

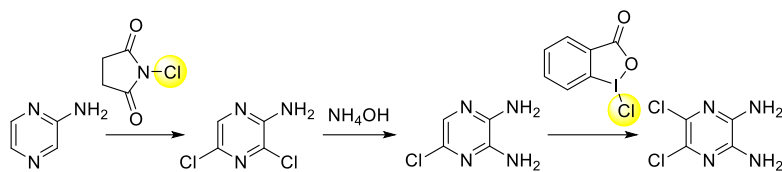
An Improved Synthesis of 2,3-Diamino-5,6-dichloropyrazine: A Useful Heterocyclic Scaffold

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1. Dichlorination 2. Regioselective amination 3. Rapid Chlorination

● No POCl₃, PCl₅ or autoclaves required ● Removes unselective amination ● Higher yielding

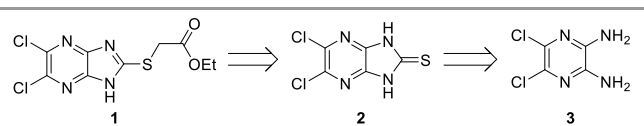
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Abstract: 2,3-Diamino-5,6-dichloropyrazine represents a valuable but underexplored heterocyclic building block. Due to the use of harsh conditions and lack of selectivity surrounding the known literature synthesis, we developed a more accessible and selective three step route from 2-aminopyrazine. Challenging conditions are avoided by using a high yielding dichlorination with NCS, which is followed by a regioselective amination. The installation of the last chlorine atom using 1-chloro-1,2-benziodoxol-3(1H)-one is rapid, enabling access to 2,3-diamino-5,6-dichloropyrazine in an improved overall yield (41%).

Key words Pyrazine, Heterocyclic building block, Synthesis, Chlorination, 2,3-diamino-5,6-dichloropyrazine

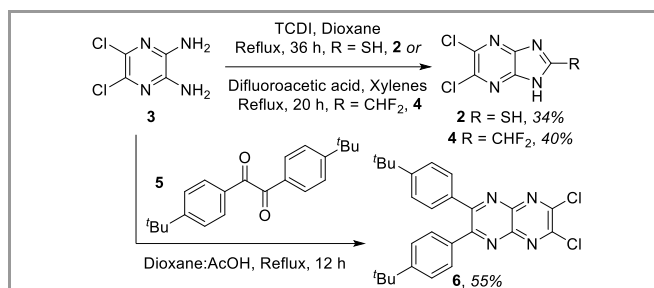
Introduction

In the course of our work studying the inhibition of WWP1 & WWP2 enzymes, NSC-217913 (**1**, Scheme 1) was identified as a hit from a HTS of NCI diversity set VI.¹ We sought to resynthesise **1** along with a library of analogues. This required us to generate 2,3-diamino-5,6-dichloropyrazine (**3**) as an intermediate in the synthesis of NSC-217913.



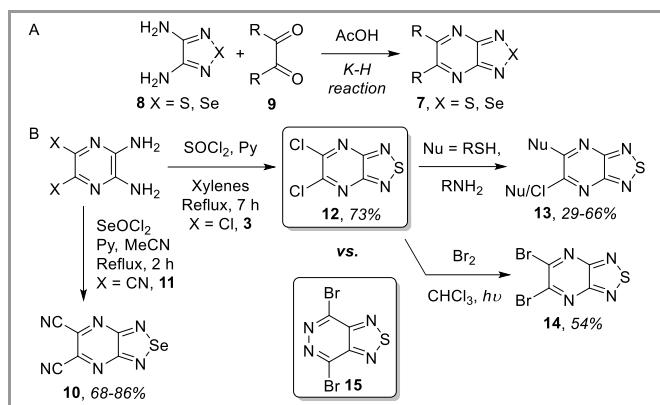
Scheme 1 Access to NSC-217913 required 2,3-diamino-5,6-dichloropyrazine.

