Homolytic aromatic substitution of acyl radicals: Oxidative coupling of 2-methylquinolines with quinoxalines

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Abstract
Oxidative coupling of 2-methylquinolines with quinoxalines via a TBHP (t-butyldihydroperoxide) and TFA (trifluoroacetic acid) mediated Minisci reaction affords quinolin-2-yl(quinoxalin-2-yl)methanone derivatives. This approach provides a simple and efficient method to construct various acyl derivatives in moderate to good yields (45%–92%) without any metal catalyst. Mechanistically, homolytic aromatic substitution (HAS) of acyl radicals mediated by TBHP is crucial for the construction of the quinolin-2-yl(quinoxalin-2-yl)methanone products.

Keywords
2-methylquinolines, homolytic aromatic substitution, quinolin-2-yl(quinoxalin-2-yl)methanones, quinoxalines, TFA/TBHP

Introduction
Acyl N-heterocycles, for example, the quinolin-2-yl (quinolin-2-yl)methanones reported in this article, play key roles in pharmaceuticals¹⁻³ and possess different biological activities such as antimicrobial,⁴ antipsychotic,⁵ antithrombotic,⁶ antitussive,⁷ and antihyperglycemic.⁸ There have been numerous reports on the preparation of electron-deficient heterocycles, but examples on their functionalization by oxidative coupling are rare. Compared to electron-rich heterocycles,⁹⁻¹³ the acylation of electron-deficient heterocycles is more difficult. It is worth mentioning that the Minisci reaction and aromatic homolytic substitution can overcome efficiently difficulties via nucleophilic acyl radical addition to protonated electron-deficient heterocycles.¹⁴,¹⁵ Recently, several researchers reported the preparation of acyl N-heterocycles using the Minisci reaction. Yuan et al.¹⁶ reported that 3-acylated quinoxalin-2(1H)-ones could be obtained by oxidative coupling of quinoxalin-2(1H)-ones with diverse aldehydes. Meanwhile, Siddaraju et al.¹⁷ reported that acylations of isoquinoline, quinoline, and quinoxaline derivatives could be accomplished by employing cross dehydrogenative coupling reactions with aldehydes using a substoichiometric amount of TBAB (tetrabutylammonium bromide) and K₂S₂O₈ as the oxidant. Zhang et al.¹⁸ showed that isoquinolin-1-yl(p-tolyl)methanones could be prepared by the reaction of isoquinoline with 4-methylbenzaldehyde catalyzed by TBHP under irradiation with blue LEDs. Furthermore, Rahim et al.¹⁹ reported that I₂/DMSO could promote the reactions of 2-methylquinolines with benzothiazoles to form 2-heteroaryl benzothiazoles under acid- and peroxide-free conditions. Also, Chen et al.²⁰ showed that TBHP/TFA could promote the reaction of

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isoquinolines with benzaldehydes to give the corresponding acyl derivatives. All these methods used aldehydes as acyl radical donors. However, Ali et al.\(^{21}\) reported that acyl radicals derived from methylenzene could be utilized for the direct acylation of N-heterocycles promoted by AlCl\(_3\) at 95 °C under N\(_2\). Inspired by these examples, we envisaged that 2-methylquinolines could be used as acyl radical donors under oxidative conditions for the acylation of quinoxalines via intermolecular homolytic aromatic substitution of acyl radicals, and our studies proved this to be the case. Therefore, in this paper, we disclose the first oxidative coupling of 2-methylquinolines with quinoxalines via TBHP (t-butyl hydroperoxide) and TFA (trifluoroacetic acid) mediated Minisci reactions to prepare quinolin-2-yl(quinoxalin-2-yl) methanones without any metal catalyst. Homolytic aromatic substitution of acyl radicals mediated by TBHP is crucial in the mechanism of this process for the construction of acyl derivatives.

