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The Nitration of 8-Methylquinoxalines in Mixed Acid

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Abstract:

8-Methylquinoxalines are nitrated surprisingly efficiently at C-5 following a simple nitration protocol with mixed acid at 40−50 °C. The implications of halogen functionalisation at C-6 and modification of the mixed acid conditions on the relative rates of conversion and process safety are discussed. Competing side reactions for 6-halo-8-methylquinoxalines involve hydrolysis at C-6 and halogenation at C-7 or C-5.

1. Introduction

5-Nitro-8-methylquinoxalines **1**, and particularly the 6-halogen derivatives **1b** and **1c**, are versatile intermediates for compounds of pharmacological interest.[1,2] Such intermediates have been prepared before from nitro-substituted 1,2-benzenediamines **2**,[2] whose synthesis, however, is not straightforward and usually involves protection as benzo-2,1,3-selenodiazoles,[2] or benzo-2,1,3-thiadiazoles,[3] for the selective introduction of the nitro group (Scheme 1). For the synthesis of **1** on a technical scale we therefore considered the direct nitration of readily accessible quinoxalines **3** as a cost-effective and less wasteful alternative.

Although the chemistry of quinoxalines is a mature area of heterocyclic chemistry,[4] over the last century there are just a few reported examples of successful electrophilic nitration reactions for this strongly deactivated heterocyclic class. Thus far, satisfactory yields have been obtained with electron-donating alkoxy- or amino-substituents either in the homo-[5] or the heterocyclic[6] ring. Regioselective mononitration at C-5 was achieved only with these heteroatom donors at C-6, while the same donors at C-8 facilitated dinitration at C-5 and C-7. Furthermore, for several 6-halo-quinoxalines, failing nitration reactions have been mentioned.[2,7]

On the basis of this precedence we reasoned that an 8-alkyl group in **3** could also exert a sufficiently activating effect for electrophilic aromatic substitution. In this study the mononitration of 8-methylquinoxalines **3** is described in a broader context, and the process optimization of the 6-chloro compound **3b** is discussed as an example. In our opinion, these nitration reactions deserve some attention because the observed relative conversion rates for **3** and the isolated by-products imply an unusual mechanistic situation with technical consequences for scale-up.

2. Nitration Experiments and a Possible Reaction Mechanism

The starting quinoxalines **3a**−**d** (6-X = H, Cl, Br, I) were readily prepared in excellent isolated yields from the nitroanilines **4a**−**d** via the classical Hinsberg condensation of the sensitive benzenediamines **5a**−**d** with glyoxal, as depicted in Scheme 1. This route was preferred because of the high regioselectivity of the halogenation reactions of **4a** with *N*-halogensuccimides in acetic acid and the simple workup for all halogenated intermediates by crystallization directly from the reaction mixtures.

The nitration of 8-methylquinoxalines **3a**−**c** proceeded smoothly at 40−50 °C in a mixture of concentrated sulfuric acid and nitric acid, 65% (1.5−1.8 equiv) to yield predominantly the 5-nitration products **1a**−**c** (Table 1) in surprisingly good yields, after a hydrolytic workup and crystallization. Under the same conditions the iodo compound **3d** was not nitrated, and side reactions accompanied by the formation of jodine sublimate occurred. Homologous quinoxalines lacking the activating 8-methyl donor (6-X = CH_3, Br, Cl) were also shown to be gradually decomposed under our forced nitration conditions, thus confirming previous literature findings.[2]

Differently from the known quinoxaline substrates with O/N-heteroatom donors at C-8,[5] the products of 5,7-dinitration were not found for **3b**−**d**, but were likely formed to some extent in the nitration mixture of **3a** (spectroscopic evidence only). Also not found were the 7-mononitrated regioisomers.[6]

While the high regioselectivity of the quinoxaline nitration at C-5 might have been expected from electron density

