



RESEARCH ARTICLE

# Site-selective and metal-free C–H nitration of biologically relevant *N*-heterocycles

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**Abstract** The site-selective and metal-free C–H nitration reaction of quinoxalinones and pyrazinones as biologically important *N*-heterocycles with *t*-butyl nitrite is described. A wide range of quinoxalinones were efficiently applied in this transformation, providing C7-nitrated quinoxalinones without undergoing C3-nitration. From the view of mechanistic point, the radical addition reaction exclusively occurred at the electron-rich aromatic region beyond electron-deficient *N*-heterocycle ring. This is a first report on the C7–H functionalization of quinoxalinones under metal-free conditions. In contrast, the nitration reaction readily takes place at the C3-position of pyrazinones. This transformation is characterized by the scale-up compatibility, mild reaction conditions, and excellent functional group tolerance. The applicability of the developed method is showcased by the selective reduction of NO<sub>2</sub> functionality on the C7-nitrated quinoxalinone product, providing aniline derivatives. Combined mechanistic investigations aided the elucidation of a plausible reaction mechanism.

**Keywords** *t*-Butyl nitrite · C–H functionalization · Regioselectivity · Heterocycles · Nitration

## Introduction

Since the landmark discovery by Mitscherlich and Laurent in 1834 (Patel et al. 2021), nitro compounds are important and versatile building blocks in organic chemistry (Ono 2001), and their derivatives are widely utilized in various pharmaceuticals, agrochemicals, pigments, and dyes as well as a variety of fine chemicals such as solvents, perfumes, explosives, and polymers, as shown in Fig. 1 (Fan et al. 2004; McNamara et al. 2011; Nepali et al. 2019). For example, chloramphenicol (Rebstock et al. 1949) and metronidazole (Freeman et al. 1997) are well-known antibiotic and anti-protozoal drugs for the treatment of a number of infectious diseases. The biological properties of these molecules are closely related with (hetero)aryl motifs tethered with nitro functionality, but vary depending on the nature and position of substituents on (hetero)aryl rings.

Traditional methods for nitration reactions rely on an excess use of nitric acid or its mixture with sulfuric acid or dinitrogen pentoxide (Olah et al. 1990). However, from a synthetic point of view, these protocols represent the limited functional group tolerance and the generation of undesirable by-products as well as incomplete regioselectivity. To overcome these limitations, new nitrating agents such as nitrate (Manna et al. 2012; Zolfigol et al. 2012), nitrite salts (Fors et al. 2009; Li et al. 2013), and *tert*-butyl nitrite (TBN) have been intensively investigated (Wu and Neumann et al. 2011; Wu and Schranck et al. 2011; Shen et al. 2014).

With great advance on C–H functionalization reactions (Mishra et al. 2017, 2018; Pandey et al. 2018; Sambaggio et al. 2018; Lee et al. 2019), direct C–H nitration of

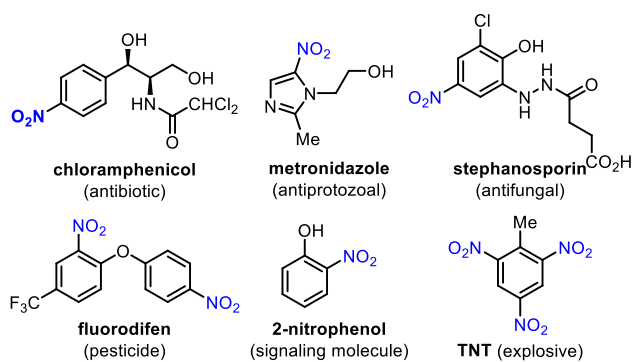
Junghyea Moon and Hyun Ku Ji have contributed equally to this work.

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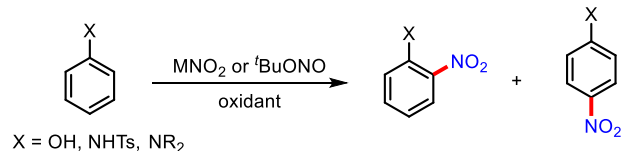
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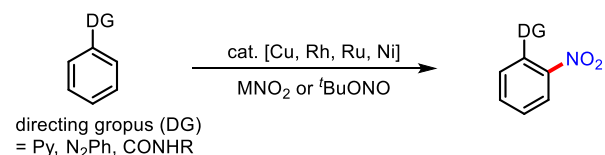


**Fig. 1** Nitro-containing pharmaceuticals and functional materials

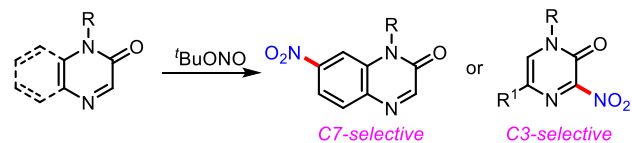
**A. metal-free C–H nitration with oxidant**



**B. transition-metal-catalyzed C–H nitration by directing groups**



**C. site-selective C–H nitration of *N*-heterocycles (this work)**



**Fig. 2** C–H nitration methods of (hetero)arenes using nitrating agents

(hetero)arenes has been recently developed. The metal-free oxidative C–H nitration of phenols or amines has been explored, as shown in Fig. 2 (Koley et al. 2009; Kilpatrick et al. 2013; Li et al. 2014). However, none of these protocols represent a general strategy to allow for complete site-selectivity between the *ortho*- and *para*-positions. A great deal of effort on site-selectivity of nitration has been devoted to the transition-metal-catalyzed *ortho*-C–H nitration of *N*-heterocycles. For example, Liu reported the Pd(II)-catalyzed *ortho*-C–H nitration of nitrogen-containing heterocycles with silver nitrite in the presence of K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> as an external oxidant (Liu et al. 2010). The *ortho*-C–H nitration of (hetero)arenes using nitrite salts was also realized with the Cu(II), Rh(III), Ru(0), and Ni(II) catalytic systems (Zhang et al. 2011; Xie et al. 2013; Katayev et al. 2014; Majhi et al. 2014; Fan and Ni 2016; Wan et al. 2017). In addition, the Pd(II)-catalyzed aerobic oxidative *ortho*-C–H nitration of arenes with *tert*-butyl nitrite and

toluene as the radical precursors was demonstrated (Liang et al. 2015). The azaindole-assisted *ortho*-C–H nitration of arenes with *tert*-butyl nitrite affording various nitrated azaindole derivatives was disclosed (Chun et al. 2018).

Despite the compelling progress on the C–H nitration reaction of various *N*-heterocycles, the site-selective nitration reaction of quinoxalinones and pyrazinones under milder reaction conditions is still unexplored. Driven by our ongoing interest in the C–H functionalization of *N*-heterocycles (Han et al. 2018; Ghosh et al. 2019, 2021; An et al. 2020; Park et al. 2021), we herein describe the metal-free and site-selective C–H nitration reaction of quinoxalinones and pyrazinones with *tert*-butyl nitrite as a readily available nitrating agent. Notably, the gram-scale reaction, selective reduction of a nitro group, and thiocarbonylation demonstrate the synthetic utility of the developed method.

