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Synthesis of 4-unsubstituted 2*H*-1,2,3-benzothiadiazine 1,1-dioxides via *ortho* lithiation of protected benzaldehyde derivatives

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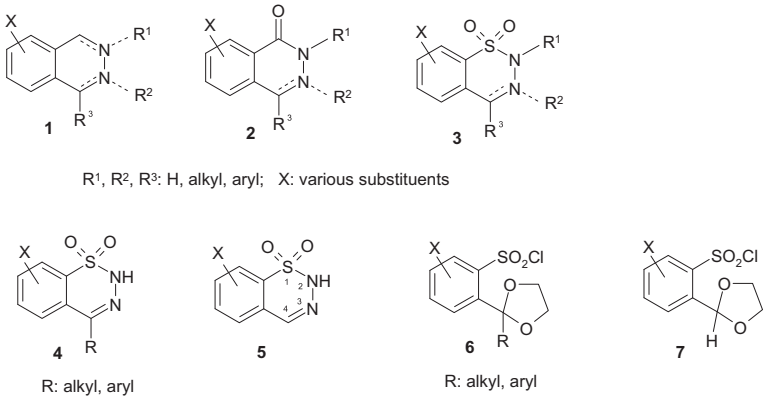
ABSTRACT

Variously substituted 2-phenyl-1,3-dioxolanes and 2-(2-bromophenyl)-1,3-dioxolanes, prepared from the corresponding benzaldehydes, were lithiated *ortho* to the acetal group. Reaction of the lithio derivatives with sulfur dioxide led to the lithium sulfinate salts, which gave, upon oxidative chlorination with sulfuryl chloride, the corresponding benzenesulfonyl chlorides. Then, depending on the aromatic substitution pattern of the molecule, several protocols were elaborated for the functional group transformations leading to the target compounds. Ring closure was performed with hydrazine hydrate or acetylhydrazine, in the latter case with one-pot removal of the acetyl group. The 4-unsubstituted 2*H*-1,2,3-benzothiadiazine 1,1-dioxides thus obtained are potential drug candidates based on their structural similarity to biologically active phthalazinones.

1. Introduction

Biological efficacy of compounds bearing a phthalazine (**1**, Scheme 1) or phthalazinone (**2**) skeleton is discussed in several papers and patent applications. Compounds **1** are known as active antiparasital agents,[1] AMPA/kainate receptor allosteric modulators[2] and phosphodiesterase-4 (PDE-4) inhibitors.[3] Also, they can potentially be used for the treatment of protein-kinase mediated diseases[4] and depression.[5] Various pharmacological and therapeutic effects are also described for compounds **2** ranging from poly (ADP-ribose) polymerase (PARP) inhibition[6] to antagonism of chemoattractant receptor-homologous molecule expressed on T helper type 2 cells (CRTH-2).[7] Other members of the family **2** exhibit anti-inflammatory effect,[8] cytoprotective properties[9] and antihistamine efficacy.[10] Certain representatives of the 1,2,3-benzothiadiazine 1,1-dioxide (**3**) family, structurally related to



Scheme 1.

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compounds **2**, also act as antagonists of the CRTH-2 receptor[7] or as bactericides and fungicides.[11]

While the syntheses of phthalazines (**1**) and phthalazinones (**2**) are well elaborated,[12] the literature on the preparation and chemistry of compounds **3**–**5** (Scheme 1) is rather scarce. Apart from the unsubstituted, C=N double bond containing congener, 2*H*-1,2,3-benzothiadiazine 1,1-dioxide (**5**, X=H),[13] only a few representatives of family **4** are described, bearing a substituted amino,[14] a hydrazino[15] or a substituted phenyl[16] moiety at position 4 (substituent R in **4**). 4-Unsubstituted congeners with various substitution patterns on the aromatic ring (**5**, X≠H) are unknown in the literature.