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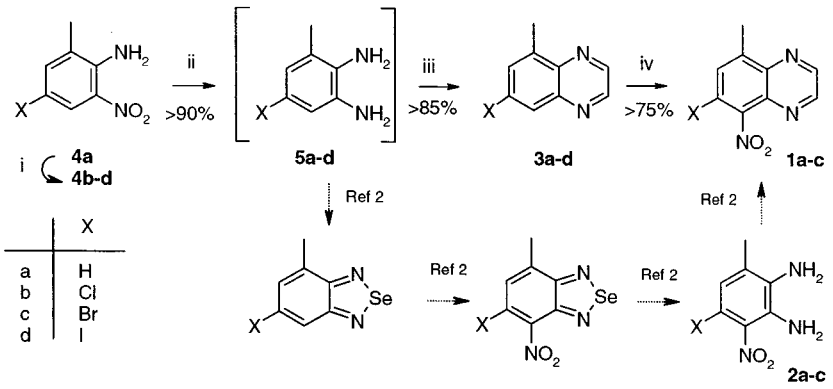
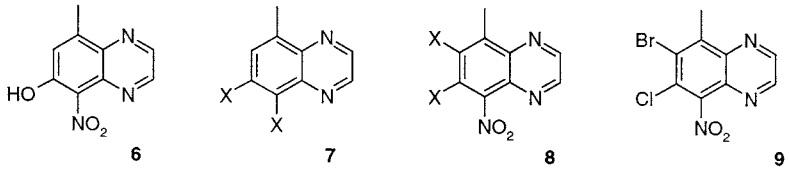
Scheme 1. **Routes to 5-nitroquinoxalines 1a−c**[a]



[a] Reaction conditions: i) *N*-Halosuccinimide (Cl, Br, I), acetic acid; 55 °C. ii) H_2, Raney-nickel, ethanol, 25 °C. iii) Glyoxal 40% (1.1 equiv); ethanol/water, $NaHCO_3$ (pH 6−8), 25 °C. iv) Sulfuric acid/nitric acid 65% (1.5−1.8 equiv), 40−50 °C.

Scheme 2. **Observed by-products in the mixed acid nitrations 3b−d at 50 °C**



7	X	
b	Cl	ca. 0.5%
c	Br	-
d	I	16%

8	X	
b	Cl	< 0.1%
c	Br	ca.10%
d	I	-

Table 1. **Nitration of quinoxalines 3a−d in mixed acid**

3	yield (%) 1	time to complete conversion (h)	main by-products (Scheme 2)
a	77	15−20[a]	two by-products
b	82	7−11[a]	**6** (ca. 10%); **7b** (ca. 0.5%)
c	79	1−3[b]	**6**; **8c** (<2%,[b] ca. 10%[a])
d	0	>20[a]	**3d**; **6**; **7d** (16%)

[a] 1.8 equiv of HNO_3; 50 °C. [b] 1.5 equiv of HNO_3; 40 °C.

considerations, the relative rates of the conversions to **1a−c** came as a surprise. A priori, we had expected that the increased steric strain between a bulky substituent at C-6 and the incoming nitronium ion at C-5 would slow the product-forming step of the electrophilic aromatic substitution in the order **3a** (H) > **3b** (Cl) > **3c** (Br) > **3d** (I). The time until complete conversion in the mixed acid decreased, however, qualitatively in the order **3c** ≫ **3b** > **3a** and only **3d** with the largest substituent followed the expectation. As an explanation we tentatively propose that the 6-halogen groups further activate the electron-deficient heterocycle (+M-effect) but in addition also exert a directing influence by coordination of the strong nitronium electrophile and that from these Friedel−Crafts related intermediates either the electrophilic aromatic nitration at C-5 or the side reactions are initiated under the strongly acidic conditions. The isolated by-products from **3b-d** (Scheme 2) substantiate this interpretation.

