entry 19), but with longer reaction time than that proceeding at 4 mA/cm^2. However, increasing the current density to 8 mA/cm^2 resulted in lower yield of **3a** (entry 20). Further screening of conducting salts indicated that $LiClO_4$ is superior since **3a** was obtained in lower yields when *n*-Bu_4NBF_4 or *n*-Bu_4NPF_6 were employed as the electrolytes (entries 21-22). Notably, without electricity, **3a** was not produced (entry 23), thereby revealing that electricity plays an essential role for the cross-dehydrogenative coupling reaction.

Table 1. Optimization of reaction conditions[a]



1a **2a** **3a**

Entry	**1a**:**2a**	Mediator (mol %)	Solvent	Additive (equiv.)	Electrodes	Yield (%)[b]
1	1:1.5	NaI (50)	DMF	-	C(+)/C(-)	21
2	1:1.5	NaI (50)	CH_3OH	-	C(+)/C(-)	8
3	1:1.5	NaI (50)	CH_3CN	-	C(+)/C(-)	Trace
4	1:1.5	NaI (50)	CH_3CN/CH_2Cl_2=2:1	-	C(+)/C(-)	Trace
5	1:1.5	NaI (50)	1,4-Dioxane/H_2O=2:1	-	C(+)/C(-)	Trace
6	1:1.5	NH_4I (50)	DMF	-	C(+)/C(-)	13
7	1:1.5	NaBr (50)	DMF	-	C(+)/C(-)	26
8	1:1.5	NH_4Br (50)	DMF	-	C(+)/C(-)	20

9	1:1.5	NaBr (50)	DMF	HOAc(2)	C(+)/C(-)	32
10	1:1.5	NaBr (50)	DMF	TsOH(2)	C(+)/C(-)	Trace
11	1:1.5	NaBr (50)	DMF	A-15(H)®	C(+)/C(-)	Trace
12[c]	1:1.5	NaBr (50)	DMF	HOAc(2)	C(+)/C(-)	52
13[c]	1:5	NaBr (50)	DMF	HOAc(2)	C(+)/C(-)	68
14[c]	1:5	-	DMF	HOAc(2)	C(+)/C(-)	73
15[d]	1:5	-	DMF	HOAc(2)	C(+)/Pt(-)	81
16[d]	1:5	-	DMF	HOAc(2)	Pt(+)/C(-)	Trace
17[d]	1:5	-	DMF	HOAc(2)	GC(+)/Pt(-)	4
18[d]	1:5	-	DMF	HOAc(2)	RVC(+)/Pt(-)	4
19[e]	1:5	-	DMF	HOAc(2)	C(+)/Pt(-)	80
20[f]	1:5	-	DMF	HOAc(2)	C(+)/Pt(-)	52
21[g]	1:5	-	DMF	HOAc(2)	C(+)/Pt(-)	72
22[h]	1:5	-	DMF	HOAc(2)	C(+)/Pt(-)	75
23[i]	1:5	-	DMF	HOAc(2)	-	0

[a] Reaction conditions: **1a** (1 mmol), amine **2a** in 8 mL of solvent, undivided cell, current density of 4 mA/cm^2, 0.1 M $LiClO_4$ as conducting salt, rt, 6 h.
[b] Isolated yield.
[c] Reaction time was 10 h.
[d] Reaction time was shortened to 7 h.
[e] J = 2 mA/cm^2, 10 h.
[f] J = 8 mA/cm^2.
[g] 0.1 M *n*-Bu_4NBF_4 as conducting salt.
[h] 0.1 M *n*-Bu_4NPF_6 as conducting salt.
[i] No electricity.

With the optimal reaction conditions in hand, we then studied the scope and the generality of the protocol by examining reactions of quinoxalinone **1a** with a variety of amines **2**. As shown in Table 2, the corresponding products **3a**-**3m** were obtained in up to 99% yield under the electrochemical conditions. For six-membered cyclic amines, such as morpholine, piperazine, piperidine and tetrahydroisoquinoline, the reactions underwent smoothly to give the corresponding 3-aminoquinoxalinones **3b-3h** in 21-81% yields. When piperazine was employed as the nitrogen source, an electron-withdrawing protecting group (**3d**) is beneficial for the yield compared with the electron-donating protecting group (**3c**). When piperidine was used as the substrate, it was found that the target products **3e-3g** were obtained with similar yields regardless of the electron-withdrawing or the electron-donating nature of substituents. In addition to six-membered cyclic amines, seven-membered and five-membered cyclic amines were also