In the course of our earlier efforts to explore 4-alkyl- (**4**, R=alkyl)[17] and 4-aryl-2*H*-1,2,3-benzothiadiazine 1,1-dioxides (**4**, R=Ph or substituted phenyl) with anxiolytic effect, we elaborated the synthesis of the precursors of the target compounds: acetophenone and benzophenone derivatives masked as 1,3-dioxolanes were chlorosulfonylated *ortho* to the protected keto group (**6**, Scheme 1) via *ortho*-lithiation chemistry.[18,19]

Now, we aimed at elaborating a versatile synthetic route for the preparation of 4-unsubstituted 2*H*-1,2,3-benzothiadiazine 1,1-dioxides (**5**). The syntheses of sodium 2-formylbenzenesulfonate as the key intermediate of the only described representative (**5**, X=H),[13b] involving either oxidation of 2-methylsulfonic acid[20] or introduction of the sulfonic acid function to 2-chlorobenzaldehyde by nucleophilic substitution with sodium sulfite[21] are not generalizable. Therefore, an alternative method was sought, which could be extended to other derivatives with various aromatic substitution patterns. *ortho*-Lithiation and subsequent chlorosulfonylation of benzaldehydes, which are temporarily protected and at the same time transformed into an *ortho*-directing group, promised to be a suitable route for the synthesis of the key intermediates of the target compounds.

Several methods are known for such an *ortho*-functionalization of benzaldehydes. Benzaldehydes protected as cyclohexylimines exhibit *ortho* directing potential in lithiation reactions.[22,23] 1,3-Dimethyl-2-phenylimidazolidine, prepared from benzaldehyde and *N*,*N*′-dimethylethylenediamine, also led to *ortho*-lithio intermediates upon reaction with butyllithium and TMEDA.[24] A more general method was described by Comins et al., who reported on the *ortho* lithiation of various lithium α-amino(phenyl)methanolates.[25] These latter were generated in situ from aromatic aldehydes and lithium dialkylamides (e.g., lithium morpholin-4-ide or lithium 4-methylpiperazin-1-ide).

Nevertheless, our synthetic approach necessitated such an *ortho* directing group that was expected to protect the carbonyl group not only in the lithiation reaction but also in the planned chlorination step leading to intermediates **7** (Scheme 1), and at the same time could be hydrolyzed under mild conditions so that the chlorosulfonyl moiety of **7** remains stable. 1,3-Dioxolanes prepared by acetalization of the corresponding benzaldehydes with ethylene glycol seemed suitable for this purpose.

2. Results and discussion

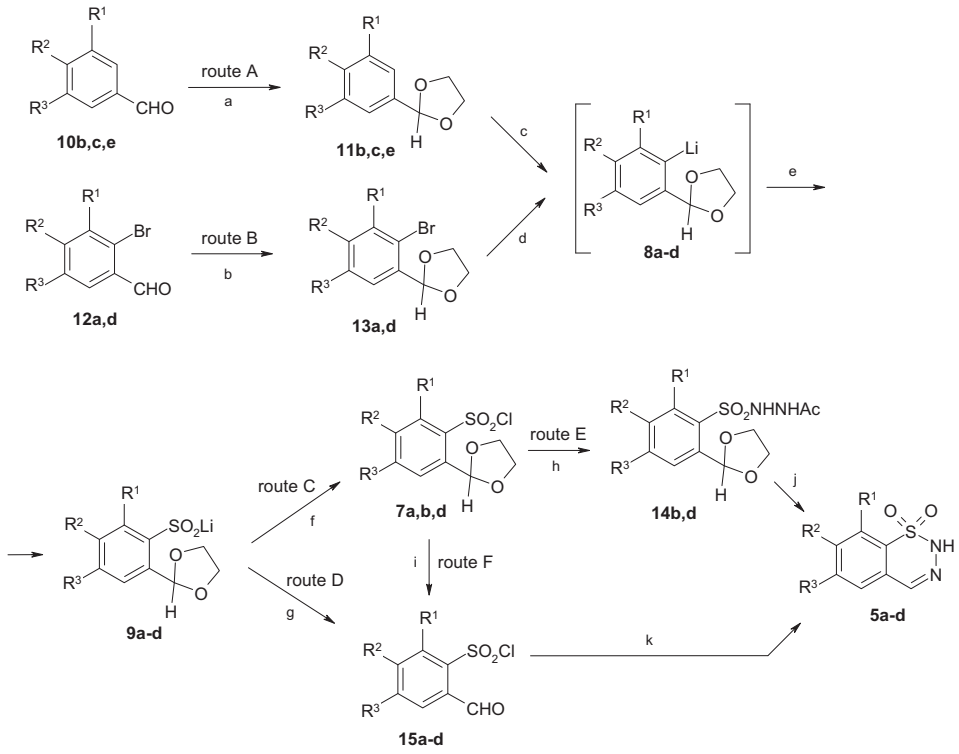
In continuation of our earlier work dealing with the lithiation of acetophenones[18] and benzophenones[19] protected as 1,3-dioxolanes we report here on the synthesis (Scheme 2) of *ortho*-chlorosulfonyl benzaldehyde acetals **7** (via *ortho*-lithio intermediates **8** and lithium sulfinates **9**) and their transformation to the corresponding 2*H*-1,2,3-benzothiadiazine 1,1-dioxides (**5**). Depending on which approach seemed more promising, two strategies were applied for the preparation of lithiated intermediate **8**: directed *ortho*-metalation (route A) or bromine–lithium exchange (route B). We will also show various alternatives for the transformation of acetal-protected lithium sulfinates **9** to target compounds **5** (routes C–F).

