One-Pot Synthesis of Azobenzene Derivatives by Oxidation of 2,3-Dihydrobenzothiadiazines

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Abstract: An oxidative route to N-substituted sulfonamidic azobenzene derivatives is reported. A mechanism, based on a rationalization of previous findings, is proposed. This simple one-pot method could be adapted to the synthesis of a range of substituted sulfonylazobenzenes with potential applications in the pharmaceutical and industrial fields.

Key words: azo compounds, sulfonamides, oxidation, ring opening, imines

The chemistry of substituted 1,2,4-benzothiadiazine 1,1-dioxides is extensively studied because such compounds represent an important scaffold in pharmaceutical chemistry that can be used as a basis for anticancer, nootropic, antihypertensive, diuretic and antiviral agents.[1–8]

Recently, we demonstrated that some chiral derivatives of 2,3-dihydrobenzothiadiazines (e.g., **1**) undergo rapid racemization at the stereogenic center C-3 in protic solvents.[9,10] It was suggested that the racemization mechanism involves an imine intermediate with the double bond at N-2 C-3 (**A**) or C-3 N-4, depending on the nature of the substituents and on the pH of the racemization solvent.[11,12]

More recently, our research group has developed a synthetic strategy to oxidize cyclic imines to azodioxy-carbonyl compounds by the action of 3-chloroperoxybenzoic acid (MCPBA).[13] Starting from the proposed racemization mechanism (Scheme 1), (±)-7-chloro-3-methyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (IDRA21, **1**), was oxidized with MCPBA.

Depending on the amount of peracid used, different products were obtained, which underlines the conclusion that the ratio IDRA21/MCPBA affects the oxidation reaction. Particularly, the oxidation reaction of IDRA21 performed with an excess of MCPBA (6 equiv.) at 0 °C in CH_2Cl_2 overnight, led only to the *N*-[(5-chloro-2-nitrophenyl)sulfonyl]acetamide (**2**), which was obtained in high yield (99%). A possible mechanism that explains the formation of **2** has been suggested (Scheme 1).

Since IDRA21 was in equilibrium with its imine intermediate **A** under the reaction conditions employed, it is likely that the iminic bond can add a molecule of water to give the corresponding carbinolamine **B**; the latter intermediate could be rapidly oxidized by one equivalent of MCPBA, to carbonyl intermediate **C**.[14] Since an excess of MCPBA was used, the reaction conditions could lead to oxidation of the amino group of intermediate **C** to give the corresponding nitroderivative **2**.[15–17]

With the aim of isolating intermediate **C**, the oxidation reaction of IDRA21 was carried out by using only one equivalent of MCPBA. However, after 12 hours, LC-MS analysis of the reaction mixture showed the formation of a new product that did not correspond to **C**, together with 70% unreacted starting material **1**, and trace amounts of nitro-derivative **2**. When the same reaction was carried out with three equivalents of MCPBA, the new product could be isolated. The product was identified as (*E*)-diazoderivative **3** (by NOESY measurement), and was probably derived from condensation of intermediate **C** with compound **2** (Scheme 1). In this regard, it has been reported that the treatment of aniline with hydrogen peroxide, under SeO_2 catalysis, leads to the formation of azobenzene.[16,17] Since the sulfonamidic group *ortho* to the aromatic amino group of intermediate **C** increases the reactivity of the amino group towards oxidative action of peracid, catalysis might not be necessary. To confirm the that the reaction also proceeded without added catalyst, 5-chloro-2-aminobenzensulfonamide (**4**) was oxidized with two equivalents of MCPBA under the same oxidation conditions described above for IDRA21. This reaction afforded the corresponding (*E*)-6,6′-(diazene-1,2-diyl)bis(3-chlorobenzenesulfonamide) (**5**) in 22% yield (Scheme 2), which is consistent with the mechanistic hypothesis presented in Scheme 1.

