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An Aniline-Mediated Regioselective Synthesis of Quinoxalin-2-ones via the Condensation of α-Ketimine Esters with 2-Aminoanilines

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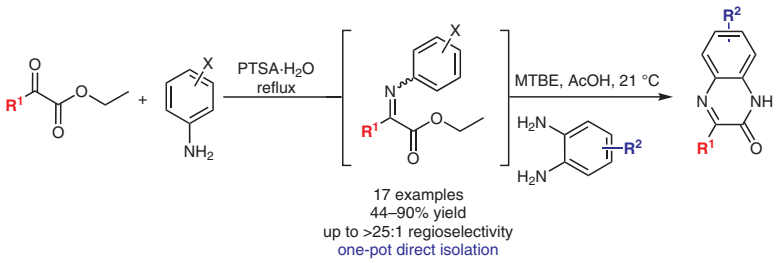

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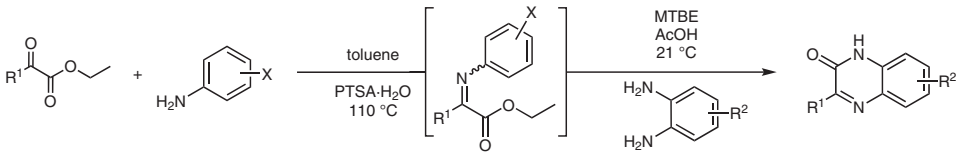
Abstract A highly regioselective method for the condensation of α-ketimine esters with 2-aminoanilines for the construction of quinoxalin-2-one derivatives is described. The substrate scope with 2-aminoaniline derivatives and different α-keto esters is explored with yields ranging from 44 to 90% and typical isolated regioselectivities between 6.4 to >25:1.

Key words quinoxalin-2-ones, 2-aminoanilines, α-ketimine esters, one-pot synthesis, transimination, regioselectivity

Quinoxalines are important nitrogen-containing heterocycles that have been utilized extensively in the pharmaceutical and specialty chemical industry. In particular, quinoxaline derivatives are desirable synthetic targets due to their extensive applications as antibiotic,[1] anticancer,[2] antiviral,[3] antimalarial,[4] and antileishmanial[5] agents. Furthermore, quinoxalines have been utilized as electroluminescent materials,[6] dyes,[7] organic semiconductors,[8] and ligands in coordination chemistry.[9]

As part of our efforts toward designing efficient routes to biologically active compounds,[10–12] we required an efficient and regioselective method for the synthesis of substituted quinoxalin-2-ones. While a survey of the literature identified several potential routes to unsymmetrical quinoxalin-2-ones, most were found to suffer from poor regioselectivity,[13] thus hindering their synthetic utility from a process chemistry point of view. Only a limited number of methods have been reported to generate quinoxalin-2-ones regioselectively; examples include the reactions of diamines with ynones via a base-promoted C-α-CH_2-extrusion,[14] the reactions of *o*-alkynylaldehydes with ring-fused diamines,[15] and the *ortho*-C–H bond activation reaction of aryl diamines with terminal alkynes.[16] Another regioselective route to quinoxalin-2-ones has been reported between an α-keto ester and unsymmetrical 2-aminoanilines, but the reaction required microwave irradiation at 200 °C and 250 psi,[17] which are not easily accessible conditions in commercial manufacturing.

Herein, we report a mild, expedient, one-pot synthesis of substituted quinoxalin-2-ones via the in situ conversion of α-keto esters into α-ketimine esters using a functionalized aniline followed by cyclocondensation with a functionalized 2-aminoaniline (Scheme 1). We envisioned that condensation of the carbonyl and amine would result in the formation of a more basic ketimine moiety, which would



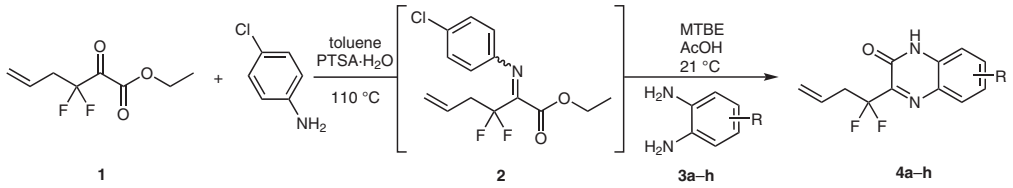
Scheme 1 General reaction for ketimine formation and transimination to quinoxalin-2-ones

facilitate selective acid-mediated protonation and activation of the ketimine versus the ester, thereby enabling selective attack of the more nucleophilic dianiline amine. This transimination would then be followed by a fast and irreversible cyclization to furnish the quinoxalin-2-one core. The design of this catalytic process hinged upon the increased Brønsted basicity of the ketimine intermediate which, upon protonation, forms a ketiminium ion with enhanced electrophilicity at the ketiminium carbon relative to the ester, thereby affording a regioselective cyclization of the 1,2-diamine.

Previously, difluoroalkylquinoxalin-2-ones were reported as important synthetic building blocks for the construction of HCV serine protease scaffolds.[1] Issues that plagued these early efforts were the low yield and poor regioselectivity of the heterocycle construction.

For this reason, we opted to utilize the β,β-difluoro-α-keto ester **1**[18] as the model substrate for our studies. Initially, a series of aliphatic and aromatic amines for ketimine formation were screened in THF with aniline-based amines exhibiting the best conversion into the ketimine. Specifically, 4-chloroaniline provided the best combination of regioselectivity, conversion, and cost (see the Supporting Information). Other solvents for the condensation step were screened (toluene, acetonitrile, dichloromethane, ethyl acetate, isopropyl acetate, *N*,*N*-dimethylformamide) with methyl *tert*-butyl ether (MTBE) showing the best combination of regioselectivity, yield, and removal of the undesired minor regioisomer.

