Chemistry of Halonitroethenes, 1: First Synthesis of Functionalized 3-Chloroquinoxalin-2(1*H*)-one 4-Oxides

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Abstract: A one-pot annulation reaction of aniline and its ring-substituted derivatives with 1,1,2-trichloro-2-nitroethene (TCNiE) was developed delivering 3-chloroquinoxalin-2(1*H*)-one 4-oxides, exclusively, in good yields. The structure was proved by X-ray analysis. The C–N cyclization, a competing reaction to the double S_NVin reaction of 1,1,2-trichloro-2-nitroethene with amines, can be controlled by the mode of addition. Some of the resulting quinoxalinones are promising candidates with respect to their prospective biological, especially pharmacological, activity.

Key words: annulation, C–N coupling, amines, halides, nitro compounds, nitrones, quinoxalinones

Halonitroalkenes are valuable building blocks for the directed synthesis of four-, five-, and six-membered heterocycles with a unique substitution pattern.[1] In particular, to date an impressive number of different reactions of pentachloro-2-nitrobuta-1,3-diene have been documented;[2] further efforts are underway to explore the whole synthetic potential of this class of compounds. The group of known halonitroethenes is still rather small, consisting of 14 members, which have been prepared by four different synthetic routes.[3,4] Synthetic applications of halonitroethenes are rare in the literature.[5] In this context we became interested in the availability and chemistry of 1,1,2-trichloro-2-nitroethene (TCNiE, **2**), a perchlorovinyl analogue of nitryl chloride, representing the reactive key unit of many polychloroalkenes. 1,1,2-Trichloro-2-nitroethene (**2**) is now easily accessible by electrophilic nitration of the inexpensive industrial solvent trichloroethene with nitric acid.[3k,4] Nitration of a solution of trichloroethene in cyclohexane in a liquid–liquid extractor with nitric acid at comparatively low temperatures leads to lower amounts of oxidative destruction and, thus, to a higher yield of **2**. Careful control of the reaction and distillation conditions allows the synthesis of **2** on a 100 g scale and with high purity.

Most reactions of **2** known in the literature start with primary Michael addition, then lead to the product of a S_NVin reaction of **3**;[6] only one synthetic example has been reported of subsequent cyclization with C–C coupling.[7] Therefore, we started with a detailed investigation of the reaction of 1,1,2-trichloro-2-nitroethene (**2**) with anilines.

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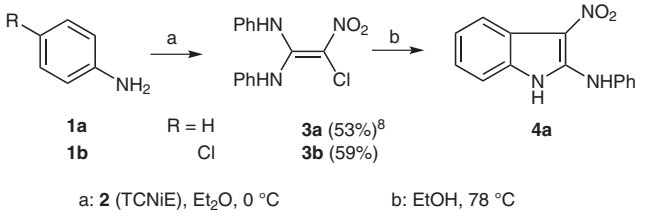
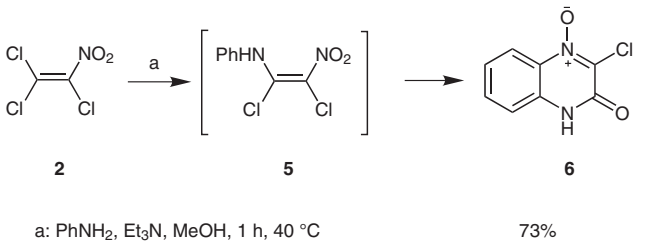
Exclusive formation of 1-chloro-1-nitro-2,2-bis(phenylamino)ethene (**3a**) as a product of a twofold S_NVin reaction has already been reported by Declerqc et al.[8] when a solution of **2** was added to excess aniline (**1a**) in a solvent such as diethyl ether at room temperature or below. This twofold substitution reaction is not restricted to the parent compound aniline itself, but also takes place with ring-substituted anilines such as 4-chloroaniline (**1b**). The mode of addition is crucial in determining the reaction product that will be formed. Successive heating of **3a** in a polar solvent such as ethanol to at least 50 °C resulted in isomerization to an amidine, generating a $CH(Cl)NO_2$ group simultaneously, which then leads to a Friedel–Crafts-type cyclization reaction forming 3-nitro-2-(phenylamino)-1*H*-indole (**4a**), as mentioned by Perekalin et al.[7a] (Scheme 1).

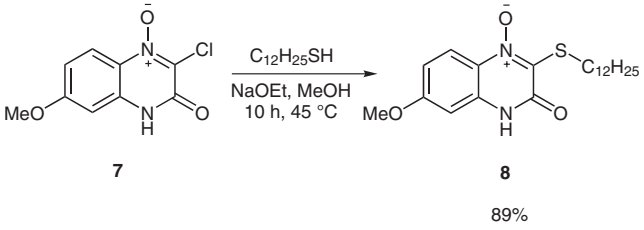
When the mode of addition is reversed, thus the aniline solution (1 equiv) is slowly added by a syringe pump to a solution of **2** (1 equiv) at temperatures between –10 and 50 °C under isothermal conditions, to our surprise a new product precipitated, independent of the solvent used (Scheme 2). Due to the 1:1 ratio of the starting materials **2** and **1a**, an intermediate such as **5** or an equivalent is formed. The low solubility of the product in combination with its high melting point and the NMR, IR, and MS spectra made formation of the 3-chloroquinoxalin-2(1*H*)-



Scheme 1 Formation of 3-nitroindole **4a** starting from **1a** and **2** (4:1)



Scheme 2 Formation of quinoxalinone 4-oxide **6** starting from **2** and **1a** (1:1)



Scheme 3 Transformation of **7** to a soluble derivative **8**

one 4-oxide (**6**) appear likely. An unambiguous spectroscopic analysis of the product proved difficult.

