

Short Note

6-Chloro-3H-benzo[*d*][1,2,3]dithiazol-2-ium Chloride

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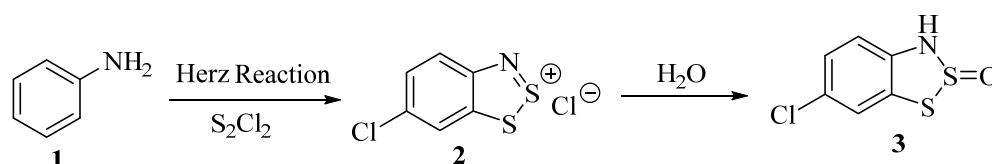
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Abstract: This short note describes the synthesis of an amorphous benzo[1,2,3]dithiazole chloride salt (commonly known as a ‘Herz salt’) by use of the Herz reaction. Hetero- and homolytic transformations of this species to a variety of useful adducts in medicinal and materials chemistry are well established, although there are limited examples of isolation in the literature, and characterisation data is even harder find. While several studies have confirmed the structure of the benzodithiazole ring beyond doubt, (having generated suitably crystalline salts with large counterions for XRD-analysis), there remains value in understanding and optimising the synthesis of the simple, amorphous polymorphs. For the first time, MS data is provided for this compound and a new mechanism of its formation is proposed based upon new experimental observations and data.

Keywords: thiazole; disulfur dichloride; Herz reaction; heterocycle formation; organic radical anion; semiconductor

1. Introduction

The Herz reaction (Scheme 1) is a unique process that transforms an electron-rich aniline starting material into an electron-deficient benzo[1,2,3]dithiazolium salt with a single reagent: disulfur dichloride. As well as heterocycle formation, a C–Cl bond is created at the 4-position of the aniline precursor aromatic ring. The product can be further derivatised by simple steps. Research into the chemistry and properties of the benzo[1,2,3]dithiazole structures, produced generally by the Herz reaction, have historically centred around their utilisation as dyes and, by extension, as medicinal building-blocks [1,2]. More recent investigations have concerned their unusual electron properties, including generation of stable radicals and their solid-state material properties [3–6]. Being a heterocycle of general interest [7–13], we considered it of value for exploring the scaled preparation of this compound optimising the outline syntheses collated from various literature sources. As such, in this short note the performance of the synthesis at higher scales is disclosed with an improved and fully optimised procedure. In addition, new data has been obtained, which adds further support to the ionic structure, compound **2**, indicated in the literature.



Scheme 1. The Herz reaction, starting with aniline (1).

2. Results

A concentrated solution of aniline in acetic acid (in demonstration, 44 wt% strength with 4.65 g of aniline was used) reacts vigorously and alongside substantial exotherm with neat disulfur dichloride. This is allowed to react with external cooling (room-temperature water bath) for 30 min and then heated at 80 °C for 4 h. After this time, the reaction forms a



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thick slurry of brown precipitate. To aid in the collection of the target solid, toluene (50 mL) is added. The filtrate contains a variety of impurities; some major components identified were 4-chloroaniline and *N*-oxidised species (e.g., azobenzene). These are removed by washing the precipitate with toluene (50 mL), followed by DCM (50 mL). The precipitate contains the title compound, although it also contains elemental sulfur and small amounts of other organic impurities. Often, crystalline forms of sulfur are collected, although the title compound is entirely amorphous (upon inspection under microscope), as per previous literature reports [13]. To form crystalline polymorphs, an ion-exchange can be performed with a sufficiently large counterion source (e.g., SbCl_6), followed by slow-growth solution-recrystallisation from polar-organic solvents [14].

While generally challenging to characterise due to its lack of solubility, the solid product can be analysed by solid-phase ASAP-MS (Figure 1). The mass peak observed corresponds to the mass of the anticipated Herz cation, and the isotope pattern is also consistent with the molecular formula $\text{C}_6\text{H}_3\text{S}_2\text{NCl}$.