Results and discussion

Quinoxaline (1\textsubscript{a}) and 2-methylquinoline (2\textsubscript{a}) were selected as model substrates to optimize the reaction conditions for the synthesis of quinolin-2-yl(quinoxalin-2-yl) methanone (3\textsubscript{a}). The effects of different additives, oxidants, solvents and temperatures were investigated and the results are summarized in Table 1. First, different oxidants such as K\(_2\)S\(_2\)O\(_8\), H\(_2\)O\(_2\), O\(_2\), and TBHP were screened and TBHP was found to be the best, affording a 60% yield of 3\textsubscript{a} (Table 1, entries 1–4). Next, different additives including AlCl\(_3\), TFA, Ac\(_2\)O, and AcOH were investigated, with TFA to be the best (Table 1, entries 4–8). The yield of 3\textsubscript{a} was only 11% without any additive (Table 1, entry 5). Next, the solvent was optimized, and PhCl was found to be the most suitable leading to a 71% yield of 3\textsubscript{a} (Table 1, entries 6 and 9–12). With PhCl as the solvent, the reaction temperature was further optimized. When the temperature was increased from room temperature to reflux, the yield of 3\textsubscript{a} increased from 24% to 73% (Table 1, entries 4, 10 and 11), which indicated that the solvent, the reaction temperature was further optimized. When electron-donating substitutents were attached at different positions of the quinoline ring, the order of the product yields was C-6 > C-8 > C-7 > C-4 > C-3 (Table 2, entries 2, 4, 6, 9, and 11). For electron-withdrawing substitutents, the order of the product yields was C-6 > C-7 > C-4 > C-3 > C-8 (Table 2, entries 3, 5, 7, 8, 10, and 12).

Subsequently, we set out to examine the substrate scope of quinoxalines 1 under the optimized conditions. The nature and the location of different R’ groups on quinoxalines 1 affected the reaction yields. At the same positions, quinoxalines substituted with electron-donating groups surpassed those derived from substrates with electron-withdrawing groups. When electron-donating substitutents were attached at different positions of the quinoline ring, the order of the product yields was C-6 > C-8 > C-7 > C-4 > C-3 (Table 2, entries 2, 4, 6, 9, and 11). For electron-withdrawing substitutents, the order of the product yields was C-6 > C-7 > C-4 > C-3 > C-8 (Table 2, entries 3, 5, 7, 8, 10, and 12).

Table 1. Optimization of the reaction conditions for the synthesis of 3a.\(^{a}\)

| Entry | Additive | Oxidant\(^{b}\) | Solvent | Temp (°C) | Yield of 3a (%)\(^{c}\) |
|-------|----------|---------------|---------|-----------|-------------------|
| 1     | AlCl\(_3\) | K\(_2\)S\(_2\)O\(_8\) | DCE     | 70        | trace             |
| 2     | AlCl\(_3\) | H\(_2\)O\(_2\) | DCE     | 70        | –                 |
| 3     | AlCl\(_3\) | O\(_2\) | DCE     | 70        | trace             |
| 4     | AlCl\(_3\) | TBHP | DCE     | 70        | 60                |
| 5     | – | TBHP | DCE     | reflux    | 11                |
| 6     | TFA | TBHP | DCE     | 70        | 65                |
| 7     | Ac\(_2\)O | TBHP | DCE     | 70        | 46                |
| 8     | AcOH | TBHP | DCE     | 70        | 40                |
| 9     | TFA | TBHP | DMSO    | 70        | 35                |
| 10    | TFA | TBHP | CH\(_3\)CN | 70        | 32                |
| 11    | TFA | TBHP | H\(_2\)O | 70        | 10                |
| 12    | TFA | TBHP | Ph\(_2\) | 70        | 71                |
| 13    | TFA | TBHP | Ph\(_2\) | r.t.      | 24                |
| 14    | TFA | TBHP | Ph\(_2\) | 100       | 72                |
| 15    | TFA | TBHP | Ph\(_2\) | reflux    | 73                |
| 16*   | TFA | TBHP | Ph\(_2\) | 70        | 76                |
| 17*   | TFA | TBHP | Ph\(_2\) | 70        | 86                |
| 18*   | TFA | TBHP | Ph\(_2\) | 70        | 85                |

\(^{a}\)Reaction conditions: 1\textsubscript{a} (1.0 mmol), 2\textsubscript{a} (3.0 mmol), additive (1.2 equiv), oxidant (2.0 equiv), solvent (8 mL), 12 h.

\(^{b}\)TBHP in decane (5–6 M).

\(^{c}\)Isolated yield.

\(^{d}\)TBHP (3.0 equiv).

\(^{e}\)TBHP (4.0 equiv).

\(^{f}\)TBHP (5.0 equiv).

