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Electrochemically C-H / S-H Oxidative Cross-Coupling between Quinoxalin-2(1*H*)-ones and Thiols for the Synthesis of 3-Thioquinoxalinones

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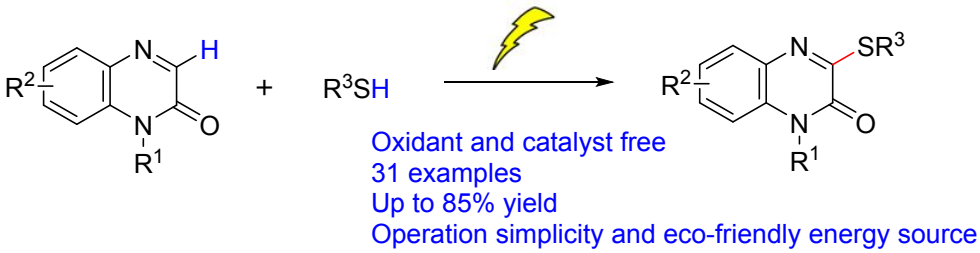


Abstract: An electrochemical method for the C(sp²)-H thioetherification of quinoxalin-2(1*H*)-ones with primary, secondary, and tertiary thiols is reported. Various quinoxalin-2(1*H*)-ones underwent this thioetherification smoothly under metal- and chemcial oxidant-free conditions, affording 3-alkylthiol substituted quinoxalin-2(1*H*)-ones in moderate to good yields.

Introduction

Aromatic thioethers are prevalent in a wide range of biologically active molecules and functional materials.[1] Meanwhile, quinoxalin-2(1*H*)-ones are extensively utilized in antineoplastic,[2] antithrombotic agents,[3] and aldose reductase inhibitors.[4] Therefore, the development of environmentally friendly and atom-economical methods for the preparation of 3-alkylthiol substituted quinoxalin-2(1*H*)-ones is of significant importance.

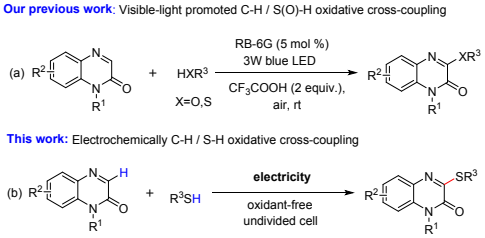
Various effective strategies,[5] including palladium-based,[6] copper-based,[7] rhodium-based,[8] nickel-based,[9] and iron-based[10] coupling reactions have been established for C−S bond construction. Nevertheless, most reported methods require specific or unstable ligands and often harsh reaction conditions. Such concerns stimulate efforts to explore alternative approaches for the formation of C−S bond. Recently, various iodine-catalyzed synthesis of aromatic thioethers were successfully developed.[11] Wherein, oxidant such as TBP, DMSO and H_2O_2 were necessary for those transformations. On the other hand, there are also reports on the addition of thiols into *p*-quinones without the use of any catalyst.[12] Among them, 1,4-quinone and thiophenols in methanol or water media at room temperature *via* the cross-dehydrogenative coupling (CDC) had been achieved in this transformation.[13] Meanwhile, considerable efforts have been made to the preparation of varied 3-substituted quinoxalin-2(1*H*)- ones, such as C3- alkylation,[14] C3-amination[15] and C3- alkoxylation[16]. However, direct C3-thioetherification of quinoxalin-2(1*H*)-ones remains scare.

In the past few decades, The fast-developing fields of photocatalysis and photoredox have recently afforded new opportunities to broaden the potential of organic chemistry,[17] including C−S bond formation.[18] More recently, our group reported the visible-light-mediated (thio)etherification of quinoxalin-2(1*H*)-ones with various alcohols and thiols (Scheme 1a).[19] He et al. also reported the visible-light-induced method for the preparation of 3-sulfenylated quinoxalin-2(1*H*)-ones.[20] Nevertheless, photoredox catalysts may introduce restrictions in terms of the sustainability and scalability of these processes.

Due to the pharmaceutical value of aromatic thioethers, a sustainable method for the preparation of aromatic thioethers is still extremely desirable. Over the past decade, the utilization of electrochemical oxidation in organic chemistry

has attracted much attention.[21] In 2017, the electrochemical dehydrogenative C–S cross-coupling of aryl isothiocyanates with amines has been developed.[22] In the same year, electrooxidation was implemented to realize the straight arylsulfonlylation of ynones with sulfinic acids without the need for an external catalyst.[23] Nevertheless, only limited examples of electrochemical C–H thioetherification of heterocyclic compounds have been well established.[24] Herein, we establish an electrochemical cross-coupling of quinoxalin-2(1*H*)-ones with thiols for the synthesis of 3-thioquinoxalones (Scheme 1b).

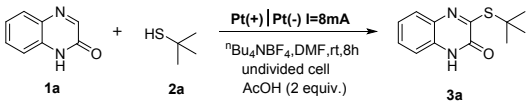
Scheme 1. (Thio)etherification of Quinoxalin-2(1*H*)-ones *via* Cross-dehydrogenative Coupling