Additionally, single crystals could not be obtained by recrystallization. Fortunately, the C–Cl group of the *C*-chloronitrone unit of **7** allowed S_N reactions. By transformation of the 7-methoxy derivative **7** into **8** using the strong nucleophile dodecane-1-thiol, the long alkyl chain improved the solubility and we were able to isolate single crystals of 3-(dodecylsulfanyl)-7-methoxyquinoxalin-2(1*H*)-one 4-oxide (**8**) (Scheme 3). X-ray analysis confirmed the structure (Figure 1).[9]

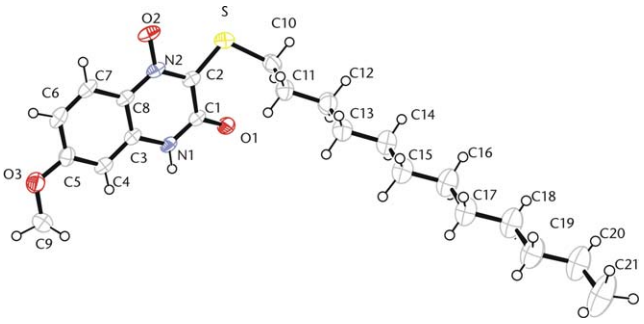
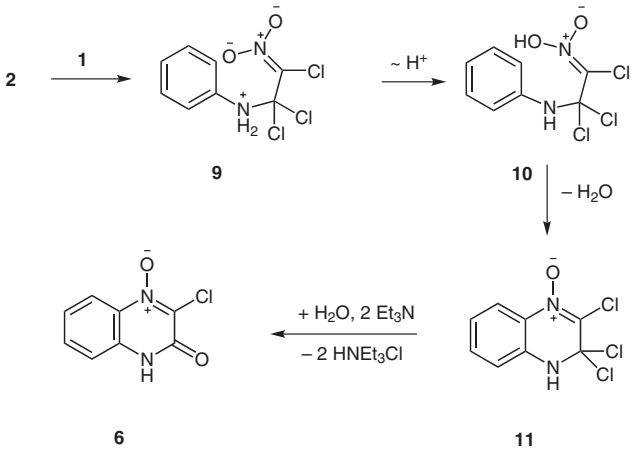


Figure 1 X-ray crystal structure of the quinoxalin-2-one derivative **8**[9]

The detailed mechanism of formation of the parent heterocycle **6** remains unclear. Apparently, the reaction starts with Michael addition of the aromatic amine at the C2 position of 1,1,2-trichloro-2-nitroethene (**2**) forming an intermediate such as **9**. *N*-Alkylanilines do not form quinoxalinones. Then a proton shift occurs: the ammonium proton migrates to the nitro group thus forming a nitronic acid **10**. In the following steps an intramolecular S_E process appears feasible under C–N cyclization and elimination of water generating 2,2,3-trichloro-1,2-dihydroquinoxaline 4-oxide (**11**). Hydrolysis of the *gem*-C2 dichloride unit in **11** by water in the reaction leads to formation of the final product **6**, even in dry solvents (Scheme 4).

Syntheses of such 3-haloquinoxalin-2(1*H*)-ones 4-oxides are completely unknown. Additionally, this type of ring-closure reaction has not previously been reported under comparable conditions. Only the cyclization of nitroenamines containing a heteroaromatic or oxido-substituted aromatic base is known, but the reaction proceeds under strong acidic conditions and in low yields.[11] Additionally, **6** represents a key compound for the synthesis of 3-substi-



Scheme 4 Postulated mechanism for the formation of **6**

tuted derivatives by means of S_N reactions. A small number of syntheses for 3-alkyl- and 3-arylquinoxalin-2(1*H*)-ones 4-oxides are known.[12]

Various bioactivities of quinoxalinones and their corresponding *N*-oxides have been reported, some examples are noteworthy: antibacterial, antiviral, anticancer, antifungal, antihelmintic, and insecticidal activities are documented[13a–13e] as well as their potential as antiallergic agents.[13f] Additionally, the variety of pharmacological agents can be illustrated by antimalarial activity.[13g] Therefore, the new heterocyclic compounds present interesting entities for biological screening.

To evaluate the synthetic scope and limitation of this annulation reaction, all reaction conditions were modified in a stepwise process. If one equivalent of aniline or a derivative and two equivalents of a tertiary amine such as triethylamine or 1,4-diazabicyclo[2.2.2]octane were added to a solution of **2** in a solvent such as methanol, tetrahydrofuran, or toluene, the new quinoxalin-2(1*H*)one 4-oxide **6** precipitated completely (Scheme 2). The product yield always depended on the reaction temperature, the addition rate of the aniline to the reaction mixture, the solvent, and the substitution pattern of the aniline.

The annulation reaction was exothermic. Under isothermal conditions the product yield increased with higher reaction temperatures. Reaction rate and yield were also dependent on the ring substituents of the aniline derivatives (Figure 2). In a number of cases the reaction was almost complete within 1–3 hours. Not all reactions were optimized with respect to time.

The product yield of **7** was not strongly dependent on the nature of the reaction solvent (Table 1); methanol and tetrahydrofuran were especially well suited. Only in the case of acetonitrile did the yield decreased.

The broad range of applicability of this annulation reaction is documented in Table 2, many different substituents are tolerated.

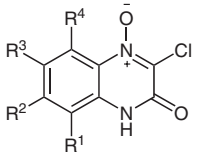
In the case of *m*-anisidine the reaction was highly regioselective. Only the 3-chloro-7-methoxyquinoxalin-2(1*H*)-

Table 1 Yields of Quinoxalinone **7** in Various Solvents[a]

Solvent	Yield (%)
MeOH	66
THF	74
toluene	62
MeCN	39

[a] Reaction conditions: Et_3N (2 equiv), r.t., 12 h.