With optimized conditions in hand, the substrate scope was next investigated. 2-Methylquinolines 2 possessing sp\(^3\) carbons and different substituents reacted with 1\textsubscript{a} via oxidative cross-dehydrogenative coupling to afford the corresponding products 3 in moderate to good yields ranging from 51% to 92% in Table 2. The electronic properties of the substituents were observed to affect the reaction yields to a degree. At the same carbons positions, 2-methylquinolines substituted with electron-donating groups (Table 2, entries 2, 4, 6, 9, and 11) gave slightly higher yields than those with electron-withdrawing groups (Table 2, entries 3, 5, 7, 8, 10, and 12), the reason for this may be that the nucleophilicities of the acyl radicals derived from substrates with electron-donating groups surpassed those derived from substrates with electron-withdrawing groups.
Table 2. Substrate scope of various 2-methylquinolines 2 having sp<sup>3</sup> carbons in the oxidative cross-dehydrogenative coupling reaction.<sup>a</sup>

| Entry | R Product<sup>b</sup> | Yield (%)<sup>c</sup> |
|-------|------------------------|---------------------|
| 1     | (2a) H 3a              | 86                  |
| 2     | (2b) 3-OCH<sub>3</sub> 3b | 59                  |
| 3     | (2c) 3-Br 3c           | 53                  |
| 4     | (2d) 4-OCH<sub>3</sub> 3d | 71                  |
| 5     | (2e) 4-Cl 3e           | 58                  |
| 6     | (2f) 6-OCH<sub>3</sub> 3f | 92                  |
| 7     | (2g) 6-Cl 3g           | 80                  |
| 8     | (2h) 6-Br 3h           | 83                  |
| 9     | (2i) 7-OCH<sub>3</sub> 3i | 73                  |
| 10    | (2j) 7-Cl 3j           | 62                  |
| 11    | (2k) 8-OCH<sub>3</sub> 3k | 79                  |
| 12    | (2l) 8-Br 3l           | 51                  |

<sup>a</sup>Reaction conditions: 1a (1.0 mmol), 2 (3.0 mmol), TFA (1.2 equiv), TBHP (4.0 equiv), PhCl (8 mL), 12 h.
<sup>b</sup>Structures were confirmed by 1H and 13C NMR spectroscopy.
<sup>c</sup>Isolated yield based on 1a.

Table 3. Substrate scope of various quinoxalines 1<sup>a</sup>.

| Entry | R′ Product<sup>b</sup> | Yield (%)<sup>c</sup> |
|-------|------------------------|---------------------|
| 1     | (1a) 2-CH<sub>3</sub> 3m | 45                  |
| 2     | (1b) 2-Cl 3n           | 49                  |
| 3     | (1c) 6-CH<sub>3</sub> 3o | 55(1:1)<sup>d</sup>
|       |                        | 3o′                 |
| 4     | (1d) 6-Cl 3p           | 61(1:1)<sup>d</sup>
|       |                        | 3p′                 |

<sup>a</sup>Reaction conditions: 1 (1.0 mmol), 2a (3.0 mmol), TFA (1.2 equiv), TBHP (4.0 equiv), PhCl (8 mL), 12 h.
<sup>b</sup>Structures were confirmed by 1H and 13C NMR spectroscopy.
<sup>c</sup>Isolated yield based on 1.
<sup>d</sup>Ratio was determined by 1H NMR (600 MHz, CDCl₃) analysis.

![Scheme 1](image1.png)

**Scheme 1.** 2-Methylpyridine (4) and quinoline (6) as substrates.

tooltip

yield ratio was 1:1, as determined by 1H NMR (600 MHz, CDCl₃) analysis (Table 3, entry 3). The same was observed for 6-chloroquinoxaline (Table 3, entry 4).

Finally, 2-methylpyridine (4) and quinoline (6) were investigated as substrates. 2-Methylpyridine 4 exhibited moderate reactivity with quinoxaline (1a) under the standard conditions and gave the corresponding product 5 in 41% yield. Quinoline (6) also exhibited moderate reactivity with 2-methylquinoline (2a) under the standard conditions and gave the corresponding product 7 in 39% yield (Scheme 1).