## Materials and methods

### General methods

Commercially available reagents were used without additional purification, unless otherwise stated. Quinoxalinones (**1a–1m**) and 5-aryl pyrazinones (**4a–4j**) were prepared according to the reported literature (Ghosh et al. 2021; Guo et al. 2021). *t*-Butyl nitrite was purchased from Aldrich, Switzerland. All the reactions were performed in an oil bath by using hot plate magnetic stirrer (IKA universal, Guangzhou city, China). Sealed tubes were purchased from Fischer Scientific (13 × 100 mm, 1495925A; Mexico) and dried in oven for overnight and cooled at room temperature prior to use. Thin layer chromatography was carried out using plates coated with silica gel 60 F<sub>254</sub> (Merck KGaA, 64271 Darmstadt, Germany). For flash column chromatography, silica gel 60 Å (230–400 mesh, Merck, Germany) was used. Nuclear magnetic resonance spectra (<sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR) were recorded on a Bruker Unity 400, 500, and 700 MHz spectrometers in CDCl<sub>3</sub>, CD<sub>3</sub>COCD<sub>3</sub>, and DMSO-*d*<sub>6</sub> solution and chemical shifts are reported as parts per million (ppm). Resonance patterns are reported with the notations s (singlet), br (broad), d (doublet), t (triplet), q (quartet), sext (sextet), dd (doublet of doublets), dt (doublet of triplets), dq (doublet of quartets), qd (quartet of doublets), td (triplet of doublets), tt (triplet of triplets), and m (multiplet). In addition, the notation br is used to indicate a broad signal. Coupling constants (*J*) are reported in hertz (Hz). IR spectra were recorded on a Varian 2000 Infrared spectrophotometer and are reported as cm<sup>−1</sup>. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-600 spectrometer.

### General procedure and characterization data for the C7-nitration of quinoxalinones (3a–3m)

To an oven-dried sealed tube charged with 1-methylquinoxalin-2(1H)-one (**1a**) (32.0 mg, 0.2 mmol, 100 mol %) was added *t*-butyl nitrite (**2a**) (71.4  $\mu$ L, 0.6 mmol, 300 mol %) and CH<sub>3</sub>CN (2 mL) under O<sub>2</sub> atmosphere at room temperature. After using O<sub>2</sub> balloon, the reaction mixture was allowed to stir at 60 °C for 20 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (4 mL) and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 10:1 to 2:1) to afford **3a** (31.2 mg) in 76% yield.

#### 1-Methyl-7-nitroquinoxalin-2(1H)-one (3a)

31.2 mg (76%); eluent (*n*-hexanes/EtOAc = 10:1 to 2:1); brown solid; mp = 228.9–231.1 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.43 (s, 1H), 8.32 (d, *J* = 2.4 Hz, 1H), 8.16 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 3.68 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  154.1, 153.9, 147.9, 136.0, 133.9, 130.9, 117.7, 110.6, 28.9; IR (KBr)  $\nu$  2924, 2854, 1666, 1587, 1512, 1462, 1354 cm<sup>-1</sup>; HRMS (quadrupole, EI) *m/z*: [M]<sup>+</sup> Calcd for C<sub>9</sub>H<sub>7</sub>N<sub>3</sub>O<sub>3</sub> 205.0487; Found 205.0486.

#### 1-Ethyl-7-nitroquinoxalin-2(1H)-one (3b)

32.9 mg (75%); eluent (*n*-hexanes/acetone = 10:1 to 1:1); brown solid; mp = 165.5–167.9 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.41 (s, 1H), 8.24 (d, *J* = 2.4 Hz, 1H), 8.18 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  154.1, 153.9, 148.7, 136.9, 132.8, 132.1, 118.1, 109.7, 37.8, 12.6; IR (KBr)  $\nu$  2989, 2924, 1668, 1589, 1523, 1471, 1442, 1344, 1244, 1103 cm<sup>-1</sup>; HRMS (quadrupole, EI) *m/z*: [M]<sup>+</sup> Calcd for C<sub>10</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub> 219.0644; Found 219.0639.

#### 1-Isobutyl-7-nitroquinoxalin-2(1H)-one (3c)

36.6 mg (74%); eluent (*n*-hexanes/acetone = 10:1 to 1:1); light brown solid; mp = 121.8–124.0 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.41 (s, 1H), 8.21 (d, *J* = 2.4 Hz, 1H), 8.15 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.02 (d, *J* = 8.8 Hz, 1H), 4.15 (d, *J* = 7.6 Hz, 2H), 2.27 (sep, *J* = 6.4 Hz, 1H), 1.04 (s, 3H), 1.02 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  154.8, 153.9, 148.5, 136.9, 133.4, 132.0, 118.1, 110.3, 49.3, 27.4, 20.2; IR (KBr)  $\nu$  3114, 2956, 2927, 2871, 1664, 1591, 1562, 1522, 1464, 1441, 1338, 1315, 1236, 1132,

1099, 1057 cm<sup>-1</sup>; HRMS (quadrupole, EI) *m/z*: [M]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub> 247.0957; Found 247.0954.

#### 1-Butyl-7-nitroquinoxalin-2(1H)-one (3d)

35.2 mg (71%); eluent (*n*-hexanes/acetone = 10:1 to 3:1); yellow solid; mp = 112.3–114.3 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.40 (s, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 8.16 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 4.28 (dd, *J* = 6.0 Hz, 2H), 1.80–1.73 (m, 2H), 1.51 (sext, *J* = 7.2 Hz, 2H), 1.02 (t, *J* = 7.6 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  154.3, 153.8, 148.6, 136.9, 133.1, 132.0, 118.1, 109.9, 42.5, 29.5, 20.3, 13.8; IR (KBr)  $\nu$  2956, 2925, 1668, 1593, 1527, 1462, 1346, 1265 cm<sup>-1</sup>; HRMS (quadrupole, EI) *m/z*: [M]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub> 247.0957; Found 247.0954.

#### 1-(4-Bromobutyl)-7-nitroquinoxalin-2(1H)-one (3e)

51.2 mg (78%); eluent (*n*-hexanes/acetone = 10:1 to 1:1); yellow solid; mp = 126.3–128.5 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.42 (s, 1H), 8.26 (d, *J* = 2.4 Hz, 1H), 8.18 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 4.33 (t, *J* = 7.6 Hz, 2H), 3.50 (t, *J* = 5.6 Hz, 2H), 2.08–1.95 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  154.3, 153.7, 148.7, 136.9, 132.9, 132.2, 118.3, 109.7, 41.6, 32.6, 29.6, 25.9; IR (KBr)  $\nu$  2922, 2854, 1666, 1593, 1564, 1525, 1444, 1344, 1317, 1103 cm<sup>-1</sup>; HRMS (quadrupole, EI) *m/z*: [M]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>12</sub>BrN<sub>3</sub>O<sub>3</sub> 325.0062; Found 325.0061.

#### 1-Benzyl-7-nitroquinoxalin-2(1H)-one (3f)

30.9 mg (55%); eluent (*n*-hexanes/EtOAc = 10:1 to 2:1); light brown solid; mp = 165.7–167.9 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.52 (s, 1H), 8.23 (d, *J* = 2.0 Hz, 1H), 8.12 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.38–1.28 (m, 5H), 5.51 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  154.6, 153.9, 148.5, 136.9, 134.2, 133.1, 131.9, 129.5, 128.5, 127.3, 118.4, 110.6, 46.1; IR (KBr)  $\nu$  2922, 2854, 1666, 1593, 1564, 1523, 1450, 1342, 1317, 1219, 1103 cm<sup>-1</sup>; HRMS (quadrupole, EI) *m/z*: [M]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub> 281.0800; Found 281.0800.

#### 3-((7-Nitro-2-oxoquinoxalin-1(2H)-yl)methyl)benzonitrile (3g)

19.2 mg (31%); eluent (*n*-hexanes/acetone = 10:1 to 2:1); yellow solid; mp = 193.8–196.1 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.53 (s, 1H), 8.17 (dd, *J* = 5.2, 1.2 Hz, 1H), 8.09 (d, *J* = 0.8 Hz, 1H), 8.08 (d, *J* = 2.8 Hz, 1H), 7.61 (dt, *J* = 4.4 Hz, 1H), 7.60–7.58 (m, 1H), 7.54–7.53 (m, 1H), 7.51 (t, *J* = 4.4 Hz, 1H), 5.53 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  154.4, 153.7, 148.7, 136.9, 135.8, 132.8, 132.4, 132.3, 131.7, 130.6, 130.3, 118.8, 118.1, 113.9, 109.9, 45.4;

IR (KBr)  $\nu$  2924, 2854, 2231, 1670, 1593, 1566, 1525, 1448, 1344  $\text{cm}^{-1}$ ; HRMS (quadrupole, EI)  $m/z$ :  $[M]^+$  Calcd for  $\text{C}_{16}\text{H}_{10}\text{N}_4\text{O}_3$  306.0753; Found 306.0748.