Table 1 Scope of Substituted 2-Aminoanilines for the Synthesis of Quinoxalin-2-ones



1 2 3a–h 4a–h

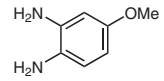
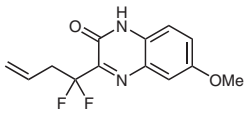
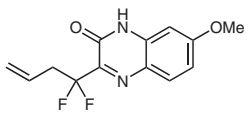
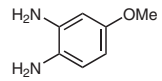
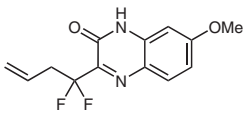
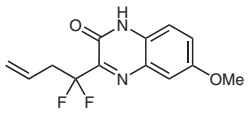
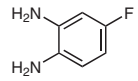
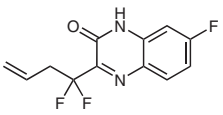
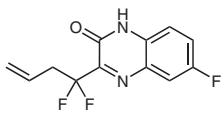
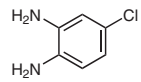
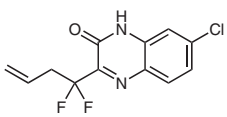
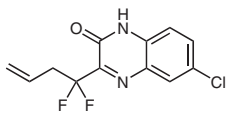
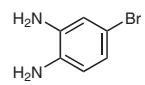
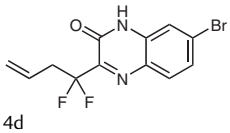
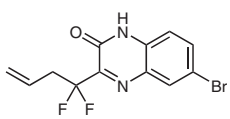
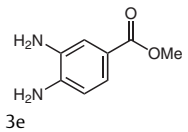
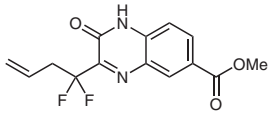
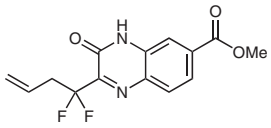
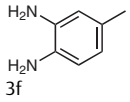
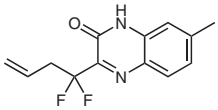
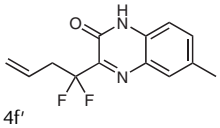
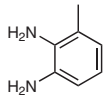
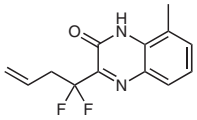
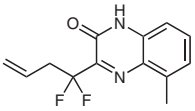
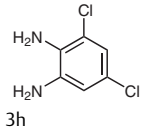
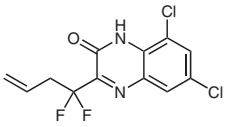
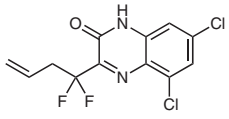
Entry	Substrate	Major product	Minor product	Regioisomer ratio (major/minor)		Yield (%)[c]
				Crude[a]	Isolated[b]	
1[d]	 3a	 4a′	 4a	2.6:1[d]	>25:1[d]	53
2	 3a	 4a	 4a′	6.3:1	>25:1	68
3	 3b	 4b	 4b′	6.1:1	6.9:1[e]	61[f]
4	 3c	 4c	 4c′	1.5:1	>25:1	50
5	 3d	 4d	 4d′	2.1:1	>25:1	44

Table 1 (continued)

Entry	Substrate	Major product	Minor product	Regioisomer ratio (major/minor)		Yield (%)[c]
				Crude[a]	Isolated[b]	
6	 3e	 4e	 4e′	4.4:1	>25:1	69
7	 3f	 4f	 4f′	1.9:1	1.5:1[e]	44[f]
8	 3g	 4g	 4g′	11.2:1	>25:1	55
9	 3h	 4h	 4h′	11.1:1	>25:1	52

[a] Determined from the ratio of products in the ^{19}F NMR (DMSO-d_6) spectrum of the reaction mixture.
[b] Determined from the ratio of products in the ^{19}F NMR (DMSO-d_6) spectrum of the isolated product.
[c] Yield of isolated product.
[d] Control reaction with no 4-chloroaniline added.
[e] Regioisomeric ratio after column chromatography.
[f] Required isolation by column chromatography.

Under the optimized conditions, the reaction proceeds by mixing 1 equivalent of the α-keto ester **1** with 1.15 equivalents of 4-chloroaniline in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate (PTSA·H_2O) in toluene at reflux to provide ketimine **2** after 16 hours. Water was removed azeotropically during the process thereby facilitating the expedient conversion into the desired ketimine intermediate. Addition of MTBE, acetic acid, and 3,4-diaminoanisole to the reaction mixture followed by stirring for an additional 16 hours at ambient temperature afforded **4a** as the major regioisomer in 68% yield with >25:1 regioselectivity after filtration of the one-pot reaction mixture (Table 1, entry 2). Notably, under the optimized conditions, no further purification of the isolated solid was required to remove any undesired minor regioisomer.

To confirm that the ketimine was the source of the enhanced regioselectivity, a control study using 3,4-diaminoanisole in the absence of 4-chloroaniline was conducted with **1** and **3a** (Table 1, entry 1). The cyclization proceeded as expected but resulted in a crude regioisomer ratio of 2.6:1 with *undesired* **4a′** as the major regioisomer. In this case, the opposite regioisomer was the major product compared to our ketimine activation protocol of 6.3:1 affording **4a** as the major isomer.

Using the optimized reaction conditions, different functionalized 2-aminoanilines were evaluated covering a range of electron-donating and electron-withdrawing substituents on the aromatic ring (Table 1). Through simple filtration and rinsing of the resulting slurry, a single regioisomer could be isolated with >25:1 regioselectivity and yields of 44-69% (entries 2, 4-6, 8-9). Only products **4b** and **4f** required further purification by column chromatography since neither quinoxalin-2-one product was amenable to direct crystallization from the reaction medium and thus, were isolated as a mixture of regioisomers. In most cases, the structures of the major regioisomers were established by NOESY and ROESY ^1H NMR with a nOe correlation between the amide proton (H_y, 12.7 ppm) and the phenyl proton doublet (H_x, 6.8 ppm) (Figure 1). Additionally, the nOe correlation was confirmed for **4g** between the amide proton and methyl proton; **4h** was assigned by analogy.