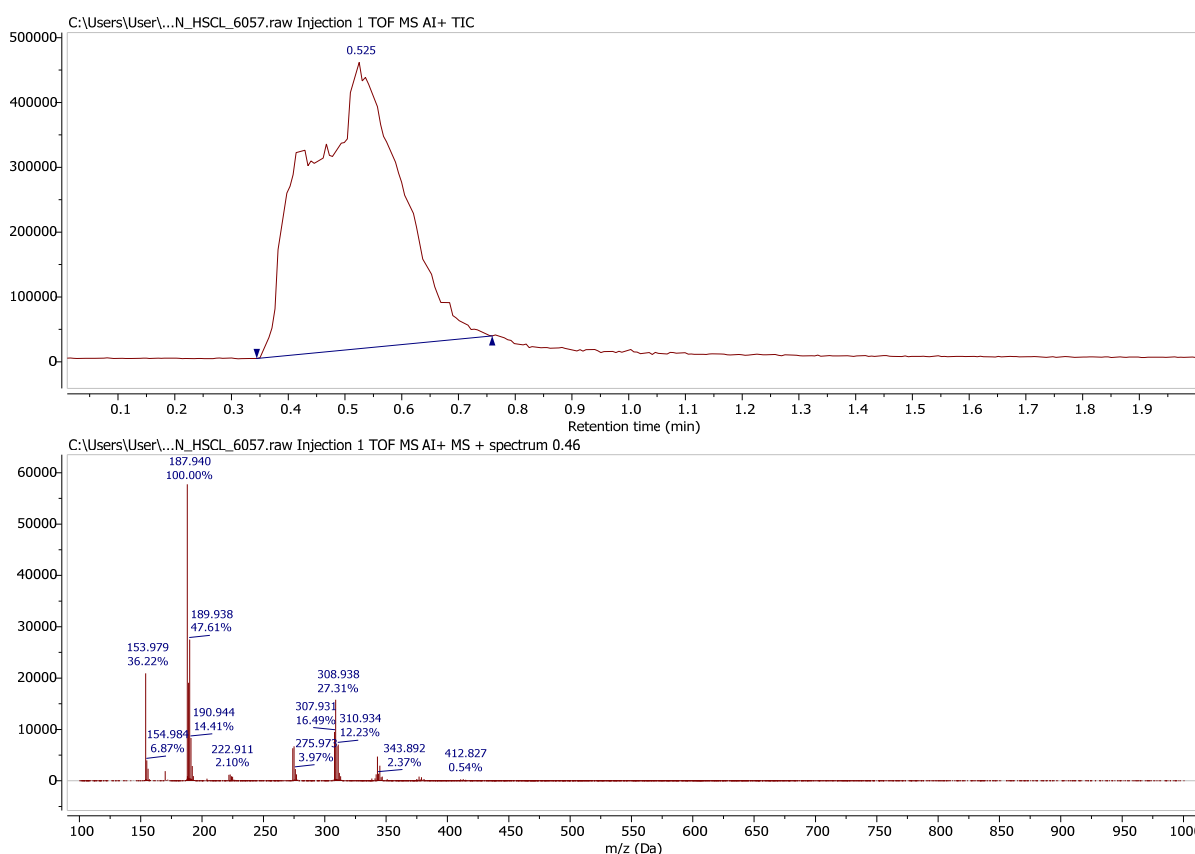


Figure 1. The full ASAP-MS spectrum obtained from the sample of (2) generated in this study according to the experimental. Y-axis is (total) ion count.

A minor impurity with a Cl-containing splitting pattern is detected with mass 308.938 Da; this is consistent with a molecular formula of $\text{C}_{12}\text{H}_6\text{ClN}_2\text{S}_3$. This impurity (like the titled compound) must be insoluble in organic solvents and could be the result of two units of (2) coupling together, with ring-opening and a nucleophilic displacement of the 4-Cl (2a, Figure 2), although there is no additional supporting evidence of this structure. After accounting for the elemental sulfur contamination, the yield of target compound 2 was 10.8 g (61% isolated yield).