*1-(4-Ethoxyphenyl)-7-nitroquinoxalin-2(1H)-one (3h)*

34.4 mg (56%); eluent (*n*-hexanes/EtOAc = 10:1 to 2:1); orange solid; mp = 182.0–183.9 °C;  $^1\text{H}$  NMR (700 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  8.40 (s, 1H), 8.14 (dd,  $J$  = 8.4, 2.1 Hz, 1H), 8.09 (d,  $J$  = 8.4 Hz, 1H), 7.56 (d,  $J$  = 2.8 Hz, 1H), 7.39 (dt,  $J$  = 9.1, 2.8 Hz, 2H), 7.20 (dt,  $J$  = 9.1, 3.5 Hz, 2H), 4.18 (q,  $J$  = 7.0 Hz, 2H), 1.44 (t,  $J$  = 7.0 Hz, 3H);  $^{13}\text{C}$  NMR (175 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  160.9, 155.6, 155.1, 149.1, 137.3, 136.6, 131.9, 130.5, 128.2, 118.4, 116.8, 111.8, 64.6, 15.1; IR (KBr)  $\nu$  2925, 2854, 1676, 1593, 1523, 1508, 1477, 1435, 1344, 1302, 1246, 1043  $\text{cm}^{-1}$ ; HRMS (quadrupole, EI)  $m/z$ :  $[M]^+$  Calcd for  $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_4$  311.0906; Found 311.0904.

*7-Nitro-1-(4-nitrophenyl)quinoxalin-2(1H)-one (3i)*

18.8 mg (30%); eluent (*n*-hexanes/EtOAc = 10:1 to 3:1); yellow solid; mp = 244.2–245.6 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.55 (dt,  $J$  = 8.8, 2.8 Hz, 2H), 8.52 (s, 1H), 8.20 (dd,  $J$  = 8.8, 2.4 Hz, 1H), 8.12 (d,  $J$  = 8.8 Hz, 1H), 7.58–7.54 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  154.0, 153.6, 148.9, 148.6, 139.6, 136.3, 133.6, 132.1, 129.8, 126.3, 119.2, 110.7; IR (KBr)  $\nu$  3111, 3082, 2924, 1680, 1595, 1523, 1435, 1348  $\text{cm}^{-1}$ ; HRMS (quadrupole, EI)  $m/z$ :  $[M]^+$  Calcd for  $\text{C}_{14}\text{H}_8\text{N}_4\text{O}_5$  312.0495; Found 312.0490.

*7-Nitro-1-(*m*-tolyl)quinoxalin-2(1H)-one (3j)*

33.8 mg (60%); eluent (*n*-hexanes/EtOAc = 10:1 to 3:1); yellow solid; mp = 183.1–185.6 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.51 (s, 1H), 8.14 (dd,  $J$  = 8.8, 2.4 Hz, 1H), 8.07 (d,  $J$  = 8.8 Hz, 1H), 7.60 (d,  $J$  = 2.4 Hz, 1H), 7.56 (td,  $J$  = 8.0, 1.6 Hz, 1H), 7.43 (d,  $J$  = 7.6 Hz, 1H), 7.10–7.08 (m, 2H), 2.47 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  154.4, 154.3, 148.5, 141.4, 136.3, 134.7, 134.1, 131.5, 130.8, 128.5, 124.9, 119.9, 118.5, 111.6, 21.6; IR (KBr)  $\nu$  2924, 2854, 1678, 1593, 1562, 1527, 1433, 1344  $\text{cm}^{-1}$ ; HRMS (quadrupole, EI)  $m/z$ :  $[M]^+$  Calcd for  $\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_3$  281.0800; Found 281.0803.

*Ethyl 3-(7-nitro-2-oxoquinoxalin-1(2H)-yl)benzoate (3k)*

29.2 mg (43%); eluent (*n*-hexanes/acetone = 10:1 to 2:1); yellow oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  8.45 (s, 1H), 8.28 (dt,  $J$  = 7.6, 1.6 Hz, 1H), 8.19–8.12 (m, 3H), 7.88 (t,  $J$  = 7.6 Hz, 1H), 7.81 (dq,  $J$  = 7.6, 1.2 Hz, 1H), 7.47 (d,  $J$  = 2.4 Hz, 1H), 7.47 (qd,  $J$  = 7.2, 1.6 Hz, 2H), 1.36 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  165.7, 155.5, 154.9, 149.1, 137.2, 136.4, 135.9, 134.1, 133.9,

132.1, 131.7, 131.6, 130.6, 118.7, 111.5, 62.0, 14.5; IR (KBr)  $\nu$  3066, 2924, 2854, 1716, 1680, 1593, 1562, 1525, 1436, 1344, 1269, 1211, 1182, 1103, 1082, 1022  $\text{cm}^{-1}$ ; HRMS (quadrupole, EI)  $m/z$ :  $[M]^+$  Calcd for  $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_5$  339.0855; Found 339.0852.

*6-Bromo-1-methyl-7-nitroquinoxalin-2(1H)-one (3l)*

19.9 mg (35%); eluent (*n*-hexanes/EtOAc = 10:1 to 2:1); light brown solid; mp = 229.4–231.2 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  8.33 (s, 1H), 8.24 (s, 1H), 8.16 (s, 1H), 3.72 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  155.3, 154.9, 147.8, 135.9, 134.9, 112.8, 106.2, 23.3; IR (KBr)  $\nu$  2922, 2852, 1664, 1585, 1554, 1533, 1456, 1344  $\text{cm}^{-1}$ ; HRMS (quadrupole, EI)  $m/z$ :  $[M]^+$  Calcd for  $\text{C}_9\text{H}_6\text{BrN}_3\text{O}_3$  282.9593; Found 282.9593.

*7-Chloro-1-methyl-5-nitroquinoxalin-2(1H)-one (3m)*

21.6 mg (45%); eluent (*n*-hexanes/EtOAc = 10:1 to 3:1); light brown solid; mp = 229.4–231.5 °C;  $^1\text{H}$  NMR (700 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  8.24 (s, 1H), 7.91 (d,  $J$  = 1.2 Hz, 1H), 7.83 (d,  $J$  = 1.2 Hz, 1H), 3.74 (s, 3H);  $^{13}\text{C}$  NMR (175 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  154.9, 153.5, 150.2, 137.0, 136.7, 124.3, 118.3, 117.4, 23.3; IR (KBr)  $\nu$  2918, 2861, 1676, 1603, 1537, 1454, 1379, 1267  $\text{cm}^{-1}$ ; HRMS (quadrupole, EI)  $m/z$ :  $[M]^+$  Calcd for  $\text{C}_9\text{H}_6\text{ClN}_3\text{O}_3$  239.0098; Found 239.0096.

**General procedure and characterization data for the C3-nitration of 5-aryl pyrazinones (5a–5j)**

To an oven-dried sealed tube charged with 1-methyl-5-phenylpyrazin-2(1H)-one (**4a**) (37.2 mg, 0.2 mmol, 100 mol %) was added *t*-butyl nitrite (**2a**) (119.0  $\mu\text{L}$ , 1.0 mmol, 500 mol %) and  $\text{CH}_3\text{CN}$  (2.5 mL) under  $\text{O}_2$  atmosphere at room temperature. After using  $\text{O}_2$  balloon, the reaction mixture was allowed to stir at 60 °C for 28 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (4 mL) and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/acetone = 10:1 to 3:1) to afford **5a** (33.4 mg) in 72% yield.