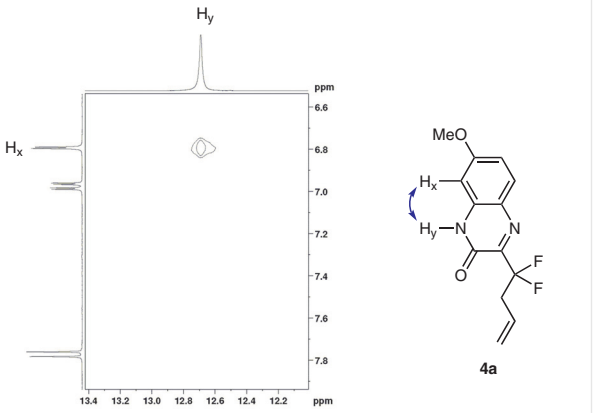


Figure 1 ^{1}H NMR NOESY evidence for the major regioisomer

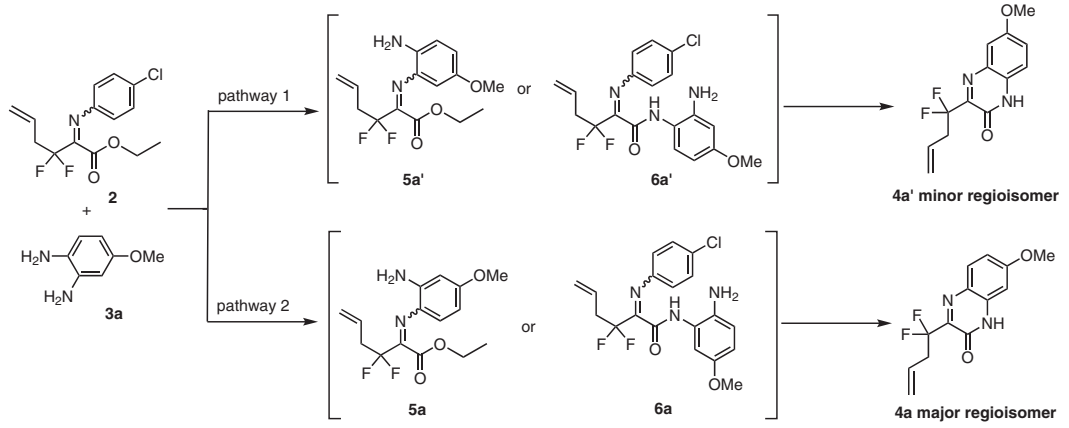
To evaluate the mechanism and the origin of the observed selectivity, electronic structure calculations were conducted at the M06-2X-D3 (PBF, methyl *tert*-butyl ether)/cc-PVTZ(-*f*)//M06-2X/LACVP** level.[19] Transition states and intermediates for the reaction of both the electron-rich methoxyaniline **3a** as well as the electron-deficient ester aniline **3e** were evaluated. In both cases, nucleophilic attack of the more electron-rich aniline nitrogen upon imine substrate **2** in a general acid-catalyzed mechanism was calculated to have the lower activation barrier; for instance, attack of the *para*-amino group is favored over the *meta*-amino group by 3.1 kcal/mol in the case of **3a**. Similarly, attack of the *meta*-amino group is favored over the *para*-amino group by 1.0 kcal/mol in the case of **3e**. Subsequent cyclocondensation then furnishes the final product that conforms to the experimentally isolated major regioisomer. It should be noted that the kinetically most facile pathway is also the most thermodynamically favorable. An alternative pathway in which attack of the *para*-NH_2 onto the ester group of **2** preceded attack at the imine carbon was ruled out due to the higher relative energy of this transition state (see the Supporting Information for more details).

On the basis of the observed results and supported by the electronic structure calculations, the following conclusions can be made. The reaction pathway and resulting regioselectivity is determined by the functional group on the 2-aminoaniline ring; electron-donating substituents increase the nucleophilicity of the *para* nitrogen, whereas electron-withdrawing groups decrease the reactivity of the *para* group relative to the *meta* nitrogen. The electronic structure calculations support pathway 2 (Scheme 2), which suggests attack will occur preferentially at the ketamine/ketiminium ion (**5a**) versus the less electrophilic ester. For example, a strong electron donor, such as the 4-methoxy group present in **3a**, leads to a 6.3:1 ratio at the end of reaction. Conversely, the regioselectivity is reversed to 4.4:1 when a strong electron-withdrawing ester, such as **3e**, is employed. In this case, the *para*-NH_2 is now deactivated resulting in the *meta*-NH_2 acting as the predominate nucleophile. Attempts to use stronger electron-withdrawing substituents such as a nitro group led to poor reactivity, presumably since both NH_2 groups are deactivated toward nucleophilic attack onto the α-ketimine ester.

Furthermore, functional groups with weak to moderate electronic effects have, as expected, a more variable impact on the reaction regioisomer ratio.

As anticipated, the sterics of the 2-aminoanilines also play a role in the regioselectivity (Table 1, entries 8 and 9), with the major product being formed via initial attack of the ketimine from the less sterically encumbered aniline. The result is a highly selective crude reaction mixture ratio of 11:1 in both cases. This steric phenomenon has also previously been reported for the condensation of 2-aminoanilines with methyl trimethoxyacetate.[20]

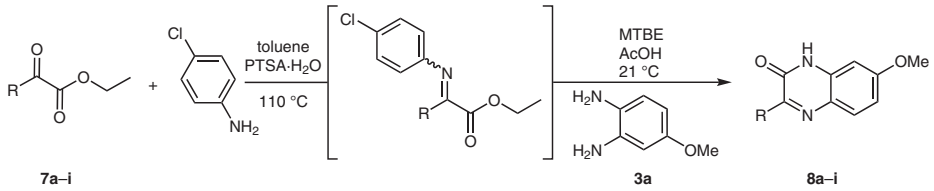
The scope of the chemistry was extended to study possible substituent effects of the α-keto ester starting material (Table 2). Additional screening of α-keto esters found that



Scheme 2 Possible intermediates leading to the quinoxalin-2-one regioisomers

those with enolizable protons resulted in complex reaction mixtures during the initial ketimine formation with 4-chloroaniline. However, functionalized aryl α-keto esters **7a–i** were found to be compatible with ketimine formation and subsequent ring-closing condensation. In these examples, the selective removal of the minor regioisomer from the reaction mixture was found to be less effective, presumably due to the decreased solubility of the products in the reaction/isolation medium, thereby resulting in the isolated product being a mixture of both quinoxalin-2-one regioisomers. The yields from these substrates ranged between 74–91% with 6.4:1 to 14.3:1 ratios of regioisomers in the isolated solids.