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suitable nitrogen sources for this amination reaction, delivering products **3i** and **3j** in 41% and 69% yields, respectively. To demonstrate the generality of this methodology, azoles as nitrogen sources were also tested. The results showed that azoles tolerated well under the optimized reaction conditions, giving the corresponding products **3k** and **3l** in 49% and 99% yields, respectively. It is noteworthy that acyclic amine was also tolerated well to give the corresponding products **3m** in 70% yield. Unfortunately, the protocol was not suitable for primary amines. For example, when cyclohexylamine or aniline were subjected to reaction with **1a**, the desired products, as well as the homo-coupling product from **1a**, were not detected. In addition, when aromatic aniline was used as a substrate, the reaction mixture became dark quickly, which might result from its polymerization.

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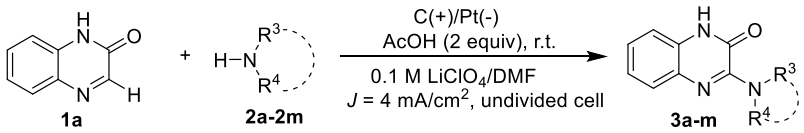
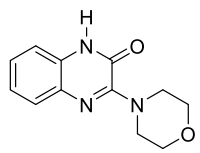
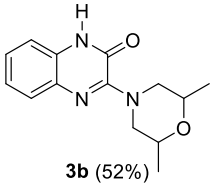
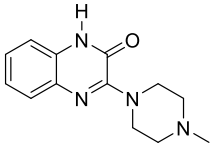
Table 2. Substrate scope with the nitrogen source[a,b]

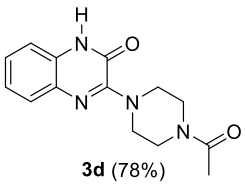


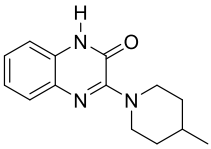
1a + 2a-2m → 3a-m

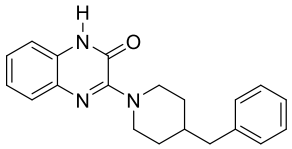

3a (81%)

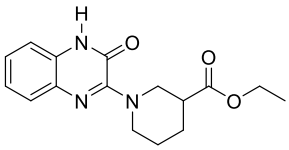

3b (52%)

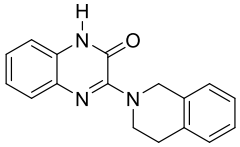

3c (21%) (29 %)[c]

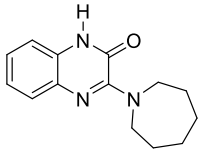

3d (78%)

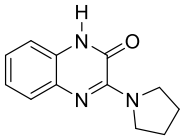

3e (76%)

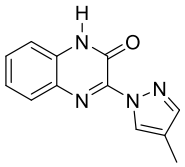

3f (71%)

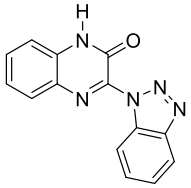

3g (72%)

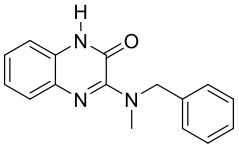

3h (47%)


3i (41%)


3j (69%)


3k (49%)


3l (99%)


3m (70%)

[a] Reaction conditions: **1a** (1 mmol), **2** (5 mmol) in 8 mL of 0.1 M $LiClO_4$/DMF, HOAc (2.0 equiv.), undivided cell, room temperature, current density of 4 mA/cm^2, graphite as an anode and platinum net as a cathode.

[b] Isolated yield.

[c] Isolated yield based on the recovered **1a**.

To further explore the potential of our methodology, the reaction of morpholine **2a** with a variety of quinoxalinone **1** was investigated, and the results are summarized in Table 3. It was found that the electronic character of the substituent on the aryl ring has a great influence on the reaction. For example, when substituents on the aryl ring were weaker electron-withdrawing groups, such as fluoro and chloro, moderate yields

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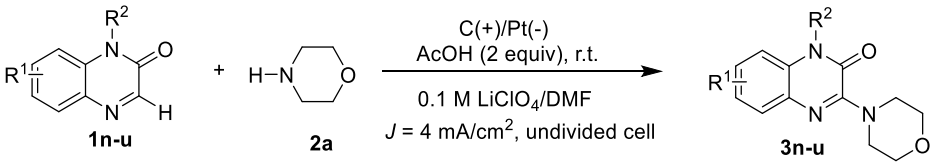
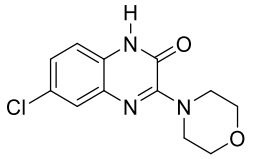
of **3n**-**3o** were obtained. However, when the substituents on the aryl ring were replaced by electron-donating groups such as methyl and methoxy, the yields of **3p** and **3r** were obtained in 31% and 33% yields, respectively. *N*-Substituted quinoxalinones such as *N*-methyl-, *N*-acetyl-, and *N*-benzyl-protected derivatives also proceeded smoothly to give the corresponding products **3s–u** in moderate to high yields. Notably, other heterocycles such as quinoxaline and coumarin did not work, and most of the starting materials were recovered.