The bromine–lithium exchange approach (route B) proved to be more advantageous for the preparation of the unsubstituted (**5a**) and 6-methoxy substituted (**5d**) target compounds. In the former case, literature data on the unsuccessful attempts for the direct lithiation of the unsubstituted derivative, 2-phenyl-1,3-dioxolane (**11a**)[26] suggested the use of the commercially available 2-bromobenzaldehyde (**12a**, route B) as the starting material instead.[27] In the latter case, lithiation of 2-(3-methoxyphenyl)-1,3-dioxolane (**11d**) with butyllithium is expected to occur primarily at the doubly activated position between the substituents,[28] therefore bromo derivative **12d** was used to achieve the required regioselective lithiation leading to the key intermediate **8d**, which could ultimately result in target compound **5d**.

Thus, benzaldehydes **10** were transformed into the corresponding 1,3-dioxolanes **11** by reaction with ethylene glycol in toluene at reflux temperature, in the presence of *para*-toluenesulfonic acid (Scheme 2, route A). 2-Bromobenzaldehyde derivatives **12** were transformed to *ortho*-brominated acetal-protected benzaldehydes **13** analogously or under microwave conditions[29] (route B). Lithiation of compounds **11** and **13** with butyllithium in THF and quenching with sulfur dioxide led to lithium sulfinates **9**. Treatment with sulfuryl chloride resulted in the formation of benzenesulfonyl chloride derivatives. This oxidative chlorination step and the subsequent work-up procedure could in certain cases be performed without hydrolysis of the dioxolane moiety, thus compounds **7a**,**b**,**d** were isolated (route C). Reaction of 2,3-dichloro (**7b**) and 4-methoxy (**7d**) derivatives with acetylhydrazine in IPA resulted in the formation of sulfonyl-acetohydrazides **14b** and **14d**, respectively (route E). Under acidic reflux conditions, removal of the acetal protecting group, deacetylation and ring closure took place in one pot giving rise to the formation of target compounds **5b** and **5d**.

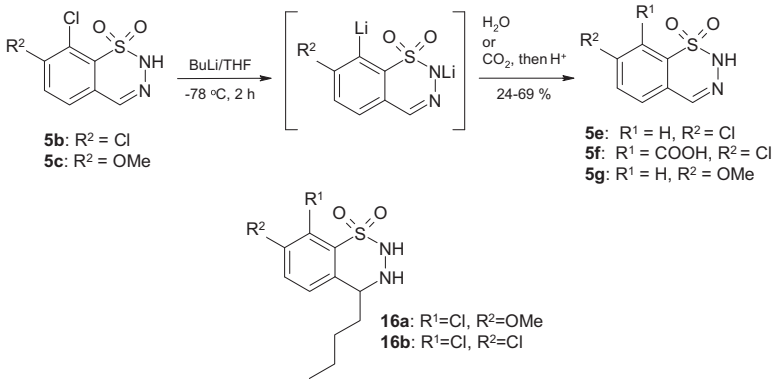
An alternative method was carried out with **7a**: the dioxolane protecting group was removed by stirring with concentrated sulfuric acid in the presence of Kieselgel (route F), leading to 2-formylbenzenesulfonyl chloride (**15a**). The same protocol could also be applied for **7b** and **7d**. However, in the case of the 2-chloro-3-methoxyphenyl (**9c**) lithium sulfinate, chlorination with sulfuryl chloride gave after work-up a mixture of acetal **7c** and its hydrolyzed derivative **15c**. Hydrolysis of the mixture to pure **15c** was completed by stirring with Kieselgel and concentrated sulfuric acid. Compounds **15a**–**d** were then treated with hydrazine hydrate to give benzothiadiazine derivatives **5a**–**d**.

