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REGIOSELECTIVE SYNTHESIS OF QUINOXALIN-2-ONE DERIVATIVES REGULATED BY ACID AND BASE

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Abstract – A concise approach for the synthesis of quinoxalin-2-one derivatives through substituted *o*-phenylenediamines and α-ketoester with high regioselectivity is developed. Interestingly, the two regioisomers can be selectively obtained and the regioselectivity can be regulated by acid and base. The typical regioisomer ratio is up to 15:1 in acidic conditions and it can be easily reversed as 1:4 in basic conditions.

INTRODUCTION

Quinoxalines belong to an important class of six-membered nitrogen heterocycles, which have a wide variety of biological activities, such as antibacterial,[1] antifungal,[2] antitumor,[3] antiviral,[4] antimalarial,[5] anti-inflammatory,[6] hypoglycemia and hyperlipidemia.[7]

Our group is committed to the synthesis of pharmaceutical intermediates. One is anti-HCV drug Grazoprevir (Figure 1), which is highly desirable to synthesize substituted quinoxalin-2-one derivatives with high regioselectivity. In fact, many researches have studied on the synthesis of quinoxalines but control of regioselectivity is still a challenge and has been rarely reported.[8-12] Only a few researches have been involved in controlling regioselectivity, which provide effective strategies including the one-pot synthesis of 2,3-substituted quinoxalines via intermolecular Michael addition/dehydrogenation coupling/base-catalyzed CH_2-α-CH_2 extrusion strategy,[13] Ru-catalyzed coupling reaction of aromatic amines with *o*-C-H bond activated terminal alkynes,[14] microwave-assisted condensation of *o*-phenylenediamines with α-ketoesters[15] and the anilines mediated condensation of α-ketimide esters with 2-aminoanilines.[16] However, these processes suffer from harsh conditions and expensive catalysts, which obviously hinder their applications. Herein, we report a concise regioselective strategy to synthesize substituted quinoxalin-2-one derivatives regulated by acid and base.

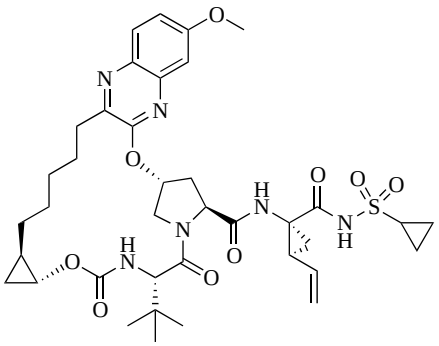
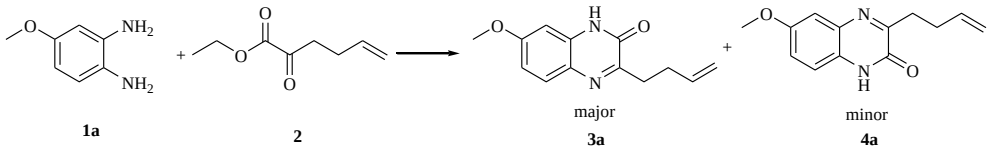


Figure 1. The structure of Grazoprevir

RESULTS AND DISCUSSION

As reported, ethyl 2-oxohex-5-enoate (**2**) and 4-methoxy-*o*-phenylenediamine (**1a**) were chosen as substrates to synthesize 3-(but-3-enyl)-7-methoxyquinoxalin-2(1*H*)-one (**3a**).[17] Nevertheless, poor reproducibility and relatively low regioselectivity were obtained even we made some improvements. Thus, we decided to pay more attention to the tough task.

Table 1. Optimization of conditions to synthesize major product **3a**[a]



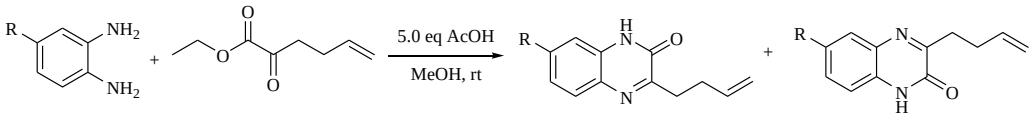
Entry	Acid	Solvent	Time (h)	Isomer ratio[b] (**3a**: **4a**)	Yield[c] (%)
1	—	EtOH	4.0	2.0:1	80
2	2.0 eq AcOH	EtOH	1.0	9.9:1	82
3	2.0 eq TsOH	EtOH	2.0	2.7:1	76
4	2.0 eq TFA	EtOH	3.0	2.5:1	53
5	2.0 eq HCl	EtOH	3.0	2.4:1	47
6	1.0 eq AcOH	EtOH	1.5	9.5:1	80
7	4.0 eq AcOH	EtOH	1.0	11.2:1	82
8	5.0 eq AcOH	EtOH	0.5	12.4:1	85
9	5.0 eq AcOH	MeOH	0.5	15.7:1	94
10	5.0 eq AcOH	MeCN	2.0	2.1:1	63
11	5.0 eq AcOH	DCM	2.0	4.6:1	70

[a]Reaction conditions: **1a** (100 mg, 1.0 eq), **2** (135.6 mg, 1.2 eq), solvent (10.0 mL), N_2, rt. [b]Determined from the reaction mixture by HPLC. [c]Isolated total yield.