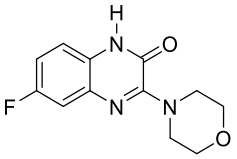
Table 3. Substrate scope with quinoxalinone[a,b]



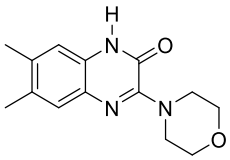
1n-u + **2a** → **3n-u**



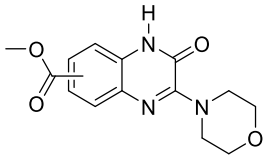
3n (69%)



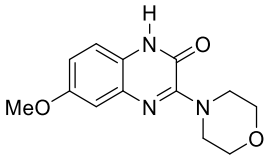
3o (71%)



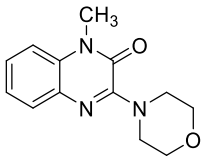
3p(31%)



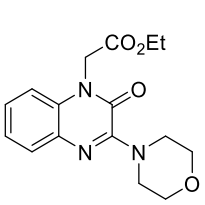
3q (37% 1:1.6)



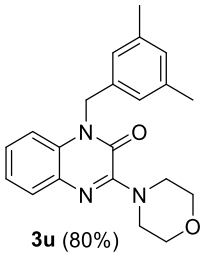
3r (33%)



3s (71%)



3t (76%)



3u (80%)

[a] Reaction conditions: **1** (1 mmol), **2a** (5 mmol) in 8 mL of 0.1 M $LiClO_4$/DMF, HOAc (2.0 equiv.), undivided cell, room temperature, current density of 4 mA/cm^2, graphite as an anode and platinum net as a cathode.

[b] Isolated yield.

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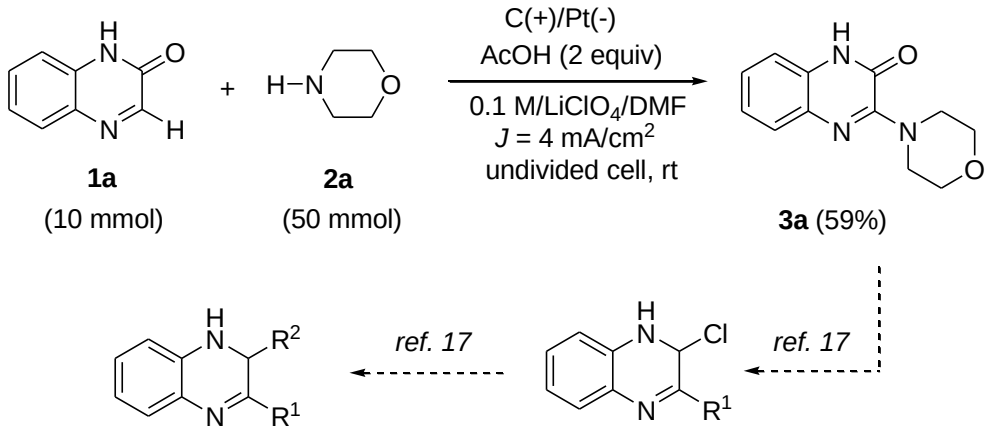
The practicability of the protocol was demonstrated by a scale-up reaction. As illustrated in Scheme 2, when 10 mmol of quinoxalinone **1a** was allowed to react with morpholine **2a** under the standard condition, the direct amination product **3a** was afforded in 59% yield. Compounds **3** are important intermediates, which could be further transformed to various quinoxaline derivatives via chlorinated intermediates (Scheme 2).[17]



Scheme 2. Scaling up and possible transformation

As for the reaction mechanism of the oxidative amination of quinoxaline-2(1*H*)-ones, both a nucleophilic addition (ionic mechanism) and a radical pathway are reported in literatures.[12d,18] Therefore, it is safe to assume that our electrochemical version may also proceed through ionic or radical pathways. As depicted in Scheme 3, the ionic mechanism starts from nucleophilic addition of the substrate amine to protonated quinoxaline-2(1*H*)-one, **1-H**, giving intermediate **A**, which after anodic oxidation and deprotonation affords product **3** (Pathway 1). In the radical pathway, the anodic oxidation of amines forms nitrogen-centered radical **B**, which is intercepted by **1-H** giving intermediate **C**. Further anodic oxidation and deprotonation give the desired products **3** (pathway 2). Simultaneously, proton is reduced at the cathode surface to generate molecular hydrogen.