Contrary to our expectations based on the former results obtained in the lithiation of 2-(4-chlorophenyl)-2-methyl-[18] and 2-(4-chlorophenyl)-2-phenyl-1,3-dioxolane[19] with butyllithium, 2-(4-chlorophenyl)-1,3-dioxolane (**11e**) could not be lithiated at the 2-position of the 4-chlorophenyl ring under the same or even harsher conditions (THF, from −78 up to +50 °C). Therefore, an alternative approach had to be elaborated for the preparation of target compound 7-chloro-2*H*-1,2,3-benzothiadiazine 1,1-dioxide (**5e**, Scheme 3). Considering that the sulfonamide moiety is a strong *ortho*-directing group,[30,31] chlorine–lithium exchange in 7,8-dichloro-2*H*-1,2,3-benzothiadiazine 1,1-dioxide (**5b**) was attempted. Indeed, reaction of **5b** with BuLi (−78 °C, 2 h) and subsequent quenching with water led to **5e** in 69% yield. Quenching of the lithium salt with dry ice gave 8-carboxy-7-chloro congener **5f**, a useful building block also for further functionalizations. When starting from the 8-chloro-7-methoxy derivative **5c**, aqueous work-up of the lithio intermediate led to the 7-methoxy target compound **5g**. Nevertheless, only a poor yield could be achieved in this latter reaction. When lithiations were carried out at −78 °C, a significant amount of the starting material could be recovered even if a fivefold excess of BuLi and a longer reaction time (5 h) was applied. If the temperature was elevated to 0 °C, 4-butyl derivative **16a** was formed as the main product, due to the addition of BuLi to the C=N double bond. It is to be noted that the formation of an analogous BuLi adduct (**16b**) could also be detected by ^{1}H NMR in crude products **5e** and **5f** as a minor impurity.



5, 7-15	R^1	R^2	R^3	Synthetic sequence applied
a	H	H	H	route B + route C + route F
b	Cl	Cl	H	route A + route C + route E *or* route A + route C + route F
c	Cl	OMe	H	route A + route D
d	H	H	OMe	route B + route C + route E *or* route B + route C + route F
e	H	Cl	H	alternative method (see Scheme 3)

Scheme 2. Reagents and conditions: (a) HO–$(CH_2)_2$–OH, toluene, reflux, 6–12 h, 84–100%; (b) HO–$(CH_2)_2$–OH, toluene, reflux, 5 h, 90%; or MW, 2 h, 77%; (c,d) BuLi, THF, −78 °C; (e) SO_2, THF, −78 °C to rt, 69–100% calculated for **11** or **13**; (f) SO_2Cl_2, hexane, −5 to 0 °C, 1 h, 74–98%; (g) step 1: SO_2Cl_2, hexane, −5 to 0 °C, 1.5 h; step 2: H_2SO_4, $CHCl_3$, Kieselgel, rt, 3 h, 3278% calculated for **11c**; (h) H_2N–NHAc, IPA, 0 °C rt, 2–12 h, 76–96%; (i) H_2SO_4, $CHCl_3$, Kieselgel, rt, 20–30 h, 54–88%; (j) 10% aq HCl, reflux, 2.5–3 h, 56–87%; (k) $N_2H_4 \cdot H_2O$, THF, rt or reflux, 1–2 h, 20–89%.



Scheme 3.

3. Conclusions

A new, versatile synthetic route is disclosed here for the synthesis 4-unsubstituted 2*H*-1,2,3-benzothiadiazine 1,1-dioxides. The key step of the synthetic route is directed *ortho* lithiation of benzaldehyde derivatives protected as dioxolanes or bromine–lithium exchange of their *ortho*-bromo congeners, followed by introduction of the sulfinate group by using sulfur dioxide as the electrophile for quenching the aromatic lithium salt. Thereafter, the slightly different behavior of the analogues variously substituted on

the aromatic ring necessitated the development of alternative methods for the further conversion of the lithium sulfinate salts to the target compounds. According to one procedure, the sulfinate group was transformed to sulfonyl-acetohydrazide via the corresponding sulfonyl chloride, while the dioxolane protecting group was kept intact until the final cyclization reaction leading to the target compounds. In the course of the other variant, the primarily prepared *ortho*-formylbenzenesulfonyl chloride was cyclized to the corresponding 2*H*-1,2,3-benzothiadiazine 1,1-dioxide. Thanks to the novel, versatile intermediates, i.e., the *ortho*-chlorosulfonylated benzaldehydes and their dioxolane counterparts, the significance of the synthetic route described above goes beyond the preparation of these particular compounds, by rendering possible the synthesis of various new compound families.