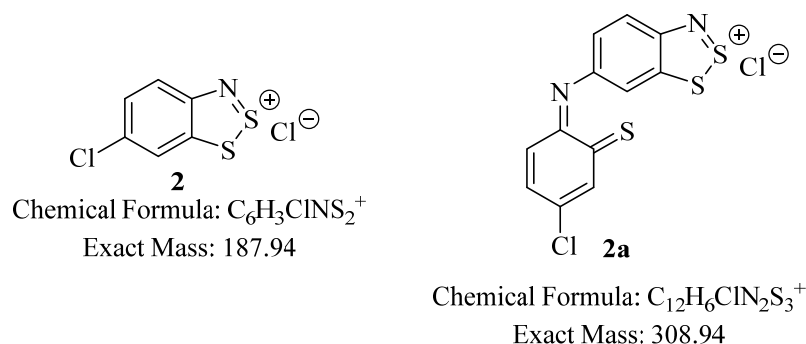


Figure 2. The structure of expected product (**2**) and a possible structure of the impurity detected by ASAP-MS.

3. Discussion

At a small scale, the dropwise addition of disulfur dichloride to the aniline solution and with the use of an external cooling bath (room-temperature water) is sufficient to control the reaction. Following further heating, the reaction time is required to complete the process. Different sources have suggested various figures, although in demonstration the optimal heating was found to be 80 °C for four hours, but only after an initial 30 min of stirring with the aforementioned external cooling in order to prevent thermal runaway.

A closer inspection of the mass spectrum of **2** corresponds perfectly to the organic cation (**2b**), confirming that the S–Cl interaction must be predominantly ionic in character (Figure 3).

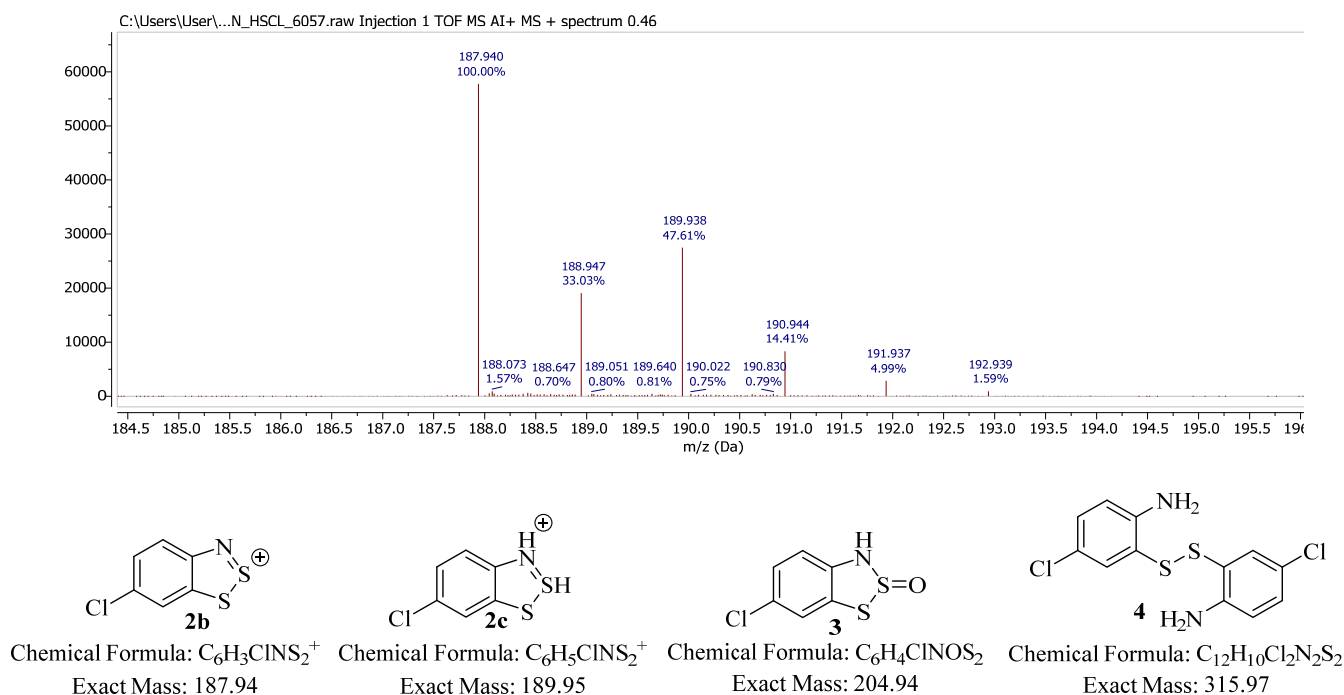
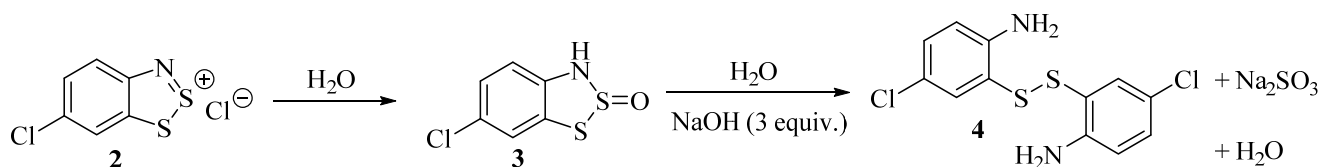