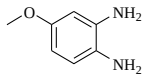
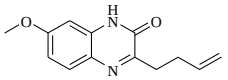
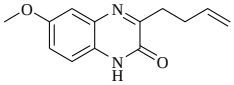
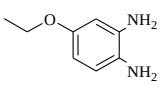
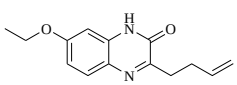
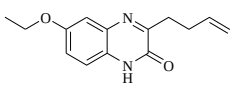
The same substrates were used in the model reaction as shown in Table 1. Obviously, acid had a great influence on the regioselectivity and the rate of the reactions (Table 1, entry 2). When 2.0 eq AcOH was added, the ratio of the two regioisomers was up to 9.9:1 compared with 2.0:1 without AcOH, and the reaction time was also shortened from 2.0 h to 1.0 h. It was found that 2.0 eq AcOH was the best choice among the acids we screened (Table 1, entries 2-5). Besides, the regioselectivity was related to the acidity of the acids, both regioselectivity and yield decreased when strong acids were used (Table 1, entries 3-5). We suggested that the formation of ammonium salt reduced the nucleophilicity of amino group, which resulted in the decrease of regioselectivity and yield. Increasing the amount of AcOH could improve the regioselectivity and the highest regioselectivity was obtained as 12.4:1 in 5.0 eq AcOH (Table 1, entry 8). The examination of solvents showed that the best result was obtained in MeOH with the highest regioselectivity 15.7:1 (Table 1, entry 9).

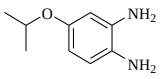
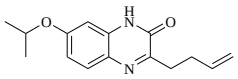
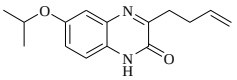
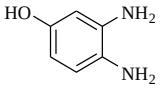
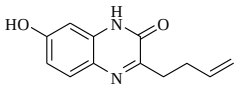
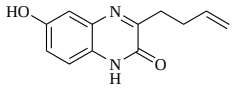
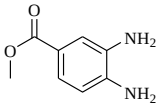
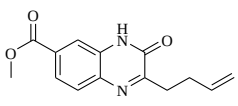
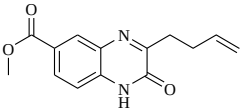
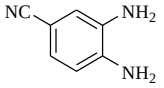
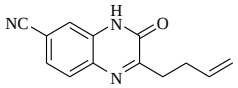
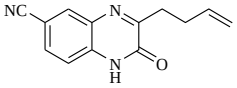
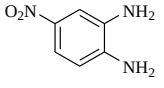
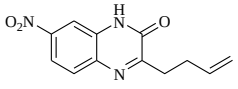
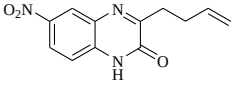
With the optimized reaction conditions in hands, different functionalized *o*-phenylenediamines were examined including electron-donating and electron-withdrawing substituents (Table 2). In the presence of AcOH, 7-substituted quinoxalin-2-one derivatives are formed as the main isomer whether the substituents are strong electron-withdrawing or electron-donating groups, but the regioselectivity of electron-donating groups is higher than that of electron-withdrawing groups. Besides, the steric hindrance of the substituents has little effect (Table 2, entries 1-4). It is worth mentioning that the electronic effect of the substituents has a significant effect on the reaction rate. The reaction rate of electron-donating groups substituted *o*-phenylenediamines is higher than that of electron-withdrawing groups. On the basis of the observed results, obviously, this method is especially suitable for electron-donating substituted *o*-phenylenediamines.

Table 2. Scope of 4-substituted *o*-phenylenediamines under acidic conditions[a]



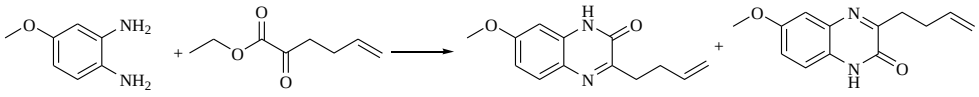
1a-g **2** **3a-g** **4a-g**

Entry	Substrate	Major product	Minor product	Regioisomer ratio[b] (**3a-g**/**4a-g**)	Time (h)	Yield[c] (%)
1	 **1a**	 **3a**	 **4a**	15.7:1	0.5	94
2	 **1b**	 **3b**	 **4b**	15.4:1	0.5	92

3	 **1c**	 **3c**	 **4c**	11.3:1	0.5	86
4	 **1d**	 **3d**	 **4d**	19.6:1	0.5	88
6	 **1e**	 **3e**	 **4e**	1.9:1	1.0	90
7	 **1f**	 **3f**	 **4f**	2.4:1	1.0	90
8	 **1g**	 **3g**	 **4g**	5.1:1	2.0	87

[a]Reaction conditions: 4-substituted *o*-phenylenediamine (100 mg, 1.0 eq), α-ketoester (1.2 eq), AcOH (5.0 eq), MeOH (10.0 mL), N_2, rt. [b]Determined from the reaction mixture by HPLC. [c]Total yield after column chromatography.