4. Experimental section

All melting points were determined on a Büchi 535 capillary melting point apparatus. IR spectra were obtained on a Bruker IFS-113v FT spectrometer in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 (200 and 50 MHz for ^{1}H and ^{13}C NMR spectra, respectively), Bruker Avance III (400 and 100 MHz for ^{1}H and ^{13}C NMR spectra, respectively) or a Varian Unity Inova 500 spectrometer (500 and 125 MHz for ^{1}H and ^{13}C NMR spectra, respectively). $CDCl_3$ or DMSO-d_6 was used as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) and coupling constants (J) are given in parts per million and in Hertz, respectively. Elemental analyses were performed on a Perkin–Elmer 2400 analyzer. The reactions were followed by analytical thin layer chromatography on silica gel 60 F_{254}. All unspecified reagents were purchased from commercial sources. The yields have not been optimized.

4.1. 2-(3,4-Dichlorophenyl)-1,3-dioxolane (11b)[32]

A solution of 3,4-dichlorobenzaldehyde (**10b**, 52.5 g, 0.30 mol), ethylene glycol (33 mL, 36.7 g, 0.59 mol) and *p*-toluenesulfonic acid (1.0 g, 0.005 mol) in toluene (300 mL) was refluxed in a Dean–Stark apparatus for 6 h. The reaction mixture was washed with aqueous sodium hydrogen carbonate solution (5 w/w%, 120 mL) and water (150 mL), dried over $MgSO_4$ and the solvent was evaporated to give **11b** (67.4 g, 100%) as colorless crystals, mp 42–47 °C. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.58 (1H, d, J=1.8 Hz), 7.45 (1H, d, J=8.1 Hz), 7.30 (1H, dd, J=8.1, 1.8 Hz), 5.77 (1H, s), 4.06 (4H, m). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 138.4, 133.0, 132.4, 130.3, 128.5, 125.8, 102.1, 65.2. IR (KBr, cm^{-1}) 2880, 1472, 1359. Anal. Calcd for $C_9H_8Cl_2O_2$ (219.08): C 49.34, H 3.68, Cl 32.37%. Found: C 49.41, H 3.76, Cl 32.04%.

4.2. 2-(3-Chloro-4-methoxyphenyl)-1,3-dioxolane (11c)

A solution of 3-chloro-4-methoxybenzaldehyde (**10c**, 11.72 g, 0.068 mol), ethylene glycol (7.56 mL, 8.39 g, 0.135 mol) and *p*-toluenesulfonic acid (0.23 g, 1.3 mmol) in toluene (70 mL) was refluxed in a Dean–Stark apparatus for 12 h. The reaction mixture was washed with aqueous sodium hydrogen carbonate solution (5 w/w%, 100 mL) and water (2×100 mL), dried over $MgSO_4$ and the solvent was evaporated to give **11c** (13.60 g, 93%) as a pale yellow oil. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.48 (1H, d, J=2.1 Hz), 7.38 (1H, dd, J=8.4, 2.1 Hz), 7.13 (1H, d, J=8.4 Hz), 5.69 (1H, s), 4.05 (2H, m), 3.93 (2H, m), 3.87 (3H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 155.3, 131.6, 128.1, 126.9, 121.1, 122.5, 102.1, 64.9, 56.2. IR (KBr, cm^{-1}) 2890, 1507, 1265. Anal. Calcd for $C_{10}H_{11}ClO_3$ (214.65): C 55.96, H 5.17, Cl 16.52%. Found: C 55.56, H 5.23, Cl 16.40%.

4.3. 2-(4-Chlorophenyl)-1,3-dioxolane (11e)

A solution of 4-chlorobenzaldehyde (**10e**, 29.0 g, 0.20 mol), ethylene glycol (40 mL, 44.5 g, 0.72 mol) and *p*-toluenesulfonic acid (0.4 g, 0.002 mol) in toluene (120 mL) was refluxed in a Dean–Stark apparatus for 6 h. The reaction mixture was washed with aqueous sodium hydrogen carbonate solution (5 w/w%, 150 mL) and water (3×150 mL), dried over $MgSO_4$ and the solvent was evaporated. The crude pale yellow oil was distilled under reduced pressure (0.2 bar) at 88–100 °C to give **11e** (30.9 g, 84%) as a colorless oil. Analytical data are in accord with the literature.[33]

4.4. 2-(2-Bromophenyl)-1,3-dioxolane (13a)[34]