*1-Methyl-3-nitro-5-phenylpyrazin-2(1H)-one (5a)*

33.4 mg (72%); eluent (*n*-hexane/acetone = 10:1 to 3:1); yellow solid; mp = 191.2–193.8 °C;  $^1\text{H}$  NMR (700 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.93 (s, 1H), 7.83–7.81 (m, 2H), 7.50–7.47 (m, 2H), 7.39 (tt,  $J$  = 7.7, 0.7 Hz, 1H), 3.69 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ )  $\delta$  148.4, 148.1, 135.9, 133.6, 128.9, 128.4, 127.9, 124.6, 38.3; IR (KBr)  $\nu$  3060, 2927, 1674, 1604, 1543, 1493, 1419, 1267  $\text{cm}^{-1}$ ; HRMS (quadrupole, EI)  $m/z$ :  $[M]^+$  Calcd for  $\text{C}_{11}\text{H}_9\text{N}_3\text{O}_3$  231.0644; Found 231.0641.

*1-Methyl-3-nitro-5-(4-(trifluoromethoxy)phenyl)pyrazin-2(1H)-one (5b)*

32.2 mg (51%); eluent (*n*-hexanes/acetone = 10:1 to 3:1); yellow oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.90 (s, 1H), 7.74 (dt,  $J = 7.2, 2.4$  Hz, 2H), 7.31–7.28 (m, 2H), 3.79 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  150.2, 149.9, 148.3, 131.8, 131.4, 129.2, 129.1 (q,  $J_{\text{C-F}} = 33.0$  Hz), 126.8, 121.7, 39.1;  $^{19}\text{F}$  NMR (470 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  –58.5 (s); IR (KBr)  $\nu$  3060, 2925, 1680, 1608, 1545, 1500, 1346, 1263, 1110  $\text{cm}^{-1}$ ; HRMS (quadrupole, EI)  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{12}\text{H}_8\text{F}_3\text{N}_3\text{O}_4$  315.0467; Found 315.0462.

*5-(4-Chlorophenyl)-1-methyl-3-nitropyrazin-2(1H)-one (5c)*

23.9 mg (45%); eluent (*n*-hexanes/acetone = 10:1 to 3:1); yellow solid; mp = 238.1–241.4 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  8.78 (s, 1H), 7.86 (dt,  $J = 8.8, 2.8$  Hz, 2H), 7.50 (dt,  $J = 8.4, 2.8$  Hz, 2H), 3.81 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  159.5, 135.5, 134.7, 133.8, 129.9, 128.3, 127.3, 105.0, 38.8; IR (KBr)  $\nu$  2925, 2856, 1678, 1606, 1543, 1489, 1340, 1267, 1196, 1086, 739  $\text{cm}^{-1}$ ; HRMS (quadrupole, EI)  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{11}\text{H}_8\text{ClN}_3\text{O}_3$  265.0254; Found 265.0250.

*1-Methyl-3-nitro-5-(3-(trifluoromethyl)phenyl)pyrazin-2(1H)-one (5d)*

34.2 mg (57%); eluent (*n*-hexanes/acetone = 10:1 to 3:1); yellow solid; mp = 159.2–161.2 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  8.93 (s, 1H), 8.17–8.13 (m, 2H), 7.73 (dd,  $J = 3.5, 1.5$  Hz, 2H), 3.83 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  150.7, 149.3, 142.5, 136.2, 131.6 (q,  $J_{\text{C-F}} = 31.2$  Hz), 130.9, 129.4, 127.8, 126.3 (q,  $J_{\text{C-F}} = 270.5$  Hz), 125.7 (q,  $J_{\text{C-F}} = 3.2$  Hz), 122.2 (d,  $J_{\text{C-F}} = 3.2$  Hz), 38.9;  $^{19}\text{F}$  NMR (470 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  –63.1 (s); IR (KBr)  $\nu$  3060, 2927, 1680, 1608, 1545, 1325, 1271, 1180, 1036  $\text{cm}^{-1}$ ; HRMS (quadrupole, EI)  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{12}\text{H}_8\text{F}_3\text{N}_3\text{O}_3$  299.0518; Found 299.0515.

*1-(Methoxymethyl)-3-nitro-5-phenylpyrazin-2(1H)-one (5e)*

27.8 mg (53%); eluent (*n*-hexanes/acetone = 10:1 to 1:1); yellow oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  8.06 (s, 1H), 7.88–7.85 (m, 2H), 7.50–7.46 (m, 2H), 7.39 (tt,  $J = 7.0, 1.5$  Hz, 1H), 5.54 (s, 2H), 3.52 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  149.1, 134.8, 131.6, 130.1, 129.9, 129.5, 125.9, 124.4, 80.9, 58.3; IR (KBr)  $\nu$  2924, 2854, 1684, 1604,

1545, 1460, 1273  $\text{cm}^{-1}$ ; HRMS (quadrupole, EI)  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_4$  261.0750; Found 261.0747.

*1-Benzyl-5-(2-methoxyphenyl)-3-nitropyrazin-2(1H)-one (5f)*

30.4 mg (45%); eluent (*n*-hexanes/acetone = 10:1 to 1:1); yellow oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  8.20 (s, 1H), 7.62 (dd,  $J = 7.6, 1.6$  Hz, 1H), 7.58 (ddd,  $J = 9.2, 7.6, 2.0$  Hz, 1H), 7.43–7.41 (m, 2H), 7.35 (td,  $J = 7.2, 2.0$  Hz, 2H), 7.27 (tt,  $J = 6.8, 1.6$  Hz, 1H), 7.14 (d,  $J = 8.4$  Hz, 1H), 7.07 (td,  $J = 7.6, 0.8$  Hz, 1H), 4.54 (d,  $J = 6.0$  Hz, 2H), 3.73 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  192.7, 165.9, 160.7, 140.0, 135.5, 131.1, 129.2, 128.6, 127.9, 126.1, 121.5, 113.3, 56.4, 43.2; IR (KBr)  $\nu$  3240, 3074, 2584, 2318, 1683, 1645, 1580, 1485, 1462, 1439, 1310, 1250, 1207, 1165, 1117, 1022, 928  $\text{cm}^{-1}$ ; HRMS (quadrupole, EI)  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_4$  337.1063; Found 337.1062.

*2-((3-Nitro-2-oxo-5-phenylpyrazin-1(2H)-yl)methyl)benzotrile (5g)*

40.6 mg (61%); eluent (*n*-hexanes/acetone = 10:1 to 3:1); yellow oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  8.90 (s, 1H), 7.88–7.85 (m, 3H), 7.73–7.67 (m, 2H), 7.58 (td,  $J = 7.6, 2.0$  Hz, 1H), 7.51–7.47 (m, 2H), 7.50 (tt,  $J = 7.2, 1.6$  Hz, 1H), 5.66 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  153.1, 148.9, 138.5, 134.8, 134.5, 134.3, 134.1, 130.4, 130.3, 129.9, 129.8, 129.5, 125.9, 117.9, 112.9, 53.7; IR (KBr)  $\nu$  2956, 2924, 2225, 1668, 1593, 1525, 1448, 1344, 1213  $\text{cm}^{-1}$ ; HRMS (quadrupole, EI)  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_3$  332.0909; Found 332.0907.