Table 3. Optimization of conditions to synthesize major product **4a**[a]



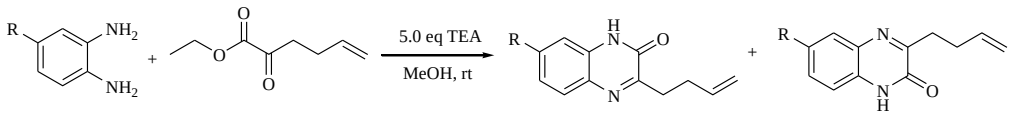
Entry	Base	Solvent	Temp (°C)	Isomer ratio[b] (**3a**:**4a**)	Yield[c] (%)
1	2.0 eq TEA	MeOH	25	1:2.0	72
2	2.0 eq DIEA	MeOH	25	1:1.3	70
3	2.0 eq $NaHCO_3$	MeOH	25	1:1.1	66
4	2.0 eq NaOH	MeOH	25	no reaction	
5	1.0 eq TEA	MeOH	25	1:1.4	70
6	5.0 eq TEA	MeOH	25	1:3.9	74
7	10.0 eq TEA	MeOH	25	1:3.3	68
8	5.0 eq TEA	EtOH	25	1:2.9	71
9	5.0 eq TEA	DCM	25	1:2.5	70
10	5.0 eq TEA	MeOH	60	1:3.0	63

[a]Reaction conditions: **1a** (100 mg, 1.0 eq), **2** (135.6 mg, 1.2 eq), solvent (10.0 mL), N_2. [b]Determined from the reaction mixture by HPLC. [c]Isolated total yield after column chromatography.

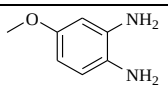
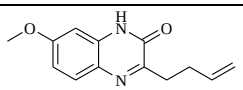
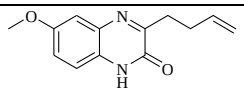
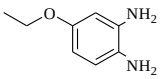
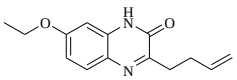
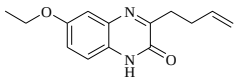
Under acidic conditions, the protonated carbonyl has higher activity so that it prefers to react with the *p*-amino group. Whether the regioselectivity will be reversed if the activity of ketonic carbonyl can be reduced and the ester carbonyl has priority to react with *p*-amino group. According to the fact that carbonyl groups are easy to isomerize to enols under basic conditions, we decided to try it under basic conditions (Table 3). To our delight, regioselectivity reversed as expected in basic conditions. It was found that 2.0 eq TEA was the best choice among the bases we screened (Table 2, entries 1-4), which gave desired isomers in 1:2.0. It should be noted that when the strong base was used, there was no target product because of the instability of substrates or intermediates (Table 3, entry 4). Regioselectivity increases first and then decreases with the increase of the dosage of base (Table 3, entries 5-7), and the best result was obtained when 5.0 eq TEA was used (Table 3, entry 6). The investigation of solvents shows that MeOH was still the best choice (Table 3, entry 6, 8-9). In addition, the regioselectivity was not increased but decreased with the increase of temperature (Table 3, entry 10).

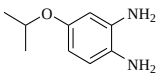
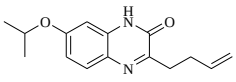
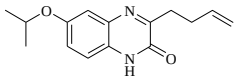
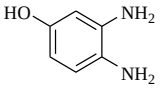
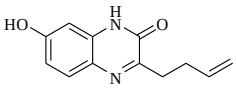
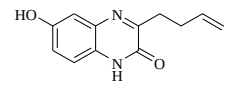
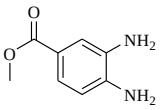
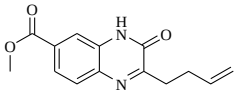
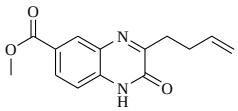
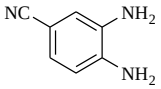
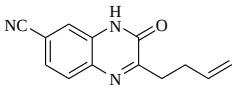
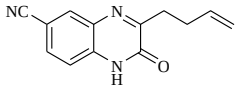
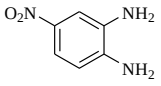
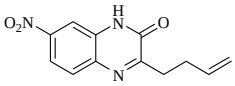
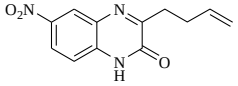
Using the optimized conditions, different substituted *o*-phenylenediamines were evaluated. Based on the obtained results, the regioselectivity in basic conditions is opposite to that in acidic conditions. 6-Substituted quinoxalin-2-one derivatives were successfully formed as main product when the substituents were electron-donating groups while strong electron-withdrawing groups such as nitro and cyano group have little reaction because of those poor reactivities even though the reaction was heated to 50 °C. However, the moderate electron-withdrawing group such as ester group does not react completely, but the regioselectivity still has been reversed obviously (Table 4, entry 5). In brief, this method is more suitable for electron-donating substituted *o*-phenylenediamines under basic conditions.