Table 2 Range of Newly Synthesized 3-Chloroquinoxalin-2(1*H*)-one 4-Oxides[a]



R^1	R^2	R^3	R^4	Product	Yield (%)
H	H	H	H	**6**	73
H	OMe	H	H	**7**	73
H	H	OMe	H	**12**	54
H	OMe	OMe	H	**13**	40
H	OH	H	H	**14**	59[b]
H	H	H	OH	**15**	6[b]
H	F	H	H	**16**	30
H	H	F	H	**17**	48
H	H	Cl	H	**18**	66
H	Cl	H	H	**19**	59
H	H	Br	H	**20**	74
H	H	I	H	**21**	79
H	H	CO_2H	H	**22**	77
H	H	CN	H	**23**	65
Cl	H	Cl	H	**24**	43
Cl	Cl	H	H	**25**	35
H	H	Me	H	**26**	16

[a] Reaction conditions: Et_3N (2 equiv), MeOH, r.t. to 30 °C, 1–62 h.
[b] Parallel formation of **14/15** from **2** and 3-aminophenol.

one 4-oxide (**7**) could be isolated from the reaction mixture. For 3-aminophenol, we obtained 3-chloro-5-hydroxyquinoxalin-2(1*H*)-one 4-oxide (**15**) in only 6% yield and the 7-hydroxy derivative **14** in 59% yield.

Under identical reaction conditions the yields of the 3-chloroquinoxalin-2(1*H*)-ones 4-oxides depend strongly on the substituents of the introduced anilines, ranging from 9 to 65%. Electron-withdrawing substituents at C6, such as the halogens F and Cl, had a negative effect on the reaction rate (Table 3) as did electron-donating methoxy groups at C6 or C7 (Figure 2).

Table 3 Yields of Various Quinoxalinones under Identical Reaction Conditions[a]

Product	Yield (%)
6	63
7	65
12	51
17	16
18	42
19	9

[a] Reaction conditions: Et_3N (2 equiv), MeOH, 30 °C, 1 h.

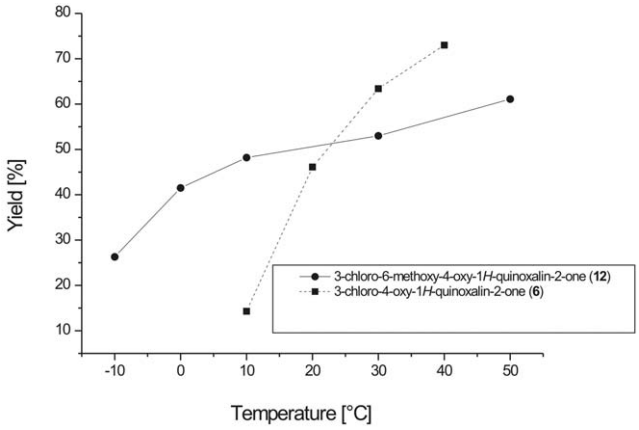


Figure 2 Correlation between yield of **6** and **12** and the reaction temperature [Et_3N (2 equiv), MeOH, 1 h]

In conclusion, we have found a novel one-pot synthesis of a broad range of substituted 3-chloroquinoxalin-2(1*H*)-ones starting from easily accessible 1,1,2-trichloro-2-nitroethene (**2**) and subsequent addition of substituted anilines. This addition mode is crucial. The structure of a long-chain derivative was proven by X-ray. The products should offer interesting biological, in particular pharmacological, properties. Therefore, corresponding tests of these promising compounds are presently underway.

All chemicals were obtained from commercial suppliers and used without further purification. MeOH was purchased as reagent grade. Melting points were determined with a Büchi apparatus 520 and are uncorrected. ^1H and ^1H-decoupled ^{13}C NMR spectra were measured on a Bruker Avance 400 (400 MHz) or Bruker DPX 200 (200 MHz) in $CDCl_3$ or DMSO-d_6. All NMR data are reported downfield from TMS as the internal standard. The ^{14}N NMR spectrum was externally referenced: $MeNO_2$, $\delta = 0.0$. IR spectral data were obtained for liquids as film and for solids as KBr discs on a Bruker Vector 22 FT-IR. Mass spectra were recorded on a Hewlett Packard MS 5989B (EI, 70 eV). In the case of chlorinated compounds, all peak values of molecular ions as well as fragments *m/z* refer to the isotope ^{35}Cl. HRMS were measured with a Finnigan MAT 95 sector field instrument (EI) or with a Bruker APEX IV 7

Tesla FT ion cyclotron resonance mass spectrometer (ESI). TLC was performed on Merck TLC plates (aluminum-backed) silica gel 60 F 254. Flash chromatography was carried out on silica gel 60 (Merck).

1,1,2-Trichloro-2-nitroethene (2)

A mixture of concd HNO_3 (900 mL, 65%) and cyclohexane (200 mL) in the extractor vessel of a rotating Normag liquid–liquid extractor for solvents lighter than H_2O was heated in an oil bath to 55 °C. Trichloroethene (250 mL, 2.81 mol) and cyclohexane (100 mL) was added to the evaporator vessel. After continuous reaction and extraction for 9 h the organic layers were separated and washed with H_2O and brine. Redistillation on a Fischer Spaltrohr column HMC 500 C gave pure **2**; yield: 96.9 g (32%) related to reisolated trichloroethene (139 g, 1.06 mol); bp 56–57 °C/25 mbar.

IR (NaCl): 2868, 2623, 2361, 2342, 1548, 1324, 1052, 933, 871, 777, 750, 707 cm^{-1}.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.5 (*C*$ClNO_2$); 128.1 (*C*Cl_2).

^{14}N NMR (28.9 MHz, $CDCl_3$): δ = –18.6.

MS (EI): *m*/*z* (%) = 177 (M^+) (44), 129 (M^+ – O) (100), 94 (M^+ – $ClNO_2$) (44).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_2Cl_3NO_2$: 174.8995; found: 174.8996.