2,3-Diamino-5,6-dichloropyrazine has been utilised in the direct production of pharmacologically relevant imidazo[4,5-*b*]pyrazine derivatives such as **4**,² and more recently in the generation of an advanced heterocyclic intermediate (**2**, Scheme 2) for the synthesis of biologically active derivatives.³ The chemistry utilising **3** towards medicinally relevant compounds has mainly been investigated in the 1970s and 80s.^{2,4,5} Several, more contemporary transformations may be envisioned from **3** using related chemistry towards novel advanced intermediates for the production of compound libraries of pharmacological relevance.^{6–9} Compound **3** has found use in the production of functional materials as exemplified by several patents.^{10–14} More recently, **3** was used in the preparation of pyrazinacenes, which exhibit interesting electronic and optical behaviours.¹⁵ By reacting **3** with di-ketone **5** (Scheme 2), the dichloro-tetraazaphthalene **6** could be produced and used as an intermediate in the synthesis of several pyrazinacenes containing 4 and 5 pyrazine units.¹⁶



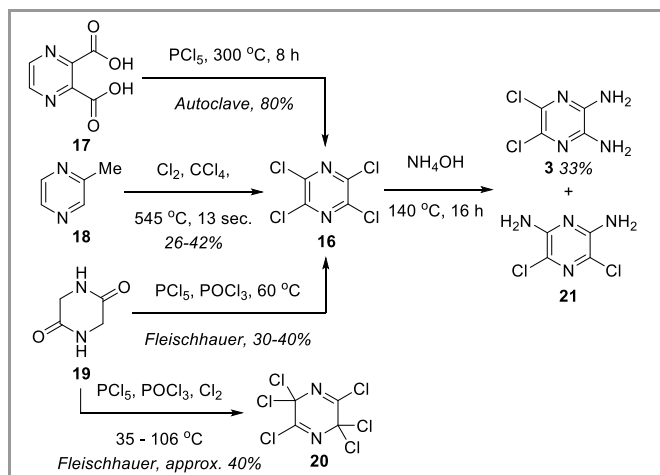
Scheme 2 2,3-Diamino-5,6-dichloropyrazine used as an intermediate in the synthesis of imidazo[4,5-*b*]pyrazine cores of pharmacological interest, and in the production of pyrazinacenes through intermediate **6**. TCDI = Thiocarbonyldiimidazole.

Furthermore, [1,2,5]thia(seleno)diazolo[3,4-*b*]pyrazines (**7**, Scheme 3, A) exhibit positive electron affinity (EA),¹⁷ which makes them amenable electron acceptors for stable radical anion (RA) generation.^{18,19} A common route to synthesise **7** with derivatisation at the 5- and 6-positions, is *via* the Körner-Hinsberg reaction between **8** and diketones **9**.^{20,21} This somewhat narrows the scope of derivatisation possible by which diketones are accessible. An alternative method for the production of these systems is the incorporation of the chalcogen atom into pre-functionalised 2,3-diaminopyrazines.¹⁷ For example, **10** was produced from **11**, and investigated for its chalcogen bonding,²² and in producing homospin RA salts with interesting magnetic properties (Scheme 3, B).²³ Further derivatisation can be proposed when useful synthetic handles (such as halides) are present at the 5- and 6-positions. 5,6-Dichloro[1,2,5]thiadiazolo[3,4-*b*]pyrazine (**12**) was previously prepared in a similar fashion from **3**, but only S_NAr (e.g. **13**) and halogen exchange reactions (**14**) were investigated.^{24,25} Its use in the production of high EA heterocycles and a Ni complex has also been reported.^{26–29} By comparison, a fuller picture of the derivatisation possible using cross-coupling reactions has been accomplished with the pyridazine analogue **15**.³⁰ A similar level of derivatisation should be possible from **12**, **14** and the Se-congeners,¹⁹ in contrast to the current limitations inherent in the synthesis of **7**. To realise this and to further develop the areas of chemistry utilising **3** mentioned above, straightforward access to **3** is desirable.