Table 4. Scope of 4-substituted *o*-phenylenediamines under basic conditions[a]



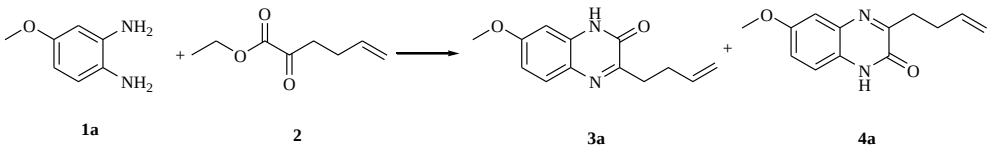
1a-g **2** minor **3a-g** major **4a-g**

Entry	Substrate	Minor product	Major product	Regioisomer ratio[b] (**3a-g**/**4a-g**)	Time (h)	Yield[c] (%)
1	 **1a**	 **3a**	 **4a**	1:3.9	8.0	74
2	 **1b**	 **3b**	 **4b**	1:4.1	10.0	70

3	 **1c**	 **3c**	 **4c**	1:4.6	12.0	69
4	 **1d**	 **3d**	 **4d**	1:3.6	5.0	67
6	 **1e**	 **3e**	 **4e**	1:11.8	24.0	64[d]
7	 **1f**	 **3f**	 **4f**	almost no reaction[e]		
8	 **1g**	 **3g**	 **4g**	almost no reaction[e]		

[a]Reaction conditions: 4-substituted *o*-phenylenediamine (100 mg, 1.0 eq), α-ketoester (1.2 eq), TEA (5.0 eq), MeOH (10.0 mL), N_2, rt. [b]Determined from the reaction mixture by HPLC. [c]Yield after column chromatography. [d]Yield after deducting recovered methyl 3,4-diaminobenzoate (**1e**). [e]There was no reaction even the reaction was heated to 50 °C for 24.0 h.

Finally, we performed the reaction on a gram scale (Scheme 1). Delightedly, the ratio of regioisomers was 14.2:1 in acidic conditions and 1:3.1 in basic conditions, which clearly demonstrates the preparative utility of this newly developed method.



Scheme 1. Gram scale experiments to synthesize **3a** and **4a**[a]

[a]Reaction conditions: **1a** (1.0 g, 1.0 eq), **2** (1.36 g, 1.2 eq), AcOH (2.17 g, 5.0 eq) or TEA (3.67 g, 5.0 eq), solvent (100.0 mL), N_2, rt.

On the basis of these results and the previous report,[18] the possible mechanism of this methodology was proposed (Figure 2). Under acidic conditions, the ketone carbonyl group is first protonated and its activity is enhanced, and then it reacts with the more nucleophilic *p*-amino group to form Schiff base followed by the elimination of H_2O. Subsequently, the *m*-amino group and the ester carbonyl group undergo an amination reaction to form 7-substituted quinoxalin-2-ones as the major regioisomer. On the contrary,

under basic conditions, the keto carbonyl group is isomerized to enol first, and its activity decreases, so the ester carbonyl group reacts with the *p*-amino group first, then the *m*-amino group reacts with the keto carbonyl group to form a Schiff base, and then H_2O was eliminated to form 6-substituted quinoxalin-2-ones as another major regioisomer.