Due to the importance of azobenzene derivatives in both pharmacology and industry,[18–21] we extended the developed synthetic strategy to the preparation of a range of N-substituted sulfonamidic azobenzenes. For this purpose, a set of C-3 substituted 2,3-dihydrobenzothiadiazines were reacted with three equivalents of MCPBA (Table 1).

Reagents **1**, **6** and **7** (Table 1, entries 1–3) allowed us to evaluate how the length of the C-3 aliphatic chain affects the reactivity of benzothiadiazine in the oxidation reaction. The yield of the azobenzene derivatives increased

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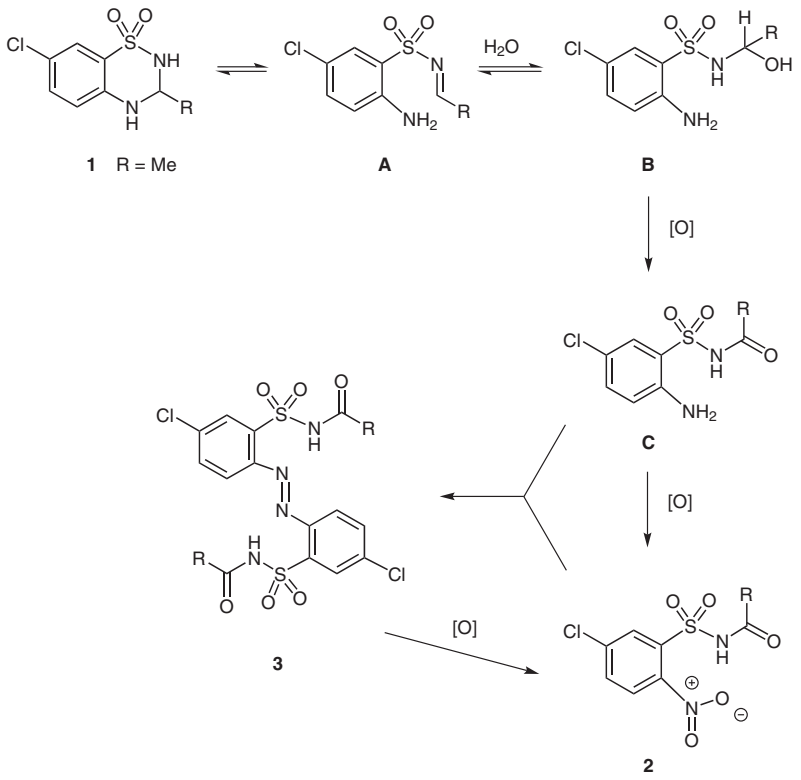
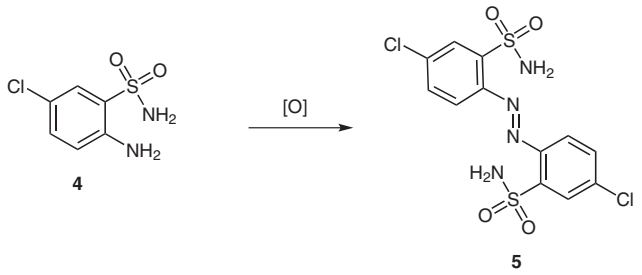


Scheme 1 Suggested oxidation mechanism of IDRA21 to nitro- and/or azo-derivative

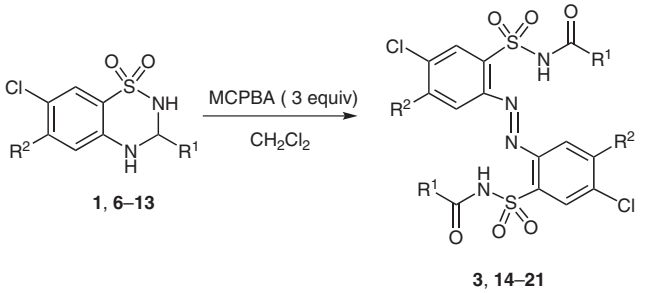


Scheme 2 Oxidation reaction of 5-chloro-2-aminobenzensulfonamide (**4**) to **5**