Figure 3. A region (185–195 Da) of the ASAP-MS spectrum obtained from the sample of (**2**) generated in this study according to the experimental. Y-axis is (total) ion count. Below are structures with their exact isotopic mass (the structure detected in this spectrum is likely **2b**).

The Herz salt (**2**) slowly reacts with moisture to form (**3**, Scheme 2) and this is accelerated by suspending the salt in an aqueous sodium acetate solution (5%) [9]. The data for the S-oxide compound (**3**) has been comprehensively presented by Neo et al. [8] for a variety of derivatives, although it should be noted that conversion from **2** to **3** is

readily monitored by ASAP-MS. Interestingly, the most intense ion observed from our solid sample of **3** is 189.95 mass units, not the expected mass of **3** but instead two units greater than the mass of **2**, suggesting that a structure equating to **2c** (Figure 3) is actually the species the spectrometer detects (which could be flanked by an undetected counterion, e.g., a hydroxide).



Scheme 2. The hydrolysis of **2** to sulfoxide **3**, followed by ring-opened thiophenol **4**.

The ASAP spectrum of compound **3** indicates that the sample contains impurities, which could not be removed effectively. One identified impurity is the ring-opened thiol **4**, a product of additional hydrolysis and dimerization (Scheme 2) [7]. Indeed, when the derivatives of **3** have been reacted in the literature, it is generally as a synthetic equivalent of **4**. Interestingly, for compound **3** the major observed ion (Figure 4) does not correspond to the expected structure, but instead to a structure such as **2c** (Figure 3).