Table 2 Scope of Substituted α-Keto Esters for the Synthesis of Quinoxalin-2-ones



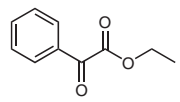
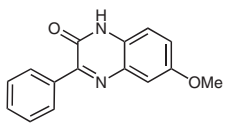
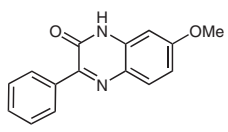
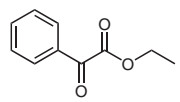
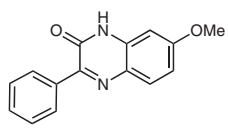
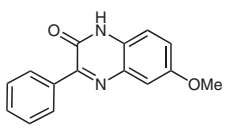
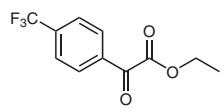
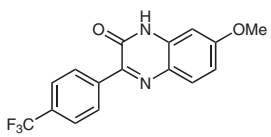
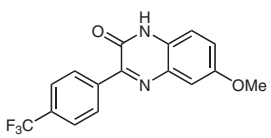
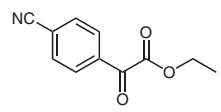
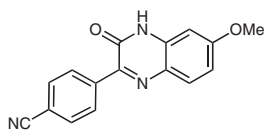
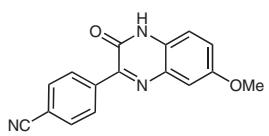
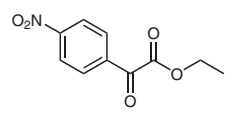
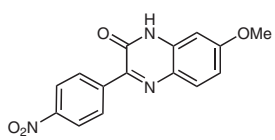
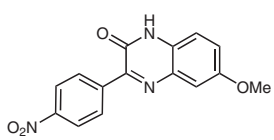
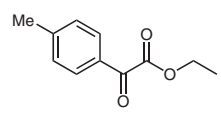
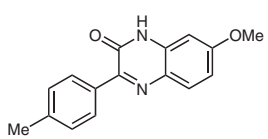
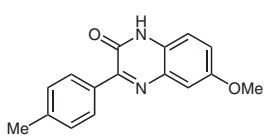
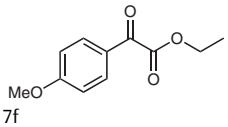
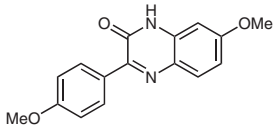
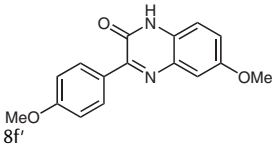
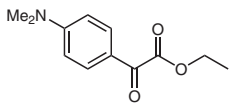
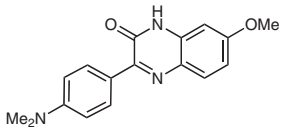
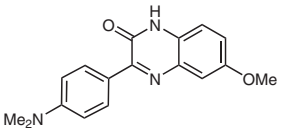
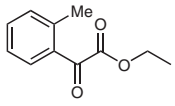
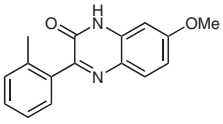
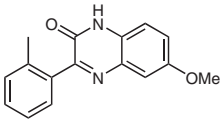
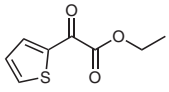
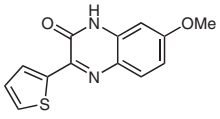
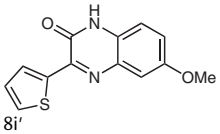
Entry	Substrate	Major product	Minor product	Regioisomer Ratio (major:minor) Crude[a]	Regioisomer Ratio (major:minor) Isolated[b]	Isolated Yield(%)[c]
1[d]	 7a	 8a′	 8a	2.1:1[d]	2.2:1[d]	89
2	 7a	 8a	 8a′	8.9:1	9.2:1	90
3	 7b	 8b	 8b′	7.3:1	14.3:1	89
4	 7c	 8c	 8c′	N/A[e]	11.5:1	91[f]
5	 7d	 8d	 8d′	N/A[e]	6.7:1	90[f]
6	 7e	 8e	 8e′	7.0:1	11.4:1	87

Table 2 (continued)

Entry	Substrate	Major product	Minor product	Regioisomer Ratio (major:minor) Crude[a]	Isolated[b]	Isolated Yield(%)[c]
7	 7f	 8f	 8f′	7.7:1	8.0:1	80[f]
8	 7g	 8g	 8g′	5.8:1	6.4:1	78
9	 7h	 8h	 8h′	7.2:1	10.1:1	74
10	 7i	 8i	 8i′	8.2:1	9.0:1	90

[a] Determined from the ratio of products in the ^{19}F NMR (DMSO-d_6) spectrum of the reaction mixture.
[b] Determined from the ratio of products in the ^{19}F NMR (DMSO-d_6) spectrum of the isolated product.
[c] Yield of isolated product.
[d] Control reaction with no 4-chloroaniline added.
[e] Sampling gave inconsistent results due to sample inhomogeneity.
[f] Required an additional slurry wash in 5.2 mL/g MTBE to remove excess 4-chloroaniline.

Indeed, the importance of preforming the ketimine is again confirmed by the reverse 2.1:1 regioisomer ratio that results from reacting **7a** directly with **3a** in the absence of 4-chloroaniline (Table 2, entry 1) compared to the 8.9:1 ratio when the ketimine is formed (entry 2). The typical regioisomeric ratios using aryl α-keto esters can range between 7.0:1 to 8.9:1 regardless of whether the ketimine is made electron-rich or deficient by arene functionalization. Contrary to the trends for substituted 2-aminoanilines, the relatively consistent crude regioisomeric ratios suggest alterations to the α-keto ester substrate electronics play a smaller role in the resulting regioisomer ratio. In addition, a heteroarene derivative was found to have a minimal impact on the reaction (entry 10), affording a comparable regioisomer ratio and yield to those of the phenyl-substituted derivatives.

A possible steric interaction is also found to have minimal impact on the resulting regioisomer ratio when there is a methyl group *ortho* to the ketamine (**7h**), affording a 7.2:1 ratio of regioisomers.

In conclusion, a simple one-pot protocol for an enhanced regioselective synthesis toward non-symmetric quinoxalin-2-ones is reported. The process relies on the reaction of an in situ formed α-ketimine ester moiety with functionalized 2-aminoanilines. When a β,β-difluoro α-keto ester substrate is utilized, the major regioisomer can typically be isolated directly from the reaction mixture in a >25:1 ratio of regioisomers, with no further purification required. In addition, the regioselectivity can be further tuned depending on the electronic nature of the 2-aminoaniline. Further investigations on the role of the dianiline electronics are ongoing.