Scheme 3 (A) Kœrner-Hinsberg reaction to access **7** with varied substituents on the 5- and 6-positions. (B) Synthesis and derivitisation of 5,6-dichloro[1,2,5]thiadiazolo[3,4-*b*]pyrazine **12**, production of **10**.

Production of **3** has historically been directly from tetrachloropyrazine (**16**, Scheme 4) *via* a double amination,³¹ which provides **3** in low yield and in an approximately 1:1 regioisomeric mixture with **21**.³² Several methods exist to access **16**, all of which use harsh conditions. One method reacts suitable precursors with PCl_5 at high temperatures (250–330 °C) using a Carius tube or an autoclave, with **17** providing the highest yield.³³ Alternatively, vapour-phase chlorination of methylpyrazine **18** can be used.^{2,34} A slightly more accessible route to **16** requires passing Cl_2 gas into a mixture of glycine anhydride **19**, PCl_5 and POCl_3 at elevated temperatures, providing apparently high (92%) yield.³⁵ Fleishauer *et al.* were unable to reproduce this, instead isolating hexachlorodihydropyrazine **20**. When the reaction was conducted without Cl_2 gas, **16** was isolated in 30–40% yields.³⁶ Tetrachloropyrazine is also commercially available but expensive for a simple heterocyclic building block.³⁷



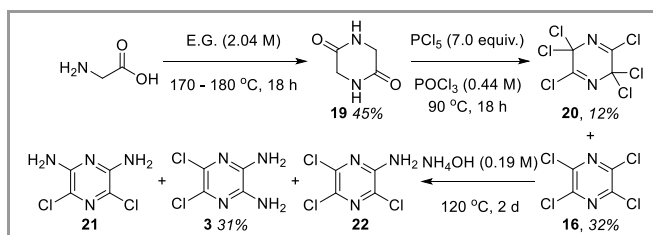
Scheme 4 Literature routes accessing 2,3-diamino-5,6-dichloropyrazine **3** from the synthetic precursor tetrachloropyrazine **16**.

Because **3** represents a valuable heterocyclic building block, an improved and more broadly accessible synthesis is therefore of interest to the research community. To this end a new route that does not require special equipment (autoclaves) is described herein.

Results and Discussion

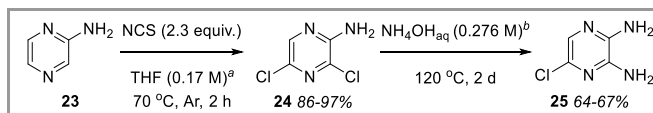
Our preliminary route to generate **3** was through known literature reactions accessible to us. Initially, **19** was easily prepared from glycine (Scheme 5).³⁸ The production of

tetrachloropyrazine **16** *via* a slightly adapted method to Fleishauer's provided a similar yield to those described in their report (32%), as well as isolation of by-product **20** (Scheme 5). The reaction releases copious amounts of HCl gas in the initial hours and requires the high temperature (200 °C) distillation and sublimation of POCl_3 and PCl_5 during workup. The best amination conditions were obtained over 2 days, providing similar yields of **3** to the literature.³² With shorter reaction times, unreacted **16** and the intermediate **22** were also observed. 2-Amino-3,5,6-trichloropyrazine **22** allows $\text{S}_\text{N}\text{Ar}$ at both the 3- and 6-positions, but with no amination at the 5-position.³⁹ Due to the low overall yield (5% over 3 steps or 10% over two) a better method for the preparation of **3** was sought.



Scheme 5 Synthesis of **3** using literature methods not requiring specialist equipment. E.G. = ethylene glycol.