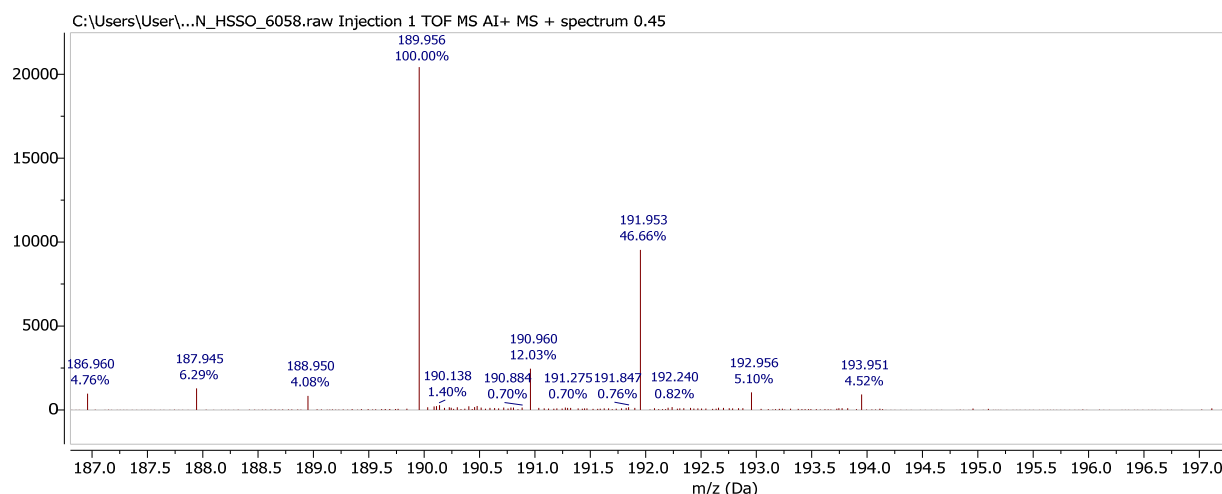
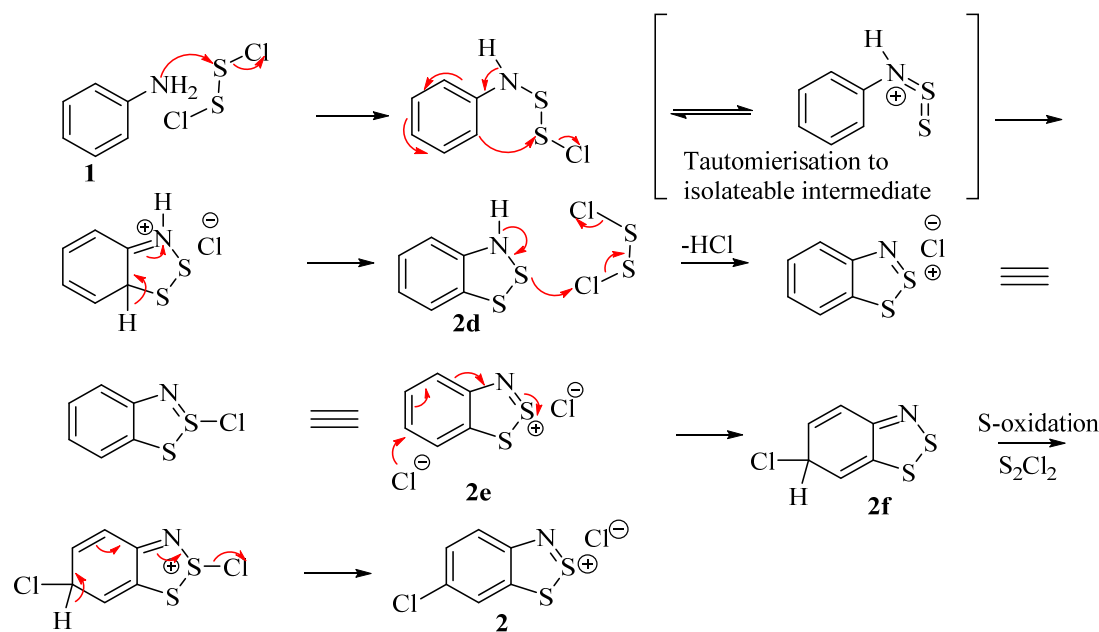


Figure 4. A region (187–197 Da) of the ASAP-MS spectrum obtained from the sample of (**3**) generated in this study according to the experimental. Y-axis is total ion count.