In the nitration of **3b**, dependent on the temperature, up to 10% of the 6-chloro functionality was hydrolytically cleaved to give the 6-hydroxy-5-nitro compound **6** together with traces of the dihalogenated impurity **7b** (ca. 0.5%). Accordingly, over the reaction period highly corrosive halogen compound(s) from the formal oxidation of chloride with nitric acid were gradually emitted into the vapor phase, presumably nitryl chloride (bp −15 °C) and chlorine, which were detected as sodium hypochlorite in a gas scrubber. We concluded, as outlined in Scheme 3, that in the formation of **6** slow hydrolysis preceded fast nitration, because at 50 °C **6** was formed quickly during the first 3 h when the mixed acid was gradually added to the **3b** solution, while under the same reaction conditions the hydrolysis of **1b** was slow.

For **3c** in addition to the nitration to **1c** and hydrolysis to **6**, also substantial bromination to **8c** (ca. 10%; dependent on temperature) occurred. Such secondary halogenation reactions competing in electrophilic aromatic nitration reactions are rare and have been reported before for strongly deactivated chloro-dinitro aromatic compounds,[8] or for nitration reactions involving nitrylhalogenides.[9] The electrophilic species from the formal oxidation of bromide with nitric acid was not bromine, since bromine added to the nitration product **1c** in the mixed acid gave no bromination to **8c**. However, added sodium bromide generated slowly **8c** from **1c**, respectively **9** from **1b** (yields approximately

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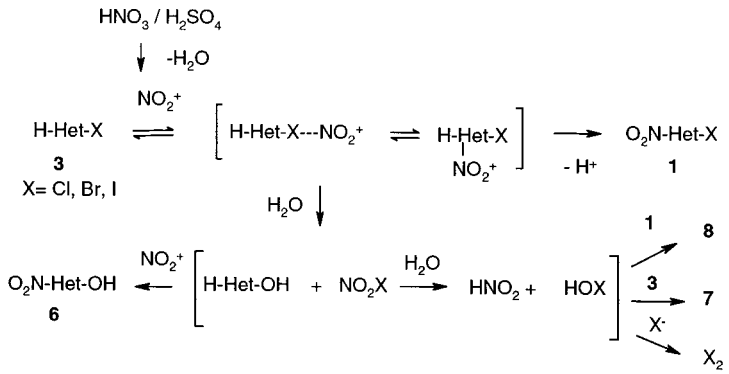
Scheme 3. **Proposed mechanism for the nitration 3 → 1**



15% after 20 h; incomplete conversion). We therefore propose that hypobromous acid, which is a strong brominating reagent in acidic solution,[10] was formed according to the formal eqs 1−3.[11]

$$Br^- + HNO_3/H_2SO_4 \rightarrow H_2O + [NO_2Br] \quad (1)$$

$$H_2O + [NO_2Br] \rightarrow HNO_2 + [HOBr] \quad (2)$$

$$[HOBr] + Br^- + H^+ \rightarrow H_2O + Br_2 \quad (3)$$

To suppress the brominating side reaction to **8** in the nitration of **3c**, the temperature was lowered to 40 °C and the excess of nitric acid reduced. After these results were determined, a related 6,7-dichloro-5-nitro compound **8b** was also detected in the 50 °C nitration mixture of **3b** at a level <0.1% (spectroscopic evidence only). Thus, the different outcome of secondary halogenation in the nitration reactions of **3b**−**d** can be tentatively interpreted as the result of different volatility and hydrolytic stability of initially formed nitryl-chloride, -bromide, or -jodide transients,[11] as depicted in Scheme 3.

3. Process Optimization of 3b

The nitration of **3b** was chosen as the preferred route for an active development project and further explored in depth. Differently to nitration reactions involving heterogeneous liquid−liquid dispersions, there were no obvious mixing related issues,[12] because **3b** was homogeneously dissolved in the sulfuric acid as the sulfate salt and the nitration reaction proceeded in the bulk of the reaction phase during the addition of the mixed acid.