We set out to improve access so that **3** could be produced in a safer fashion, without by-products and in higher yields. We wanted to avoid the use of **16** as this intermediate required harsh conditions to produce and in the amination provides no selectivity between **3** and **21**. By adapting literature procedure, 2-aminopyrazine **23** was dichlorinated in high yield using NCS in THF to provide 2-amino-3,5-dichloropyrazine (**24**, Scheme 6).⁴⁰ An 86% yield was achieved on a 0.168 mol scale to afford 23.7 g of **24** in 2 h reaction time. Subsequent amination was performed by heating **24** with 25% ammonium hydroxide solution in a sealed microwave vial, which allowed access to 2,3-diamino-5-chloropyrazine **25** in 64% yield.⁸ The best yields were obtained when the reaction was performed over two days, as with shorter reaction times (18 h) significant amounts of unreacted **24** was observed (see experimental procedure). Performing the reaction at a higher concentration (0.61 M) provided a 67% yield (see experimental procedure). No vessel failures under these conditions were observed over multiple reactions.

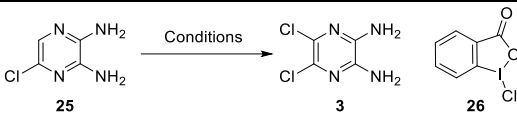


Scheme 6 Access to 2,3-diamino-5-chloropyrazine **25** from 2-aminopyrazine. ^a THF (0.2 M) was used on 0.168 mol scale, ^b NH_4OH (0.61 M) was used on a 0.143 mol scale.

To install the chlorine atom at the 6-position, treating **25** with NCS at RT overnight provided 9% isolated yield, along with significant degradation (entry 1, Table 1). The reaction was initially sluggish and HCl was added at 1 h, but full conversion was not observed by TLC. A slightly improved yield was found by lowering the concentration and heating to 40 °C, to provide 12% isolated yield in 0.5 h (entry 2). After investigating several variables using NCS (equivalency, temperature, time, concentration), the isolation of **3** was achieved only in low yields (the best results given in entries 3 and 4). Changing the chlorination reagent to 1-chloro-1,2-benziodoxol-3(1*H*)-one **26**,

and adapting literature conditions,⁴¹ gave an improved 38% yield (entry 5). When the concentration was lowered to 0.075 M in DMF and timed to 2.5 min., a further improved isolated yield of 63% resulted (entry 6). This was reproducible on a 1.0 g scale, with an average isolated yield of 60% over two reactions (entry 7). As stated in the report where this reaction was adapted, recovery of 2-iodobenzoic acid should be possible. On a 10 g scale we sought to reduce the amount of DMF used (0.15 M), but this led to a diminished yield of 45%, providing access to 5.6 g of **3** (entry 8). The analytical data of **3** matched that of the material previously produced (Scheme 5). Approximately 29 g of **26** was easily prepared from readily available 2-iodobenzoic acid for this reaction, following literature procedure.⁴²

Table 1 Tested chlorination conditions of **25** to give **3**:

					
Entry	Reagents ^a	Solvent (M)	T (°C)	Time	Yield ^d
1	NCS (1.0) ^b	THF (0.15)	RT	18 h ^c	9%
2	NCS (1.0) ^e	THF (0.075)	40	0.5 h ^c	12%
3	NCS (1.1)	THF (0.15)	40	0.5 h ^c	21%
4	NCS (1.3) ^e	THF (0.15)	66	0.5 h ^c	29%
5	26 (1.2)	DMF (0.15)	RT	5 min ^c	38%
6	26 (1.2)	DMF (0.075)	RT	2.5 min	63%
7 ^f	26 (1.2)	DMF (0.075)	RT	2.5 min	60%
8 ^g	26 (1.2)	DMF (0.15)	RT	2.5 min	45%

Reactions conducted on a 50 mg (0.345 mmol) scale of **25** unless stated otherwise.