RESULTS AND DISCUSSION

We initiated our researches by exploring reaction conditions for the C(sp^2)-H thioetherification of quinoxalin-2(1*H*)-one (**1a**) with 2-methylpropane-2-thiol (**2a**) (Table 1). In an undivided three-necked flask equipped with platinum electrodes as both the anode and cathode, quinoxalin-2(1*H*)-one (**1a**) (0.5 mmol), 2-methylpropane-2-thiol (**2a**) (1.5 mmol), $^nBu_4NBF_4$ (0.1 mmol), DMF (4 mL) and CH_3COOH (1.0 mmol) were added. The reaction mixture was stirred and electrolyzed at a constant current of 8 mA (corresponding voltage applied is about 13V) under room temperature for 8 h, giving the thioetherification product **3a** in 85% yield (Table 1, entry 1). Notably, both decreasing and increasing the constant current led to a lower reaction yield (Table 1, entries 2 and 3). Without electricity, **3a** was not detected (Table 1, entry 4), thus revealing that electricity plays a crucial role in this CDC reaction. The electrolyte also had a major influence on this CDC reaction. Other electrolytes such as TBAI, TBAB, and KI were much less active, only afforded a trace amount of **3a** (compare entries 5, 6, and 7 with entry 1). The possible reason is that the electrolyte containing Br^- and I^-, such as TBAI, TBBI, and KI, may lose electrons at the anode and take part in the reaction.[25] Further screening of solvents revealed that other solvents such as CH_3CN, CH_3CH_2OH, DMSO, NMP (*N*-Methyl pyrrolidone), DMA (*N,N*-dimethylacetamide) and GVL (gamma-Valerolactone) gave worse yields than DMF (Table 1, entries 8-13). Lower yields of **3a** were obtained when platinum was replaced with carbon as either the cathode or anode (Table 1, entries 14 and 15). Switching the acid additive from CH_3COOH to CF_3COOH, a complicated mixture was obtained (Table 1, entry 16). When $Zn(CH_3COO)_2$ was employed as an additive, the trace product was obtained (Table 1 entry 17). Replacing CH_3COOH with $(CH_3)_3CCOOH$, a slightly decreased yield was obtained (Table 1 entry 18). An inferior reaction yield was observed in the absence of CH_3CO_2H (Table 1, entry 19). The yield was not further improved, when increasing CH_3CO_2H to 4 equiv (Table 1, entry 20). The effect of the temperature was also explored, only trace amount of **3a** was detected, when the reaction was performed at 0 °C (Table 1, entry 21). When raising the temperature to 60 °C, more impurities generated (Table 1, entry 22). When the reaction was carried out under N_2 atmosphere, a comparable yield (83%) was obtained (Table 1 entry 23).

Table 1. Reaction Conditions Optimization[a]



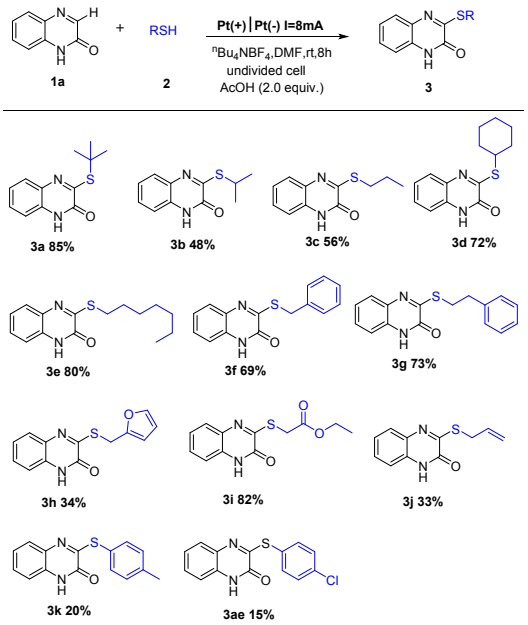
Entry	Variation from the standard conditions	Yield [%][b]
1	**None**	85
2	4、6、10 mA instead of 8 mA	32、75、55
3	12、14、16 mA instead of 8 mA	mixture
4	without electric current	N.D.
5	TBAI instead of $^nBu_4NBF_4$	trace
6	TBAB instead of $^nBu_4NBF_4$	trace
7	KI instead of $^nBu_4NBF_4$	trace
8	MeCN instead of DMF	trace
9	CH_3CH_2OH instead of DMF	trace
10	DMSO instead of DMF	trace
11	NMP instead of DMF	trace
12	DMA instead of DMF	N.R.
13	GVL instead of DMF	N.R.
14	C (+) | Pt (-) instead of Pt (+) | Pt (-)	trace

15	C (+) | C (-) instead of Pt (+) | Pt (-)	33
16	CF_3COOH instead of CH_3COOH	mixture
17	$Zn(CH_3COO)_2$ instead of CH_3COOH	trace
18	$(CH_3)_3CCOOH$ instead of CH_3COOH	82
19	without CH_3COOH	69
20	CH_3COOH (4 equiv.) was used	60
21	0 ℃ instead of rt	trace
22	60 ℃ instead of rt	mixture
23	under N_2	83

[a] Standard conditions: Pt anode, Pt cathode, constant current=8 mA, **1a** (0.5 mmol), **2a** (1.5mmol), $^nBu_4NBF_4$ (0.1 mmol), DMF (4.0 mL), CH_3COOH (1.0mmol), at room temperature for 8 h (4.8F, 35% efficiency). [b]Isolated yields based on **1a**.

With the optimized reaction conditions in hand, diverse thiols were applied to this electrochemical reaction. As shown in Scheme 2, the corresponding products **3a–3k** were achieved in up to 85% yield under the electrochemical system. Aliphatic thiols (tertiary, secondary, and primary) such as 2-methylpropane-2-thiol, propane-2-thiol, propane-1-thiol, and cyclohexanethiol were all compatible with the reaction, and the corresponding products (**3a**, **3b**, **3c**, and **3d**) were obtained in 48-85% yields. Thiols containing a long aliphatic chain or benzene ring were conducted, and the corresponding products (**3e**, **3f**, and **3g**) were obtained in 69-80% yields. In addition, primary aliphatic thiol bearing furyl substituent gave **3h** in a slightly decreased reaction yield. Ester and enyl groups were also tolerated, the corresponding product **3i** and **3j** was obtained. When thiophenol was employed, showed poor reactivity in this transformation, respectively giving **3k** and **3ae** in 20% and 15% yield, along with about 65% and 69% yield of disulfides, respectively. **3ae** can be used to synthesize 2-(3-((4-chlorophenyl)thio)-2-oxoquinoxalin-1(2H)-yl)acetic acid (CTPOQA), which is an aldose reductase (ALR2) inhibitor.[26]