A solution of 2-bromobenzaldehyde (**12a**, 37.1 g, 0.20 mol), ethylene glycol (50 mL, 55.6 g, 0.90 mol) and *p*-toluenesulfonic acid (1.0 g, 0.005 mol) in toluene (200 mL) was refluxed in a Dean–Stark apparatus (bp 118–120 °C) in a microwave reactor under irradiation with a constant 650 W energy for 2 h.[29] The reaction mixture was washed with aqueous sodium hydrogen carbonate solution (5 w/w %, 200 mL) and water (200 mL), dried over $MgSO_4$ and the solvent was evaporated. The crude pale yellow oil was distilled under reduced pressure (0.04 mbar) at 86–88 °C to give **13a** (35.15 g, 77%) as a colorless oil. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.63 (1H, dd, J=8.1, 1.2 Hz), 7.58 (1H, dd, J=7.3, 1.8 Hz), 7.43 (1H, td, J=8.1, 1.2 Hz), 7.34 (1H, td, J=7.3, 1.8 Hz), 5.95 (1H, s), 4.08 (2H, m), 3.98 (2H, m). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 136.7, 132.9, 131.2, 128.3, 127.8, 122.3, 101.9, 65.1. IR (KBr, cm^{-1}) 2889, 1472, 1352. Anal. Calcd for $C_9H_9BrO_2$ (229.07): C 47.19, H 3.96, Br 34.88%. Found: C 46.69, H 4.07, Br 34.83%.

4.5. 2-(2-Bromo-5-methoxyphenyl)-1,3-dioxolane (13d)[35]

A solution of 2-bromo-5-methoxybenzaldehyde (**12d**, 5.38 g, 25 mmol), ethylene glycol (6.45 mL, 7.17 g, 0.115 mol) and *p*-toluenesulfonic acid (0.25 g, 1.3 mmol) in toluene (25 mL) was refluxed in a Dean–Stark apparatus for 5 h. The reaction mixture was washed with aqueous sodium hydrogen carbonate solution (5 w/w%, 2×20 mL) and water (20 mL), dried over $MgSO_4$ and the solvent was evaporated to give **13d** (5.85 g, 90%) as a pale yellow oil. ^{1}H NMR data are in accord with the literature.[35b] ^{13}C NMR (DMSO-d_6, 100 MHz) δ 158.8, 137.7, 134.9, 128.4, 116.7, 113.8, 101.8, 65.0, 55.5. IR (KBr, cm^{-1}) 2890, 1474, 1293. Anal. Calcd for $C_{10}H_{11}BrO_3$ (259.11): C 46.35, H 4.28, Br 30.84%. Found: C 46.24, H 4.24, Br 30.64%.

4.6. 2-(1,3-Dioxolan-2-yl)benzenesulfonyl chloride (7a)

Butyllithium (15 mL of a 2.5 M solution in hexane, 37.5 mmol) was added to a solution of 2-(2-bromophenyl)-1,3-dioxolane (**13a**, 6.87 g, 30.0 mmol) in THF (60 mL) under argon at −78 °C and the mixture was stirred for 40 min at −50 °C. The resulting suspension was added to a stirred solution of sulfur dioxide (13.7 g, 214.0 mmol) in THF (36 mL) cooled to −78 °C. The mixture was stirred at ambient temperature for 2 h and the solid product was filtered to give lithium sulfinate **9a** (5.92 g, 90%) as colorless crystals. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.71 (1H, dd, J=7.6, 0.8 Hz), 7.39 (1H, d, J=7.5 Hz), 7.34 (1H, td, J=7.4, 0.8 Hz), 7.23 (1H, td, J=7.4, 0.8 Hz), 6.58 (1H, s), 3.99 (4H, m).

Sulfuryl chloride (2.3 mL, 3.75 g, 28.0 mmol) in hexane (30 mL) was added dropwise over a period of 10 min to the suspension of the lithium sulfinate **9a** (4.40 g, 20.0 mmol) in hexane (54 mL) at −5 °C. After addition of sulfuryl chloride, the solvent was immediately evaporated in vacuo. The residue was stirred for 30 min at 0–5 °C with water (50 mL) and the crystalline product was filtered to give **7a** (4.88 g, 98%) as colorless crystals, mp 59–60 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.74 (1H, dd, J=7.5, 1.1 Hz), 7.49 (1H, dd, J=7.5, 1.1 Hz), 7.33 (2H, m), 6.64 (1H, s), 4.08 (2H, m) 3.85 (2H, m).

^{13}C NMR δ (DMSO-d_6, 100 MHz) 150.2, 133.2, 132.7, 129.3, 127.0, 126.5, 63.0. IR (KBr, cm^{-1}) 2884, 1475, 1381. Anal. Calcd for $C_9H_9ClO_4S$ (248.69): C 43.47, H 3.65, Cl 14.26, S 12.89%. Found C 43.03, H 3.70, Cl 13.62, S 12.27%.