To further explore the mechanism of the oxidative coupling of 2-methylquinolines with quinoxalines, several control experiments were carried out. First, when adding the radical scavenger TEMPO (1.0 equiv) to the standard reaction, product 3a was only obtained in a trace amount (Scheme 2-a), which suggested that the reaction proceeded through a radical intermediate. Second, when 2a alone was subjected to the standard reaction conditions, a 95% yield of quinoline-2-carbaldehyde (8a) was observed (Scheme 2-b). Finally, when 1a was reacted with quinoline-2-carbaldehyde (8a) under the standard conditions, an 85% yield of 3a was obtained (Scheme 2-c), suggesting that quinoline-2-carbaldehyde was a crucial intermediate in this reaction.

Based on these observations and related references, a plausible mechanism for the cross-dehydrogenative coupling process is proposed in Scheme 3. TFA can coordinate with quinoxaline leading to the protonated intermediate (9a), which makes the quinoxaline ring more electron-deficient and increases the electrophilicity. TBHP undergoes
homolytic cleavage to give a methyl radical along with a hydroxyl radical on heating. On the other hand, in the presence of excess TBHP, 2-methylquinoline (2a) is oxidized to quinolin-2-ylmethanol (10a) and is subsequently transformed into quinoline-2-carbaldehyde (8a). Next, 8a undergoes C–H bond homolysis and is transformed into acyl radical (11a) upon attack of the methyl radical or hydroxyl radical. This nucleophilic acyl radical (11a) can then attack smoothly at the high electrophilic C-1 site of the protonated intermediate (9a) and generates radical-cation intermediate (12a). A single-electron transfer (SET) from (12a) releases the N⁺ intermediate (13a). Simultaneously, the methyl radical or hydroxyl radical captures a single electron. Finally, oxidative coupling target product (3a) can be obtained by deprotonation of (13a).

Conclusion

In conclusion, we have developed a procedure for the oxidative coupling of 2-methylquinolines with quinoxaline via a TBHP/TFA-mediated Minisci reaction for the synthesis of quinolin-2-yl(quinoxalin-2-yl)methanones without any metal catalyst. This works shows that 2-methylquinolines can be used as acyl radical donors under oxidative conditions and be utilized for the acylation of quinoxalines via intermolecular homolytic aromatic substitution of acyl radicals. The reaction temperature is 70 °C, below the alarm temperature 75 °C and autoignition temperature 88 °C of TBHP, which shows that the reaction condition is relatively safe. This approach encompasses relatively mild reaction conditions and affords moderate to good yields.

Experimental

Melting points were measured on a Büchi B-540 capillary melting point apparatus and are uncorrected. Mass spectra (ESI-MS) were recorded on a Thermo Finnigan LCQ-Advantage spectrometer. High-resolution mass spectrometry (ESI-HRMS) was performed using an Agilent 6210 TOF instrument. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker-600 spectrometer (600 MHz), δ in ppm per million, J in Hertz, and using TMS as the internal standard. Signal multiplicities are assigned as singlet (s), doublet (d), multiplet (m). All analytical reagents were commercially available and were used directly without further purification.

Synthesis of quinolin-2-yl(quinoxalin-2-yl)methanones (3a selected as an example); typical procedure

A mixture of quinoxaline (1a) (0.13 g, 1.0 mmol), 2-methylquinoline (2a) (0.42 g, 3 mmol), TFA (0.14 g, 1.2 mmol) and TBHP (0.36 g, 4.0 mmol, in decane 5–6 M) in PhCl (8 mL) was stirred at 70 °C for 12 hours until the total consumption of (1a) was monitored by TLC. After cooling, the reaction mixture was washed with brine (20 mL) and extracted with CH₂Cl₂ (2×20 mL). The combined organic extract was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether/EtOAc = 10:1) to afford the target product 3a (white solid, 86%, 0.24 g).

Quinolin-2-yl(quinoxalin-2-yl)methanone (3a): White solid; 86%, 0.24 g; mp 193–194 °C. ¹H NMR (600 MHz, CDCl₃): δ = 9.60 (s, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.28–8.26 (m, 2H), 8.24 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 9.2 Hz, 1H), 7.92 (d, J = 7.6 Hz, 1H), 7.84 (t, J = 7.6 Hz, 1H), 7.43 (m, 2H), 7.14 (d, J = 2.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 191.8, 160.1, 150.6, 150.1, 146.0, 143.2, 142.9, 141.8, 135.6, 132.1, 131.7, 131.1, 130.6, 130.4, 129.3, 123.5, 121.1, 104.8. MS (ESI): m/z (%)([M+H]⁺, 100). HRMS (ESI): m/z [M+H]⁺ calcd for C₁₈H₁₂N₃O: 286.0980; found: 286.0985.