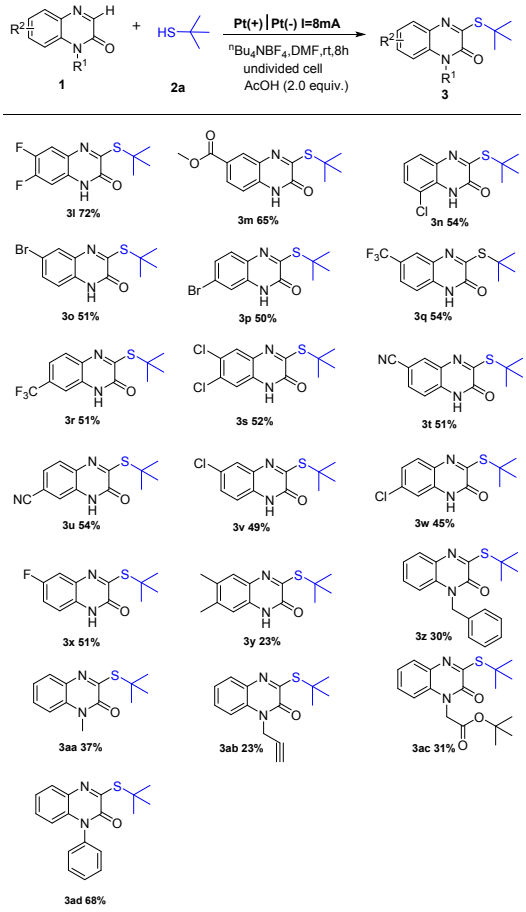
Scheme 2. Substrate Scope with Thiols[a]



[a] Reaction conditions are Pt anode, Pt cathode, constant current=8 mA, quinoxalin-2(1*H*)-one **1a** (0.5 mmol), thiols **2** (1.5 mmol), $^nBu_4NBF_4$ (0.1 mmol), DMF (4.0 mL), CH_3COOH (1.0 mmol), at room temperature for 8 h (4.8F); yields of isolated product.

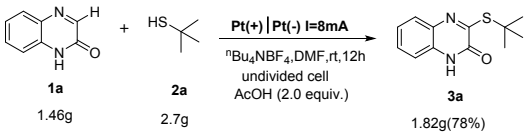
In addition, we explored the scope of quinoxalin-2(1*H*)-ones as shown in Scheme 3. A variety of quinoxalin-2(1*H*)-ones, such as F, Cl, Br, CO_2Me, CF_3, and CN at 6 or 7-position of the aromatic rings, reacted with 2-methylpropane-2-thiol facilely to generate the aimed products (**3l, 3m, 3o-3x**) in moderate yields. The reaction of 6,7-dimethylquinoxalin-2(1*H*)-one gave **3y** in a decreased yield, which might be the result of electron-donating effect of the methyl group. A 5-Cl substituted quinoxalin-2(1*H*)-one was also compatible, giving the desired product **3n** in 54% yield. Various *N*-protected quinoxalin-2(1*H*)-one, such as *N*-benzyl, *N*-methyl, *N*-propynyl, *N*-esteryl, and *N*-phenyl showed slightly lower reaction efficiency than *N*-unprotected ones, providing the expected products (**3z, 3aa, 3ab, 3ac** and **3ad**) in the yield of 30%, 37%, 23%, 31% and 68% respectively.

Scheme 3. Substrate Scope with Quinoxalin-2(1*H*)-ones[a]



[a] Reaction conditions are Pt anode, Pt cathode, constant current=8 mA, quinoxalin-2(1*H*)-ones **1** (0.5 mmol), 2-methylpropane-2-thiol **2a** (1.5mmol), $^{n}Bu_4NBF_4$ (0.1 mmol), DMF (4.0 mL), CH_3COOH (1.0mmol), at room temperature for 8 h (4.8F); yields of isolated product.

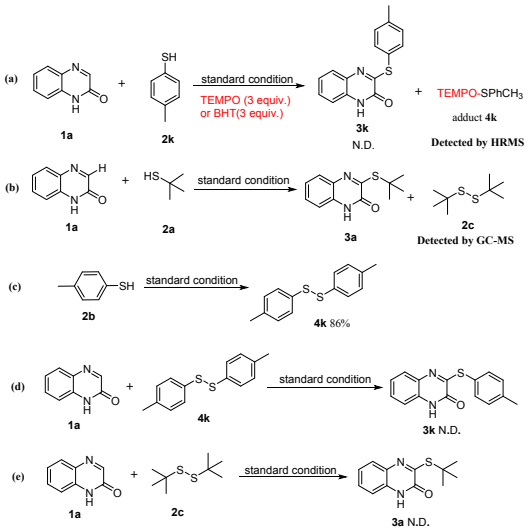
In addition, we explored the reaction efficiency at a larger scale by performing 1.46 g of **1a**, **3a** was also isolated in 78 % yield (Scheme 4).



Scheme 4. Scale-up of the CDC Reaction.

Some control experiments were conducted to explore the possible reaction mechanism. When radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (2,6-di-*tert*-butyl-4methylphenol) was added into the reaction system. No desired product **3k** was observed, and the TEMPO−$SPhCH_3$ adduct **4k** was detected by high resolution mass spectrometer (HRMS). Thus, radical intermediates may be involved under the electrocatalytic system (Scheme 5a). We conducted the reaction under standard condition, the ditertbutyldisulfide **2c** was detected by GC-MS (Scheme 5b). In addition, in the absence of quinoxalin substrates, 4-methylbenzenethiol underwent a quickly dimerization to generate disulfide **4k** in 86% yield (Scheme 5c). Due to the disulfides were formed under the standard conditions, the reaction between disulfide (**4k** or **2c**) and **1a** was performed, the corresponding C-S bond formation product **3k** and **3a** was not detected (Scheme 5d and 5e), these results demonstrate that disulfide may not participate in the C-S bond formation.

Scheme 5. Mechanistic Studies.