^a Equivalents bracketed, ^b HCl (2.0 M, 1 drop) added at the 1 h mark. ^c monitored by TLC (7:3 Hex.:EtOAc), ^d isolated yields, ^e HCl (2.0 M) added (1 drop). ^f 1.0 g (6.92 mmol) scale of **25**, yield is an average of two runs, see experimental section for details. ^g 10 g (69.17 mmol) scale of **25**.

Conclusion

2,3-Diamino-5,6-dichloropyrazine **3** was prepared in a more accessible and safer manner compared to the routes previously available in good overall yield (up to 41%). To the best of our knowledge the route provides an improved yield over the historical methods and compares well to our preliminary route to access **3** (5% over three steps). The use of PCl₅ and POCl₃ are avoided and special equipment to affect high pressure chlorinations is not required. The presented amination is regioselective, and using **26**, the installation of the last chlorine atom is rapid to give 60–63% isolated yields of **3** using optimised conditions. The synthetic route is highly practical, with all reagents readily available or easily produced, reactions easy to set up and run, and isolation of products straightforward. Of course, further improvements to the final chlorination can be envisioned, for example substituting DMF as solvent, and further improving yield. 1-Chloro-1,2-benziodoxol-3(1H)-one **26** can be easily prepared in several ways from 2-iodobenzoic acid on large scales,^{41,42} and is easily handled and stored. It is hoped that easier access to this heterocyclic building block can allow further investigation into both the synthesis of highly decorated pyrazine systems in medicinal chemistry and as an intermediate for the production of functional materials.

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Unless specified, all reagents and starting materials were purchased from Sigma-Aldrich (Merck Life Sciences) or Fluorochem (Doug Discovery) and used as received. *N,N*-dimethylformamide (DMF) was stored over activated 4 Å molecular sieves for 24 h prior to use. All other solvents and

reagents were used as supplied unless otherwise stated. Thin-layer chromatography was performed on Merck silica gel 60 F254 plates and visualised by UV absorption, purchased from VWR International. Flash column chromatography was carried out using Silica Gel 60 purchased from Material Harvest. Water refers to deionised water. NMR spectra were recorded on 400 or 500 MHz Bruker NMR spectrometers using the deuterated solvent stated in the reported data. ¹H, ¹³C, NMR samples were prepared by dissolving compound in 0.4 mL – 0.7 mL deuterated solvent. All deuterated solvents were purchased from Cambridge Isotopes and used as received, solvents were stored under activated 4 Å molecular sieves after opening. All spectra were referenced to the residual solvent peaks of the solvent used.⁴³ NMR spectra chemical shifts (δ) are reported in ppm and coupling constants (*J*) reported in hertz (Hz). Abbreviations for NMR splitting are s (singlet), d (doublet), t (triplet) and m (multiplet). Infrared spectra were recorded using a Perkin Elmer Spectrum Two LITA. High resolution mass spectrometry was performed at the University of East Anglia using a UPLC-HRMS (ACQUITY H-Class PLUS UPLC and Waters SYNAPT XS High Resolution Mass Spectrometer) setup with electrospray ionisation using ca. 1 µg mL⁻¹ solution in acetonitrile or methanol. Melting points (not corrected) were recorded on a Büchi Melting Point B-545 using capillary melting point tubes made in house. See supplementary information for synthetic procedures of **16**, **19**, **20**, **21** and **26**.

Procedures

2-Amino-3,5-dichloropyrazine **24**, [CAS: 873-42-7]