(3-Methoxyquinolin-2-yl)(quinoxalin-2-yl)methanone (3b): White solid; 86%, 0.24 g; mp 193–194 °C. ¹H NMR (600 MHz, CDCl₃): δ = 9.60 (s, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.28–8.26 (m, 2H), 8.24 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 9.2 Hz, 1H), 7.92 (d, J = 7.6 Hz, 1H), 7.84 (t, J = 7.6 Hz, 1H), 7.43 (m, 2H), 7.14 (d, J = 2.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 191.8, 160.1, 150.6, 150.1, 146.0, 143.2, 142.9, 141.8, 135.6, 132.1, 131.7, 131.1, 130.6, 130.4, 129.3, 123.5, 121.1, 104.8. MS (ESI): m/z (%)([M+H]⁺, 100). HRMS (ESI): m/z [M+H]⁺ calcd for C₁₈H₁₂N₃O: 286.0980; found: 286.0985.
2.6 Hz, 1H), 7.65 (dd, J = 7.6, 1.8 Hz, 1H), 7.45 (dd, J = 7.6, 1.8 Hz, 1H), 3.98 (s, 3H). 13C NMR (100 MHz, CDCl3): δ = 191.6, 160.7, 150.6, 150.1, 146.0, 143.3, 142.6, 141.9, 135.7, 132.3, 131.7, 131.1, 130.6, 130.5, 129.1, 123.6, 121.1, 104.5, 55.8. MS (ESI): m/z (%): 316.1 ([M+H]+, 100). HRMS (ESI): m/z [M+H]+ calcd for C19H14N3O2: 316.1064; found: 316.1069.

(3-Bromoquinolin-2-yl)(quinoxalin-2-yl)methanone (3c): White solid; 53%, 0.22 g; mp 153–154 °C. 1H NMR (600 MHz, CDCl3): δ = 9.60 (s, 1H), 8.41 (d, J = 8.3 Hz, 1H), 8.30–8.28 (m, 2H), 8.24 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 2.6 Hz, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.83 (m, 1H), 7.71 (dd, J = 7.6, 1.8 Hz, 1H), 7.52 (dd, J = 7.6, 1.8 Hz, 1H), 7.01 (m, 1H), 6.99 (s, 3H). 13C NMR (100 MHz, CDCl3): δ = 191.7, 155.7, 150.4, 150.1, 146.0, 143.3, 142.6, 141.9, 138.4, 135.8, 132.4, 131.7, 131.3, 130.6, 129.1, 123.6, 120.9. MS (ESI): m/z (%) = 364.0 ([M+H]+, 51), 366.0 ([M+H]+, 49). HRMS (ESI): m/z [M+H]+ calcd for C18H11BrN3O: 364.0085; found: 364.0090; C18H11BrN3O: 366.0065; found: 366.0070.

(4-Methoxyquinolin-2-yl)(quinoxalin-2-yl)methanone (3d): White solid; 71%, 0.22 g; mp 153–154 °C. 1H NMR (600 MHz, CDCl3): δ = 9.61 (s, 1H), 8.29–8.27 (m, 2H), 8.26–8.23 (m, 3H), 8.15 (s, 1H), 8.09 (dd, J = 7.8, 2.6 Hz, 1H), 7.79 (dd, J = 7.6, 2.8 Hz, 1H), 7.63–7.61 (m, 1H), 3.99 (s, 3H). 13C NMR (100 MHz, CDCl3): δ = 191.7, 160.7, 150.6, 150.1, 146.0, 143.1, 142.9, 141.9, 135.6, 132.4, 131.7, 131.2, 130.6, 129.1, 123.6, 121.1, 104.8, 55.7. MS (ESI): m/z (%) = 364.0 ([M+H]+, 51), 366.0 ([M+H]+, 49). HRMS (ESI): m/z [M+H]+ calcd for C18H11BrN3O: 364.0085; found: 364.0090; C18H11BrN3O: 366.0065; found: 366.0070.