1-Chloro-2,2-bis(4-chlorophenylamino)-1-nitroethene (3b)

To a mixture of 4-chloroaniline (**1b**, 5.19 g, 41.9 mmol) in anhyd MeOH (10 mL) at 10 °C was added dropwise over 1 h a soln of **2** (1.76 g, 10 mmol) in anhyd MeOH (10 mL). The resulting brown soln was stirred for an additional 2 h. Subsequently, an N_2 stream was passed through the mixture to remove the solvent. The precipitate was isolated and washed with H_2O (50 mL), aq 4 M HCl (20 mL), and H_2O (30 mL), and finally dried in vacuo to give a green solid; yield: 2.13 g (59%); mp 129–130 °C (dec).

IR (KBr): 3060, 3014, 2878, 1679, 1590, 1571, 1471, 1442, 1415, 1319, 1271, 1203, 1130, 1071, 1035, 1004, 941, 867, 819, 798, 749 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 10.43 (br s, 2 H, NH), 7.29 (d, *J* = 8.8 Hz, 4 H, $H3_{Ph}$, $H3'_{Ph}$, $H5_{Ph}$, $H5'_{Ph}$), 7.11 (d, *J* = 8.8 Hz, 4 H, $H2_{Ph}$, $H2'_{Ph}$, $H6_{Ph}$, $H6'_{Ph}$).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 149.3 (1 C, NCN), 137.4 (2 C, $C1_{Ph}$, $C1'_{Ph}$), 129.0 [4 C, $C3_{Ph}$, $C3'_{Ph}$, $C5_{Ph}$, $C5'_{Ph}$), 128.7 (2 C, $C4_{Ph}$, $C4'_{Ph}$), 123.0 (4 C, $C2_{Ph}$, $C2'_{Ph}$, $C6_{Ph}$, $C6'_{Ph}$), 106.4 (1 C, $ClCNO_2$).

MS (EI): *m*/*z* (%) = 356 (M^+) (13), 312 (M^+ – NO_2) (22), 127 ($C_6H_6NCl^+$) (100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{10}Cl_3N_3O_2$: 356.9839; found: 356.9839.

3-Chloroquinoxalin-2(1*H*)-one 4-Oxide (6); Typical Procedure I

Under N_2 at 40 °C a soln of aniline (**1a**, 0.46 mL, 5 mmol) and Et_3N (1.44 mL, 10 mmol) in anhyd MeOH (15 mL) was added via syringe pump over 1 h with stirring to a soln of **2** (0.88 g, 5 mmol) in anhyd MeOH (5 mL). The product precipitated from the mixture and was isolated by filtration with suction. The solid was washed with MeOH, diluted aq HCl, H_2O, and MeOH and subsequently dried in vacuo to give **6** as a pale beige solid; yield: 0.72 g (73%); mp 225–226 °C (dec).

IR (KBr): 2979, 2943, 2902, 2824, 1665 (C=O), 1603, 1530, 1489, 1440, 1407, 1373, 1353, 1273, 1222, 1132, 1026, 847, 772, 677, 549 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.77 (br s, 1 H, NH), 8.12 (dd, *J* = 8.5,1.3 Hz, 1 H, H5), 7.88 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1 H, H6), 7.40 (dd, *J* = 8.3, 0.5 Hz, 1 H, H7), 7.36 (ddd, *J* = 8.6, 7.4, 1.0 Hz, 1 H, H8).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.4 (C2), 133.9, 132.5, 131.0 (C3), 130.4, 123.9, 119.4, 116.6.

MS (EI): *m*/*z* (%) = 196 (M^+) (100), 180 (M^+ – O) (5), 166 (M^+ – NO) (58).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_6ClN_2O_2$: 197.01122; found: 197.01123.

3-Chloro-7-methoxyquinoxalin-2(1*H*)-one 4-Oxide (7); Typical Procedure II

Under N_2 at r.t. a soln of *m*-anisidine (1.11 mL, 10 mmol) and Et_3N (2.88 mL, 20 mmol) in anhyd MeOH (20 mL) was added via syringe pump over 12 h with stirring to a soln of **2** (1.76 g, 10 mmol) in anhyd MeOH (10 mL). The product precipitated from the mixture and was isolated by filtration with suction. The solid was washed with MeOH, dil aq HCl, H_2O, and Et_2O and subsequently dried in vacuo to give **7** as a pale green solid; yield: 1.67 g (73%); mp 246–247 °C (dec).

IR (KBr): 3122, 3085, 3029, 2948, 2914, 1679 (C=O), 1613, 1534, 1494, 1439, 1385, 1341, 1307, 1233, 1217, 1171, 1110, 1024, 838, 587 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 12.65 (br s, 1 H, NH), 8.05 (d, *J* = 9.3 Hz, 1 H, H5), 6.98 (dd, *J* = 9.3, 2.5 Hz, 1 H, H6), 6.82 (d, *J* = 2.5 Hz, 1 H, H8), 3.85 (s, 3 H, OCH_3).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 162.1 (C2), 153.7 (C7), 132.9 (C9), 131.4 (C3), 125.0 (C10), 121.1(C5), 112.3 (C6), 98.8 (C8), 56.1 (OCH_3).

MS (EI): *m*/*z* (%) = 226 (M^+) (95), 210 (M^+ – O) (7), 196 (M^+ – NO) (100).

Anal. Calcd for $C_9H_7ClN_2O_3$ (226.62): C, 47.70; H, 3.11; Cl, 15.64; N, 12.36. Found: C, 47.71; H, 3.12; Cl, 15.78; N, 12.33.