4.7. 6-(1,3-Dioxolan-2-yl)-2,3-dichlorobenzenesulfonyl chloride (7b)

Butyllithium (140 mL of a 2.5 M solution in hexane, 0.35 mol) was added to a solution of 2-(3,4-dichlorophenyl)-1,3-dioxolane (**11b**, 63.4 g, 0.29 mol) in THF (155 mL) under argon at −78 °C and the mixture was stirred for 2 h at this temperature. The resulting suspension was added to a stirred solution of sulfur dioxide (56.1 g, 0.87 mol) in THF (105 mL) cooled to −78 °C. The mixture was stirred at ambient temperature for 2 h and the solid product was filtered to give lithium sulfinate **9b** (77.2 g, 92%) as colorless crystals. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.41 (2H, s), 7.35 (1H, s), 3.86 (4H, m).

Sulfuryl chloride (43.3 mL, 72.1 g, 0.534 mol) in hexane (100 mL) was added dropwise over a period of 70 min to the suspension of the lithium sulfinate **9b** (77.2 g, 0.267 mol) in hexane (600 mL) at −5 °C. After stirring at 0 °C for 1 h, the solvent was evaporated, water (500 mL) was added to the residue and the mixture was stirred for 30 min. The crystalline product was filtered to give **7b** (62.7 g, 74%) as colorless crystals. An analytical sample was recrystallized from acetonitrile to give colorless crystals, mp 68–72 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.57 (1H, d, J=8.5 Hz), 7.52 (1H, d, J=8.5 Hz), 7.02 (1H, s), 4.03 (2H, m), 3.88 (2H, m). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 147.0, 137.4, 134.2, 131.0, 130.0, 127.7, 99.2, 65.1. IR (KBr, cm^{-1}) 2879, 1430, 1384. Anal. Calcd for $C_8H_7Cl_3O_4S$ (317.59): C 34.04, H 2.22, Cl 33.49, S 10.10%. Found: C 34.12, H 2.29, Cl 33.21, S 9.98%.

4.8. 2-(1,3-Dioxolan-2-yl)-4-methoxybenzenesulfonyl chloride (7d)

Butyllithium (100 mL of a 2.5 M solution in hexane, 0.25 mol) was added to a solution of 2-(2-bromo-5-methoxyphenyl)-1,3-dioxolane (**13d**, 40.5 g, 0.156 mol) in THF (150 mL) under argon at −78 °C and the mixture was stirred for 2 h at this temperature. The resulting suspension was added to a stirred solution of sulfur dioxide (41.7 g, 0.65 mol) in THF (155 mL) cooled to −78 °C. The mixture was stirred at ambient temperature for 2 h and the solid product was filtered to give crude lithium sulfinate (**9d**, 45.2 g, >100%) as colorless crystals. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.65 (1H, d, J=9.1 Hz), 7.91 (2H, m), 6.54 (1H, s), 4.07 (2H, m), 3.90 (2H, m), 3.73 (3H, s).

Sulfuryl chloride (18.7 mL, 31.1 g, 0.23 mol) in hexane (225 mL) was added dropwise over a period of 70 min to the suspension of the lithium sulfinate **9d** (45.2 g) in hexane (330 mL) at −5 °C. After stirring at 0 °C for 1 h, the solvent was evaporated in vacuo, hexane (200 mL) was added to the residue and the mixture was stirred for 30 min. The crystalline product was filtered to give **7d** (42.2 g, 97%) as pale yellow crystals, mp 53–56 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.66 (1H, d, J=8.6 Hz), 6.97 (1H, d, J=2.7 Hz), 6.86 (1H, dd, J=8.6, 2.7 Hz), 6.53 (1H, s), 4.07 (2H, m), 3.85 (2H, m), 3.75 (3H, s). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.7, 139.5, 137.5, 128.5, 118.6, 113.4, 99.3, 65.1, 55.5. IR (KBr, cm^{-1}) 2888, 1601, 1571, 1364. Anal. Calcd for $C_{10}H_{11}ClO_5S$ (278.71): C 43.09, H 3.98, Cl 12.72, S 11.51%. Found: C 43.16, H 4.04, Cl 12.67, S 11.41%.