*1-(4-Methoxyphenyl)-3-nitro-5-phenylpyrazin-2(1H)-one (5h)*

33.2 mg (51%); eluent (*n*-hexanes/acetone = 10:1 to 3:1); yellow solid; mp = 149.4–150.6 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.92 (s, 1H), 7.75–7.72 (m, 2H), 7.47–7.38 (m, 5H), 7.05 (dt,  $J = 8.8, 3.6$  Hz, 2H), 3.88 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  162.5, 160.9, 147.9, 133.1, 131.1, 130.5, 130.4, 129.3, 127.0, 125.3, 121.6, 115.2, 55.9; IR (KBr)  $\nu$  3060, 1682, 1606, 1512, 1467, 1265  $\text{cm}^{-1}$ ; HRMS (quadrupole, EI)  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_4$  323.0906; Found 323.0906.

*1-(4-Acetylphenyl)-3-nitro-5-phenylpyrazin-2(1H)-one (5i)*

30.2 mg (45%); eluent (*n*-hexanes/acetone = 10:1 to 4:1); yellow oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  8.63 (s, 1H), 8.21 (dt,  $J = 9.0, 2.0$  Hz, 2H), 7.91 (dq,  $J = 8.5, 1.0$  Hz, 2H), 7.88 (dt,  $J = 8.5, 2.5$  Hz, 2H), 7.50–7.46 (m, 2H), 7.40 (tt,  $J = 7.5, 1.0$  Hz, 1H), 2.68 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,

CD<sub>3</sub>COCD<sub>3</sub>) δ 197.2, 148.6, 143.2, 138.9, 134.7, 132.9, 130.2, 130.1, 129.8, 129.5, 127.8 (two carbons overlap), 126.0, 26.9; IR (KBr) ν 2924, 2854, 1685, 1599, 1545, 1360, 1265, 1194 cm<sup>-1</sup>; HRMS (quadrupole, EI) *m/z*: [M]<sup>+</sup> Calcd for C<sub>18</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub> 335.0906; Found 335.0905.

### 3-Nitro-5-phenyl-1-(*m*-tolyl)pyrazin-2(1*H*)-one (5*j*)

31.4 mg (51%); eluent (*n*-hexanes/acetone = 10:1 to 4:1); yellow solid; mp = 141.3–144.1 °C; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>) δ 8.56 (s, 1H), 7.93–7.90 (m, 2H), 7.53–7.52 (m, 1H), 7.50–7.49 (m, 2H), 7.47–7.44 (m, 2H), 7.39 (tt, *J* = 7.2, 1.2 Hz, 2H), 2.44 (s, 3H); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>COCD<sub>3</sub>) δ 150.2, 148.7, 140.4, 139.9, 134.8, 133.4, 131.2, 130.1, 129.8, 129.4, 127.7, 125.9, 124.8, 124.3, 21.2; IR (KBr) ν 3059, 2925, 2854, 1684, 1603, 1545, 1489, 1454, 1342, 1269, 1194 cm<sup>-1</sup>; HRMS (quadrupole, EI) *m/z*: [M]<sup>+</sup> Calcd for C<sub>17</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub> 307.0957; Found 307.0956.

### General procedure for the gram scale experiment of 1a

To an oven-dried round bottom flask charged with 1-methylquinoxalin-2(1*H*)-one (**1a**) (1.0 g, 6.3 mmol, 100 mol %) was added *t*-butyl nitrite (**2a**) (2.25 mL, 18.9 mmol, 300 mol %) and CH<sub>3</sub>CN (60 mL) under O<sub>2</sub> atmosphere at room temperature. After using O<sub>2</sub> balloon, the reaction mixture was allowed to stir at 60 °C for 20 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (25 mL) and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 10:1 to 2:1) to afford **3a** (0.69 g) in 68% yield.

### General procedure for the gram scale experiment of 4a

To an oven-dried sealed tube charged with 1-methyl-5-phenylpyrazin-2(1*H*)-one (**4a**) (1.0 g, 5.4 mmol, 100 mol %) was added *t*-butyl nitrite (**2a**) (3.2 mL, 27.0 mmol, 500 mol %) and CH<sub>3</sub>CN (65 mL) under O<sub>2</sub> atmosphere at room temperature. After using O<sub>2</sub> balloon, the reaction mixture was allowed to stir at 60 °C for 28 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (25 mL) and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/acetone = 10:1 to 3:1) to afford **5a** (0.81 g) in 65% yield.

### General procedure and characterization data for the reduction of nitro group on 3a

To an oven-dried sealed tube charged with 1-methyl-7-nitroquinoxalin-2(1*H*)-one (**3a**) (41.0 mg, 0.2 mmol, 100 mol %), iron (46.9 mg, 0.84 mmol, 420 mol %), ammonium chloride powder (71.7 mg, 1.34 mmol, 670 mol %) were added MeOH/THF/H<sub>2</sub>O (1:1:1, 4.5 mL) at room temperature. The

reaction mixture was allowed to stir in an oil bath for 12 h at 60 °C. The reaction mixture was cooled to room temperature, filtered through Celite, rinsing with methanol, and the volatiles were removed under reduced pressure. The aqueous residue was diluted with water, saturated NaHCO<sub>3</sub> solution, and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/acetone = 10:1 to 2:1) to afford **6a** (22.8 mg) in 65% yield.

### 7-Amino-1-methylquinoxalin-2(1*H*)-one (6a)

22.8 mg (65%); eluent (*n*-hexanes/acetone = 10:1 to 2:1); brown oil; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.74 (s, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 6.60 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.47 (d, *J* = 2.4 Hz, 1H), 6.13 (brs, 2H), 3.46 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 155.0, 152.1, 141.3, 135.4, 130.9, 125.2, 111.3, 95.6, 28.2; IR (KBr) ν 3367, 3197, 2924, 2854, 1732, 1604, 1535, 1462, 1379, 1342, 1267 cm<sup>-1</sup>; HRMS (quadrupole, EI) *m/z*: [M]<sup>+</sup> Calcd for C<sub>9</sub>H<sub>9</sub>N<sub>3</sub>O 175.0746; Found 175.0744.

### General procedure and characterization data for the thiocarbonylation of 3a into 6b

To an oven-dried sealed tube charged with 1-methyl-7-nitroquinoxalin-2(1*H*)-one (**3a**) (41.0 mg, 0.2 mmol, 100 mol %) and Lawesson's reagent (242.7 mg, 0.6 mmol, 300 mol %) was added toluene (2 mL) under air at room temperature. The reaction mixture was allowed to stir in an oil bath for 12 h at 120 °C. The reaction mixture was cooled to room temperature, diluted with EtOAc (5 mL) and concentrated in vacuo. The aqueous residue was extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/acetone = 10:1 to 1:2) to afford **6b** (25.8 mg) in 58% yield.

### 1-Methyl-7-nitroquinoxaline-2(1*H*)-thione (6b)

25.8 mg (58%); eluent (*n*-hexanes/acetone = 10:1 to 1:2); orange oil; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>) δ 8.79 (s, 1H), 8.60 (d, *J* = 2.4 Hz, 1H), 8.27 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 4.30 (s, 3H); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>COCD<sub>3</sub>) δ 179.7, 160.1, 140.9, 132.3 (two carbons overlap), 120.5, 112.4 (two carbons overlap), 37.7; IR (KBr) ν 3060, 2924, 2854, 1684, 1550, 1516, 1460, 1350, 1267, 1103 cm<sup>-1</sup>; HRMS (quadrupole, EI) *m/z*: [M]<sup>+</sup> Calcd for C<sub>9</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub>S 221.0259; Found 221.0256.

### General procedures for the control experiment using a radical scavenger TEMPO

To an oven-dried sealed tube charged with 1-methylquinoxalin-2(1*H*)-one (**1a**) (32.0 mg, 0.2 mmol, 100 mol %) and TEMPO (312.5 mg, 2.0 mmol, 10.0 equiv.) were added *t*-butyl nitrite (**2a**) (71.4  $\mu$ L, 0.6 mmol, 300 mol %) and CH<sub>3</sub>CN (2 mL) under O<sub>2</sub> atmosphere at room temperature. After using O<sub>2</sub> balloon, the reaction mixture was allowed to stir in an oil bath for 8 h at 60 °C. The reaction mixture was cooled to room temperature, diluted with EtOAc (4 mL) and concentrated in vacuo. On TLC the desired product **3a** was not detected.