The excess of nitric acid in the nitration mixture of **3b** and a temperature above 40 °C were necessary to achieve complete conversion within reasonable time. When in the nitration of **3b** the 65% nitric acid was replaced with sodium nitrate or with fuming nitric acid, an approximately 2-fold rate acceleration occurred. Interestingly, adding the mixed acid to a mixture of **3b** and sodium sulfate in sulfuric acid caused a short induction period of approximately 30 min, followed by a slightly accelerated reaction, because the sulfuric acid initially was buffered. With regard to yield, purity, or simplicity of operation none of these process modifications, aiming at a variation of the water activity in the nitration mixture, had an obvious advantage over the use of 65% nitric acid. Furthermore, neither nitration nor the side reactions of **3b** took place when sulfuric acid, in the mixture with nitric acid or sodium nitrate, was replaced with trifluoroacetic acid, although the weakly basic **3b** readily formed a trifluoroacetate salt. Therefore, we interpreted these results of a particularly marked dependence of the nitration reaction of the electron-deficient heterocycle **3b** on the acid strength and the water concentration as a further indication of the importance of the nitronium ion concentration, generated in the well-known protonation equilibrium between nitric acid and sulfuric acid.

In the technical evaluation, we decided against the use of sodium nitrate for practical reasons. Adding a solid reagent at elevated temperatures to a reaction mixture that released corrosive and noxious gases was deemed to be a potentially hazardous operation in standard pilot-plant equipment, as similarly discussed in a recently reported scale-up study of a nitration reaction.[13] On the basis of the results of reaction calorimetry and thermal stability experiments, we furthermore preferred the scale-up runs to be a diluted semi-batch process with slow addition of the premixed acids to the sulfuric acid solution of **3b**, as was precedented also in other industrial nitration reactions.[14] Thus, at low nitric acid concentrations throughout the reaction time, the enthalpy of the nitration reaction ($\Delta H_R = -140$ kJ/mol; theoretical adiabatic temperature rise 65 °C) could be conveniently controlled without the interference of the strong mixing enthalpies, which were observed when, for example, the 65% nitric acid was added directly. The rational for this cautious approach was (a) the markedly lowered onset of the highly exothermic decomposition of the nitro product **1b** (DSC, $\Delta H \approx -2000$ J/g; onset 334 °C) in the nitration mixture by more than 150 °C and (b) a further moderate exothermic event in the range of the working temperature (see Supporting

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Table 2. **Reaction calorimetric measurements for the mixed acid nitration of 3b[a]**

process operation	reaction enthalpy ΔH_R, kJ/kg	adiabatic temperature rise [°C]		accumulation %
		based on ΔH_R	at end of addition	
dissolving **3b** in H_2SO_4	−102	85	13	15
adding mixed acid at 50 °C	−75	65	7	10
inverse hydrolysis	−169	70	0	0

[a] Experimental setup as detailled in the Experimental Section.

Information) which we tentatively explained as the shifted decomposition on-set of by-product **6** (DSC: $\Delta H \approx -1500$ J/g; onset 179 °C). Similar examples for the destabilization of nitration products in mixed acid and associated preparative hazards have been recently presented in an excellent review.[15] In our opinion, the early exothermic event in the DSC thermostability measurements is associated with the product-forming reactions to **1b** and **6**. It builds up during the addition period of the mixed acid and shifts to higher (!) temperatures in parallel to the formation of **6** (see charts in Supporting Information); thus, it is not a clue for the accumulation of an unstable 6-*O*-nitrate[16] formed from **6** with the excess of nitric acid. The data of the calorimetric work (Table 2) illustrate that the diluted process with the break-down of the procedure in heat-producing unit operations considerably enhanced the thermal process safety. At the end of mixed acid addition there was only 10% heat accumulation with a theoretical adiabatic temperature rise of 7 °C.

4. Conclusions

In summary we have established a new straightforward access to the versatile 8-methyl-5-nitroquinoxalines, **1a**−**c**, by direct nitration. The observed reactivity pattern of rather slow nitration and hydrolysis reactions indicates that the donor strength of the 8-alkyl group is just sufficient to favor the desired mononitration. By eliminating two chemical steps this work had a strong impact on the productivity, mass balance, and cost-structure of an active development project using **1b** as an intermediate. The new quinoxaline nitration process was considered to be safe under diluted conditions in adequate equipment and measurements taken to remove **6** from the aqueous waste stream. Thus far, it was scaled up on a mol scale and is foreseen as the preferred supply route in the pilot plant for future drug demand. The observation of secondarily generated halogen pollutants in the process exhaust or in the reaction solution, asks for further process optimization to minimize the risks associated with these highly corrosive and noxious substances.