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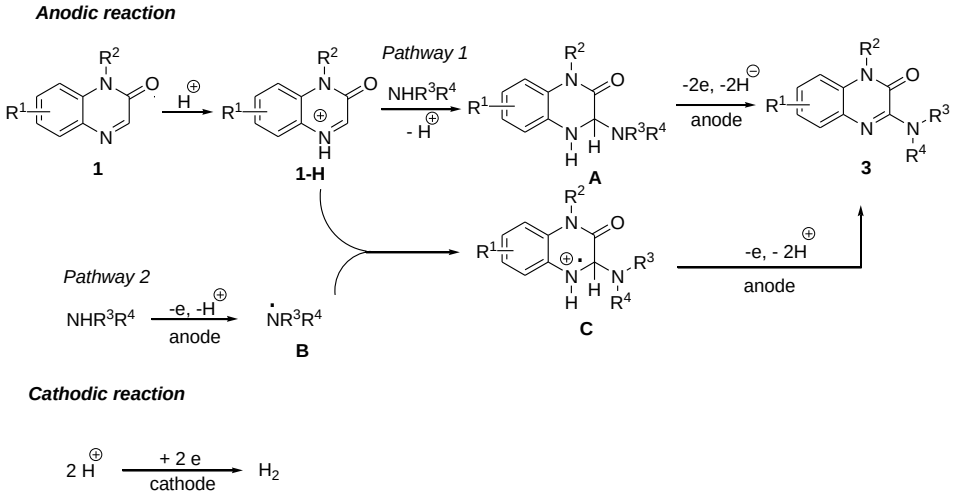
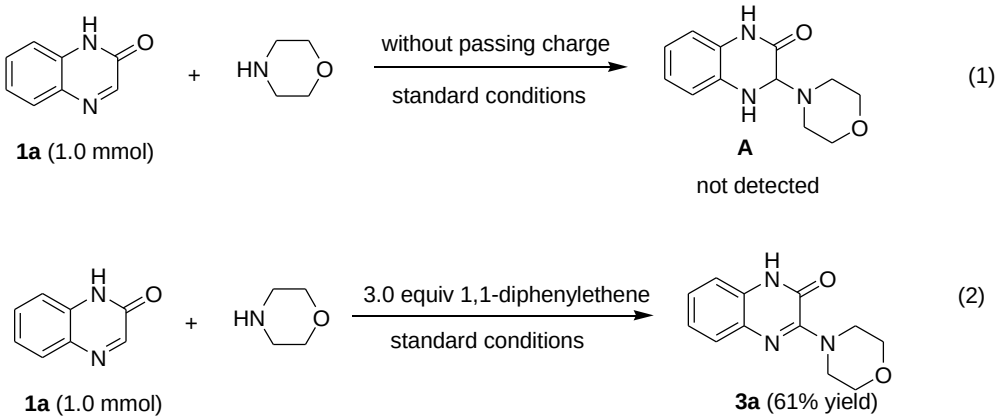


Scheme 3. Two possible pathways for the electrochemical oxidative amination of quinoxaline-2(1*H*)-ones

To identify which pathway is predominant, control experiments were performed and the results were summarized in Scheme 4. When the reaction of **1a** and **2a** was repeated under standard conditions, but without electricity, the assumed intermediate **A** was not detected and all the starting material **1a** and **2a** were recovered. Since the generation of intermediate **A** is significantly essential for pathway 1, this observation indicates that the ionic mechanism may not be involved. On the other hand, the electrochemically oxidative amination of **1a** with **2a** under the standard conditions was a little restrained and only 61% yield of **3a** was isolated in the presence of 3.0 equiv of 1,1-diphenylethene, a radical trapping reagent. Cyclic voltammetry measurements were also performed to understand the possible mechanism. As shown in Fig. 1, the oxidation peak potential of **2a** (1.30 V vs $Ag/AgNO_3$ in 0.1 M in CH_3CN, curve c) is much lower than that of **1a** (no peak potential in the range of more than 2.0 V vs $Ag/AgNO_3$ in 0.1 M in CH_3CN, curve b); therefore, amine **2a** is more easily oxidized at the surface of the anode. Moreover, the oxidation potential of the mixture of **1a** with **2a** is approximately 0.7 V lower than the oxidation potential of amine **2a**, which indicates direct radical transfer in the process. Based on these results and related literature,[12d,18] we suggest that the electrochemical oxidative amination might involves a radical process, although more evidence is required.