with the chain length, giving 19, 44 and 70% yield for R^1 = Me, Et and Pr, respectively (Table 1, entries 1–3). Presumably, the greater electron-donating effect of the aliphatic group and better solubility of the starting material with increasing C-3 chain length, positively influences the efficiency of the reaction. In contrast, benzothiadiazine **8** did not react, probably due to the strong electron-withdrawing effect of the trifluoromethyl group. This result supports the hypothesis that electron-donating substituents on C-3 of the benzothiadiazine increase reactivity (Table 1, entry 4). In addition, C-3 aryl-substituted benzothiadiazines **9**–**12** reacted with MCPBA to give the corresponding azobenzene derivatives **17**–**20** (Table 1, entries 5–8).

Compounds **9**–**12** were chosen to assess the influence of the C-3 aryl substituent on the reaction. Comparison of the reaction yields revealed that the yield increased by using

Table 1 Azobenzene Derivatives Obtained by Oxidation of 2,3-Dihydrobenzothiadiazines



Entry	Reagent	R^1	R^2	Product	Yield (%)
1	**1**	Me	H	**3**	19
2	**6**	Et	H	**14**	44
3	**7**	*n*-Pr	H	**15**	70
4	**8**	CF_3	H	**16**	–
5	**9**	Ph	H	**17**	72
6	**10**	3-ClC_6H_4	H	**18**	60
7	**11**	2-$MeOC_6H_4$	H	**19**	75
8	**12**	4-HOC_6H_4	H	**20**	75
9	**13**	Me	Cl	**21**	29

aryl substituents with an electron-donating effect on the C-3 of the benzothiadiazine (Table 1, entries 5–8). Furthermore, the reaction yields shown in Table 1 indicate that benzothiadiazines with a C-3 aryl substituent are more reactive than those with C-3 alkyl substituents. These results are consistent with previous studies regarding enantiomerization rates of 2,3-dihydrobenzothiadiazines.[9,10] Specifically, it was suggested that 3-alkylbenzothiadiazines possess an enantiomerization barrier higher than that of 3-phenyl-substituted benzothiadiazines. The resultant enantiomerization rates were consistent with an interconversion mechanism that involves the same imine intermediate with the double bond between N-2 and C-3 proposed to account the formation of azobenzene derivatives from benzothiadiazines.[9,10] In addition, a comparison between reagent **1** and **13** shows that a chloro substituent on C-6 of the benzothiadiazine does not affect the reaction yield (Table 1, entries 1 and 9).

In summary, a new synthetic pathway, based on the oxidation of 2,3-dihydrobenzothiadiazines with MCPBA, to produce sulfonamidic azobenzene derivatives was developed. 2,3-Dihydrobenzothiadiazines are easily prepared in high yields (99%) by ring closure of commercially available substituted benzenesulfonamides with selected aldehydes, under catalytic acid conditions.[1]

Moreover, in accordance with our previously published results, a reaction mechanism was proposed. This simple one-pot method could be adapted to the synthesis of a range of substituted sulfonylazobenzenes.

Because of the importance of azobenzenes,[18–23] this synthetic pathway seems to be an attractive strategy and an economic approach to the preparation of products with potential in both pharmaceutical and industrial fields. In particular, azobenzene is widely used as a photoswitch in biological systems to drive functional changes in peptides, proteins, nucleic acids, lipids, and carbohydrates.[21–23]

Finally, it is noteworthy that azobenzene derivatives are employed as prodrugs because they are rapidly metabolized into the corresponding aromatic amino derivatives by azoreducatase enzymes within the body.[18] A common system for measuring metabolism uses liver microsomes, a subcellular fraction containing major drug-metabolizing enzymes, including the cytochrome P450 family and flavin monooxygenase. For this reason, the microsomial metabolism of the obtained azobenzenes is under investigation and the results will be the object of another publication.