In the next step, we conducted the CV (cyclic voltammetry) experiments to research the redox potential of the substrates. As shown in Figure 1, the oxidation peak potential of 2-methylpropane-2-thiol (**2a**) (1.60 V vs Ag/AgCl in 0.1 M in DMF) is much lower than that of **1a** (no peak potential in the range of more than 2.0 V vs Ag/AgCl in 0.1 M in DMF).[19, 27] Therefore, 2-methylpropane-2-thiol (**2a**) may be more easily oxidized at the surface of the anode. When the CDC reaction was carrying out at applied constant voltage 1.60 V, almost no desired product was obtained. Further improving the voltage to 1.80 V, trace amount of the product was detected, the result was consistent with the CV experiments.

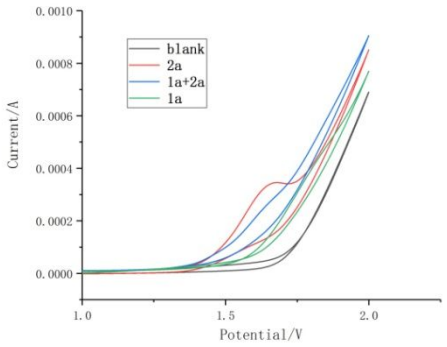
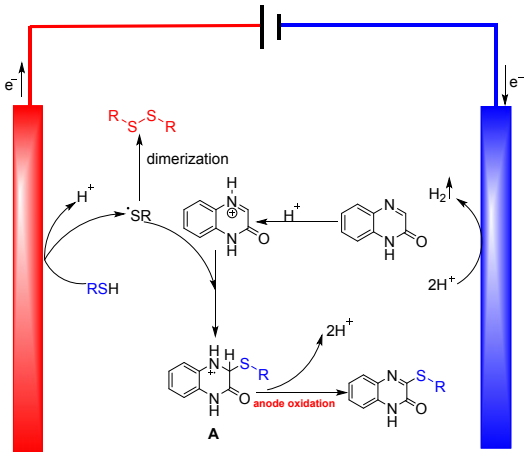


Figure 1. Cyclic voltammograms of related compounds in 0.1 M $^{n}Bu_4NBF_4$/DMF using glass carbon as the working electrode, Pt wire and Ag/AgCl (0.1 M in DMF) as the counter and reference electrode at a scan rate of 0.1V/s: (1) blank: 0.1 M $^{n}Bu_4NBF_4$/DMF (2) **1a** (10 mmol/L) (3) **2a** (10 mmol/L) (4) **1a**+**2a** (1:1)(10 mmol/L)

Based on the above radical-trapping experiments and earlier reports.[27, 28] We proposed a plausible mechanism in Scheme 6. Initially, the thiol is oxidized at anode *via* a single-electron-transfer (SET) process to give sulfur radical. Meanwhile, the sulfur radical is intercepted by the protonated quinoxaline-2(1*H*)-one to form the intermediate **A**. Further anodic oxidation and deprotonation of **A** affords the 3-thioquinoxalinones. Simultaneously, proton is reduced to generate H_2 at the cathode (see supporting information for detail). In this transformation, the dimerization of the sulfur radical is inevitable.

Scheme 6. Proposed Reaction Mechanism



In summary, a direct and simple tactics to 3-thioquinoxalinones *via* an electrochemical dehydrogenation coupling of quinoxalin-2(1*H*)-ones with thiols under undivided electrolytic conditions has been developed. This protocol provides an efficient method to acquire diverse 3-thioquinoxalinones, which is of great synthetic value due to its desirable features including catalyst and oxidant-free, mild conditions, operation simplicity, high atom economy, and eco-friendly energy source.

EXPERIMENTAL SECTION

General methods: All purchased chemicals were used as received without further purification. All reactions were monitored by TLC with silica gel-coated plates. ^{1}H (400, 500, or 600 MHz) NMR and $^{13}C\{^{1}H\}$ (101, 126, or 151 MHz) NMR spectra were recorded on a Varian spectrometer in $CDCl_3$ or DMSO-d_6 using tetramethylsilane (TMS) as internal standards. Data are reported as follows: Chemical shift (number of protons, multiplicity, coupling constants). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, hept = heptet, br = broad. High-resolution mass spectra (HRMS) were obtained using electrospray ionization (ESI) [quantitative time-of-flight (Q-TOF)] ionization sources. The cyclic voltammetry measurements were detected by using a CHI 600E electrochemical workstation.

General procedures for preparation of quinoxalin-2(1*H*)-ones:

A mixture of substituted *o*-phenylenediamine (5 mmol), ethyl 2-oxoacetate (6 mmol) and ethanol (20 mL) was taken in a dried round-bottom flask. The mixture was stirred at reflux for 1 h. After cooling, the precipitated solid was filtered, washed with ethanol and then dried to afford *N*-free protected quinoxalin-2(1*H*)-ones. The *N*-free protected quinoxalin-2(1*H*)-ones was dissolved in DMF (20 mL), followed by addition of potassium carbonate (1.2 equiv.) and corresponding halogenoalkane (1.6 equiv.). The mixture was then stirred at room temperature overnight. After the reaction was completed, EtOAc and water were added. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with a saturated solution of NH_4Cl, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue is purified by flash chromatography over silica gel to afford the desired quinoxalin-2(1*H*)-ones.

General procedures for preparation of 3-thioquinoxalinones:

In an oven-dried undivided three-necked bottle (25 mL) equipped with a stir bar, quinoxalin-2(1*H*)-ones (0.50 mmol), thiols (1.5 mmol), $^{n}Bu_4NBF_4$ (33 mg, 0.1 mmol), CH_3COOH (1.0mmol), and DMF (4 mL) were added. The bottle was equipped with platinum electrodes (1.5×1.5 cm^2) as both the anode and cathode. The reaction mixture was stirred and electrolyzed at a constant current of 8 mA (The dual display potentiostat was operating in constant current mode) under room temperature for 8 h. When the reaction was finished, the solvent（DMF） was removed with a rotary evaporator（Another method：when the reaction was finished, EtOAc and water were added. The aqueous layer was extracted twice with EtOAc. The combined organic layer was dried with Na_2SO_4, filtered. The solvent was removed with a rotary evaporator）. The pure product was obtained by flash column chromatography on silica gel.