5. Experimental Section

Reagents and solvents were obtained from commercial sources and used as received. All reactions were carried out under an atmosphere of nitrogen in standard glass reactors with appropriate stirring. Temperatures were internally measured. Chromatography for side-product isolation was performed using silica gel (Merck, Grade 60, particle size 0.040−0.063 mm, 230−400 mesh ASTM) with the eluent indicated. HPLC column: Machery Nagel, Nucleosil CC 100-5 C18; 250 mm × 4 mm; gradient: water/acetonitrile. Reaction calometry experiments were performed in a Mettler RC1 reactor and thermal stability measurements in SEDEX- and DSC equipment (Systag, Mettler).

General Procedure for 4-Halogenation of Nitroaniline 4a. A stirred suspension of *N*-halosuccinimide NXS (X = Br, Cl, I; 1.05 equiv) in acetic acid (1.42 mL per g NXS) at 25 °C was added in 60 min, via a transferline and subtle application of nitrogen pressure, to a solution of 2-methyl-6-nitroaniline (**4a**, 1 equiv) in acetic acid (2.7 mL per g **4a**) at 50 °C, at such a rate to maintain the temperature below 55 °C. Acetic acid was used for rinsing (1.05 mL per g of NXS) and combined with the reaction mixture. After another 5 h at 55 °C the reaction was complete as judged by HPLC analysis. The suspension was cooled to 45 °C, and water (8.53 mL per g of **4a**) was added during 120 min at this temperature. The solids were collected after gradually cooling to 0−5 °C by filtration, washed with water (total 5.1 mL per g **4a**), and dried under reduced pressure at 50 °C.

4-Chloro-6-methyl-2-nitroaniline, 4b. The general procedure above with *N*-chlorosuccinimide and **4a** (0.23 mol) yielded **4b** (39.8 g, 92%) as orange brown crystals, mp 128−129 °C (lit.[17a] 129−130). HPLC purity > 98%.

4-Bromo-6-methyl-2-nitroaniline, 4c. The general procedure above with *N*-bromosuccinimide and **4a** (0.14 mol) yielded **4c** (29.4 g, 93%) as orange red crystals, mp 143−145 °C (lit.[17b] 145 °C). HPLC purity > 99%.

4-Iodo-6-methyl-2-nitroaniline, 4d. The general procedure above with *N*-iodosuccinimide and **4a** (0.038 mol) yielded **4d** (10.4 g, 97%) as orange crystals, mp 139−140 °C. HPLC purity > 99%. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 2.06 (s, 3H), 6.03 (br, 2H), 7.37 (s, 1H), 8.18 (s, 1H).

General Procedure for Hydrogenation of Nitroanilines 4 and Hinsberg Condensation of Phenylenediamines 5. A solution of **4** (1 equiv) in ethanol 95% (6 mL per g **4**) was hydrogenated at 50 °C over Raney-nickel (Degussa B113W; ca. 0.1 g per g **4**). [*Caution: The pyrophoric catalyst (fresh or spent) should be handled with adequate care.*] After the hydrogenation was complete as judged by the hydrogen uptake and TLC analysis, the catalyst was removed by filtration and washed with ethanol; the combined filtrate was

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(16) In the mixed-acid nitration of phenols, such protonated *O*-nitrate transients either rearrange rapidly to the nitrophenol products or dissociate in *homogeneous* acid mixtures to the corresponding phenol and nitronium ions. They may however accumulate in *heterogeneous* systems as do other nitrate esters (Boschan, R.; Merrow, R. T.; Van Dolah, R. W. *Chem. Rev.* **1955**, *55*, 485−510). Some phenol nitrate compounds had been isolated in acid-free "trans-esterification" experiments with thionylnitrates (Hakimelahi, G. H.; Shargi, H.; Zarrinmayeh, H.; Khalafii-Nezhad A. *Helv. Chim. Acta* **1984**, *67*, 906−915) or copper nitrate/acetic acid anhydride (Bagade, M. B.; Ghiya, B. J. *Indian J. Chem. B* **1991**, *30*, 71−74).