All reactions involving air-sensitive reagents were performed under an atmosphere of nitrogen in oven-dried glassware by using syringe/septum cap techniques. CH_2Cl_2 was distilled from calcium hydride before use. Petroleum ether refers to the 40–60 °C boiling fraction. 2-Amino-5-chlorobenzenesulfonamide (**4**) and *m*-chloroperbenzoic acid (MCPBA) were of commercial grade (Aldrich) and used without further purification. 2,3-Dihydrobenzothiadiazines **1**, **6-12** were obtained by ring closure of **4** with a selected aldehyde, under catalytic acid conditions, following reported synthetic protocols.[1] Dihydrobenzothiadiazine (**13**) was obtained by ring closure of the commercially available 2-amino-4,5-dichlorobenzenesulfonamide with acetaldehyde.[1] The ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance 400 apparatus (400.13 and 100.62 MHz, for ^1H and ^{13}C, respectively) with $CDCl_3$ as the solvent and TMS as an internal standard (δ = 7.26 ppm for ^1H spectra; δ = 77.0 ppm for ^{13}C spectra). The IR spectra were recorded with a Digilab Scimitar Series FTS 2000 FTIR spectrophotometer. LC–MS analyses were performed using an Agilent 1260 Infinity Series HPLC system coupled to Agilent 6420 triple quadrupole detector equipped with electrospray ionization (ESI). The electrospray ionization [HRMS (ESI)] experiments were carried out in a hybrid QqTOF mass spectrometer (PE SCIEX–QSTAR) equipped with an ion-spray ionization source. MS (+) spectra were acquired by direct infusion (5 μL·min^{-1}) of a solution containing the appropriate sample (10 pmol·μL^{-1}) dissolved in a solution of 0.1% AcOH, MeOH–H_2O (50:50) at the optimum ion voltage of 4800 V. The nitrogen gas flow was set at 30 psi and the potentials of the orifice, the focusing ring and the skimmer were kept at 30, 50 and 25 V relative to ground, respectively. Melting points were determined with an Electrothermal melting point apparatus and are uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; viewing was by UV light (254 nm). Column chromatography was performed on silica gel (63–200 mm) using petroleum ether–EtOAc mixtures as eluents.

_N_-Acetyl-5-chloro-2-nitrobenzenesulfonamide (2)

To an ice-cooled solution of **1** (233 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise an excess of MCPBA (1478 mg, 6.0 mmol, 70%) in CH_2Cl_2 (10 mL) previously cooled in an ice bath. The mixture was allowed to gradually warm to r.t., with stirring, over 12 h. TLC and LC-MS analyses were used to monitor reaction progress. When the reaction was complete, the solution was stirred with excess powered anhydrous Na_2CO_3 until carbon dioxide evolution ceased. After filtration, the mixture was concentrated in vacuo at r.t. to give pure **2**.

Yield: 275 mg (99%); yellow solid; mp 160−163 °C.

IR (KBr): 3160, 3101, 2990, 1600, 1550, 1350, 850 cm^{-1}.

^1H NMR (400.13 MHz, $CDCl_3$): δ = 2.48 (s, 3 H, CH_3), 7.63 (d, *J* = 9.0 Hz, 1 H, ArH), 7.98 (d, *J* = 9.0 Hz, 1 H, ArH), 8.06 (s, 1 H, ArH), 9.25 (br s, 1 H, NH).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.8, 125.4, 126.9, 133.0, 135.8, 138.1, 143.5, 165.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_7ClN_2O_5S$: 278.9842; found: 278.9840.

(*E*)-6,6′-(Diazene-1,2-diyl)bis(3-chlorobenzenesulfonamide) (5)

To an ice-cooled solution of 2-amino-5-chlorobenzenesulfonamide (**4**; 206 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise an excess of MCPBA (493 mg, 2.0 mmol, 70%) in CH_2Cl_2 (10 mL) previously cooled in an ice bath. The mixture was allowed to gradually warm to r.t., with stirring, over 12 h. TLC and LC-MS analyses were used to monitor reaction progress. The solution was then evaporated to dryness, in vacuo at r.t., to give the crude material, which was purified by chromatography on silica gel (petroleum ether–EtOAc, 50:50).