### General procedure and characterization data for the reaction of **1a** and **2a** with radical polymerization mediator 1,1-diphenylethylene (**2b**)

To an oven-dried sealed tube charged with 1-methylquinoxalin-2(1*H*)-one (**1a**) (32.0 mg, 0.2 mmol, 100 mol %) and 1,1-diphenylethylene (**2b**) (72.1 mg, 0.4 mmol, 200 mol %) were added *t*-butyl nitrite (**2a**) (71.4  $\mu$ L, 0.6 mmol, 300 mol %) and CH<sub>3</sub>CN (2 mL) under O<sub>2</sub> atmosphere at room temperature. After using O<sub>2</sub> balloon, the reaction mixture was allowed to stir in an oil bath for 8 h at 60 °C. The reaction mixture was cooled to room temperature, diluted with EtOAc (5 mL) and concentrated in vacuo. The aqueous residue was extracted with EtOAc (3  $\times$  15 mL). The combined organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/acetone = 10:1 to 4:1) to afford **7a** (25.2 mg) in 56% yield.

#### (2-Nitroethene-1,1-diyl)dibenzene (**7a**)

25.2 mg (56%); eluent (*n*-hexanes/acetone = 10:1 to 4:1); yellow oil; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>)  $\delta$  7.72 (s, 1H), 7.51–7.42 (m, 6H), 7.40–7.37 (m, 2H), 7.27–7.24 (m, 2H); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>COCD<sub>3</sub>)  $\delta$  149.9, 137.9, 136.9, 136.0, 131.6, 129.8, 129.7, 129.6, 129.5, 129.3; IR (KBr)  $\nu$  3059, 2925, 2854, 1610, 1574, 1510, 1495, 1444, 1308, 1267 cm<sup>-1</sup>; HRMS (quadrupole, EI) *m/z*: [M]<sup>+</sup> Calcd for C<sub>14</sub>H<sub>11</sub>NO<sub>2</sub> 225.0790; Found 225.0791.

## Results

Our optimization was performed by investigating the coupling reaction of 1-methylquinoxalin-2(1*H*)-one (**1a**) with *tert*-butyl nitrite (**2a**), as shown in Table 1.

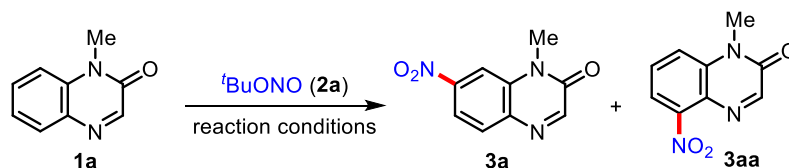
The nitration reaction of **1a** was initiated by using *tert*-butyl nitrite (**2a**) to deliver C7-nitrated quinoxalinone **3a** in 12% yield, and no formation of other regioisomers including

C5-nitrated adduct **3aa** was observed (Table 1, entry 1). The chemical structure of C7-nitrated quinoxalinone **3a** (CCDC 2099185) was elucidated by the X-ray crystallographic analysis (Fig. 3).

Solvent screening revealed that this coupling reaction displayed the increased reactivity in CH<sub>3</sub>CN solvent to give **3a** in 40% yield (Table 1, entries 2–4). Addition of oxidants such as K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, and AgNO<sub>2</sub> were found to be unsatisfactory in this transformation (Table 1, entries 5–7). To our delight, this reaction smoothly proceeded with three equiv. of **2a** to afford the desired product **3a** in 76% yield along with C5-nitrated compound **3aa** in 9% yield (Table 1, entry 8). The reaction temperature is quite pivotal for this transformation, as shown in entries 9 and 10. It should be noted that molecular oxygen was needed for the formation of both **3a** and **3aa** (Table 1, entry 11), revealing that a NO radical, derived from the decomposition of *tert*-butyl nitrite, could be readily oxidized into a reactive NO<sub>2</sub> radical by molecular oxygen (O<sub>2</sub> gas). Finally, when the reaction was performed with increased loading of **2a**, the lower formation of our desired product was observed (Table 1, entries 12 and 13).

With the optimal reaction conditions in hand, the scope of quinoxalinones was examined as shown in Table 2. The linear and branched *N*-alkylated quinoxalinones **1b**–**1e** were found to be suitable substrates for this coupling reaction to afford C7-nitrated quinoxalinones **3b**–**3e** in high yields. It is noteworthy that a linear alkyl halide **1e** was completely compatible under the current reaction conditions, and the tolerance of bromo moiety presents valuable opportunities for further versatile synthetic transformations. In addition, *N*-benzylated quinoxalinones **1f** and **1g** were also coupled with **2a** to provide the corresponding products **3f** (55%) and **3g** (31%). To our pleasure, the current protocol could be applied to *N*-arylated quinoxalinones **1h**–**1k**, producing the desired products **3h**–**3k** without undergoing the C–H nitration on the *N*-aryl ring. It is mentioned that electron-deficient NO<sub>2</sub> (**1i**) and CO<sub>2</sub>Et (**1k**) groups on the *N*-aryl moiety were found to be comparatively less reactive in this transformation, presumably due to the destabilization of radical and carbocation intermediates. To observe the steric and electronic effects on the quinoxalinone framework, the reactions of **1l** with **2a** under the standard and modified reaction conditions were subjected to afford the C7-nitrated adduct **3l** in 20% and 35% yields. It should be mentioned that the nitration reaction of C7-substituted quinoxalinone **1m** preferentially occurred at the C5-position, affording the nitrated product **3m** as a single regioisomer in 45% yield.

With successfully screening results of quinoxalinone substrates, the substrate scope of various 5-aryl pyrazin-2-ones **4a**–**4j** was evaluated, as shown in Table 3. The reaction of 5-phenyl pyrazinone **4a** with **2a** under the modified reaction conditions (5 equiv. of **2a**, 28 h) provided **5a** in 72% yield.

**Table 1** Selected optimization of the reaction conditions

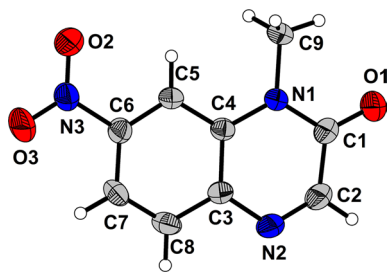
Entry	2a (Equiv.)	Additive (Equiv.)	<i>T</i> °C	Solvent	Yield (%) <sup>a</sup>	
					3a	3aa
1	2a (2)	–	60	PhCl	12	N.R.
2	2a (2)	–	60	ClCH <sub>2</sub> CH <sub>2</sub> Cl	25	5
3	2a (2)	–	60	1,4-Dioxane	Trace	N.R.
4	2a (2)	–	60	CH <sub>3</sub> CN	40	8
5	2a (2)	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (1)	60	CH <sub>3</sub> CN	40	14
6	2a (2)	Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (1)	60	CH <sub>3</sub> CN	Trace	5
7	2a (2)	AgNO <sub>2</sub> (1)	60	CH <sub>3</sub> CN	35	10
<b>8</b>	<b>2a (3)</b>	–	<b>60</b>	<b>CH<sub>3</sub>CN</b>	<b>76</b>	<b>9</b>
9	2a (3)	–	40	CH <sub>3</sub> CN	30	5
10	2a (3)	–	80	CH <sub>3</sub> CN	55	12
11 <sup>b</sup>	2a (3)	–	60	CH <sub>3</sub> CN	22	4
12	2a (4)	–	60	CH <sub>3</sub> CN	68	9
13	2a (5)	–	60	CH <sub>3</sub> CN	65	9