All reactions were performed in dry glassware under an atmosphere of nitrogen unless otherwise noted. Melting points (mp) were measured with a Büchi Melting Point B-545 instrument and are uncorrected. IR spectra were recorded using a Nicolet iS50 FT spectrometer, with the absorption bands given in cm^{-1}. NMR spectra were obtained with a Bruker ASCEND 400 spectrometer at 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR, and 377 MHz for ^{19}F NMR. Chemical shifts (δ) are

given in parts per million (ppm) relative to the residual solvent peak [δ = 2.54 (^{1}H NMR) and δ = 39.51 (^{13}C NMR) in DMSO-d_6] with coupling constants (J) in Hertz (Hz). ^{19}F NMR spectra were recorded using a proton decoupled method with no internal reference. The multiplicities are indicated as standard abbreviations. High-resolution mass spectra (HRMS) were measured with a Thermo LTQ Orbitrap XL instrument.

Quinoxalin-2-ones; General Procedure

To the appropriate α-keto ester (9.5 mmol) in toluene (22.5 mL) were added *p*-toluenesulfonic acid monohydrate (18.2 mg, 0.095 mmol) and 4-chloroaniline (1.40 g, 11.0 mmol) at 21 °C. After heating the reaction mixture at 110 °C for 1 d using a Dean–Stark apparatus, the reaction mixture was distilled to a volume of 6 mL. Next, at 21 °C, the appropriate diamine (1.2 equiv), MTBE (12.4 mL) and AcOH (1.3 mL) were combined with the reaction mixture. After stirring for 1–4 d, the resulting slurry was filtered and rinsed with MTBE (2 × 6 mL). The solid was dried in a vacuum oven at 40 °C (with N_2 purging) to afford the desired quinoxalin-2-one. No further purification was required unless otherwise stated.

Control Reaction; General Procedure

To the appropriate α-keto ester (9.5 mmol) in toluene (6 mL) were added *p*-toluenesulfonic acid monohydrate (22.1 mg, 0.12 mmol), 3,4-diaminoanisole (1.2 equiv), MTBE (10 mL) and AcOH (1.3 mL). After stirring for 1 d, the resulting slurry was filtered and rinsed with MTBE (2 × 6 mL). The solid was dried in a vacuum oven at 40 °C (with N_2 purging) to afford the desired quinoxalin-2-one.

3-(1,1-Difluorobut-3-en-1-yl)-6-methoxyquinoxalin-2-one (4a′)

The cyclization required 16 h.

Yield: 1.46 g (53%); beige solid; mp 180–181 °C.

IR (ATR): 1665, 1495, 1376, 1127, 1028, 1002, 831 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.80 (s, 1 H), 7.43 (br s, 1 H), 7.34 (br s, 2 H), 5.75–5.86 (m, 1 H), 5.26 (d, J = 25.8 Hz, 1 H), 5.23 (d, J = 18.8 Hz, 1 H), 3.87 (s, 3 H), 3.29 (dt, J = 7.1, 17.1 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.7, 152.1, 150.4 (t, J = 24.6 Hz), 130.9, 128.8 (t, J = 5.0 Hz), 127.3, 122.1, 121.0, 119.3 (t, J = 244.0 Hz), 118.4, 116.5, 110.4, 55.7.

^{19}F NMR (377 MHz, DMSO-d_6): δ = –99.7 (s, 2 F).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{13}F_2N_2O_2$: 267.0945; found: 267.0961.

3-(1,1-Difluorobut-3-en-1-yl)-7-methoxyquinoxalin-2-one (4a)[12]

The ketimine formation required 16 h and the cyclization required 16 h.

Yield: 5.22 g (68%); off-white solid; mp 161–162 °C.

IR (ATR): 1659, 1615, 1512, 1199, 1172, 1124, 1017, 834 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.68 (s, 1 H), 7.73 (d, J = 8.8 Hz, 1 H), 6.92 (dd, J = 2.0, 9.2 Hz, 1 H), 6.75 (d, J = 2.4 Hz, 1 H), 5.71–5.82 (m, 1 H), 5.15–5.25 (m, 2 H), 3.84 (s, 3 H), 3.21 (dt, J = 7.2, 17.2 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.1, 152.8, 146.4 (t, J = 25.0 Hz), 134.9, 130.9, 129.0 (t, J = 5.0 Hz), 125.3, 120.8, 119.4, 112.9 (t, J = 243.0 Hz), 97.5, 55.7, 39.2 (t, J = 31.0 Hz).

^{19}F NMR (377 MHz, DMSO-d_6): δ = –99.2 (s, 2 F).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{13}F_2N_2O_2$: 267.0945; found: 267.0940.

3-(1,1-Difluorobut-3-en-1-yl)-7-fluoroquinoxalin-2-one (4b)

The ketimine formation required 16 h and the cyclization required 72 h. The final solids was isolated by column chromatography using a 3% MeOH in DCM eluent.

Yield: 2.0 g (61%); light orange solid; mp 129–130 °C.

IR (ATR): 1676, 1614, 1510, 1152, 1008, 812 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.93 (s, 1 H), 7.92 (dd, J = 3.2, 9.0 Hz, 1H), 7.24 (dt, J = 2.8, 8.8 Hz, 1H), 7.07 (dd, J = 2.8, 9.4 Hz, 1 H), 5.77 (m, 1 H), 5.22 (m, 2 H), 3.24 (dt, J = 7.2, 10.0 Hz, 2 H). Isolated as a 6.9:1 regioisomer ratio; only signals of the major regioisomer are listed.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.7, 162.3, 159.1, 156.7, 153.4, 152.2, 149.4 (t, J = 28.0 Hz), 134.7 (d, J = 13.0 Hz), 132.2 (d, J = 11.0 Hz), 130.0, 128.7 (m), 127.4, 121.0, 120.3 (d, J = 24.0 Hz), 119.1 (t, J = 243.0 Hz), 117.1 (d, J = 9.0 Hz), 114.5 (d, J = 23.0 Hz), 112.1 (d, J = 24.0 Hz), 101.4 (d, J = 27.0 Hz), 39.1 (t, J = 25.0 Hz). Isolated as a 6.9:1 ratio of regioisomers; both sets of signals are listed.