The following mechanism (Scheme 3) was recently proposed and published, aiming to take into account the literature results as well as the data collected in this study [6]. The consequences of the mechanism include the consumption of an excess of disulfur dichloride, although the precise extent of this is unclear. Regardless, when considering scale-up, this has severe consequences on the cost of the inputs and the amount of waste generated (not to mention the corrosive HCl fumes released from the reaction of S_2Cl_2). The Herz reaction is a remarkable transformation for its ability to not only introduce an *ortho*-sulfur to an aniline ring, but also activate it to nucleophilic attack at the 4-position (via the introduced chloride); it is surprising that only a handful of publications have made use of this unique feature [11,12].



Scheme 3. A proposed mechanism for the formation of title compound (2) by the Herz reaction.

4. Materials and Methods

All solid-state Carbon-13 magic-angle spinning measurements were carried out at 100.6 MHz using a Bruker Avance III HD spectrometer (Karlsruhe, Germany) and 4 mm (rotor o.d.) probe. The spectra were acquired at a spin rate of 10 kHz. The cross-polarisation (CP) spectra were recorded with TOSS spinning sideband suppression, 1 ms contact time and with a recycle delay of 1 s. The recycle delay and contact time were optimised for each sample. Carbon spectral referencing is relative to neat tetramethylsilane and carried out by setting the high-frequency signal from an external sample of adamantane to 38.5 ppm.

In addition to the CPTOSS spectrum, we used phase-inverted (cp_{pi}_toss) experiments to attempt to assist with identification and characterisation of the signals. This gave negative CH₂, null CH and positive C and CH₃ signals. Unfortunately, all of the carbon signals bunched tightly at approximately 130 ppm, meaning that assured identification was not possible (Figure 5).

Aniline (1, 50 mmol, 4.65 g, 1 equiv.) was added to acetic acid (10 mL) in a flask surrounded by a water bath (ambient temperature, 21 °C). Disulfur dichloride (200 mmol, 32.4 g, 4 equiv.) was added dropwise, evacuating the emitted fumes. The mixture was stirred for 30 min at room temperature and then heated at 80 °C for 4 h. Toluene (125 mL) was added to precipitate the 6-chloro-3H-benzo[d][1,2,3]dithiazolium chloride (2) as a dark red powder, contaminated with elemental sulfur (10.8 g, 96% recovery and 61% purity based upon elemental analysis), isolated by filtration from a brown liquor and washed with dry toluene (50 mL) followed by dry dichloromethane (50 mL), then dried *in vacuo*. IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 3019 (m, N-H), 1705 (m, N-H), 1574 (s, C=N), 1499 (m, Ar C-C), 1302 (s), 1299 (s), 1120 (m), 1103 (m), 945 (m), 823 (m), 751 (s), 658 (m), 523.5 (w), 406.4 (m). ASAP-MS: Rt = 0.67 min, m/z 187.940 ([M]⁺, 100%). HR-MS: calculated for: 187.9395, C₆H₃NS₂³⁵Cl, found: 187.9398 (Δ −1.6 ppm, −0.3 mDa). Elemental analysis found: C 20.06% (20.44), H 1.26% (0.86), N 3.38% (3.97).