To a 1 L 3-neck RBF attached with two glass stoppers and a reflux condenser, was added 2-aminopyrazine (8.08 g, 85.0 mmol) and placed under an argon atmosphere with low stirring. THF (500 mL, over mol. sieves, 0.17 M) was then added. *N*-chlorosuccinimide (26.11 g, 195.4 mmol, 2.30 equiv.) was added in one batch to the solution, the mixture placed in a preheated 80 °C syn and monitored by TLC (7:3 Hex. : EtOAc, R_f = 0.61). After 2 h TLC indicated full dichlorination of starting material, the vessel was cooled to RT. The reaction mixture was filtered through a pad of Celite® and washed with excess EtOAc. The solvent was reduced *in vacuo* and the residue dry loaded and purified by column chromatography (8:2 to 7:3 hexane : EtOAc) to provide 2-amino-3,5-dichloropyrazine (13.48 g, 82.2 mmol, 97%) as yellow crystals. Conditions were adapted for a 0.168 mol scale, 2-aminopyrazine (16.0 g, 0.168 mol), NCS (51.66 g, 2.3 equiv.), THF (840 mL, 0.2 M), for an 86% (23.72 g) isolated yield. Purified in the same manner as above. Adapted from literature procedure.⁴⁰ Data in-line with literature data.⁴¹

¹H NMR (400 MHz, CDCl₃) δ 7.97 (s, 1H), 5.01 (br s, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 150.5, 140.2, 134.8, 131.6.

IR (cm⁻¹) 3435, 3167.

M.P. 115 – 118 °C (lit.),⁴¹ 126.9 – 127.3 °C.

2,3-Diamino-5-chloropyrazine **25**, [CAS: 1259479-81-6]

To eighteen 30 mL microwave vials was added 2-amino-3,5-dichloropyrazine (9.00 g total (54.9 mmol), approx. 0.5 g per vial) and a stirrer bar. To each vial was added 25% aqueous ammonium hydroxide solution (12.5 mL, 0.276 M) and crimp sealed. Vials were placed in a sand bath and heated with stirring at 120 °C (sand temp.) for 2 days (A precautionary blast shield is recommended). The vessels were allowed to cool to RT, contents transferred to a separatory funnel and extracted with EtOAc (8x 100 mL). The organic extracts were collected and washed with brine (100 mL) and dried (MgSO₄). The solvent was removed *in vacuo*, the material was purified by column chromatography (5:5 -> 2:8 -> 0:1 Hex. : EtOAc) to provide 2,3-diamino-5-chloropyrazine (5.06 g, 35.0 mmol, 64%) as an off-white solid. R_f (6:4 Pet. E : EtOAc, after two runs) = 0.27. Conditions adapted slightly to react 23.5 g (0.143 mol) of **24**. Eighteen 30 mL microwave vials were charged with **24** (approx. 1.25 g each), 25% NH₄OH_{aq} solution (12.5 mL, 0.61 M). Provided 2,3-diamino-5-chloropyrazine (15.72 g, 67%, 0.109 mol) after reaction and purification in the same manner as above. Shorter reaction times: 2-amino-3,5-dichloropyrazine (1.0 g), NH₄OH_{aq} solution (0.25 M), 120 °C, 18 h. Provided **25** (0.45 g, 50%) and **24** 0.23 g, 23%). Adapted from literature procedure.⁸

¹H NMR (400 MHz, Acetone-*d*₆) δ 7.24 (s, 1H), 5.72 (br s, 2H), 5.47 (br s, 2H).

¹³C NMR (101 MHz, Acetone-*d*₆) δ 144.5, 143.5, 134.3, 127.7.

IR (cm⁻¹) 3440, 3375, 1646.

M.P. 222.7 – 223.1 °C (deg.).

2,3-Diamino-5,6-dichloropyrazine 3, [CAS: 13484-57-6]