Radical-Trapping Experiments. In an oven-dried undivided three-necked bottle (25 mL) equipped with platinum electrodes (1.0×1.0 cm^2) as both the anode and cathode, quinoxalin-2(1*H*)-one **1a** (0.50 mmol), 4-methylbenzenethiol **2k** (1.5 mmol), $^{n}Bu_4NBF_4$ (0.1 mmol), CH_3COOH (1.0mmol), TEMPO (1.5mmol) and DMF (4 mL) were added. The reaction mixture was stirred and electrolyzed at a constant current of 8 mA for 8 h. It was found that TEMPO captured the sulfur radical and the addduct **4k** was confirmed by HRMS (ESI): m/z calcd for $C_{16}H_{25}NNaOS$ $[M + Na]^+$: 302.1549, found: 302.1553.

Cyclic voltammetry (CV) measurements. The cyclic voltammetry (CV) measurements (Ag/AgCl as a reference electrode) were determined by using tetrabutylammonium tetrafluoroborate (0.1 M in DMF) as electrolyte. The quinoxalin-2(1*H*)-one (**1a**)， 2-methylpropane-2-thiol (**2a**) were prepared with 0.1 mmol in 10.0 mL of 0.1 M tetrabutylammonium tetrafluoroborate in DMF. The applied potential range is 2.0 to 0 V vs Ag/AgCl at a sweep rate of 0.1 V/s.

Characterization of the Products.

3-(Tert-butylthio)quinoxalin-2(1*H*)-one (3a). 85 % yield (99.5 mg, petroleum ether/ethyl acetate = 6:1 as an eluent). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.38 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.35 – 7.31 (m, 1H), 1.74 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 160.2, 155.1, 133.2, 128.8, 128.3, 127.3, 124.3, 116.3, 47.5, 29.6 (3C); HRMS (ESI): m/z calcd for $C_{12}H_{14}N_2NaOS$ $[M + Na]^+$: 257.0719, found: 257.0720.

3-(Isopropylthio)quinoxalin-2(1*H*)-one (3b). 48% yield (52.8 mg, petroleum ether/ethyl acetate = 6:1 as an eluent). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H), 7.67 – 7.62 (m, 1H), 7.45 – 7.38 (m, 1H), 7.29 – 7.24 (m, 2H), 3.89 (hept, *J* = 6.8 Hz, 1H), 1.39 (d, *J* = 6.8 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 160.7, 153.2, 132.7, 130.3, 128.7, 127.2, 123.9, 116.0, 34.1, 22.8 (2C); HRMS (ESI): m/z calcd for $C_{11}H_{13}N_2OS$ $[M + H]^+$: 221.0743, found: 221.0745.

3-(Propylthio)quinoxalin-2(1*H*)-one (3c). 56% yield (61.6 mg, petroleum ether/ethyl acetate = 6:1 as an eluent). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 7.66 – 7.64 (m, 1H), 7.43 – 7.39 (m, 1H), 7.29 – 7.24 (m, 2H), 3.10 (t, *J* = 7.2 Hz, 2H), 1.75 – 1.65 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 160.8, 153.3, 132.7, 130.4, 128.7, 127.2, 123.8, 116.0, 30.9, 22.1, 13.9; HRMS (ESI): m/z calcd for $C_{11}H_{13}N_2OS$ $[M + H]^+$: 221.0743, found: 221.0743.

3-(Cyclohexylthio)quinoxalin-2(1*H*)-one (3d). 72% yield (93.6 mg, petroleum ether/ethyl acetate = 6:1 as an eluent). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.27 (dd, *J* = 12.3, 5.4 Hz, 2H), 3.79 (s, 1H), 2.03 (d, *J* = 9.1 Hz, 2H), 1.77 – 1.66 (m, 2H), 1.63 – 1.38 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 160.3, 153.2, 132.7, 130.3, 128.7, 127.2, 123.9, 115.9, 41.8, 32.5 (2C), 25.9 (2C), 25.7; HRMS (ESI): m/z calcd for $C_{14}H_{17}N_2OS$ $[M + H]^+$: 261.1056, found: 261.1058.

3-(Heptylthio)quinoxalin-2(1*H*)-one (3e). 80% yield (110.4 mg, petroleum ether/ethyl acetate = 6:1 as an eluent). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H), 7.64 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.43 – 7.39 (m,1H), 7.33 – 7.22 (m, 2H), 3.10 (t, *J* = 7.3 Hz, 2H), 2.51 (d, *J* = 1.8 Hz, 2H), 1.67 (ddd, *J* = 14.8, 8.1, 6.7 Hz, 2H), 1.47 – 1.24 (m, 6H), 0.88 – 0.81 (m, 3H).; $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 160.8, 153.3, 132.7, 130.4, 128.7, 127.2, 123.9, 116.0, 31.6, 28.9, 28.8, 28.7, 28.6, 22.5, 14.4; HRMS (ESI): m/z calcd for $C_{15}H_{21}N_2OS$ $[M + H]^+$: 277.1369, found: 277.1378.

3-(Benzylthio)quinoxalin-2(1*H*)-one (3f). 69% yield (92.4 mg, petroleum ether/ethyl acetate = 6:1 as an eluent). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.53 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.46 – 7.41 (m, 1H), 7.34

– 7.22 (m, 5H), 4.39 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ: 160.1, 153.2, 138.0, 132.6, 130.6, 129.6 (2C), 128.9, 128.8 (2C), 127.5, 127.3, 124.0, 116.1, 33.2; HRMS (ESI): m/z calcd for $C_{15}H_{13}N_2OS$ [M + H]$^+$: 269.0743, found: 269.0744.

3-(Phenethylthio)quinoxalin-2(1*H*)-one (3g). 73% yield (102.9 mg, petroleum ether/ethyl acetate = 6:1 as an eluent). ^1H NMR (400 MHz, $CDCl_3$) δ 12.23 (s, 1H), 7.82 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.48 –7.42 (m, 2H), 7.39 –7.34 (m, 5H), 7.36 – 7.29 (m, 1H), 3.54 – 3.45 (m, 2H), 3.16 – 3.06 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ: 159.4, 154.9, 140.5, 133.5, 129.1, 128.7 (2C), 128.6 (2C), 128.5, 127.4, 126.5, 124.5, 116.2, 35.1, 30.9; HRMS (ESI): m/z calcd for $C_{16}H_{15}N_2OS$ [M + H]$^+$: 283.0900, found: 283.0903.