^{19}F NMR (377 MHz, DMSO-d_6): δ (major regioisomer) = –99.9 (s, 2 F), –106.0 (s, 1 F); δ (minor regioisomer) = –100.1 (s, 2 F), –118.4 (s, 1 F).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{10}F_3N_2O$: 255.0745; found: 255.0742.

7-Chloro-3-(1,1-difluorobut-3-en-1-yl)quinoxalin-2-one (4c)

The ketimine formation required 16 h and the cyclization required 96 h.

Yield: 1.65 g (50%); dark purple solid; mp 179–186 °C.

IR (ATR): 1662, 1645, 996, 927, 834 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.88 (s, 1 H), 7.87 (d, J = 8.8 Hz, 1 H), 7.35–7.40 (m, 2 H), 5.51–5.75 (m, 1 H), 5.18–5.27 (m, 2 H), 3.22 (dt, J = 24.0, 31.2 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.2, 150.6 (t, J = 26.0 Hz), 136.4, 134.1, 131.2, 129.0, 128.7 (t, J = 5.0 Hz), 123.9, 121.1, 119.1 (t, J = 243.0 Hz), 114.8, 39.3 (unresolved triplet due to solvent).

^{19}F NMR (377 MHz, DMSO-d_6): δ = –100.0 (s, 2 F).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{10}ClF_2N_2O$: 271.0450; found: 271.0444.

7-Bromo-3-(1,1-difluorobut-3-en-1-yl)quinoxalin-2-one (4d)

The ketimine formation required 16 h and the cyclization required 72 h.

Yield: 1.30 g (44%); brown-tan solid; mp 186–187 °C.

IR (ATR): 1663, 1644, 1151, 1044, 1001, 836 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.86 (s, 1 H), 7.80 (d, J = 8.4 Hz, 1 H), 7.50–7.53 (m, 2 H), 5.73–5.83 (m, 1 H), 5.18–5.27 (m, 2 H), 3.22 (dt, J = 7.1, 17.3 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.2, 150.8 (t, J = 26.0 Hz), 134.2, 131.3, 129.3, 128.6 (t, J = 5.0 Hz), 126.7, 125.1, 121.1, 119.1 (t, J = 244.0 Hz), 117.8, 39.1 (t, J = 24.0 Hz).

^{19}F NMR (377 MHz, DMSO-d_6): δ = –100.1 (s, 2 F).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{10}BrF_2N_2O$: 314.9945; found: 314.9939.

Methyl 3-(1,1-Difluorobut-3-en-1-yl)-2-hydroxyquinoxaline-6-carboxylate (4e)

The ketimine formation required 16 h and the cyclization required 96 h.

Yield: 2.13 g (69%); tan solid; mp 171–173 °C.

IR (ATR): 1721, 1662, 1612, 1274, 1101, 1071, 765 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.09 (s, 1 H), 8.33 (s, 1 H), 8.15 (d, J = 8.4 Hz, 1 H), 7.43 (d, J = 8.4 Hz, 1 H), 5.77–5.84 (m, 1 H), 5.19–5.29 (m, 2 H), 3.88 (s, 3 H), 3.23 (dt, J = 6.8, 17.2 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.2, 152.5, 151.6 (t, J = 26.0 Hz), 136.5, 132.1, 130.8, 129.5, 128.7 (t, J = 5.0 Hz), 124.8, 121.1, 119.0 (t, J = 243.0 Hz), 116.1, 52.3, 39.1 (t, J = 27.0 Hz).

^{19}F NMR (377 MHz, DMSO-d_6): δ = –100.2 (s, 2 F).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{13}F_2N_2O_3$: 295.0894; found: 295.0888.

3-(1,1-Difluorobut-3-en-1-yl)-7-methylquinoxalin-2-one (4f)

The ketimine formation required 16 h and the cyclization required 18 h. The final solids was isolated by column chromatography using a 4:1 heptanes:EtOAc eluent.

Yield: 1.98 g (44%); light orange solid; mp 122–123 °C.

IR (ATR): 1667, 1029, 993, 819 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.74 (s, 1 H), 7.70–7.72 (m, 1 H), 7.22–7.25 (m, 1 H), 7.11–7.17 (m, 1 H), 5.72–5.82 (m, 1 H), 5.16–5.25 (m, 2 H), 3.23 (dt, J = 7.2, 17.2 Hz, 2 H), 2.41 (3 H). Isolated as a 1.5:1 ratio of regioisomers; only signals of the major regioisomer are listed.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.6, 152.4, 150.1 (t, J = 25.4 Hz), 149.0 (t, J = 25.4 Hz), 142.9, 133.4, 133.2, 132.9, 130.8, 130.2, 129.2, 128.9 (m), 128.6, 125.3, 120.9, 119.3 (t, J = 243.0 Hz), 115.3, 115.0, 39.2 (t, J = 25.0 Hz), 21.4, 20.3. Isolated as a 1.5:1 ratio of regioisomers; both sets of signals are listed.

^{19}F NMR (377 MHz, DMSO-d_6): δ (major regioisomer) = –99.6 (s, 2 F); δ (minor regioisomer) = –99.7 (s, 2 F). Isolated as a 1.5:1 ratio of regioisomers; both sets of signals are listed.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{13}F_2N_2O$: 251.0996; found: 251.0991.

3-(1,1-Difluorobut-3-en-1-yl)-8-methyl-quinoxalin-2-one (4g)

The ketimine formation required 16 h and the cyclization required 18 h.

Yield: 1.98 g (55%); pale yellow solid; mp 150–151 °C.

IR (ATR): 1660, 1600, 1018, 875 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.13 (s, 1 H), 7.69 (d, J = 7.8 Hz, 1 H), 7.47 (d, J = 7.6 Hz, 1 H), 7.25–7.29 (m, 1 H), 5.73–5.83 (m, 1 H), 5.17–5.27 (m, 2 H), 3.26 (dt, J = 7.2, 17.2 Hz, 2 H), 2.44 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.0, 149.8 (t, J = 27.5 Hz), 133.2, 131.5, 130.4, 128.8 (t, J = 5.0 Hz), 127.5, 124.4, 123.4, 121.0, 119.2 (t, J = 243.0 Hz), 39.2 (t, J = 24.0 Hz), 16.8.

^{19}F NMR (377 MHz, DMSO-d_6): δ = –99.8 (s, 2 F).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{13}F_2N_2O$: 251.0996; found: 251.0991.