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concentrated (end-volume 2.7 mL per g **4**) by distillation under reduced pressure at 40−50 °C. After cooling to 20−25 °C sodium hydrogen carbonate (0.08 equiv) was added to adjust pH to 6−8. Glyoxal, 40% (1.07 equiv) was diluted with water (2.76 g per g of glyoxal, 40%) and added during 75 min to the ethanol solution containing the phenylenediamine **5**, at a rate so that 25 °C was maintained. After 1 h the reaction was complete as judged by TLC, and the suspension was heated to 50 °C for another 30 min and gradually cooled to 0−5 °C. The solids were collected by filtration, washed with ethanol 40% (1.93 mL per g **4**), and dried under reduced pressure at 40 °C.

8-Methylquinoxaline, 3a.[18] Following the procedure described above with **4a** (0.1 mol) via **5a**, yielded, after extraction with toluene and removal of solvent, **3a** (12.9 g, 90%) as a brown viscous oil. HPLC purity > 95%. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 2.94 (s, 3H), 7.72−7.81 (m, 2H), 8.08 (br d, J = 8.3 Hz, 1H), 8.97 (dd, J = 4.6 Hz, J = 1.8 Hz, 2H).

6-Chloro-8-methylquinoxaline, 3b. Following the procedure described above with **4b** (0.08 mol) via **5b**, yielded **3b** (13.1 g, 92%) as red-brown crystals, mp 81−83 °C. HPLC purity > 97%; Ni < 300 ppm. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 2.62 (s, 3H), 7.41 (br s, 1H), 7.78 (br s, 1H), 8.67 (br s, 2H). Anal. Calcd for $C_9H_7N_2Cl$: C 60.52; H 3.95; N 15.68; Cl 19.85. Found: C 60.39; H 3.80; N 15.64; Cl 19.63.

6-Bromo-8-methylquinoxaline, 3c. Following the procedure described above, **4c** (0.10 mol) via **5c**, yielded **3c** (20.6 g, 92%) as slightly brown crystals, mp 89−91 °C. HPLC purity > 98%. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 2.80 (s, 3H), 7.74 (br s, 1H), 8.15 (br s, 1H), 8.85 (br s, 1H), 8.86 (br s, 1H). MS (EI): *m*/*z* (%) 222 (M^+, 100), 168 (13), 143 (84), 116, 89, 63. Anal. Calcd for $C_9H_7N_2Br$: C 48.46; H 3.16; N 12.56; Br 35.82. Found: C 48.26; H 3.16; N 12.53; Br 35.58.

6-Iodo-8-methylquinoxaline, 3d. Following the procedure described above, **4d** (0.028 mol) via **5d**, yielded **3d** (6.7 g, 88%) as slightly brown crystals. HPLC purity > 99%. %. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 2.78 (s, 3H), 7.92 (s, 1H), 8.40 (s, 1H), 8.63 (s, 1H), 8.87 (s, 1H).