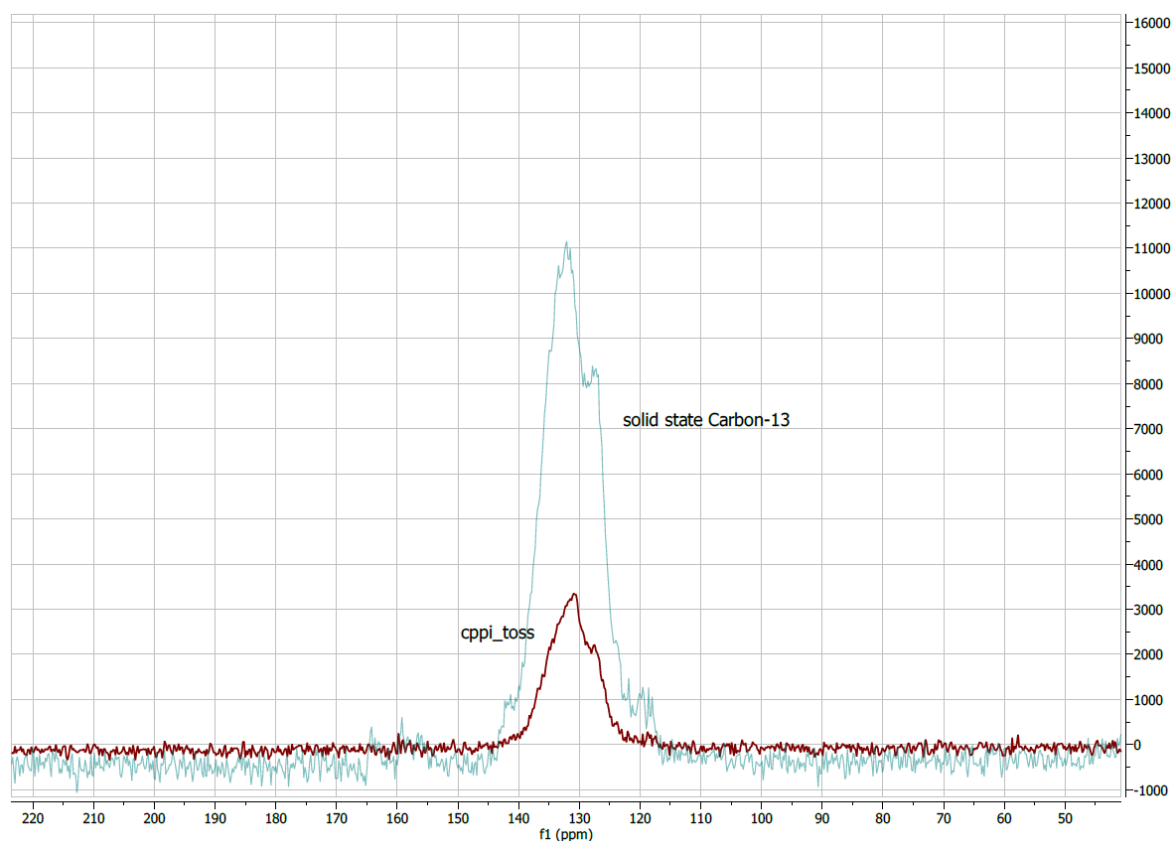


Figure 5. A region (50–220 ppm) of the solid-state ^{13}C NMR and CPTOSS spectrum of compound **2**.

Based upon the small-scale preparation, a large-scale synthesis was conducted.

A 2 L jacketed reactor connected to an external Huber Chiller set to maintain a working $15\text{ }^{\circ}\text{C}$ internal temperature and fitted with a mechanical stirrer and nitrogen purge line (Purge outlet to NaOH scrubber solution) was charged with acetic acid (200 mL). To the reactor was added aniline (**1**, 1 mol, 93.13 g, 1 equiv.), and the solution was stirred until an internal temperature of $15\text{ }^{\circ}\text{C}$ was reached (~ 15 min). Disulfur dichloride (319.6 mL, 4 mol, 4 equiv.) was added over 1 h dropwise (pressure equalised dropping funnel). Liberation of gas accompanied by a strong exotherm, with temperature reaching and remaining at $25\text{ }^{\circ}\text{C}$ for the duration of the controlled addition, was encountered. Following the addition, the mixture was stirred for an additional 45 min at $25\text{ }^{\circ}\text{C}$, and then the temperature was raised over 45 min and the mixture heated at $80\text{ }^{\circ}\text{C}$ for 4 h. The mixture was cooled to $35\text{ }^{\circ}\text{C}$ and diluted by the addition of a 8:2 mixture of toluene:DCM (1 L). The solution was further cooled to $10\text{ }^{\circ}\text{C}$, furnishing 6-chloro-3*H*-benzo[*d*][1,2,3]dithiazolium chloride (**2**) as a dark red suspension. The material was dispensed onto a sintered filter bed and agitated (nitrogen bubbling and stirring) with additional portions of toluene (2×500 mL) then dichloromethane (500 mL), with intermediate filtration. The solid was dried in vacuo at $40\text{ }^{\circ}\text{C}$ for 8 h. The solid (213.9 g, 95% recovery and 91% purity based upon elemental analysis) had identical spectroscopic data to the small-scale reaction but indicated a higher overall purity and darker red colour. Elemental analysis found: C 29.21% (32.16), H 1.12% (1.35), N 5.88% (6.25).