Scheme 3. A plausible mechanism for the formation of quinolin-2-yl(quinoxalin-2-yl)methanones.
(6-Bromoquinolin-2-yl)(quinoxalin-2-yl)methanone (3h): White solid; 83%, 0.30 g; mp 167–168 °C. 1H NMR (600 MHz, CDCl3): δ = 9.60 (s, 1H), 8.36–8.33 (m, 2H), 8.26–8.23 (m, 2H), 8.16–8.14 (m, 1H), 7.92–7.90 (m, 1H), 7.87–7.84 (m, 1H), 7.57–7.54 (m, 2H). 13C NMR (100 MHz, CDCl3): δ = 191.7, 160.4, 152.3, 151.2, 149.2, 145.6, 144.3, 141.5, 136.6, 133.2, 132.0, 130.4, 130.2, 130.1, 129.1, 121.3, 120.5, 110.2. MS (ESI): m/z (%) = 364.0 ([M+H]+), 51, 366.0 ([M+H]+), 49. HRMS (ESI): m/z [M+H]+ ccalc for C18H1135ClN3O: 364.0845; found: 364.0848; C18H1115ClN3O: 364.0685; found: 364.0675.

(7-Methoxyquinolin-2-yl)(quinoxalin-2-yl)methanone (3i): White solid; 70%, 0.23 g; mp 166–167 °C. 1H NMR (600 MHz, CDCl3): δ = 9.71 (s, 1H), 8.28 (d, J = 8.6 Hz, 1H), 8.28–8.26 (m, 2H), 8.23 (d, J = 8.4 Hz, –1H), 8.02 (d, J = 9.2 Hz, 1H), 7.92 (s, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.42 (dd, J = 9.2, 2.5 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 3.98 (s, 3H). 13C NMR (100 MHz, CDCl3): δ = 191.7, 160.1, 150.6, 146.0, 143.3, 142.9, 141.9, 135.4, 132.3, 131.7, 131.1, 130.6, 130.5, 129.3, 123.1, 121.1, 104.8, 55.8. MS (ESI): m/z (%) = 361. ([M+H]+, 100). HRMS (ESI): m/z [M+H]+ ccalc for C18H1135ClN3O: 351.0343; found: 351.0346.

(3-Methylquinolin-2-yl)(quinolin-2-yl)methanone (3m): White solid; 49%, 0.16 g; mp 130–131 °C. 1H NMR (600 MHz, CDCl3): δ = 8.44 (d, J = 8.4 Hz, 1H), 8.36–8.34 (m, 1H), 8.17 (dd, J = 8.3, 2.6 Hz, 1H), 8.11 (d, J = 8.2 Hz, 1H), 8.08–8.06 (m, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.82–7.78 (m, 2H), 7.68–7.66 (m, 1H). 13C NMR (100 MHz, CDCl3): δ = 191.2, 154.0, 149.2, 147.3, 145.7, 143.6, 141.7, 141.0, 137.2, 134.0, 131.7, 130.2, 129.3, 129.5, 128.8, 127.6, 122.7, 121.3. MS (ESI): m/z (%) = 320.1 ([M+H]+), 75, 322.1 ([M+H]+), 25. HRMS (ESI): m/z [M+H]+ ccalc for C18H1135ClN3O: 322.0591; found: 322.0597; C18H1135ClN3O: 322.0561; found: 322.0567.

(8-Methoxyquinolin-2-yl)(quinolin-2-yl)methanone (3k): White solid; 79%, 0.24 g; mp 105–106 °C. 1H NMR (600 MHz, CDCl3): δ = 9.61 (s, 1H), 8.34 (d, J = 8.5 Hz, 1H), 8.27–8.25 (m, 2H), 8.23 (d, J = 8.3 Hz, 1H), 8.06 (d, J = 7.6 Hz, 1H), 7.81 (dd, J = 7.8, 2.6 Hz, 1H), 7.70 (dd, J = 7.8, 2.6 Hz, 1H), 7.44 (dd, J = 7.6, 1.8 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 3.98 (s, 3H). 13C NMR (100 MHz, CDCl3): δ = 191.7, 160.1, 150.6, 150.1, 146.0, 143.3, 142.9, 141.7, 135.5, 132.3, 131.7, 131.1, 130.6, 130.5, 129.3, 123.6, 121.2, 107.9, 55.8. MS (ESI): m/z (%) = 361. ([M+H]+, 100). HRMS (ESI): m/z [M+H]+ ccalc for C18H1135ClN3O: 366.1064; found: 366.1064. 13C NMR (100 MHz, CDCl3): δ = 191.7, 160.8, 158.7, 151.2, 146.4, 143.4, 142.9, 141.4, 135.7, 132.4, 131.6, 131.1, 130.7, 130.5, 129.1, 123.5, 121.2, 112.0. MS (ESI): m/z (%) = 360.4 ([M+H]+), 51, 366.0 ([M+H]+), 49. HRMS (ESI): m/z [M+H]+ ccalc for C18H1135ClN3O: 364.0845; found: 364.0809; C18H1135ClN3O: 366.0665; found: 366.0670.