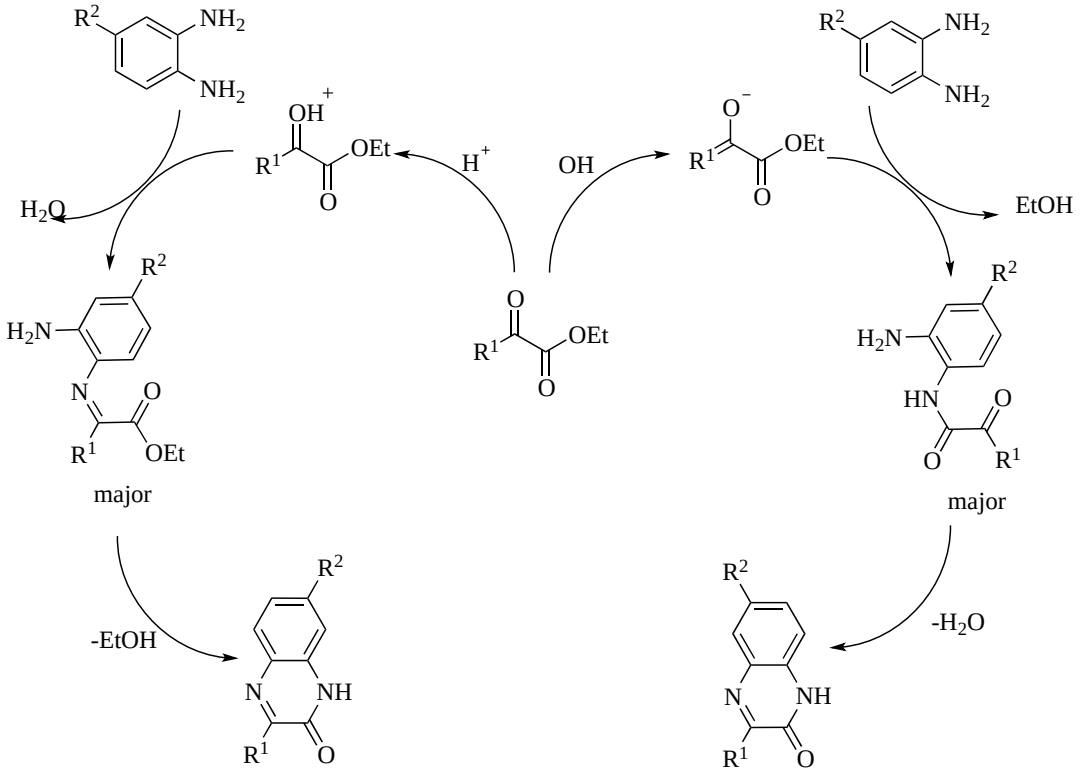


Figure 2. The possible mechanism of this method

In summary, a simple methodology for regioselective synthesis of asymmetric quinoxalin-2-one derivatives is proposed here. The regioselectivity of the reaction can be easily adjusted by adding AcOH or TEA. And this method has a certain range of substrates. Under acidic conditions, this method is compatible with both electron-donating and electron-withdrawing groups. While under basic conditions, it is more suitable for electron-donating groups.

EXPERIMENTAL

All reagents used are from commercial sources unless otherwise specified. All reactions were performed in dry glassware under an atmosphere of nitrogen unless otherwise noted. The IR was recorded in the solid state as KBr dispersion medium using Shimadzu IR Affinity-1 FT-IR spectrophotometer. HRMS was conducted on Thermo Dionex Ultimate-3000 and Thermo TSQ Quantum Access MAX. The HPLC was operated at Rigol L-3000 and RP-HPLC was operated at Agilent Technologies 1260 Infinity-11 or

Shimadzu LC-20A system. NMR spectra were obtained using Bruker ASCEND 400 spectrometer at 400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) in Hertz (Hz).

Ethyl 2-oxohex-5-enoate (2). Compound **2** was prepared according to the previous procedure.[19] In a flask, magnesium turnings (6.25 g, 0.26 mol) were stirred vigorously overnight under nitrogen. A solution of 4-bromo-1-butene (22.0 mL, 0.22 mol) in anhydrous THF (200 mL) was added in dropwise aliquots over 1.0 h to the magnesium turnings under nitrogen, ensuring that the THF did not boil, then stirred for 0.5 h. The solution was carefully drawn up in a dropping funnel, leaving unreacted magnesium in the flask. The Grignard solution was added dropwise to a flask at -70 °C containing diethyl oxalate (31.7 g, 0.22 mol) dissolved in anhydrous THF (200 mL) and stirred for 3.0 h at -70 °C. The reaction was quenched with NH_4Cl aqueous (150 mL) at -70 °C. After quenching, the mixture of EtOAc (EA) and petroleum ether (PE) (100 mL) was added to the flask and the flask was allowed to warm to room temperature. The two layers were separated, and the aqueous layer was extracted with EA (100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo with the rotary evaporator under 40 °C. The residue was purified by flash chromatography to give the target product as slightly yellow oil (27.2 g, 80.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, J = 16.8, 10.2, 6.5 Hz, 1H), 5.03 (ddd, J = 17.1, 3.1, 1.5 Hz, 1H), 4.97 (dd, J = 10.2, 1.3 Hz, 1H), 4.35 – 4.20 (m, 2H), 2.99 – 2.82 (m, 2H), 2.45 – 2.25 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H).