3-((Furan-2-ylmethyl)thio)quinoxalin-2(1*H*)-one (3h). 34% yield (43.8 mg, petroleum ether/ethyl acetate = 6:1 as an eluent). ^1H NMR (400 MHz, DMSO-d_6) δ 12.58 (s, 1H), 7.78 – 7.62 (m, 1H), 7.65 – 7.53 (m, 1H), 7.51 – 7.36 (m, 1H), 7.35 – 7.06 (m, 2H), 6.43 – 6.38 (m, 2H), 4.46 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ: 159.4, 153.3, 150.7, 143.0, 132.5, 130.5, 129.1, 127.4, 124.1, 116.1, 111.2, 108.9, 25.7; HRMS (ESI): m/z calcd for $C_{13}H_{10}N_2NaO_2S$ [M + Na]$^+$: 281.0355, found: 281.0358.

Ethyl 2-((3-Oxo-3,4-dihydroquinoxalin-2-yl)thio)acetate (3i). 82% yield (108.2 mg, petroleum ether/ethyl acetate = 6:1 as an eluent). ^1H NMR (400 MHz, DMSO-d_6) δ 12.60 (s, 1H), 7.58 – 7.56 (m, 1H), 7.46 – 7.42 (m, 1H), 7.31 – 7.26 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 2H), 1.21 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ: 169.1, 159.7, 153.2, 132.4, 130.5, 129.1, 127.2, 124.1, 116.1, 61.5, 32.1, 14.6; HRMS (ESI): m/z calcd for $C_{12}H_{12}N_2NaO_3S$ [M + Na]$^+$: 287.0461, found: 287.0460.

3-(Allylthio)quinoxalin-2(1*H*)-one (3j). 33% yield (35.9 mg, petroleum ether/ethyl acetate = 6:1 as an eluent). ^1H NMR (400 MHz, DMSO-d_6) δ 12.53 (s, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.30 – 7.26 (m, 2H), 6.01 – 5.91 (m, 1H), 5.41 – 5.36 (m, 1H), 5.16 – 5.14 (m, 1H), 3.82 (d, *J* = 6.9 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ: 159.9, 153.3, 133.7, 132.6, 130.5, 128.9, 127.3, 123.9, 118.8, 116.1, 31.8; HRMS (ESI): m/z calcd for $C_{11}H_{11}N_2OS$ [M + H]$^+$: 219.0587, found: 219.0587.

3-(P-tolylthio)quinoxalin-2(1*H*)-one (3k). 20% yield (26.8 mg, petroleum ether/ethyl acetate = 6:1 as an eluent). ^1H NMR (400 MHz, DMSO-d_6) δ 12.61 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.45 – 7.27 (m, 5H), 7.20 – 7.18 (m, 1H), 2.39 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ: 160.5, 153.1, 139.5, 135.5 (2C), 132.5, 130.9, 130.4 (2C), 129.1, 127.5, 124.9, 123.9, 116.0, 21.4; HRMS (ESI): m/z calcd for $C_{15}H_{13}N_2OS$ [M + H]$^+$: 269.0743, found: 269.0756.

3-(Tert-butylthio)-6,7-difluoroquinoxalin-2(1*H*)-one (3l). 72% yield (97.2 mg, petroleum ether/ethyl acetate = 6:1 as an eluent). ^1H NMR (400 MHz, DMSO-d_6) δ 12.49 (s, 1H), 7.70 (dd, *J* = 11.2, 8.0 Hz, 1H), 7.15 (dd, *J* = 11.2, 7.6 Hz, 1H), 1.59 (s, 9H); $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ: 162.3, 152.8, 149.4 (dd, *J* = 247.7, 14.6 Hz), 146.2 (dd, *J* = 242.3, 14.1 Hz), 128.7 (dd, *J* = 9.9, 2.4 Hz), 127.3 (d, *J* = 10.1 Hz), 115.0 (d, *J* = 18.4 Hz), 103.8 (d, *J* = 21.9 Hz), 47.2, 29.7 (3C); HRMS (ESI): m/z calcd for $C_{12}H_{13}F_2N_2OS$ [M + H]$^+$ 271.0711, found: 271.0710.

Methyl 3-(Tert-butylthio)-2-oxo-1,2-dihydroquinoxaline-6-carboxylate (3m). 65% yield (94.9 mg, petroleum ether/ethyl acetate = 8:1 as an eluent). ^1H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 7.87 (d, *J* = 1.4 Hz, 1H), 7.81– 7.78 (m, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 3.89 (s, 3H), 1.63 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ: 165.9, 164.6, 153.1, 134.9, 130.0, 128.8, 127.4, 124.2, 117.3, 52.9, 47.4, 29.6 (3C); HRMS (ESI): m/z calcd for $C_{14}H_{17}N_2O_3S$ [M + H]$^+$ 293.0954, found 293.0951.

3-(Tert-butylthio)-8-chloroquinoxalin-2(1*H*)-one (3n). 54% yield (72.4 mg, petroleum ether/ethyl acetate = 8:1 as an eluent). ^1H NMR (400 MHz, DMSO-d_6) δ 12.00 (s, 1H), 7.63 – 7.52 (m, 2H), 7.26 (t, *J* = 7.6 Hz, 1H), 1.62 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ: 162.7, 153.6, 133.3, 128.7, 127.5, 126.4, 124.2, 118.9, 47.2, 29.7 (3C); HRMS (ESI): m/z calcd for $C_{12}H_{13}ClN_2NaOS$ [M + Na]$^+$: 291.0329, found: 291.0322.