Scheme 4. Control Experiments

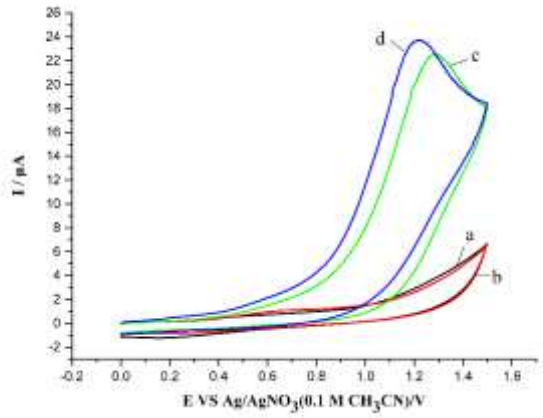


Fig. 1 Cyclic voltammograms of related compounds in 0.1 M $LiClO_4$/DMF using glass carbon as the working electrode, Pt wire, and $Ag/AgNO_3$ (0.1 M in CH_3CN) as the counter and reference electrode, respectively, at a scan rate of 100 mV s^{-1}: (a) background, (b) **1a** (5.0 mmol L^{-1}), (c) **2a** (5.0 mmol L^{-1}), (d) **1a** + **2a** (1:1) (5.0 mmol L^{-1}).

Conclusion

In summary, we have developed oxidative C-H amination of quinoxalin-2(1*H*)-ones under electrochemical conditions. With aliphatic amines and azoles as the nitrogen sources, a variety of 3-aminoquinoxalinones were obtained in up to 99% yield. Compared with the previous reports on 3-aminoquinoxalinone synthesis, this electrochemically dehydrogenative cross-coupling method avoids the use of transition metals and external oxidants, thus providing an appealing alternative for 3-

aminoquinoxalinone synthesis.

Experimental Section

Instruments and reagents

All melting points were measured with an electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded using a 400 MHz (400 MHz ^{1}H frequency, 100 MHz ^{13}C frequency). Chemical shifts are given as δ values (internal standard: TMS). Coupling constants are reported in Hz. The chemical shifts were referenced to signals at 7.28 ppm. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). All starting materials and solvents were obtained from commercial sources and used without further purification. Products were purified by chromatography on silica gel (petroleum ether/EtOAc). The starting quinoxalin-2(1*H*)-ones were prepared according to known procedure.[19]

Typical procedure for the electrochemical synthesis of 3-aminoquinoxalinones

An undivided cell was equipped with a carbon anode (2.0×1.5 cm^2) and a platinum net (2.0×1.5 cm^2) and connected to a DC regulated power supply. To the cell was added the quinoxalinone (1.0 mmol), morpholine (5.0 mmol) and 8.0 mL of 0.1 M $LiClO_4$/DMF. The mixture was electrolyzed using constant current conditions (4 mA/cm^2) at room temperature under magnetic stirring. When TLC analysis indicated that the electrolysis was complete (witnessed by the disappearance of the quinoxalinone), the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford the desired pure product.

3-(Morpholin-4-yl)quinoxalin-2(1*H*)-one (3a)[5] White solid; 187 mg; Yield 81%; m.p.: 204-205 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (t, *J* = 4.4 Hz, 4H), 4.06 (t, *J* = 4.8 Hz, 4H), 7.16-7.18 (m, 1H), 7.25-7.28 (m, 2H), 7.55-7.57 (m, 1H), 11.47 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.2, 66.5, 114.8, 123.6, 125.2, 125.6, 129.8, 132.6, 151.5, 152.5.

3-(2,6-Dimethylmorpholino)quinoxalin-2(1*H*)-one (3b)[7] White solid; 135 mg; Yield 52%; m.p.: 208-209 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, *J* = 6.4 Hz, 6H), 2.71-2.77 (m, 2H), 3.82-3.86 (m, 2H), 4.90 (d, *J* = 12.8 Hz, 2H), 7.15-7.17 (m, 1H), 7.24-7.26 (m, 2H), 7.55-7.57 (m, 1H), 11.34-11.40 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.5, 47.3, 66.6, 110.1, 118.8, 120.4, 120.9, 125.0, 127.9, 146.5, 147.7.