6,8-Dichloro-3-(1,1-difluorobut-3-en-1-yl)quinoxalin-2-one (4h)

The ketimine formation required 16 h and the cyclization required 16 h.

Yield: 1.51 g (52%); pale yellow solid; mp 170–173 °C.

IR (ATR): 1668, 1480, 1064, 1009, 937 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.62 (s, 1 H), 7.98 (s, 2 H), 5.74–5.83 (m, 1 H), 5.19–5.29 (m, 2 H), 3.23 (dt, J = 7.2, 17.6 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.8, 131.7 (br s), 131.4, 130.1, 128.5 (t, J = 4.8 Hz), 127.9, 127.3 (br s), 121.4, 121.2, 120.0 (br s), 116.5, 39. 4.

^{19}F NMR (377 MHz, DMSO-d_6): δ = –100.3 (s, 2 F).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_9Cl_2F_2N_2O$: 305.0060; found: 305.0055.

7-Methoxy-3-phenyl-quinoxalin-2-one (8a)[21]

The ketimine formation required 25 h and the cyclization required 96 h.

Yield: 2.55 g (90%); light yellow solid; mp 232–233 °C (dec.).

IR (ATR): 1658, 1615, 1273, 1252, 1177, 827 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.46 (s, 1 H), 8.27–8.28 (m, 2 H), 7.74 (d, J = 8.8 Hz, 1 H), 7.46–7.48 (m, 3 H), 6.93 (dd, J = 2.8, 8.8 Hz, 1 H), 6.79 (d, J = 2.8 Hz, 1 H), 3.84 (s, 3 H). Isolated as a 9.2:1 ratio of regioisomers; only signals of the major regioisomer are listed.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.7, 155.4, 154.8, 154.22, 154.16, 150.4, 135.9, 135.8, 133.7, 132.7, 130.1, 129.6, 129.2, 128.9, 128.1, 127.8, 127.1, 126.3, 125.6, 119.8, 116.0, 112.2, 110.0, 97.3, 55.6, 55.5. Isolated as a 9.2:1 ratio of regioisomers; both sets of signals are listed.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{13}N_2O_2$: 253.0977; found: 253.0972.

7-Methoxy-3-[4-(trifluoromethyl)phenyl]quinoxalin-2-one (8b)

The ketimine formation required 17 h and the cyclization required 48 h.

Yield: 2.25 g (89%); light yellow solid; mp 280–287 °C (dec.).

IR (ATR): 1661, 1324, 1109, 1070, 1016, 828 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.59 (s, 1 H), 8.50 (d, J = 8.4 Hz, 2 H), 7.83 (d, J = 8.4 Hz, 2 H), 7.77 (d, J = 8.8 Hz, 1 H), 6.96 (dd, J = 2.8, 8.8 Hz, 1 H), 6.79 (d, J = 2.4 Hz, 1 H), 3.85 (s, 3 H). Isolated as a 14.3:1 ratio of regioisomers; only signals of the major regioisomer are listed.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.3, 154.7, 154.1, 148.7, 139.6, 134.0, 130.5, 129.9, 129.6, 129.5, 129.3, 129.0, 128.3, 127.0, 125.6, 124.7 (m), 122.9, 120.7, 120.2, 112.6, 110.1, 97.3, 55.7. Isolated as a 14.3:1 ratio of regioisomers; both sets of signals are listed.

^{19}F NMR (377 MHz, DMSO-d_6): δ (major regioisomer) = –61.2 (s, 3 F); δ (minor regioisomer) = –61.2 (s, 3 F).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{12}F_3N_2O_2$: 321.0851; found: 321.0845.

4-(6-Methoxy-3-oxo-3,4-dihydroquinoxalin-2-yl)benzonitrile (8c)

The ketimine formation required 21 h and the cyclization required 18 h. The final solids required an additional slurry wash in 5.2 mL/g MTBE to remove residual 4-chloroaniline.

Yield: 1.73 g (91%); yellow solid; mp >300 °C (dec.).

IR (ATR): 1659, 1620, 1273, 1207, 1033, 819 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.61 (s, 1 H), 8.47 (d, J = 8.8 Hz, 2 H), 7.93 (d, J = 8.8 Hz, 2 H), 7.78 (d, J = 9.2 Hz, 1 H), 6.97 (dd, J = 2.4, 8.8 Hz, 1 H), 6.80 (d, J = 2.4 Hz, 1 H), 3.86 (s, 3 H). Isolated as an 11.5:1 ratio of regioisomers; only signals of the major regioisomer are listed.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.5, 155.6, 154.7, 154.1, 152.5, 148.4, 140.0, 139.9, 134.2, 133.0, 132.6, 131.8, 130.6, 129.8, 129.4, 128.5, 127.1, 126.7, 125.5, 120.9, 118.8, 118.7, 116.2, 115.3, 112.8, 112.2, 111.7, 110.1, 97.3, 55.8, 55.7. Isolated as an 11.5:1 ratio of regioisomers; both sets of signals are listed.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{12}N_3O_2$: 278.0930; found: 278.0924.

7-Methoxy-3-(4-nitrophenyl)quinoxalin-2-one (8d)

The ketimine formation required 21 h and the cyclization required 18 h. The final solids required an additional slurry wash in 5.2 mL/g MTBE to remove residual 4-chloroaniline.

Yield: 1.92 g (90%); yellow solid; mp >300 °C (dec.).

IR (ATR): 1663, 1621, 1508, 1346, 1279, 1205, 1031, 826 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.71 (s, 1 H), 8.62 (d, *J* = 9.2 Hz, 2 H), 8.37 (d, *J* = 8.8 Hz, 2 H), 7.85 (d, *J* = 8.8 Hz, 1 H), 7.03 (dd, *J* = 2.8, 9.2 Hz, 1 H), 6.86 (d, *J* = 2.4 Hz, 1 H), 3.91 (s, 3 H). Isolated as a 6.7:1 ratio of regioisomer; only signals of the major regioisomer are listed.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.6, 155.6, 154.6, 154.0, 148.0, 147.9, 147.6, 141.7, 141.6, 134.2, 132.6, 130.6, 130.2, 129.8, 127.1, 122.9, 121.0, 116.1, 112.7, 110.2, 97.4, 55.7, 55.6. Isolated as a 6.7:1 ratio of regioisomer; both sets of signals are listed.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}N_3O_4$: 298.0828; found: 298.0822.