Yield: 45 mg (22%); yellow solid; mp 198−200 °C.

IR (KBr): 3160, 3100, 2990, 1600, 1495, 1210, 840 cm^{-1}.

^1H NMR (400.13 MHz, acetone-d_6): δ = 6.65 (dd, *J* = 9.0, 2.1 Hz, 2 H, ArH), 7.09 (s, 2 H, ArH), 7.50 (d, *J* = 9.0 Hz, 2 H, ArH), 8.70 (br s, 4 H, NH_2).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 115.8, 119.0, 122.7, 131.3, 132.6, 136.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}Cl_2N_4O_4S_2$: 408.9599; found: 408.9598.

Azobenezene Derivatives 3 and 14–21; General Procedure
To an ice-cooled solution of 2,3-dihydrobenzothiadiazine **1** or **6**–**13** (1.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise an excess of MCPBA (739 mg, 3.0 mmol, 70%) in CH_2Cl_2 (10 mL) previously cooled in an ice bath. The mixture was allowed to gradually warm to r.t., with stirring, over 12 h. TLC and LC-MS analyses were used to monitor reaction progress. The solution was then evaporated to dryness, in vacuo at r.t., to give the crude material. The reaction mixture was purified by chromatography on silica gel (petroleum ether–EtOAc, 60:40).

Compound 3
Yield: 46 mg (19%); light-yellow solid; mp 190−192 °C.

IR (KBr): 3212, 3108, 3076, 2984, 2943, 1744, 1582, 1462, 1380, 1288, 1175, 862 cm^{-1}.

^1H NMR (400.13 MHz, $CDCl_3$): δ = 2.47 (s, 6 H, CH_3), 7.33 (d, *J* = 9.0 Hz, 2 H, ArH), 7.47 (dd, *J* = 9.0, 2.1 Hz, 2 H, ArH), 7.64 (d, *J* = 2.1 Hz, 2 H, ArH), 8.95 (br s, 2 H, NH).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 20.0, 115.6, 120.9, 122.6, 131.2, 132.5, 134.0, 162.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{15}Cl_2N_4O_6S_2$: 492.9810; found: 492.9812.

Compound 14
Yield: 114 mg (44%); light-yellow solid; mp 187−190 °C.

IR (KBr): 3211, 3110, 3076, 2984, 2945, 1744, 1580, 1463, 1420, 1290, 1175, 860 cm^{-1}.

^1H NMR (400.13 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.4 Hz, 6 H, CH_3), 2.74 (q, *J* = 7.4 Hz, 4 H, CH_2), 7.32 (d, *J* = 9.0 Hz, 2 H, ArH), 7.46 (dd, *J* = 9.0, 2.1 Hz, 2 H, ArH), 7.63 (d, *J* = 2.1 Hz, 2 H, ArH), 8.95 (br s, 2 H, NH).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 9.1, 27.0, 116.7, 121.9, 123.6, 132.2, 133.5, 135.0, 163.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{19}Cl_2N_4O_6S_2$: 521.0123; found: 521.0125.

Compound 15
Yield: 192 mg (70%); light-yellow solid; mp 180.5−182 °C.

IR (KBr): 3232, 3110, 3079, 2964, 2933, 2873, 1698, 1580, 1541, 1462, 1416, 1374, 1287, 1175, 899 cm^{-1}.

^1H NMR (400.13 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.4 Hz, 6 H, CH_3), 1.63 (sext, *J* = 7.4 Hz, 4 H, CH_2CH_3), 2.62 (t, *J* = 7.4 Hz, 4 H, $COCH_2$), 7.34 (d, *J* = 9.0 Hz, 2 H, ArH), 7.47 (dd, *J* = 9.0, 2.1 Hz, 2 H, ArH), 7.66 (d, *J* = 2.1 Hz, 2 H, ArH), 8.98 (br s, 2 H, NH).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 13.4, 18.6, 35.2, 116.8, 121.9, 123.6, 132.3, 133.5, 135.1, 162.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{23}Cl_2N_4O_6S_2$: 549.0436; found: 549.0439.