3-Chloro-6-methoxyquinoxalin-2(1*H*)-one 4-Oxide (12); Typical Procedure III

Under N_2 at r.t. a soln of *p*-anisidine (1.23 g, 10 mmol) and DABCO (1.12 g, 10 mmol) in anhyd MeOH (20 mL) was added via syringe pump over 12 h with stirring to a soln of **2** (1.76 g, 10 mmol) in anhyd MeOH (10 mL). The product precipitated from the mixture and was isolated by filtration with suction. The solid was washed with MeOH, dil aq HCl, H_2O, and Et_2O and subsequently dried in vacuo to give **12** as a green solid; yield: 1.23 g (54%); mp 234–235 °C (dec).

IR (KBr): 2979, 2943, 2902, 2824, 1665 (C=O), 1603, 1530, 1489, 1440, 1407, 1373, 1353, 1273, 1222, 1132, 1026, 847, 772, 677, 549 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 12.70 (br s, 1 H, NH), 7.49 (d, *J* = 1.4 Hz, 1 H, H5), 7.28–7.38 (m, 2 H, H7, H8), 3.83 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.9 (C2), 152.8 (C6), 134.2 (C3), 130.9 (C9 or C10), 125.1 (C9 or C10), 121.7, 118.0, 101.0, 56.0 (OCH_3).

MS (EI): *m*/*z* (%) = 226 (M^+) (100), 210 (M^+ – O) (7), 196 (M^+ – NO) (18).

Anal. Calcd for $C_9H_7ClN_2O_3$ (226.62): C, 47.70; H, 3.11; Cl, 15.64; N, 12.36. Found: C, 47.60; H, 3.10; Cl, 15.36; N, 12.26.

3-Chloro-6,7-dimethoxyquinoxalin-2(1*H*)-one 4-Oxide (13)

Following typical procedure I gave **13** as a pale green solid; yield: 40%; mp 268–269 °C (dec).

IR (KBr): 3138, 3083, 3038, 2942, 1672 (C=O), 1630, 1604, 1527, 1511, 1460, 1442, 1426, 1411, 1379, 1333, 1307, 1256, 1213, 1187,

1119, 1030, 1003, 927, 855, 830, 792, 769, 723, 688, 664, 624, 575, 541, 527 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.64 (br s, 1 H, NH), 7.52 (s, 1 H, H5), 6.82 (s, 1 H, H8), 3.84 (s, 3 H, OCH_3). 3.83 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.2 (C6), 153.0 (C7) 146.5 (C2), 131.6 (C3), 126.1, 124.2, 100.3, 98.0, 56.3 (OCH_3), 56.2 (OCH_3).

MS (EI): *m*/*z* (%) = 256 (M^+) (100), 24 (M^+ – O) (10), 226 (M^+ – NO) (60), 150 (30).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{10}ClN_2O_4$: 257.03236; found: 257.03236.

3-(Dodecylsulfanyl)-7-methoxyquinoxalin-2(1*H*)-one 4-Oxide (8)

Under N_2 at r.t. a suspension of 3-chloro-7-methoxyquinoxalin-2(1*H*)-one 4-oxide (**7**, 1.00 g, 4.41 mmol), NaOEt (0.721 g, 10.59 mmol), and dodecane-1-thiol (1.95 g, 9.71 mmol) in anhyd MeOH (10 mL) was stirred for 1 h. Subsequently, the mixture was heated to 50 °C for 10 h. After cooling to r.t., dil aq HCl was added. The product precipitated from the mixture and was isolated by filtration with suction. The solid was washed with dil aq HCl, H_2O, and MeOH and then dried in vacuo to obtain **8** as a yellow solid; yield: 1.56 g (89%); mp 138–140 °C.

IR (KBr): 3129, 3078, 3038, 2954, 2920, 2851, 1666 (C=O), 1657, 1616, 1530, 1467, 1378, 1333, 1308, 1264, 1251, 1220, 1182, 1158, 1033, 961, 868, 843, 816, 768, 735, 721, 694, 647, 530 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 12.38 (br s, 1 H, NH), 8.20 (d, *J* = 9.3 Hz, 1 H, H5), 6.92 (dd, *J* = 9.3, 2.5 Hz, 1 H, H6), 6.83 (d, *J* = 2.5 Hz, 1 H, H8), 3.92 (s, 3 H, OCH_3), 3.48 (t, *J* = 7.4 Hz, 2 H, SCH_2), 1.60–1.74 (m, 2 H, SCH_2CH_2), 1.36–1.50 (m, 2 H, $SCH_2CH_2CH_2$), 1.16–1.28 (m, 16 H, H_{Alkyl}), 0.87 (t, *J* = 6.8 Hz, 3 H, CH_2CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 162.0, 158.4, 138.0, 131.5, 125.9, 121.0, 113.2, 98.6, 55.9 (OCH_3), 31.9, 31.8, 30.5, 29.6, 29.6, 29.5, 29.4, 29.3, 29.1, 28.8, 22.6, 14.1.

Anal. Calcd for $C_{21}H_{32}N_2O_3S$ (392.56): C, 64.25; H, 8.22; N, 7.14; S, 8.17. Found: C, 64.37; H, 8.17; N, 7.04; S 8.44.

3-Chloro-7-hydroxyquinoxalin-2(1*H*)-one 4-Oxide (14) and 3-Chloro-5-hydroxyquinoxalin-2(1*H*)-one 4-Oxide (15)

Following typical procedure II, addition time 62 h. The precipitated solid was a mixture of 2 regioisomers. The 7-hydroxyquinoxalinone **14** was separated by washing the solid with $CHCl_3$ (50 mL) and acetone (50 mL). Subsequently, the second isomer **15** was isolated by evaporating the solvents.

3-Chloro-7-hydroxyquinoxalin-2(1*H*)-one 4-Oxide (14)

Red-brown solid; yield: 59%; mp 276–277 °C.