6-chloro-3*H*-benzo[*d*][1,2,3]dithiazolium chloride (**2**) (with the equivalent of 4S contamination as determined by elemental analysis) (31 mmol, 10.8 g, 1 equiv.) was suspended in a solution of sodium acetate trihydrate (62 mmol, 10.3 g, 2 equiv.) in water (125 mL) and stirred vigorously for 14 h. A purple solid was obtained by filtration from a mauve liquor and washed with water (50 mL) followed by EtOAc (50 mL). The purple solid was dissolved in boiling MeOH (800 mL), failing to crystallise and instead precipitating upon cooling to ambient temperature. A 6-chloro-3*H*-benzo[*d*][1,2,3]dithiazole-2-oxide

contamination of S₈ (9.3 g, 94%) was obtained as a dark purple solid. Sulfur removal was attempted by washing the purple solid with hot THF using a Soxhlet procedure, but this had little impact on the sulfur content. The NMR data in CDCl₃ is identical to that reported previously [8]. Greater solubility in DMSO allows a better quality of spectra: ¹H NMR (400 MHz; DMSO-*d*₆) 7.50–7.68 (2H, m, Ar-H), 7.13–7.28 (1H, m, Ar-H), 7.18 (1H, s, N-H) [8]. Solubility was insufficient for the resolved ¹³C NMR. IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 2785 (m, N-H), 2547 (m, N-H), 1600 (s, C=N), 1572 (m, Ar CC), 1467 (s), 1377 (s), 1098 (m), 1018 (m), 817 (m), 615 (m), 492 (s), 447 m. ASAP-MS: Rt = 0.44 min, *m/z* 189.955 ([M]⁺, 100%). Accurate Mass found 189.9539. C₆H₅NS₂ ³⁵Cl = 189.9552. (−1.3 mDa, Δ 6.8 ppm). Melting point 178.1–182.4 °C (MeOH). Literature: 113–114 °C (in absence of sulfur, MeOH) [8]. Elemental analysis found: C 21.55% (21.57), H 1.57% (1.21), N 3.56% (4.19). Solid state NMR data to be found in the Supplementary Materials.

5. Conclusions

As benzo[1,2,3]dithiazole appears more and more frequently in materials chemistry literature, the importance of understanding the processes that create it becomes greater. The first and most simple product of the Herz reaction has been synthesised on scale and identified using methods such as ASAP-MS and IR spectroscopy. The characteristics of the reaction and their implications at greater scales have been studied and considered. A mechanism of action has been proposed to explain the experimental and literature findings. The Herz reaction remains a valuable tool to generate benzo[1,2,3]dithiazole structures for research into new organic materials, although there remain barriers and expenses towards its adoption in large-scale synthesis.

Supplementary Materials: The following are available online: solid state NMR spectra for compound 2.

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Data Availability Statement: Supporting data available (link to Supporting Data File submitted).

Conflicts of Interest: The authors declare no conflict of interest.

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