6-Bromo-3-(tert-butylthio)quinoxalin-2(1*H*)-one (3o). 51% yield (79.5 mg, petroleum ether/ethyl acetate = 8:1 as an eluent). ^1H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.41 (s, 2H), 1.61 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ: 162.1, 152.9, 131.5, 131.4, 128.9, 126.7, 120.8, 118.2, 47.2, 29.7 (3C); HRMS (ESI): m/z calcd for $C_{12}H_{14}BrN_2OS$ [M + H]$^+$: 313.0005 , found: 313.0014.

7-Bromo-3-(tert-butylthio)quinoxalin-2(1*H*)-one (3p). 50% yield (77.9 mg, petroleum ether/ethyl acetate = 8:1 as an eluent). ^1H NMR (400 MHz, DMSO-d_6) δ 12.52 (s, 1H),

7.83 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 1.61 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ: 163.1, 153.0, 133.2, 131.2, 129.5, 129.2, 117.9, 115.2, 47.3, 29.7 (3C); HRMS (ESI): m/z calcd for $C_{12}H_{14}BrN_2OS$ [M + H]$^+$: 313.0005, found: 313.0003.

3-(Tert-butylthio)-6-(trifluoromethyl)quinoxalin-2(1*H*)-one (3q). 54 % yield (81.5 mg, petroleum ether/ethyl acetate = 8:1 as an eluent). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.61 (s, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 9.4 Hz, 2H), 1.61 (s, 9H); $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ: 164.8, 153.0, 134.2, 130.3, 128.2, 128.1 (q, *J* = 32.3 Hz), 124.3 (q, *J* = 273.2 Hz), 120.0 (q, *J* = 3.5 Hz), 113.1 (q, *J* = 4.1 Hz), 47.4, 29.6 (3C); HRMS (ESI): m/z calcd for $C_{13}H_{13}F_3N_2NaOS$ [M + Na]$^+$:325.0593, found:325.0590.

3-(Tert-butylthio)-7-(trifluoromethyl)quinoxalin-2(1*H*)-one (3r). 51% yield (77.0 mg, petroleum ether/ethyl acetate = 8:1 as an eluent). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.71 (s, 1H), 7.94 (s, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 1.63 (s, 9H); $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ: 163.6, 153.3, 133.1, 131.6, 127.2 (q, *J* = 271.7 Hz), 124.8 (q, *J* = 3.6 Hz), 124.2 (q, *J* = 4.0 Hz), 123.9 (q, *J* = 32.6 Hz), 117.2, 47.4, 29.7 (3C); HRMS (ESI): m/z calcd for $C_{13}H_{13}F_3N_2NaOS$ [M + Na]$^+$: 325.0593, found: 325.0599.

3-(Tert-butylthio)-6,7-dichloroquinoxalin-2(1*H*)-one (3s). 52% yield (78.5 mg, petroleum ether/ethyl acetate = 8:1 as an eluent). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.53 (s, 1H), 7.85 (s, 1H), 7.36 (s, 1H), 1.60 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ: 163.6, 152.8, 131.7, 130.3, 130.1, 128.0, 125.5, 116.9, 47.4, 29.7 (3C); HRMS (ESI): m/z calcd for $C_{12}H_{12}Cl_2N_2NaOS$ [M + Na]$^+$: 324.9940, found: 324.9944.

3-(Tert-butylthio)-2-oxo-1,2-dihydroquinoxaline-6-carbonitrile (3t). 51% yield (66.1 mg, petroleum ether/ethyl acetate = 8:1 as an eluent). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.74 (s, 1H), 8.13 (s, 1H), 7.789 – 7.76 (m, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 1.62 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ: 165.5, 152.9, 134.5, 130.6, 128.3, 126.9, 120.0, 118.9, 110.0, 47.6, 29.6 (3C); HRMS (ESI): m/z calcd for $C_{13}H_{13}N_3NaOS$ [M + Na]$^+$: 282.0672, found: 282.0671.

2-(Tert-butylthio)-3-oxo-3,4-dihydroquinoxaline-6-carbonitrile (3u). 54% yield (69.9 mg, petroleum ether/ethyl acetate = 8:1 as an eluent).^{1}H NMR (400 MHz, DMSO-d_6) δ 12.64 (s, 1H), 7.78 (s, 1H), 7.61 (d, *J* = 23.2 Hz, 2H), 1.63 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ: 163.8, 153.1, 133.9, 131.8, 131.6, 131.4, 118.9, 117.3, 105.9, 47.5, 29.7 (3C); HRMS (ESI): m/z calcd for $C_{13}H_{13}N_3NaOS$ [M + Na]$^+$: 282.0672, found: 282.0677.

3-(Tert-butylthio)-6-chloroquinoxalin-2(1*H*)-one (3v). 49% yield (65.6 mg, petroleum ether/ethyl acetate = 8:1 as an eluent). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.27 – 7.24 (m, 2H), 1.60 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ: 163.2, 153.0, 132.9, 129.1, 128.5, 127.5, 126.3, 117.6, 47.3, 29.7 (3C); HRMS (ESI): m/z calcd for $C_{12}H_{13}ClN_2NaOS$ [M + Na]$^+$:291.0329, found: 291.0315.

3-(Tert-butylthio)-7-chloroquinoxalin-2(1*H*)-one (3w). 45% yield (60.3 mg, petroleum ether/ethyl acetate = 8:1 as an eluent). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H), 7.47 (dd, *J* = 9.4, 2.6 Hz, 1H), 7.34 – 7.25 (m, 2H), 1.61 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ: 161.9, 152.9, 132.5, 131.2, 131.1, 128.8, 123.8, 115.2, 47.1, 29.7 (3C); HRMS (ESI): m/z calcd for $C_{12}H_{13}ClN_2NaOS$ [M + Na]$^+$: 291.0329, found: 291.0322.