General Procedure for the Mixed Acid Nitration of Quinoxalines 3. The quinoxaline **3** (1 equiv) was added in portions to concentrated sulfuric acid (7.4 equiv; density: 1.83) at 25 °C and heated to 50 °C. Cold mixed acid, freshly prepared at −15 °C from concentrated sulfuric acid (7.4 equiv) and nitric acid, ca. 65% (1.8 equiv; density: 1.39), was gradually added over 3 h (2/3 in 60 min and 1/3 in 120 min) to the solution of **3** at 50 °C. [*Caution: Above 60 °C the decomposition of mixed acid producing brown nitrous gases is obvious. Throughout the reaction with a weak nitrogen stream the process vapors were washed into a series of gas scrubbers (water/sodium hydroxide) to avoid emission of highly toxic and corrosive reaction gases.*] The reaction was kept at 50 °C until HPLC or TLC analysis (or both) indicated complete conversion (1−21 h). The reaction mixture was cooled to 20 °C and transferred slowly over 45−60 min to a a well-stirred solution of sulfaminic acid (0.5−0.8 equiv) in water (10 mL per g of **3**) of 5 °C, and ethyl acetate (1 mL per g of **3**), at a rate so that 20 °C was not exceeded and the gas evolution accompanied by by-product precipitation could be conveniently controlled. [*Caution: A pressure rise with heavy emission of nitrous gases may occur if the rate of addition in this strongly exothermic hydrolysis is not observed*]. After completed addition the suspension was kept at 25 °C for another 1−3 h. The solids were collected by filtration at 5 °C, washed with water (3.5 mL per g of **3**) and dried under reduced pressure at 50 °C. The crude product was dissolved in ethanol 95% (5−7 mL per g **3**) at 60 °C, crystallized during cooling to 5 °C. The solids were collected by filtration, washed with cold ethanol 80% (1.5 mL per g of **3**) and dried under reduced pressure at 50 °C. [Alternatively, the nitration products were isolated by extraction of the hydrolyzed reaction mixture with ethyl acetate (ca. 10−15 mL per g of **3**). The ethyl acetate layer was washed with brine and concentrated under reduced pressure, and the residue was recrystallized from ethanol 95%, or alternatively, separated by chromatography on silica gel (hexane/ethyl acetate).]

8-Methyl-5-nitroquinoxaline, 1a. The nitration procedure above with **3a** (0.012 mol) gave, after extractive work up and recrystallization from ethanol, **1a** (1.76 g, 77%) as slightly yellow crystals, mp 134−136 °C. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 2.97 (s, 3H), 7.79 (AB, 1H, J = 7.7 Hz), 8.22 (AB, 1H, J = 7.7 Hz), 9.07 (br s, 1H), 9.12 (br s, 1H). MS (EI): *m*/*z* (%) 189 (M^+, 100), 159 (52), 143 (62), 116 (37), 77, 63. (Note: The crude sample of **1a** contained traces of a dinitro impurity (*m*/*z*: 234).)

6-Chloro-8-methyl-5-nitroquinoxaline, 1b. The general nitration procedure above with **3b** (0.1 mol) gave, after filtration and recrystallization from ethanol, **1b** (18.7 g, 82%) as slightly yellow crystals, mp 122−123 °C (lit.[2] 119.5−120.5 °C). HPLC purity > 99%; Ni < 1 ppm. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 2.91 (s, 3H), 7.76 (s, 1H), 9.01 (br s, 1H) 9.03 (br s, 1H). MS (EI): *m*/*z* (%) 223 (M^+, 69), 193 (100), 177 (26), 165 (35), 142 (84), 114, 87, 63. Anal. Calcd for $C_9H_6N_3O_2Cl$: C 48.34; H 2.70; N 18.79; Cl 15.85; O 14.31. Found: C 48.13; H 2.47; N 18.74; Cl 15.70; O 14.63.

From the mother liquor of **1b** by chromatography **6-hydroxy-8-methyl-5-nitroquinoxaline**, **6**, (0.26 g; ca. 1%) was isolated as a brownish solid, mp 153−154 °C dec. ^{1}H NMR (400 MHz; DMSO-d_6): δ = 2.73 (s, 3H), 7.99 (s, 1H); 9.09 (br s, 1H), 9.12 (br s, 1H). MS (EI): *m*/*z* (%) 212 (M^+, 100), 177 (75), 148, 123, 89, 63. (Note: The main amount of **6** is found in the aqueous filtrate after hydrolysis of the nitration mixture and is removed, e.g., by extraction with *n*-butanol).