IR (KBr): 3343, 3094, 3010, 2941, 2843, 1661 (C=O), 1630, 1608, 1543, 1489, 1432, 1347, 1324, 1291, 1239, 1182, 1107, 850, 602, 498 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 12.56 (br s, 1 H, NH), 10.66 (s, 1 H, OH), 7.97 (d, *J* = 9.1 Hz, 1 H, H5), 6.73–6.82 (m, 2 H, H6, H8).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.1 (C2), 153.7 (C7), 132.7 (C10), 130.7 (C3), 124.2 (C9), 121.2 (C5), 113.3 (C6), 100.5 (C8).

MS (EI): *m*/*z* (%) = 212 (M^+) (100), 196 (M^+ – O) (5), 182 (M^+ – NO) (100).

Anal. Calcd for $C_8H_5ClN_2O_3$ (212.59): C, 45.20; H, 2.37; Cl, 16.68; N, 13.18. Found: C, 44.92; H, 2.41; Cl, 16.66; N, 12.81.

3-Chloro-5-hydroxyquinoxalin-2(1*H*)-one 4-Oxide (15)

Orange solid; yield: 6%; mp 274–275 °C (dec).

IR (KBr): 3423, 3121, 3019, 2929, 2862, 1665 (C=O), 1625, 1608, 1513, 1450, 1374, 1338, 1306, 1238, 1174, 1144, 1130, 1088, 866, 810, 758, 596 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 13.02 (s, 1 H, OH), 12.82 (br s, 1 H, NH), 7.47 (dd, *J* = 8.3, 8.3 Hz, 1 H, H7), 6.79 (dd, *J* = 8.3, 1.2 Hz, 1 H, H6 or H8) 6.72 (dd, *J* = 8.3, 1.2 Hz, 1 H, H6 or H8).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.8 (C2), 152.4 (C5), 133.7 (C3), 133.4 (C7), 132.4 (C10), 117.6 (C9), 110.6 (C8), 106.2 (C6).

MS (EI): *m*/*z* (%) = 212 (M^+) (72), 196 (M^+ – O) (22), 182 (M^+ – NO) (100).

Anal. Calcd for $C_8H_5ClN_2O_3$ (212.59): C, 45.20; H, 2.37; Cl, 16.68; N, 13.18. Found: C, 45.15; H, 2.37; Cl, 16.52; N, 12.78.

3-Chloro-7-fluoroquinoxalin-2(1*H*)-one 4-Oxide (16)

Following typical procedure I gave **16** as a white solid; yield: 30%; mp 218–219 °C (dec).

IR (KBr): 3072, 2987, 2908, 2863, 2819, 2706, 1667 (C=O), 1627, 1611, 1535, 1492, 1439, 1367, 1317, 1267, 1128, 1103, 1090, 974, 876, 861, 823, 798, 733, 656, 592, 483 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.83 (br s, 1 H, NH), 8.16 (dd, *J* = 9.4 Hz, J_{HF} = 5.5 Hz, 1 H, H5), 7.19–7.25 (m, 1 H, H6), 7.11 (dd, *J* = 2.7 Hz, J_{HF} = 9.2 Hz, 1 H, C8).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.5 (d, *J* = 249.4 Hz, C7), 153.6 (C2), 133.4 (C3), 132.7 (d, *J* = 13.2 Hz, C9), 127.5 (d, *J* = 1.5 Hz, C10), 122.4 (d, *J* = 11.0 Hz, C5), 111.8 (d, *J* = 24.2 Hz, C6), 102.6 (d, *J* = 27.1 Hz, C8).

MS (EI): *m*/*z* (%) = 214 (M^+) (100), 198 (M^+ – O) (45), 184 (M^+ – NO) (70), 108 (M^+ – C_2NO_2Cl) (48).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_8H_4ClFN_2O_2$: 213.9945; found: 213.9945.

3-Chloro-6-fluoroquinoxalin-2(1*H*)-one 4-Oxide (17)

Following typical procedure I gave **17** as a green solid; yield: 48%; mp 214–215 °C (dec).

IR (KBr): 2990, 2947, 2902, 1653 (C=O), 1524, 1483, 1441, 1404, 1349, 1295, 1256, 1203, 1124, 1075, 880, 830, 781, 672, 640, 535 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.83 (br s, 1 H, NH), 7.89 (dd, J_{HF} = 9.2 Hz, *J* = 2.9 Hz, 1 H, H5), 7.63–7.57 (m, 1 H, H7), 7.43 (dd, *J* = 9.1 Hz, J_{HF} = 4.8 Hz, 1 H, H8).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.1 (d, *J* = 242.1 Hz, C6), 153.2 (C2), 135.0 (C3), 130.8 (d, *J* = 10.2 Hz, C10), 128.0 (d, *J* = 1.5 Hz, C9), 120.7 (d, *J* = 24.2 Hz, C7), 118.7 (d, *J* = 8.8 Hz, C8), 105.7 (d, *J* = 28.6 Hz, C5).

MS (EI): *m*/*z* (%) = 214 (M^+) (100), 198 (M^+ – O) (45), 184 (M^+ – NO) (70), 108 (M^+ – C_2NO_2Cl) (48).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_8H_4ClFN_2O_2$: 213.9945; found: 213.9945.

3,6-Dichloroquinoxalin-2(1*H*)-one 4-Oxide (18)

Following typical procedure I gave **18** as a green solid; yield: 66%; mp 242–243 °C (dec).

IR (KBr): 2995, 2926, 2892, 2854, 2697, 1651 (C=O), 1620, 1517, 1473, 1441, 1395, 1351, 1299, 1261, 1135, 1113, 885, 820, 670, 518 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.86 (br s, 1 H, NH), 8.06 (s, 1 H, H5), 7.71 (dd, *J* = 8.8, 2.1 Hz, 1 H, H7), 7.38 (d, *J* = 8.8 Hz, 1 H, H8).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.2 (C2), 134.9 (C3), 132.5 (C5), 130.9, 130.1, 127.7, 118.7 (C7 or C8), 118.6 (C7 or C8).