3-(4-Methylpiperazin-1-yl)quinoxalin-2(1*H*)-one (3c)[20] White solid; 51 mg; Yield 21%; m.p.: 190-195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.65 (t, *J* = 4.8 Hz, 4H), 4.09 (s, 4H), 7.11-7.13 (m, 1H), 7.22-7.25 (m, 2H), 7.53-7.56 (m, 1H), 10.70 (br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.7, 46.1, 54.7, 114.8, 123.6, 125.2, 125.6, 129.8, 132.7, 151.5, 152.5.

3-(4-Acetylpiperazin-1-yl)quinoxalin-2(1*H*)-one (3d)[7] Yellowish solid; 212 mg; Yield 78%; m.p.: 230-231 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 3.66 (t, *J* = 4.8 Hz, 2H), 3.82 (t, *J* = 4.8 Hz, 2H), 4.01-4.07 (m, 4H), 7.16-7.19 (m, 1H), 7.26-7.28 (m, 2H), 7.55-7.58 (m, 1H), 11.14 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.7, 41.2, 45.9, 46.4, 46.8, 114.9, 123.6, 125.3, 125.6, 129.8, 132.6, 151.5, 152.5, 168.9.

3-(4-Metylpiperidin-1-yl)quinoxalin-2(1*H*)-one (3e)[6] White solid; 185 mg; Yield 76%; m.p.: 168-169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.4 Hz, 3H), 1.35-1.45 (m, 2H), 1.68-1.74 (m, 1H), 1.78-1.82 (m, 2H), 3.00 (t, *J* = 12.4 Hz, 2H), 4.96 (d, *J* = 12.8 Hz, 2H), 7.15-7.25 (m, 3H), 7.53-7.55 (m, 1H), 11.26-11.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 31.1, 34.4, 47.0, 114.7, 123.5, 124.7, 125.4, 129.7, 133.0, 151.6, 152.6.

3-(4-Benzylpiperidin-1-yl)quinoxalin-2(1*H*)-one (3f)[7] Yellow solid; 226 mg; Yield 71%; m.p.: 170-171 °C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42-1.51 (m, 2H), 1.81-1.91 (m, 3H), 2.62 (d, *J* = 6.8 Hz, 2H), 2.95 (t, *J* = 12.8 Hz, 2H), 5.00 (d, *J* = 12.8 Hz, 2H), 7.15-7.16 (m, 1H), 7.20-7.26 (m, 5H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.53-7.55 (m, 1H), 11.36 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.5, 33.4, 38.0, 42.1, 110.0, 118.7, 120.0,

120.6, 121.5, 123.8, 124.7, 124.9, 128.2, 135.8, 146.9, 147.8.

Ethyl 1-(3-oxo-3,4-dihydroquinoxalin-2-yl)piperidine-4-carboxylate (3g) White solid; 217 mg; Yield 72%; m.p.: 128-129 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3H), 1.71-1.91 (m, 3H), 2.15-2.18 (m, 1H), 2.75-2.80 (m, 1H), 3.17-3.23 (m, 1H), 3.33-3.38 (m, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.78 (d, *J* = 13.2 Hz, 1H), 5.00 (d, *J* = 12.8 Hz, 1H), 7.19-7.26 (m, 3H), 7.54-7.57 (m, 1H), 11.56 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 9.7, 19.5, 22.8, 36.4, 42.2, 43.7, 55.7, 110.0, 118.7, 120.2, 120.7, 125.0, 128.0, 146.9, 147.7, 168.7. HRMS (ESI) m/z calculated for $C_{16}H_{19}O_3N_3$ $(M+H)^+$ 302.1499, Found 302.1497.

3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)quinoxalin-2(1*H*)-one (3h) Yellowish solid; 130 mg; Yield 47%; m.p.: 170-174 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) 2.94 (m, 2H) (m, 2H), 4.16 (t, *J* = 5.6 Hz, 2H), 4.99 (s, 2H), 7.13-7.21 (m, 7H), 7.41-7.43 (m, 1H), 12.12 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.9, 44.6, 48.8, 114.8, 123.6, 124.9, 125.5, 126.4, 126.7, 126.9, 129.0, 129.7, 132.9, 134.7, 135.1, 151.4, 152.6. HRMS (ESI) m/z calculated for $C_{17}H_{15}ON_3$ $(M+H)^+$ 278.1288, Found 278.1286.