As a further by-product **5,6-dichloro-8-methylquinoxaline**, **7b**, (0.16 g, ca. 0.2%) was isolated from the mother liquor of a 0.6 mol nitration batch by chromatography. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 2.81 (s, 3H), 7.44 (s, 1H); 8.82 (br s, 1H), 9.00 (br s, 1H), 11.42 (b, 1H). MS (EI): *m*/*z* (%) 205 (M^+, 100), 175 (34), 147 (67), 131 (39), 103, 76. (Note: The sample of compound **7b** contained as a trace impurity 5,7-dichloro-8-methyl-5-nitroquinoxaline (**8b**; *m*/*z* = 257).)

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6-Bromo-8-methyl-5-nitroquinoxaline, 1c. The general nitration procedure above with **3c** (0.022 mol) at 40 °C and 1.5 equiv of nitric acid, gave after extractive work up and recrystallization from ethanol, **1c** (4.8 g, 79%) as light yellow crystals, mp 134−136 °C. ^{1}H NMR (400 MHz; DMSO-d_6): δ = 2.76 (s, 3H), 8.14 (br s, 1H), 9.07 (br s, 1H), 9.15 (br s, 1H). MS (EI): *m*/*z* (%) 267 (M^+, 61), 237 (56), 221 (17), 142 (100), 87, 63. Anal. Calcd for $C_9H_6N_3O_2Br$: C 40.32; H 2.26; N 15.68; Br 29.81; O 11.94. Found: C 40.56; H 2.15; N 16.02; Br 30.08; O 12.03.

6,7-Dibromo-8-methyl-5-nitroquinoxaline, 8c. The general nitration procedure above with **3c** (0.018 mol) at 50 °C and 1.8 equiv nitric acid, yielded after extractive work up, crystallization, and chromatography of the crude crystallisate, **1c** (2.6 g, 54%) and **8c** (0.35 g, 6%). Slightly yellow crystals, mp 167−170 °C. ^{1}H NMR (400 MHz; DMSO-d_6): δ = 2.92 (s, 3H), 9.07 (br s, 1H), 9.18 (br s, 1H). MS (EI): *m*/*z* (%) 347 (M^+, 100), 317 (59), 301 (15), 220 (50), 141 (37).

5,6-Diiodo-8-methyl-quinoxaline, 7d. The general nitration procedure above with **3d** (0.022 mol) yielded after filtration of the hydrolyzed nitration mixture **7d** (1.1 g, 16%) as light yellow crystals, mp 185−188 °C. ^{1}H NMR (400 MHz; DMSO-d_6): δ = 2.60 (s, 3H), 8.23 (s, 1H), 8.92 (s, 2H).). MS (EI): *m*/*z* (%) 396 (M^+, 100%), 269 (29), 142 (82), 115, 88, 63. (Note: In the ethyl acetate extract of the filtrate of the nitration batch unreacted **3d** and **6** were identified.)

7-Bromo-6-chloro-8-methyl-5-nitroquinoxaline, 9. To **1b** (2.2 g, 10 mmol) in concentrated sulfuric acid (14 mL) at 50 °C was added nitric acid (65%, 0.75 mL) within 15 min. Sodium bromide (1.0 g, 10 mmol) was added in small portions over 60 min [*Caution: Bromine vapors*!] and the mixture kept at 50 °C for 18 h. After hydrolysis and extraction with ethyl acetate, a solid residue was obtained which was separated by chromatography (heptane/ethyl acetate) in **1b** (1.2 g, 55%) and **9** (0.4 g, 13%), slightly yellow crystals, mp 160−162 °C. ^{1}H NMR (400 MHz; DMSO-d_6): δ = 2.86 (s, 3H), 9.10 (br s, 1H), 9.14 (br s, 1H). MS (EI): *m*/*z* (%) 303 (M^+, 100), 273 (60), 176 (95), 164 (38), 141 (30), 114, 87, 63. (Note: compound **9** contained as a trace impurity 5,7-dibromo-6-chloroquinoxaline (*m*/*z* = 336).)

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Supporting Information Available

Some selected charts from reaction calorimetry and DSC thermostability measurements for the nitration of **3b** to illustrate the conclusions of this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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