MS (EI): *m*/*z* (%) = 230 (M^+) (100), 214 (M^+ – O) (12), 200 (M^+ – NO) (63).

Anal. Calcd for $C_8H_4Cl_2N_2O_2$ (229.96): C, 41.59; H, 1.75; Cl, 30.69; N, 12.13. Found: C, 41.43; H, 1.71; Cl, 30.54; N, 12.02.

3,7-Dichloroquinoxalin-2(1*H*)-one 4-Oxide (19)
Following typical procedure I gave **19** as a green solid; yield: 59%; mp 242–243 °C (dec).

IR (KBr): 3442, 3141, 3084, 2604, 1677 (C=O), 1619, 1480, 1429, 1360, 1236, 1134, 1081, 1036, 933, 871, 808, 732, 686, 634, 558, 472 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 12.95 (br s, 1 H, NH), 8.11–8.15 (s, 1 H, H5), 7.39–7.45 (m, 2 H, H6 and H8).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 153.2, 136.3, 133.9, 131.8, 129.1, 123.6, 121.2, 115.5.

MS (EI): *m*/*z* (%) = 230 (M^+) (50), 214 (M^+ – O) (10), 200 (M^+ – NO) (70), 77 ($C_6H_5^+$) (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_5Cl_2N_2O_2$: 230.97229; found: 230.97226.

6-Bromo-3-chloroquinoxalin-2(1*H*)-one 4-Oxide (20)
Following typical procedure I gave **20** as a yellow solid; yield: 74%; mp 245 °C (dec).

IR (KBr): 3110, 3035, 2993, 2851, 2808, 2697, 1904, 1759, 1655 (C=O), 1615, 1515, 1471, 1440, 1389, 1349, 1304, 1279, 1262, 1229, 1176, 1157, 1134, 1109, 954, 902, 883, 859, 817, 733, 699, 505 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 13.11 (br s, 1 H, NH), 8.52 (d, *J* = 1.8 Hz, 1 H, H5), 8.05 (dd, *J* = 8.6, 1.8 Hz, 1 H, H7), 7.49 (d, *J* = 8.6 Hz, 1 H, H8).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 153.5 (C2), 135.2 (C5), 134.6 (C3), 130.3, 124.5 (C7), 118.0, 117.9 (C8), 105.8.

MS (EI): *m*/*z* (%) = 276 (M^+) (100), 260 (M^+ – O) (21), 246 (M^+ – NO) (55).

Anal. Calcd for $C_8H_4ClBrN_2O_2$ (275.49): C, 34.88; H, 1.46; Cl, 12.87; Br, 29.00; N, 12.87. Found: C, 34.88; H, 1.48; Cl, 12.75; Br, 29.14; N, 12.75.

3-Chloro-6-iodoquinoxalin-2(1*H*)-one 4-Oxide (21)
Following typical procedure I gave **21** as a green solid; yield: 79%; mp 243 °C (dec).

IR (KBr): 3186, 3056, 3005, 2896, 2816, 2700, 1674 (C=O), 1615, 1513, 1469, 1437, 1386, 1352, 1262, 1227, 1162, 1137, 1110, 955, 909, 899, 823, 782, 738, 691, 667, 636, 559, 545, 499, 441, 426 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 12.85 (br s, 1 H, NH), 8.32 (d, *J* = 1.8 Hz, 1 H, H5), 7.93 (dd, *J* = 8.6, 1.8 Hz, 1 H, H7), 7.18 (d, *J* = 8.6 Hz, 1 H, H8).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 153.2 (C2), 140.7 (C8), 134.4 (C3), 131.2 (C9 or C10), 130.7 (C9 or C10), 127.2 (C7), 118.7 (C5), 86.8 (C6).

MS (EI): *m*/*z* (%) = 321 (M^+) (100), 305 (M^+ – O) (30), 291 (M^+ – NO) (35).

Anal. Calcd for $C_8H_4ClIN_2O_2$ (321.90): C, 29.80; H, 1.25; Cl, 10.99; N, 8.69. Found: C, 29.76; H, 1.22; Cl, 11.06; N, 8.67.

3-Chloro-2-oxo-1,2-dihydroquinoxaline-6-carboxylic Acid 4-Oxide (22)
Following typical procedure I gave **22** as a yellow solid; yield: 77%; mp 234 °C (dec).

IR (KBr): 3454 (O–H), 3165, 3105, 2960, 2702, 2627, 2551, 1904, 1699 (C=O), 1627, 1536, 1491, 1432, 1402, 1346, 1288, 1259, 1234, 1170, 1143, 1109, 1077, 1003, 954, 920, 849, 788, 768, 740, 685, 672, 633, 571, 444 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 13.30 (br s, 1 H, NH), 13.00 (br s, 1 H, COOH), 8.60 (d, *J* = 1.9 Hz, 1 H, H5), 8.15 (dd, *J* = 8.6, 1.9 Hz, 1 H, H7) 7.44 (d, *J* = 8.6 Hz, 1 H, H8).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 166.2 (COOH), 153.6 (C2), 134.6 (C3), 134.3, 132.7, 130.2, 125.9, 121.0, 117.1.

MS (EI): *m*/*z* (%) = 240 (M^+) (45), 210 (M^+ – NO) (31), 204 (M^+ – HCl).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_9H_5ClN_2O_4$: 239.9938; found: 239.9938.

3-Chloro-2-oxo-1,2-dihydroquinoxaline-6-carbonitrile 4-Oxide (23)
Following typical procedure I gave **23** as a yellow solid; yield: 65%; mp 243 °C (dec).