To an 8 mL microwave vial was added 2,3-diamino-5-chloropyrazine (50 mg, 0.345 mmol) and a stirrer bar. Anhydrous DMF (4.6 mL, 0.075 M) was added *via* syringe. 1-Chloro-1,2-benziodoxol-3(1H)-one (0.117 g, 1.2 equiv.) was added in one batch with vigorous stirring. Timing was started at addition for 2.5 minutes, with a significant colour change of the reaction mixture from light yellow to black occurring. The reaction mixture was quenched immediately following the 2.5-minute mark with NaHCO₃ sat. solution (3 mL) and the reaction mixture transferred to a separatory funnel, washing with water. This was extracted with EtOAc (3x 15 mL), the organic layers were collected and washed with water (2x 15 mL), dried (Na₂SO₄) and the solvent removed *in vacuo*. The residue was purified using column chromatography (6:4 Pet. E : EtOAc) to provide 2,3-diamino-5,6-dichloropyrazine as a light-brown solid (38.9 mg, 0.21 mmol, 63%). R_f (6:4 Pet. E : EtOAc, after 2 runs) = 0.47. For reactions on 1.0 g and 10 g scale, additional extractions from the reaction mixture with EtOAc and extractions from the organic phase using brine : water (1:3) were performed to obtain a solid after removing the organic solvent for dry loading prior to column chromatography. May be repeated on a 1 g scale, **25** (1.0 g, 6.917 mmol), **26** (2.34 g, 1.2 equiv.), DMF (93 mL, 0.075 M). Isolated **3** in the same manner as above (1st run = 784 mg, 63%, 2nd run = 708 mg, 57%). Adapted on a 10 g scale, **25** (10.0 g, 69.17 mmol), **26** (20.61 g, 1.2 equiv.), DMF (400 mL, 0.15 M). Used *ca.* 400 mL NaHCO₃ sat. soln. to quench. Eluted using 7:3 -> 6:4 hex. : EtOAc. Isolated 2,3-diamino-5,6-dichloropyrazine (5.6 g, 45%, 31.26 mmol).

¹H NMR (400 MHz, DMSO-*d*₆) δ 6.55 (br s, 4H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 142.6, 126.2.

IR (cm⁻¹) 3435, 3202, 1625.

M.P. >250 °C (lit.),³² 275.7 – 276.1 °C.

HRMS ES+ m/z calcd for C₄H₅³⁵Cl₂N₄ (M+H)⁺: 178.9891, found: 179.9888.

2,3-Diamino-5,6-dichloropyrazine may be stored in a freezer (-20 °C) protected from light for extended periods. Adapted from literature conditions.⁴¹

1-Chloro-1,2-benziodoxol-3(1H)-one **26**, [CAS: 59457-26-0]

To a 250 mL RBF was added 2-iodobenzoic acid (2.0 g, 8.06 mmol), sodium chlorite (2.19 g, 24.2 mmol, 80% pure, 3.0 equiv.), a stirrer bar and H₂O (40 mL, 0.2 M). The suspension was stirred and to an attached dropping funnel was added concentrated hydrochloric acid (37%, 16.2 mL, 0.5 M). This was added dropwise at RT with vigorous stirring, which was continued for 18 h after addition. The precipitated solid was filtered and washed with H₂O and Pet E., the solid was placed under vacuum to provide 1-chloro-1,2-benziodoxol-3(1H)-one as a light-yellow powder (2.18 g, 7.72 mmol, 96%).

¹H NMR (500 MHz, CDCl₃) δ 8.30 – 8.24 (m, 1H), 8.24 – 8.18 (m, 1H), 8.00 (tdd, J = 6.9, 3.2, 1.6 Hz, 1H), 7.80 (tt, J = 6.0, 2.9 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 167.3, 136.8, 133.6, 132.0, 128.8, 127.0, 117.2.

IR (cm⁻¹): 1724.

M.P. 172 – 173 °C (lit.),⁴² 173.4 – 175.0 °C.

May be repeated in the same manner on a 0.106 mol scale. 2-iodobenzoic acid (26.34 g, 0.106 mol), NaClO₂ (35.95 g, 80% pure, 3.0 equiv.), H₂O (530 mL, 0.2 M), Conc. HCl (212 mL, 37%, 0.5 M). Provided 29.34 g (0.104 mol, 98%) of 1-chloro-1,2-benziodoxol-3(1H)-one.

Followed literature procedure, data matches literature data.⁴²

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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