Typical synthesis of substituted quinoxalin-2-one derivatives: Appropriate 4-substituted *o*-phenylenediamine (100 mg, 1.0 eq) was dissolved in MeOH (10.0 mL) in a round-bottomed flask with three-necks and AcOH or TEA (5.0 eq) was added into the mixture slowly. Then the α-ketoester (1.2 eq) was added dropwise and the reaction mixture was stirred at room temperature. The reaction was checked by thin-layer chromatography (TLC) using iodine and phosphomolybdic acid as chromogenic reagents and the ratio of the two regioisomers was recorded by HPLC or RP-HPLC. After the reaction was completed, the reaction was quenched with water and extracted with EA, washed with saturated sodium bicarbonate aqueous (when AcOH was used as catalyst) or NH_4Cl aqueous (when TEA was used as catalyst) and saturated brine, dried by anhydrous sodium sulfate and the solvent was evaporated at 40 °C under vacuum environment. The residual solids were purified on silica gel column to obtain the target products.

3-(But-3-enyl)-7-methoxyquinoxalin-2(1*H*)-one (3a):[20] The cyclization required 0.5 h in acidic conditions while 8.0 h in basic conditions. The target product **3a** was obtained as an off-white solid. Mp 190-193 °C. FT-IR: 2926, 2851, 1659, 1501, 1412, 1362, 1287, 1252, 1200, 1163, 1033, 914, 842 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ =12.21 (s, 1H), 7.62 (d, J = 8.9 Hz, 1H), 6.87 (dd, J = 8.9, 2.7 Hz, 1H), 6.74 (d, J = 2.7 Hz, 1H), 5.91 (ddt, J = 16.8, 10.2, 6.5 Hz, 1H), 5.07 (ddd, J = 17.2, 3.6, 1.6 Hz, 1H), 4.97

(ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 3.82 (s, 3H), 2.82 (dd, *J* = 8.5, 6.7 Hz, 2H), 2.45 (ddd, *J* = 14.1, 6.4, 1.3 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) *δ* 160.42, 157.76, 155.29, 138.50, 133.67, 129.83, 126.99, 115.53, 111.89, 98.25, 55.99, 32.16, 30.62. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}N_2O_2$: 231.1134, found: 231.1141.

3-(But-3-enyl)-6-methoxyquinoxalin-2(1*H*)-one (4a):[20] The cyclization required 0.5 h in acidic conditions while 8.0 h in basic conditions. The target product 4a was obtained as an off-white solid. Mp 166-172 °C. FT-IR: 3075, 2841, 1659, 1618, 1557, 1514, 1447, 1366, 1288, 1238, 1215, 1176, 1117, 1034, 912, 816 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) *δ* 12.24 (s, 1H), 7.24 (d, *J* = 2.7 Hz, 1H), 7.22 (d, *J* = 8.9 Hz, 1H), 7.13 (dd, *J* = 8.9, 2.8 Hz, 1H), 5.93 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.08 (ddd, *J* = 17.2, 3.5, 1.6 Hz, 1H), 5.02 – 4.94 (m, 1H), 3.82 (s, 3H), 2.88 (dd, *J* = 8.5, 6.7 Hz, 2H), 2.51 – 2.43 (m, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) *δ* 161.83, 155.70, 154.66, 138.43, 132.72, 126.26, 119.01, 116.51, 115.56, 110.33, 55.98, 32.46, 30.50. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}N_2O_2$: 231.1134, found: 231.1137.

3-(But-3-enyl)-7-ethoxyquinoxalin-2(1*H*)-one (3b): The cyclization required 0.5 h in acidic conditions while 10.0 h in basic conditions. The target product was obtained as an off-white solid. Mp 169-172 °C. FT-IR: 2976, 1655, 1501, 1287, 1244, 1209, 1121, 1049, 912, 818 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) *δ* 12.17 (s, 1H), 7.59 (d, *J* = 8.9 Hz, 1H), 6.83 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.70 (d, *J* = 2.7 Hz, 1H), 5.89 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.05 (ddd, *J* = 17.2, 3.5, 1.7 Hz, 1H), 4.95 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 4.10 – 3.99 (m, 2H), 2.80 (dd, *J* = 8.6, 6.7 Hz, 2H), 2.43 (dt, *J* = 7.5, 6.5 Hz, 2H), 1.34 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) *δ* 159.70, 157.67, 155.30, 138.51, 133.66, 129.81, 126.92, 115.52, 112.17, 98.74, 64.05, 32.16, 30.63, 14.98. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}N_2O_2$: 245.1290, found: 245.1302.