Compound 17
Yield: 222 mg (72%); light-yellow solid; melts with decomposition.

IR (KBr): 3184, 2923, 2853, 1599, 1510, 1414, 1374, 1286, 827 cm^{-1}.

^1H NMR (400.13 MHz, acetone-d_6): δ = 7.52–7.56 (m, 6 H, ArH), 7.85–7.90 (m, 10 H, ArH), 11.37 (br s, 2 H, NH).

^{13}C NMR (100.62 MHz, acetone-d_6): δ = 117.7, 123.2, 124.5, 128.0, 130.0, 131.4, 131.6, 131.7, 133.3, 136.7, 157.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{19}Cl_2N_4O_6S_2$: 617.0123; found: 617.0125.

Compound 18
Yield: 206 mg (60%); light-yellow solid; mp 228−231 °C.

IR (KBr): 3176, 2963, 2923, 1696, 1574, 1515, 1472, 1427, 1370, 1291, 1164, 1114, 828 cm^{-1}.

^1H NMR (400.13 MHz, acetone-d_6): δ = 7.57–7.67 (m, 4 H, ArH), 7.84–7.94 (m, 10 H, ArH), 11.35 (br s, 2 H, NH).

^{13}C NMR (100.62 MHz, acetone-d_6): δ = 117.8, 123.3, 124.4, 128.5, 129.7, 129.9, 131.4, 131.6, 133.4, 133.5, 136.5, 155.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{17}Cl_4N_4O_6S_2$: 684.9344; found: 684.9346.

Compound 19
Yield: 254 mg (75%); light-yellow solid; mp 195−198 °C.

IR (KBr): 3160, 3072, 2974, 2944, 1703, 1600, 1584, 1518, 1489, 1417, 1190, 833 cm^{-1}.

^1H NMR (400.13 MHz, $CDCl_3$): δ = 3.96 (s, 6 H, OCH_3), 7.04 (d, *J* = 8.2 Hz, 2 H, ArH), 7.14 (dt, *J* = 7.6, 0.8 Hz, 2 H, ArH), 7.54–7.66 (m, 8 H, ArH), 7.86 (d, *J* = 2.1 Hz, 2 H, ArH), 8.24 (br s, 2 H, NH).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 56.8, 111.5, 117.0, 121.0, 122.2, 123.3, 124.0, 131.7, 132.5, 133.3, 133.6, 135.2, 155.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{23}Cl_2N_4O_8S_2$: 677.0334; found: 677.0336.

Compound 20
Yield: 243 mg (75%); light-yellow solid; mp 228–230 °C.

IR (KBr): 3169, 3105, 3076, 2924, 1608, 1586, 1498, 1414, 1374, 1287, 1114, 835 cm^{-1}.

^1H NMR (400.13 MHz, acetone-d_6): δ = 6.96 (d, *J* = 8.9 Hz, 4 H, ArH), 7.79–7.90 (m, 10 H, ArH), 9.32 (br s, 2 H, OH), 11.09 (br s, 2 H, NH).

^{13}C NMR (100.62 MHz, acetone-d_6): δ = 115.7, 118.6, 123.0, 123.9, 125.6, 132.0, 133.6, 133.9 (2C), 137.8, 161.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{19}Cl_2N_4O_8S_2$: 649.0021; found: 649.0020.

Compound 21
Yield: 81 mg (29%); light-yellow solid; mp 226−229 °C.

IR (KBr): 3076, 2963, 2923, 1697, 1577, 1515, 1472, 1428, 1370, 1291, 1165, 1114, 829 cm^{-1}.

^1H NMR (400.13 MHz, $CDCl_3$): δ = 2.49 (s, 6 H, CH_3), 7.52 (s, 2 H, ArH), 7.77 (s, 2 H, ArH), 8.97 (br s, 2 H, NH).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.8, 116.8, 120.4, 125.6, 131.5, 135.2, 138.9, 160.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{13}Cl_4N_4O_6S_2$: 560.9031; found: 560.9029.

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