IR (KBr): 3163, 3075, 2933, 2230 (C≡N), 1665 (C=O), 1621, 1526, 1473, 1441, 1403, 1352, 1299, 1262, 1202, 1153, 1124, 1091, 953, 920, 890, 848, 809, 741, 677, 642, 598, 588, 556, 517 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.12 (br s, 1 H, NH), 8.54 (d, *J* = 1.9 Hz, 1 H, H5), 8.05 (dd, *J* = 8.6, 1.9 Hz, 1 H, H7) 7.50 (d, *J* = 8.6 Hz, 1 H, H8).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.6 (C2), 135.2, 134.6, 130.4, 124.5, 118.1 (CN), 117.9, 105.8. C3 was not detected.

MS (EI): *m*/*z* (%) = 221 (M^+) (85), 205 (M^+ – O)(100), 191 (M^+ – NO) (42), 185 (M^+ – HCl), 177 (M^+ – N_2O) (95).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_9H_4ClN_3O_2$: 220.9992; found: 220.9992.

3,6,8-Trichloroquinoxalin-2(1*H*)-one 4-Oxide (24)
Following typical procedure I gave **24** as a yellow solid; yield: 43%; mp 235 °C (dec).

IR (KBr): 3085, 3036, 2908, 2814, 1866, 1808, 1782, 1752, 1656 (C=O), 1611, 1511, 1438, 1420, 1395, 1344, 1312, 1294, 1250, 1198, 1177, 1122, 944, 909, 894, 878, 827, 735, 708, 659, 607, 570, 523, 499, 474 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.56 (br s, 1 H, NH), 8.14 (d, *J* = 2.4 Hz, 1 H, H5), 8.06 (d, *J* = 2.4 Hz, 1 H, H7).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.6 (C2), 135.2 (C3), 132.0 (C7), 129.1, 128.5, 127.6, 121.3, 118.3 (C5).

MS (EI): *m*/*z* (%) = 264 (M^+) (78), 248 (M^+ – O) (100), 234 (M^+ – NO) (57).

Anal. Calcd for $C_8H_3Cl_3N_2O_2$ (263.93): C, 36.19; H, 1.14; Cl, 40.06; N, 10.55. Found: C, 36.37; H, 1.13; Cl, 39.96; N, 10.58.

3,7,8-Trichloroquinoxalin-2(1*H*)-one 4-Oxide (25)
Following typical procedure I gave **25** as a beige solid; yield: 35%; mp 236 °C (dec).

IR (KBr): 3188, 3130, 3078, 3022, 1924, 1666 (C=O), 1601, 1589, 1502, 1456, 1439, 1350, 1293, 1252, 1165, 1119, 954, 899, 827, 813, 784, 739, 729, 654, 577, 526, 472 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.53 (br s, 1 H, NH), 8.12 (d, *J* = 9.2 Hz, 1 H, H5), 7.61 (d, *J* = 9.2 Hz, 1 H, H6).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.8 (C2), 135.4 (C3), 134.3, 130.6, 130.5, 124.3, 119.4, 118.5 (C5).

MS (EI): *m*/*z* (%) = 264 (M^+) (91), 248 (M^+ – O) (12), 234 (M^+ – NO) (100).

Anal. Calcd for $C_8H_3Cl_3N_2O_2$ (263.93): C, 36.19; H, 1.14; Cl, 40.06; N, 10.55. Found: C, 36.28; H, 1.14; Cl, 39.74; N, 10.49.

3-Chloro-6-methylquinoxalin-2(1*H*)-one 4-Oxide (26)

Following typical procedure I gave **26** as a beige solid; yield: 16%; mp 230 °C (dec).

IR (KBr): 3113, 2992, 2951, 2907, 2863, 1673 (C=O), 1601, 1532, 1484, 1439, 1398, 1355, 1268, 1250, 1148, 1130, 1093,1037, 945, 819, 739, 676, 644, 552, 536, 457 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.71 (br s, 1 H, NH), 7.94 (s, Hz, 1 H, H5), 7.50 (dd, *J* = 8.3, 1.5 Hz, 1 H, H7), 7.30 (d, *J* = 8.3 Hz, 1 H, H8), 2.39 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.2 (C2), 133.8 (C3), 133.7, 133.6, 130.2, 128.8, 118.8, 116.5 (C5), 20.7 (CH_3).

MS (EI): *m*/*z* (%) = 210 (M^+) (100), 194 (M^+ – O) (32), 180 (M^+ – NO) (70).

Anal. Calcd for $C_9H_7ClN_2O_2$ (210.02): C, 51.32; H, 3.35; Cl, 16.83; N, 13.30;. Found: C, 51.32; H, 3.33; Cl, 16.82; N, 12.51.

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(9) X-ray crystallographic analysis of $C_{21}H_{32}N_2O_3S$ was performed at 223(2) K by using a STOE IPDS II diffractometer with MoKα radiation (λ = 0.71073 Å) and a graphite monochromator. Crystal system: triclinic, $P\bar{1}$ (No. 2), *Z* = 1, *a* = 632.32(13) pm, *b* = 900.7(2) pm, *c* = 1935.2(4) pm, α = 84.236(19), β = 83.827(17), γ = 77.126(18), VEZ = 1064.9(4) 10^6 pm^3. The structure was solved by direct methods (SHELXS-97)[10a] using 3704 independent reflections. Structure refinement: full matrix least-squares methods on F^2 using SHELXL-97[10b] all nonhydrogen atoms with anisotropic displacement parameters. All hydrogen atoms were taken from a difference Fourier synthesis and were isotropically refined. The refinement converged to a final *wR*2 = 0.1223 for 3704 unique reflections and *R*1 = 0.0540 for 2420 observed reflections [$I_0 > 2\sigma(I_0)$] and 373 refined parameters with a goodness-of-fit of 1.053. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-679570. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033, e-mail: deposit@ccdc.cam.ac.uk].

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