3-(But-3-enyl)-6-ethoxyquinoxalin-2(1*H*)-one (4b): The cyclization required 0.5 h in acidic conditions while 10.0 h in basic conditions. The target product was obtained as an off-white solid. Mp 145-149 °C. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 12.23 (s, 1H), 7.28 (d, *J* = 3.0 Hz, 1H), 7.26 (d, *J* = 3.3 Hz, 1H), 7.13 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.05 – 5.93 (m, 1H), 5.14 (ddd, *J* = 17.1, 3.3, 1.6 Hz, 1H), 5.02 (dd, *J* = 10.2, 1.7 Hz, 1H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.09 (dd, *J* = 8.6, 6.8 Hz, 2H), 2.62 (dt, *J* = 7.6, 6.5 Hz, 2H), 1.46 (t, *J* = 6.9 Hz, 3H). HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}N_2O_2$: 245.1290, found: 245.1288.

3-(But-3-enyl)-7-isopropoxyquinoxalin-2(1*H*)-one (3c): The cyclization required 0.5 h in acidic conditions while 12.0 h in basic conditions. The target product was obtained as an off-white solid. Mp 174-179 °C. FT-IR: 2974, 2806, 1667, 1626, 1557, 1516, 1300, 1186, 1134, 1111, 993, 901, 851, 820 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) *δ* 12.15 (s, 1H), 7.60 (d, *J* = 8.9 Hz, 1H), 6.85 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.73 (d, *J* = 2.6 Hz, 1H), 5.91 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.06 (ddd, *J* = 17.2, 3.4, 1.6 Hz, 1H),

5.00 – 4.93 (m, 1H), 4.63 (dt, *J* = 12.1, 6.0 Hz, 1H), 2.82 (dd, *J* = 8.5, 6.7 Hz, 2H), 2.44 (dt, *J* = 14.1, 7.0 Hz, 2H), 1.31 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 158.66, 157.66, 155.28, 138.51, 133.72, 129.86, 126.83, 115.54, 112.84, 99.97, 70.42, 32.16, 30.67, 22.15. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_2$: 259.1447, found: 259.1441.

3-(But-3-enyl)-6-isopropoxyquinoxalin-2(1*H*)-one (4c): The cyclization required 0.5 h in acidic conditions while 12.0 h in basic conditions. The target product was obtained as an off-white solid. Mp 153-158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.45 (s, 1H), 7.31 – 7.25 (m, 2H), 7.11 (dd, *J* = 8.9, 2.6 Hz, 1H), 5.99 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.14 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.61 (dt, *J* = 12.1, 6.0 Hz, 1H), 3.13 – 3.05 (m, 2H), 2.62 (dd, *J* = 14.5, 7.4 Hz, 2H), 1.38 (d, *J* = 6.1 Hz, 6H). HRMS(ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_2$: 259.1447, found: 259.1449.

3-(But-3-enyl)-7-hydroxyquinoxalin-2(1*H*)-one (3d): The cyclization required 0.5 h in acidic conditions while 5.0 h in basic conditions. The target product was a pale solid. Mp 240-244 °C. IR: 3246, 1647, 1620, 1566, 1514, 1489, 1418, 1321, 1250, 1180, 1118, 902, 845, 820 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.05 (s, 1H), 10.08 (s, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 6.64 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.59 (d, *J* = 2.5 Hz, 1H), 5.84 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 4.99 (ddd, *J* = 17.2, 3.6, 1.6 Hz, 1H), 4.89 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 2.73 (dd, *J* = 8.6, 6.7 Hz, 2H), 2.37 (dt, *J* = 7.6, 6.4 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 159.09, 156.51, 155.41, 138.57, 133.78, 129.89, 126.28, 115.48, 112.89, 100.01, 32.11, 30.72. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{13}N_2O_2$: 217.0977, found: 217.0982.

3-(But-3-enyl)-6-hydroxyquinoxalin-2(1*H*)-one (4d): The cyclization required 0.5 h in acidic conditions while 5.0 h in basic conditions. The target product was a pale solid. Mp 223-226 °C. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.12 (s, 1H), 9.53 (s, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 7.05 (d, *J* = 2.6 Hz, 1H), 6.97 (dd, *J* = 8.7, 2.6 Hz, 1H), 5.96 – 5.83 (m, 1H), 5.06 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.00 – 4.91 (m, 1H), 2.88 – 2.82 (m, 2H), 2.44 (dd, *J* = 14.4, 7.4 Hz, 2H). HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{13}N_2O_2$: 217.0977, found: 217.0991.

Methyl 2-(but-3-enyl)-3,4-dihydro-3-oxoquinoxaline-7-carboxylate (3e): The cyclization required 0.5 h in acidic conditions while there is still a surplus of raw materials in basic conditions after 24.0 h. The target product was obtained as an off-white solid. Mp 158-163 °C. IR: 2949, 1722, 1662, 1610, 1435, 1298, 1261, 1211, 1092, 991, 914, 768 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.60 (s, 1H), 8.20 (d, *J* = 1.8 Hz, 1H), 8.00 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 5.93 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.09 (dd, *J* = 17.2, 1.8 Hz, 1H), 4.99 (dd, *J* = 10.2, 1.8 Hz, 1H), 3.88 (s, 3H), 2.92 – 2.85 (m, 2H), 2.48 (dd, *J* = 10.9, 4.2 Hz, 2H). Only signals of the major regioisomer are listed. ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 165.99, 162.81, 155.09, 138.33, 135.93, 131.31, 130.13, 129.83, 124.60, 116.10, 115.66,

52.67, 32.29, 30.15. Only signals of the major regioisomer are listed. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_3$: 259.1083, found: 259.1076.