Reaction conditions: **1a** (0.2 mmol), **2a** (quantity noted), additive (quantity noted), solvent (2 mL) under O<sub>2</sub> atmosphere at indicated temperature for 20 h in reaction tubes

<sup>a</sup>Isolated yield by flash column chromatography

<sup>b</sup>The reaction was performed under N<sub>2</sub> atmosphere. N.R. = no reaction

Entry 8 is the final optimized reaction conditions

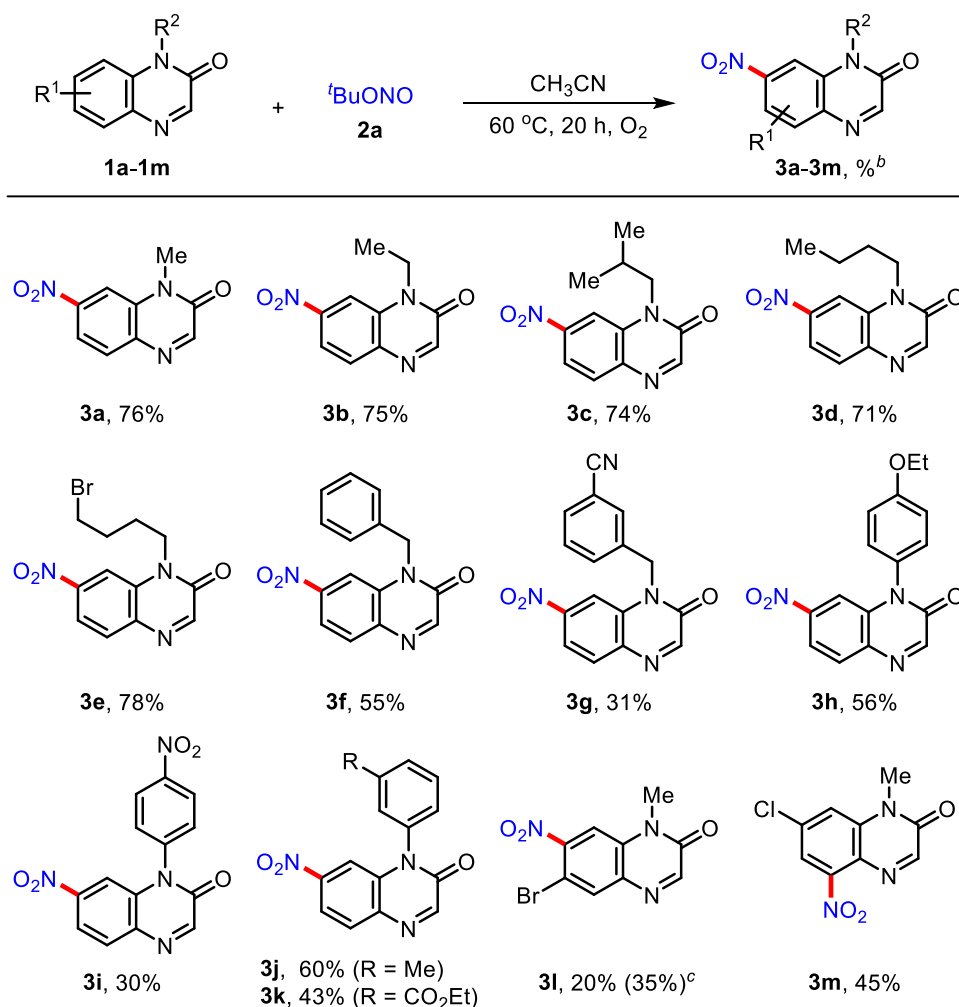
**Fig. 3** X-ray crystallographic data of **3a**

Additionally, *N*-alkyl-5-aryl-substituted pyrazinones **4b–4e** reacted with **2a** to afford C3-nitrated pyrazinone adducts **5b–5e** in moderate to good yields. In addition, *N*-benzyl-substituted pyrazinones **4f** and **4g** were also compatible under the current reaction conditions to give the corresponding products **5f** (45%) and **5g** (61%). The complete regioselectivity was observed in all cases. Finally, the C3-nitration

reaction of *N*-aryl-substituted pyrazinones **4h–4j** smoothly proceeded, resulting in the formation of the desired products **5h–5j**. The functional group compatibility of nitrile and acetyl moieties (**5g** and **5i**) allows further synthetic elaboration of the products.

To demonstrate the robustness and practicality of this process, the scale-up experiments and synthetic transformations were performed (Fig. 4). The nitration reaction of **1a** was readily scaled up to 1 g (6.3 mmol) for the formation of **3a** (0.69 g) in 68% yield. In addition, the gram-scale reaction of **4a** (1 g, 5.4 mmol) with **2a** was successfully achieved to afford 0.81 g of **5a** in 65% yield. Meanwhile, the selective reduction of a nitro moiety of the product **3a** was performed by the single electron reduction protocol using by Fe/NH<sub>4</sub>Cl to furnish the desired aniline adduct **6a** in 65% yield. Moreover, treatment of **3a** with Lawesson's reagent resulted in the formation of 7-nitroquinoxaline-2(1*H*)-thione **6b** in 58% yield.



**Table 2** Scope of quinoxalinones<sup>a</sup>

<sup>a</sup>Reaction conditions: **1a–1m** (0.2 mmol), **2a** (0.6 mmol, 3 equiv.), CH<sub>3</sub>CN (2 mL) under O<sub>2</sub> atmosphere at 60 °C for 20 h in reaction tubes

<sup>b</sup>Isolated yield by flash column chromatography

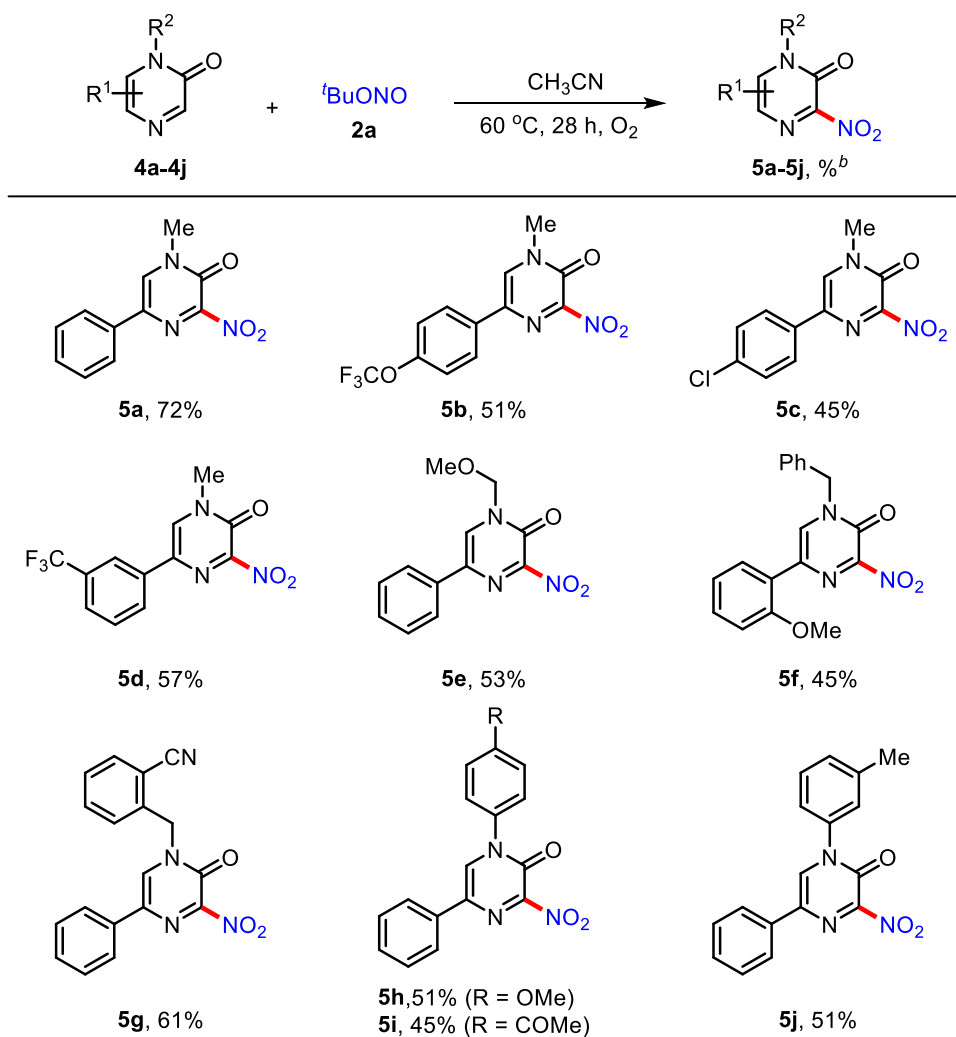
<sup>c</sup>**2a** (1.0 mmol, 5 equiv.) was used