3-(Tert-butylthio)-6-fluoroquinoxalin-2(1*H*)-one (3x). 51% yield (63.7 mg, petroleum ether/ethyl acetate = 8:1 as an eluent). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.53 (s, 1H), 7.71 (d, *J* = 2.2 Hz, 1H), 7.48 – 7.45 (m, 1H), 7.27 (d, *J* = 8.7 Hz, 1H), 1.62 (s, 9H); $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 163.2, 158.5 (d, *J* = 239.5 Hz), 152.9, 132.6 (d, *J* = 11.9 Hz), 126.9, 117.3 (d, *J* = 9.3 Hz), 116.4 (d, *J* = 24.3 Hz), 112.5 (d, *J* = 22.8 Hz), 47.2, 29.7 (3C); HRMS (ESI): m/z calcd for $C_{12}H_{13}FN_2NaOS$ [M + Na]$^+$: 275.0625, found: 275.0617.

3-(Tert-butylthio)-6,7-dimethylquinoxalin-2(1*H*)-one (3y). 23% yield (30.3 mg, petroleum ether/ethyl acetate = 8:1 as an eluent). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 (s, 1H), 7.43 (s, 1H), 7.01 (s, 1H), 2.27 (s, 6H), 1.61 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ: 159.9, 153.3, 127.9, 132.4, 130.9, 128.0, 127.3, 116.0, 46.7, 29.8 (3C), 20.1, 19.3; HRMS (ESI): m/z calcd for $C_{14}H_{19}N_2OS$ [M + H]$^+$: 263.1213, found: 263.1204.

1-Benzyl-3-(tert-butylthio)quinoxalin-2(1*H*)-one (3z). 30% yield (48.6 mg, petroleum ether/ethyl acetate = 40:1 as an eluent). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 4 Hz, 2H), 7.34 – 7.30 (m, 3H), 7.26 – 7.24 (m, 3H), 5.48 (s, 2H), 1.65 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ: 160.4, 153.0, 136.1, 133.1, 130.5, 129.2 (2C), 128.9, 128.2, 127.9, 127.3 (2C), 124.3, 115.6, 47.3, 45.7, 29.7 (3C); HRMS (ESI): m/z calcd for $C_{19}H_{20}N_2NaOS$

[M + H]$^+$: 347.1189, found: 347.1196.

3-(Tert-butylthio)-1-methylquinoxalin-2(1*H*)-one (3aa). 37% yield (45.8 mg, petroleum ether/ethyl acetate = 5:1 as an eluent). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (d, J = 7.6 Hz, 1H), 7.54 (d, J = 3.6 Hz, 2H), 7.38 – 7.34 (m, 1H), 3.62 (s, 3H), 1.63 (s, 9H).; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ:160.2, 152.8, 132.8, 131.5, 128.9, 127.9, 124.1, 115.3, 47.0, 29.8 (3C), 29.7; HRMS (ESI): m/z calcd for $C_{13}H_{17}N_2OS$ [M + H]$^+$: 249.1056, found: 249.1057.

3-(Tert-butylthio)-1-(prop-2-yn-1-yl)quinoxalin-2(1*H*)-one (3ab). 23% yield (31.2 mg, petroleum ether/ethyl acetate = 40:1 as an eluent). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 7.6 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.40 – 7.36 (m, 1H), 5.07 (d, J = 2.4 Hz, 2H), 3.36 (t, J = 2.4 Hz, 1H), 1.62 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 160.0, 151.9, 132.9, 129.8, 129.1, 128.1, 124.6, 115.5, 78.2, 75.8, 47.3, 32.0, 29.7 (3C). HRMS (ESI): m/z calcd for $C_{15}H_{16}N_2NaOS$ [M + Na]$^+$: 295.0876, found: 295.0887.

Tert-butyl 2-(3-(tert-butylthio)-2-oxoquinoxalin-1(2*H*)-yl)acetate (3ac). 31% yield (53.9 mg, petroleum ether/ethyl acetate = 40:1 as an eluent). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.75 (m, 1H), 7.43 – 7.38 (m, 1H), 7.32 – 7.28 (m, 1H), 7.03 (d, J = 8.4 Hz, 1H), 4.92 (s, 2H), 1.69 (s, 9H), 1.46 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 165.9, 160.2, 152.9, 133.2, 130.4, 128.5, 123.9, 113.2, 83.1, 63.3, 47.3, 44.2, 29.6 (3C), 27.9 (3C); HRMS (ESI): m/z calcd for $C_{18}H_{24}N_2NaO_3S$ [M + Na]$^+$: 371.1400, found: 371.1406.

3-(Tert-butylthio)-1-phenylquinoxalin-2(1*H*)-one (3ad). 68% yield (105.4mg, petroleum ether/ethyl acetate = 20:1 as an eluent). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, J = 7.9, 1.7 Hz, 1H), 7.64 – 7.53 (m, 3H), 7.33 – 7.23 (m, 4H), 6.66 (dd, J = 8.2, 1.6 Hz, 1H), 1.75 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.3, 152.9, 135.6, 133.0, 132.1, 130.2 (2C), 129.4, 128.3 (2C), 127.9, 127.7, 123.8, 115.5, 47.3, 29.6 (3C); HRMS (ESI): m/z calcd for $C_{18}H_{18}N_2NaOS$, [M + Na]$^+$: 333.1034, found: 333.1032.

3-((4-Chlorophenyl)thio)quinoxalin-2(1*H*)-one (3ae). 15% yield (21.6mg, petroleum ether/ethyl acetate = 15:1 as an eluent). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.67 (s, 1H), 7.67 – 7.54 (m, 4H), 7.48 – 7.36 (m, 2H), 7.30 (dd, J = 8.0, 1.5 Hz, 1H), 7.24 – 7.18 (m, 1H); ^{13}C{1H} NMR (100 MHz, DMSO-d_6) δ 159.7, 153.1, 137.3 (2C), 134.7, 132.4, 130.9, 129.7 (2C), 129.3, 127.6, 127.5, 123.9, 116.1; HRMS (ESI): m/z calcd for $C_{14}H_{10}ClN_2OS$ [M + H]$^+$: 289.0192, found: 289.0197.

ASSOCIATED CONTENT

Supporting Information

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^{1}H and ^{13}C spectra for all products and mechanism research (PDF)

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Notes

The authors declare no competing financial interest.

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