3-(Azepan-1-yl)quinoxalin-2(1*H*)-one (3i) White solid; 100 mg; Yield 41%; m.p.: 183-184 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63-1.64 (m, 4H), 1.93 (s, 4H), 4.05 (t, *J* = 5.6 Hz, 4H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.12-7.21 (m, 2H), 7.48 (d, *J* = 7.6 Hz, 1H), 10.95 (br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.7, 28.8, 50.5, 114.5, 123.4, 123.7, 124.9, 129.2, 133.5, 150.5, 152.5. HRMS (ESI) m/z calculated for $C_{14}H_{17}ON_3$ $(M+H)^+$ 244.1444, Found 244.1444.

3-(Pyrrolidin-1-yl)quinoxalin-2(1*H*)-one (3j)[7] Yellowish solid; 148 mg; Yield 69%; m.p.: 204-205 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (s, 4H), 4.01 (br, 4H), 7.07-7.19 (m, 3H), 7.48 (d, *J* = 8.0 Hz, 1H), 11.32 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 49.5, 114.5, 123.3, 124.0, 124.9, 127.8, 134.6, 149.3, 154.1.

3-(4-Methyl-1*H*-imidazol-1-yl)quinoxalin-2(1*H*)-one (3k) Yellow solid; 111 mg; Yield 49%; m.p.: 190-195 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.12 (s, 3H), 7.33-7.37 (m, 2H), 7.51-7.55 (m, 1H), 7.70 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 8.71 (s, 1H), 12.91 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 9.0, 115.6, 118.0, 124.3, 128.4, 129.1, 129.9, 131.0, 131.3, 131.9, 144.0, 151.1. HRMS (ESI) m/z calculated for $C_{12}H_{10}ON_4$ $(M+H)^+$ 227.0927, Found 227.0929.

3-(1H-benzo[d][1,2,3]triazol-1-yl)quinoxalin-2(1*H*)-one (3l) Yellowish solid; 260 mg; Yield 99%; m.p.: 250-254 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41-7.48 (m, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 2H), 7.91 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 13.12 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 109.4, 111.3, 115.0, 119.7, 120.7, 124.3, 124.5, 125.9, 127.2, 128.2, 128.5, 140.3, 140.6, 146.6. HRMS (ESI) m/z calculated for $C_{14}H_9ON_5$ $(M+H)^+$ 264.0880, Found 264.0887.

3-[Benzyl(methyl)amino]quinoxalin-2(1*H*)-one (3m)[7] White solid; 186 mg; Yield 70%; m.p.: 170-171 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.31 (s, 3H), 5.24 (s, 2H), 6.99 (d, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.28-7.32 (m, 1H), 7.35-7.41 (m, 4H), 7.53 (d, *J* = 8.0 Hz, 1H), 11.48 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.1, 55.1, 114.6, 124.1, 124.5, 125.5, 127.1, 127.7, 128.3, 128.5, 133.7, 138.8, 150.8, 154.1.

6-Chloro-3-(morpholin-4-yl)quinoxalin-2(1*H*)-one (3n) Yellowish solid; 183 mg; Yield 69%; m.p.: 268-271 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.70 (t, *J* = 4.8 Hz, 4H), 3.94 (br, 4H), 7.14-7.22 (m, 2H), 7.38 (d, *J* = 2.0 Hz, 1H), 12.23 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.1, 66.5, 116.2, 124.4, 124.6, 127.3, 128.6, 133.8, 151.7, 152.3. HRMS (ESI) m/z calculated for $C_{14}H_9ON_2Cl$ $(M+H)^+$ 266.0691, Found 266.0699.

6-Fluoro-3-(morpholin-4-yl)quinoxalin-2(1*H*)-one (3o)[7] White solid; 177 mg;

Yield 71%; m.p.: 237-238 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.70 (t, J = 4.4 Hz, 4H), 3.93 (d, J = 4.4 Hz, 4H), 7.01-7.03 (m, 1H), 7.12-7.17 (m, 2H), 12.17 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.1, 66.6, 110.7 (d, J_{CF} = 22.0 Hz), 112.3 (d, J_{CF} = 24.0 Hz), 115.8 (d, J_{CF} = 9.0 Hz), 126.4, 133.6 (d, J_{CF} = 12.0 Hz), 151.8, 152.1, 158.7 (d, J_{CF} = 237.0 Hz).

6, 7-Dimethyl-3-morpholinoquinoxalin-2(1*H*)-one (3p)[5] White solid; 80 mg; Yield 31%; m.p.: 214-216 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.33 (s, 3H), 3.88-3.90 (m, 4H), 3.97-3.99 (m, 4H), 6.91 (s, 1H), 7.35 (s, 1H), 10.83 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.4, 19.8, 47.3, 66.5, 115.1, 126.1, 127.8, 130.7, 131.8, 134.1, 151.3, 152.5.