## Discussion

To support the mechanistic pathway for this reaction, the nitration reaction of **1a** and **2a** was performed in the presence of a radical scavenger TEMPO (Fig. 5). No formation of C7-nitrated quinoxalinone **3a** was observed. The nitration reaction was completely inhibited by 1,1-diphenylethylene (**2b**) as a radical polymerization mediator, and 1,1-diphenyl-2-nitroethylene (**7a**) was obtained in 56% yield. These results support that a radical pathway is involved in this process.

Based on preliminary mechanistic investigation and reported literatures (Liang et al. 2015; Chun et al. 2018), a proposed reaction mechanism is outlined in Fig. 6. In the

presence of molecular oxygen, a reactive NO<sub>2</sub> radical can be derived from the thermal decomposition of tBuONO, followed by subsequent aerobic oxidation of a NO radical. A NO<sub>2</sub> radical can undergo the radical addition into the C7-position on quinoxalinone **1a**, affording intermediate **A**. The single-electron transfer (SET) process by the assistance of NO<sub>2</sub> or tBuO radical followed by aromatization provides the C7-nitrated product **3a**. In case of the nitration of pyrazinone **4a**, the radical addition can occur at the C3-position, delivering a nitrogen radical species **C**, which further undergoes the SET reaction and elimination reaction to produce **6a**. The site-selectivity between the C7- and C3-positions of quinoxalinone **1a** can be rationalized by the electronic density between the electron-rich aromatic ring

**Table 3** Scope of 5-aryl pyrazin-2-ones<sup>a</sup>

<sup>a</sup>Reaction conditions: **4a–4j** (0.2 mmol), **2a** (1.0 mmol, 5 equiv.),  $\text{CH}_3\text{CN}$  (2.5 mL) under  $\text{O}_2$  atmosphere at  $60\text{ }^\circ\text{C}$  for 28 h in reaction tubes

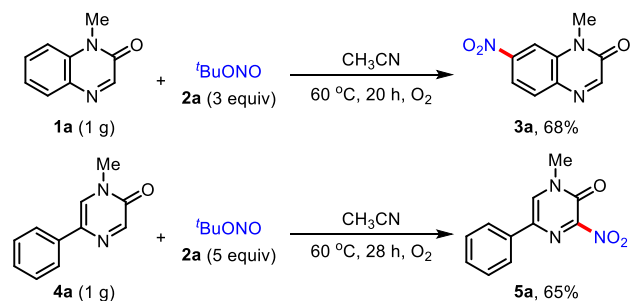
<sup>b</sup>Isolated yield by flash column chromatography

and electron-deficient *N*-heterocycle ring in the electrophilic radical addition step. Moreover, the C7-selectivity over C6,C8-positions on aromatic ring of **1a** can be explained by the relative stability of a radical intermediate **A**. However, the site-selectivity between C7- and C5-position still remains unclear, and the detailed mechanistic investigations on the site-selectivity of this process are underway.

In summary, we described the synthesis of biologically relevant C7-nitrated quinoxalinones and C3-nitrated pyrazinones through metal-free C–H nitration with *t*-butyl nitrite. From the mechanistic point of view, the radical

addition to quinoxalinones with *t*-butyl nitrite exclusively occurred at the electron-rich aromatic region beyond electron-deficient *N*-heterocycle ring. In contrast, the nitration reaction of pyrazinones readily takes place at the C3-position via the single electron transfer process of a nitrogen radical intermediate followed by elimination reaction. This protocol is characterized by the scale-up compatibility, mild reaction conditions, and excellent functional group tolerance. The selective reduction of a  $\text{NO}_2$  group and thiocarbonylation on the synthesized products highlight the importance of the developed methodology.

## A. scale-up experiments



## B. synthetic transformations

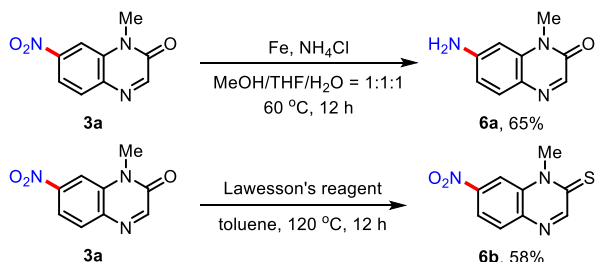


Fig. 4 Scale-up experiments and synthetic transformations

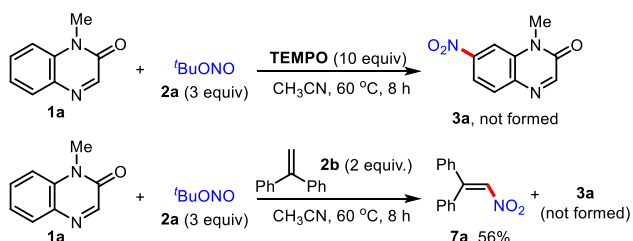


Fig. 5 Mechanistic investigations

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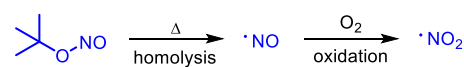
**Funding** This study was funded by National Research Foundation of Korea (Nos. 2019R1A4A2001451 and 2020R1A2C3005357).

## Declarations

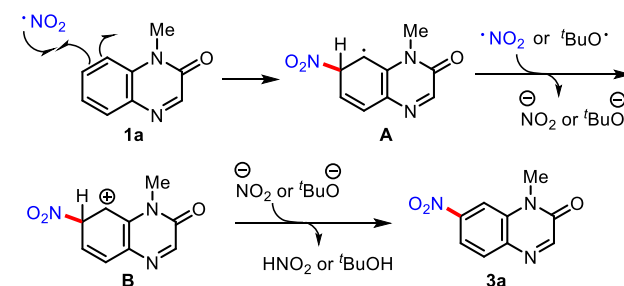
**Conflict of interest** There are no conflicts to declare relevant to this work.

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## a. generation of nitrite radical



## b. addition of nitrite radical into quinoxalines



## c. addition of nitrite radical into pyrazinones

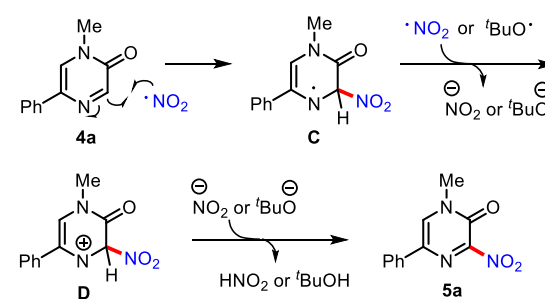


Fig. 6 Proposed reaction mechanism for the site-selective C–H nitration

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