Methyl 2-(but-3-enyl)-3,4-dihydro-3-oxoquinoxaline-6-carboxylate (4e): The cyclization required 0.5 h in acidic conditions while there is still a surplus of raw materials in basic conditions after 24.0 h. The target product was obtained as an off-white solid. Mp 134-139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.84 (s, 1H), 8.04 (d, *J* = 1.5 Hz, 1H), 7.99 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 6.00 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.16 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.04 (d, *J* = 10.2 Hz, 1H), 4.01 (s, 3H), 3.18 – 3.10 (m, 2H), 2.65 (dd, *J* = 14.7, 7.0 Hz, 2H). HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_3$: 259.1083, found: 259.1092.

2-(But-3-enyl)-3,4-dihydro-3-oxoquinoxaline-7-carbonitrile (3f): The cyclization required 0.5 h in acidic conditions while there is little reaction in basic conditions after 24.0 h under 50 °C. The target product was obtained as a faint yellow solid. Mp 200-204 °C. IR: 2918, 2849, 2224, 1663, 1611, 1566, 1497, 1414, 1140, 910, 829 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.67 (s, 1H), 8.20 (d, *J* = 1.8 Hz, 1H), 7.86 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 5.92 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.08 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.02 – 4.92 (m, 1H), 2.89 (dd, *J* = 8.4, 6.8 Hz, 2H), 2.50 – 2.43 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.80, 154.91, 138.21, 135.96, 133.09, 132.71, 131.53, 118.99, 117.07, 115.75, 105.64, 32.42, 30.21.HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{12}N_3O$: 226.0980, found: 226.0985.

2-(But-3-enyl)-3,4-dihydro-3-oxoquinoxaline-6-carbonitrile (4f): The cyclization required 0.5 h in acidic conditions while there is little reaction in basic conditions after 24.0 h under 50 °C. The target product was obtained as a faint yellow solid. Mp 193-196 °C. IR: 2922, 2845, 2234, 1670, 1612, 1566, 1398, 1142, 1117, 1001, 920, 831 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.65 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.60 (d, *J* = 1.7 Hz, 1H), 5.92 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.08 (ddd, *J* = 17.2, 3.5, 1.7 Hz, 1H), 5.01 – 4.96 (m, 1H), 2.91 (dd, *J* = 8.3, 6.9 Hz, 2H), 2.51 – 2.43 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.30, 154.67, 138.19, 134.31, 132.60, 129.76, 126.39, 119.78, 118.75, 115.75, 111.52, 32.60, 30.16. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{12}N_3O$: 226.0980, found: 226.0986.

3-(But-3-enyl)-7-nitroquinoxalin-2(1*H*)-one (3g): The cyclization required 0.5 h in acidic conditions while there is little reaction in basic conditions after 24.0 h under 50 °C. The target product was obtained as a faint yellow solid. Mp 201-204 °C. IR: 2924, 2853, 1670, 1618, 1539, 1342, 1146, 1078, 914, 837 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.82 (s, 1H), 8.44 (d, *J* = 2.5 Hz, 1H), 8.31 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.41 (d, *J* = 9.0 Hz, 1H), 5.94 (dd, *J* = 17.1, 10.3 Hz, 1H), 5.09 (ddd, *J* = 17.2, 3.5, 1.6 Hz, 1H), 5.03 – 4.97 (m, 1H), 2.95 – 2.86 (m, 2H), 2.51 – 2.45 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.34,

154.97, 142.85, 138.20, 137.56, 130.88, 124.65, 124.00, 116.70, 115.77, 32.38, 30.06. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{12}N_3O_3$: 246.0879, found: 246.0863.

3-(But-3-enyl)-6-nitroquinoxalin-2(1*H*)-one (4g): The cyclization required 2 h in acidic conditions while there is little reaction in basic conditions after 24.0 h under 50 °C. The target product was obtained as a light yellow solid. Mp 179-181 °C. IR: 3188, 1678, 1668, 1522, 1246, 1252, 1140, 1084, 895, 847 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 11.36 (s, 1H), 8.20 – 8.13 (m, 2H), 8.01 – 7.96 (m, 1H), 5.97 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.14 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.04 (dd, *J* = 10.2, 1.5 Hz, 1H), 3.18 – 3.11 (m, 2H), 2.64 (dt, *J* = 13.8, 6.8 Hz, 2H). HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{12}N_3O_3$: 246.0879, found: 246.0881.

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