Methyl 2-morpholino-3-oxo-3,4-dihydroquinoxaline-6-carboxylate (3q) and methyl 2-morpholino-3-oxo-3,4-dihydroquinoxaline-7-carboxylate (3q') Yellowish solid; 107 mg; Yield 37%; m.p.: 226-230 °C; ^{1}H NMR for **(3q)** (400 MHz, DMSO-d_6) δ 3.71 (t, J = 4.8 Hz, 4H), 3.84 (s, 3H), 3.91-3.92 (m, 4H), 7.22 (d, J = 8.4 Hz, 1H), 7.73-7.77 (m, 1H), 7.91 (d, J = 1.2 Hz, 1H), 12.41 (s, 1H); ^{1}H NMR for **(3q')** (400 MHz, DMSO-d_6) δ 3.71 (t, J = 4.8 Hz, 4H), 3.84 (s, 3H), 4.01 (br, 4H), 7.41 (d, J = 8.4 Hz, 1H), 7.67-7.70 (m, 1H), 7.73-7.77 (m, 1H), 12.27 (s, 1H); ^{13}C NMR of **3q** and **3q'** (100 MHz, DMSO-d_6) δ 47.1, 52.4, 66.5, 66.6, 114.9, 115.9, 124.2, 124.7, 125.1, 125.2, 125.6, 126.6, 129.3, 132.2, 133.5, 136.5, 151.6, 152.0, 152.4, 152.6, 166.3, 166.4. HRMS (ESI) m/z calculated for $C_{14}H_{15}N_3O_4$ $(M+H)^+$ 290.1135, Found 290.1142.

6-Methoxy-3-morpholinoquinoxalin-2(1*H*)-one (3r) White solid; 86 mg; Yield 33%; m.p.: 248-249 °C ; ^{1}H NMR for the mixture (400 MHz, DMSO-d_6) δ 3.69-3.72 (m, 4H), 3.76 (s, 3H), 3.88-3.89 (m, 4H), 6.83 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 12.04 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.2, 55.8, 66.6, 108.2, 113.8, 115.6, 123.8, 133.4, 151.8, 152.0, 156.1. HRMS (ESI) m/z calculated for $C_{13}H_{15}N_3O_3$ $(M+H)^+$ 262.1186, Found 262.1189.

1-Methyl-3-morpholinoquinoxalin-2(1*H*)-one (3s)[7] White solid; 174 mg; Yield 71%; m.p.: 101-102 ºC ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.83-3.85 (m, 4H), 3.94-3.97 (m, 4H), 7.19 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 7.22-7.31 (m, 2H), 7.54 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.3, 47.5, 67.0, 113.3, 123.8, 125.3, 126.8, 130.8, 133.0, 150.6, 152.1.

Ethyl 2-(3-morpholino-2-oxoquinoxalin-1(2*H*)-yl)acetate (3t)[5] White solid; 241 mg; Yield 76%; m.p.: 133-136 ºC ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3H), 3.83-3.85 (m, 4H), 3.96-3.98 (m, 4H), 4.25 (q, *J* = 7.2 Hz, 2H), 4.98 (s, 2H), 6.94-6.99 (m, 1H), 7.22-7.26 (m, 2H), 7.54-7.58 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 43.8, 47.5, 61.9, 66.9, 112.7, 124.1, 125.4, 127.1, 130.0, 133.1, 150.2, 152.0, 167.3.

1-(3,5-Dimethylbenzyl)-3-morpholinoquinoxalin-2(1*H*)-one (3u) White solid; 279 mg; Yield 80%; m.p.: 135-139 ºC ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 6H), 3.85-3.88 (m, 4H), 3.98-4.01 (m, 4H), 5.39 (s, 2H), 6.81 (s, 2H), 6.87 (s, 1H), 7.13-7.23 (m, 3H), 7.55-7.57 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 46.2, 47.7, 67.0, 114.3, 123.9, 124.4, 125.5, 126.9, 129.3, 130.4, 133.2, 135.4, 138.5, 150.8, 152.3. HRMS (ESI) m/z calculated for $C_{21}H_{23}N_3O_2$ $(M+H)^+$ 350.1863, Found 350.1855.

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The authors declare no competing financial interest.

Supporting Information Available: Copies of ^{1}H NMR, ^{13}C NMR spectral and HRMS.

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