7-Methoxy-3-(*p*-tolyl)quinoxalin-2-one (8e)

The ketimine formation required 17 h and the cyclization required 48 h.

Yield: 2.35 g (87%); light yellow solid; mp 253–254 °C (dec.).

IR (ATR): 1653, 1619, 1288, 1169, 1137, 1036, 816 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.43 (s, 1 H), 8.23 (d, *J* = 8.0 Hz, 2 H), 7.73 (d, *J* = 8.8 Hz, 1 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 6.93 (dd, *J* = 2.8, 8.8 Hz, 1 H), 6.79 (d, *J* = 2.4 Hz, 1 H), 3.84 (s, 3 H), 2.38 (s, 3 H). Isolated as an 11.4:1 ratio of regioisomers; only signals of the major regioisomer are listed.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.6, 155.4, 154.9, 154.3, 153.8, 150.1, 140.0, 139.4, 133.5, 133.1, 133.0, 132.7, 130.0, 129.2, 128.9, 128.4, 127.0, 126.2, 119.5, 115.9, 112.1, 109.9, 67.3, 55.6, 55.5, 21.0. Isolated as an 11.4:1 ratio of regioisomers; both sets of signals are listed.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2O_2$: 267.1134; found: 267.1128.

7-Methoxy-3-(4-methoxyphenyl)quinoxalin-2-one (8f)

The ketimine formation required 18 h and the cyclization required 23 h. The final solids required an additional slurry wash in 5.2 mL/g MTBE to remove residual 4-chloroaniline.

Yield: 1.81 g (80%); yellow solid; mp 230–231 °C.

IR (ATR): 1666, 1286, 1170, 1026, 827 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.39 (s, 1 H), 8.35 (d, *J* = 9.2 Hz, 2 H), 7.71 (d, *J* = 8.8 Hz, 1 H), 7.02 (d, *J* = 8.8 Hz, 2 H), 6.92 (dd, *J* = 2.8, 9.2 Hz, 1 H), 6.78 (d, *J* = 2.4 Hz, 1 H), 3.83–3.84 (m, 6 H). Isolated as an 8.0:1 ratio of regioisomers; only signals of the major regioisomer are listed.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.0, 160.6, 160.3, 155.5, 154.9, 154.3, 149.6, 133.3, 132.7, 131.0, 130.6, 129.8, 128.5, 128.4, 128.3, 127.0, 126.0, 119.2, 115.8, 113.2, 112.1, 109.8, 97.3, 55.6, 55.3, 55.2. Isolated as an 8.0:1 ratio of regioisomers; both sets of signals are listed.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2O_3$: 283.1083; found: 283.1077.

3-[4-(Dimethylamino)phenyl]-7-methoxy-quinoxalin-2-one (8g)

The ketimine formation required 41 h and the cyclization required 72 h.

Yield: 2.03 g (78%); light yellow solid; mp 233–244 °C (dec.).

IR (ATR): 1656, 1602, 1529, 1297, 1187, 1128, 1033, 802 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.25 (s, 1 H), 8.34 (d, *J* = 8.0 Hz, 2 H), 7.66 (d, *J* = 9.2 Hz, 1 H), 6.89 (dd, *J* = 2.8, 9.2 Hz, 1 H), 6.75–6.77 (m, 3 H), 3.83 (s, 3 H), 2.99 (s, 6 H). Isolated as a 6.4:1 ratio of regioisomers; only signals of the major regioisomer are listed.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.7, 155.4, 155.1, 154.6, 153.0, 151.6, 151.2, 149.7, 133.0, 132.8, 130.7, 130.2, 129.3, 128.2, 128.1, 127.2, 125.5, 123.4, 123.1, 118.1, 115.6, 111.8, 110.9, 110.8, 109.5, 97.4, 55.5. Isolated as a 6.4:1 ratio of regioisomers; both sets of signals are listed.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_3O_2$: 296.1399; found: 296.1394.

7-Methoxy-3-(*o*-tolyl)quinoxalin-2-one (8h)

The ketimine formation required 72 h and the cyclization required 23 h.

Yield: 1.78 g (74%); light yellow solid; mp 182–183 °C.

IR (ATR): 1660, 1624, 1515, 1295, 1173, 1034, 846 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.44 (s, 1 H), 7.70 (d, *J* = 8.8 Hz, 1 H), 7.22–7.41 (m, 4 H), 6.93 (dd, *J* = 2.8, 8.8 Hz, 1 H), 6.81 (d, *J* = 2.4 Hz, 1 H), 3.85 (s, 3 H), 2.23 (s, 3 H). Isolated as a 10.1:1 ratio of regioisomers; only signals of the major regioisomer are listed..

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.8, 155.4, 154.5, 153.9, 147.7, 136.5, 136.3, 133.8, 132.6, 130.1, 129.9, 129.5, 129.4, 128.8, 128.6, 128.5, 126.9, 125.1, 119.7, 118.7, 116.2, 115.2, 112.0, 110.2, 97.7, 55.6, 55.6, 19.5. Isolated as a 10.1:1 ratio of regioisomers; both sets of signals are listed.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2O_2$: 267.1134; found: 267.1128.

7-Methoxy-3-(2-thienyl)quinoxalin-2-one (8i)[12]

The ketimine formation required 48 h and the cyclization required 72 h.

Yield: 2.51 g (90%); light yellow solid; mp 246–247 °C (dec.).

IR (ATR): 1658, 1615, 1259, 1181, 818 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.58 (s, 1 H), 8.40 (d, *J* = 1.2 Hz, 1 H), 7.82–7.83 (m, 1 H), 7.68 (d, *J* = 9.2 Hz, 1 H), 7.20–7.23 (m, 1 H), 6.93 (dd, *J* = 2.8, 8.8 Hz, 1 H), 6.80 (d, *J* = 2.8 Hz, 1 H), 3.84 (s, 3 H). Isolated as a 9.0:1 ratio of regioisomers; only signals of the major regioisomer are listed.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.4, 155.7, 153.6, 153.0, 145.7, 139.3, 139.1, 133.0, 132.6, 132.1, 131.3, 130.9, 130.2, 129.5, 128.0, 127.9, 126.8, 125.7, 119.5, 116.2, 112.5, 109.2, 97.6, 55.6, 55.6. Isolated as a 9.0:1 ratio of regioisomers; both sets of signals are listed.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}N_2O_2S$: 259.0541; found: 259.0536.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609345.

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