(6-Bromoquinolin-2-yl)(quinolin-2-yl)methanone (3o): White solid; 62%, 0.25 g; mp 175–176 °C. 1H NMR (600 MHz, CDCl3): δ = 9.19 (s, 1H), 8.40 (s, 1H), 8.33 (d, J = 7.8 Hz, 1H), 8.28–8.26 (m, 2H), 8.23 (d, J = 8.4 Hz, 1H), 8.07 (dd, J = 7.6, 2.6 Hz, 1H), 7.94 (dd, J = 7.6, 2.8 Hz, 1H), 7.63–7.61 (m, 2H). 13C NMR (100 MHz, CDCl3): δ = 191.7, 160.8, 158.5, 151.2, 146.4, 143.4, 142.8, 141.4, 135.6, 132.4, 131.6, 131.2, 130.7, 130.3, 129.1, 123.5, 121.0, 111.5. MS (ESI): m/z (%) = 320.1 ([M+H]+, 75), 322.1 ([M+H]+), 25. HRMS (ESI): m/z [M+H]+ ccalc for C18H1135ClN3O: 320.0591; found: 320.0597; C18H1135ClN3O: 322.0561; found: 322.0567.

Pyridin-2-yl(quinoxalin-2-yl)methanone (5): White solid; 41%, 0.10 g; mp 178–179 °C. 1H NMR (600 MHz, CDCl3): δ = 9.64 (s, 1H), 8.90 (d, J = 8.4 Hz, 1H), 8.36 (d,
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J = 8.6 Hz, 1H), 8.28–8.25 (m, 2H), 8.23 (d, J = 8.6 Hz, 1H), 8.21–8.19 (m, 2H), 8.20 (dd, J = 7.8, 2.2 Hz, 1H), 8.10–8.08 (m, 1H), 7.71–7.69 (m, 1H). 13C NMR (100 MHz, CDCl3): δ = 191.2, 160.3, 150.7, 150.3, 146.1, 142.7, 135.4, 131.6, 130.5, 130.1, 128.8, 128.5, 123.5, 122.7. MS (ESI): m/z (%) = 236.1 ([M+H]+, 100). HRMS (ESI): m/z [M+H]+ calcd for C14H10N3O: 236.0824; found: 236.0829.

Diquinolin-2-ylmethanone (7): White solid; 39%, 0.11 g; mp 198–199 °C. 1H NMR (600 MHz, CDCl3): δ = 8.06 (d, J = 8.6 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H), 7.97 (dd, J = 8.4, 2.6 Hz, 2H), 7.83–7.79 (m, 4H), 7.69–7.66 (m, 2H). 13C NMR (100 MHz, CDCl3): δ = 191.7, 153.1, 147.2, 143.2, 141.0, 134.1, 131.1, 129.4, 127.6, 121.1. MS (ESI): m/z (%) = 285.1 ([M+H]+, 100). HRMS (ESI): m/z [M+H]+ calcd for C19H13N2O: 285.1028; found: 285.1033.

Quinoline-2-carbaldehyde (8a): Pale yellow solid; 95%, 0.15 g; mp 66–67 °C. 1H NMR (600 MHz, CDCl3): δ = 10.24 (s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.83 (t, J = 8.2 Hz, 1H), 7.70 (t, J = 7.5 Hz, 1H). 13C NMR (100 MHz, CDCl3): δ = 193.7, 152.6, 147.9, 137.4, 130.5, 130.4, 130.1, 129.2, 127.9, 117.3.

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