4.9. *N′*-{[2,3-Dichloro-6-(1,3-dioxolan-2-yl)phenyl]sulfonyl} acetohydrazide (14b)

2,3-Dichloro-6-(1,3-dioxolane-2-yl)benzenesulfonyl chloride (**7b**, 15.88 g, 0.05 mol) was dissolved in 2-propanol (100 mL) and to this solution acetylhydrazine (8.15 g, 0.11 mol) was added at 0 °C. After stirring at room temperature for 2 h, the solvent was evaporated in vacuo, to the residue ice-water (100 g) was added, the precipitate was filtered to give **14b** (13.5 g, 76%) as colorless crystals, mp 141–143 °C (2-propanol). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.06 (2H, br s), 7.89 (1H, d, J=8.8 Hz), 7.69 (1H, d, J=8.8 Hz), 6.63 (1H, s), 4.02 (2H, m), 3.93 (2H, m), 1.68 (3H, s). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 168.6, 140.1, 139.0, 134.9, 133.5, 132.0, 127.2, 99.0, 65.1, 20.2. IR (KBr, cm^{-1}) 3306, 3145, 1686, 1517. Anal. Calcd for $C_{11}H_{12}Cl_2N_2O_5S$ (355.20): C 37.20, H 3.41, Cl 19.96, N 7.89, S 9.03%. Found: C 37.24, H 3.45, Cl 19.88, N 7.82, S 8.93%.

4.10. *N′*-{[2-(1,3-Dioxolan-2-yl)-4-methoxyphenyl]sulfonyl} acetohydrazide (14d)

2-(1,3-Dioxolan-2-yl)-4-methoxybenzenesulfonyl chloride (**7d**, 25.1 g, 0.09 mol) was dissolved in 2-propanol (270 mL) and to this solution acetylhydrazine (26.6 g, 0.36 mol) was added at 10 °C. After stirring for 12 h, the solid was filtered to give **14d** (27.3 g, 96%) as colorless crystals, mp 153–154 °C (ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.06 (1H, br s), 9.26 (1H, br s) 7.79 (1H, d, J=8.8 Hz), 7.15 (1H, d, J=2.7 Hz), 7.08 (1H, dd, J=8.8, 2.7 Hz), 6.48 (1H, s), 4.08 (2H, m), 3.95 (2H, m), 3.84 (3H, s), 1.69 (3H, s). ^{13}C NMR (DMSO-d_6, 400 MHz) δ 167.9, 162.5, 139.8, 132.3, 128.6, 113.5, 98.7, 64.8, 55.7, 20.1. IR (KBr, cm^{-1}) 3223, 3010, 1667, 1595. Anal. Calcd for $C_{12}H_{16}N_2O_6S$ (316.34): C 45.56, H 5.10, N 8.86, S 10.14%. Found: C 45.25, H 5.13, N 8.74, S 10.02%.

4.11. 2-Formyl-benzenesulfonyl chloride (15a)[36]

To a suspension of Kieselgel (11.0 g) in chloroform (170 mL), concentrated sulfuric acid (3.8 mL) was added and stirred at room temperature for 10 min. After the addition of 2-(1,3-dioxolan-2-yl) benzenesulfonyl chloride (**7a**, 5.52 g, 22.4 mmol) the suspension was stirred for 30 h at room temperature. After filtration, the filtrate was washed with aqueous sodium hydrogen carbonate solution (5 w/w%, 50 mL) and water (50 mL), dried, and concentrated in vacuo to give pure **15a** (2.50 g, 54%) as a yellow oil. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.90 (1H, s), 7.83 (1H, dd, J=7.7, 1.3 Hz), 7.77 (1H, dd, J=7.7, 1.4 Hz), 7.63 (1H, dd, J=7.5, 1.4 Hz), 7.50 (1H, dt, J=7.5, 1.3 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 194.6, 150.2, 134.4, 133.8, 130.7, 128.0, 127.9. IR (KBr, cm^{-1}) 3096, 1704, 1376, 1183. Anal. Calcd for $C_7H_5ClO_3S$ (204.63): C 41.09, H 2.46, Cl 17.33, S 15.67%. Found: C 41.00, H 2.44, Cl 17.40, S 15.51%.

4.12. 2-Formyl-5,6-dichlorobenzenesulfonyl chloride (15b)

To a suspension of Kieselgel (11.0 g) in chloroform (224 mL), concentrated sulfuric acid (3.8 mL) was added and stirred at room temperature for 10 min. After the addition of 6-(1,3-dioxolan-2-yl)-2,3-dichlorobenzenesulfonyl chloride (**7b**, 5.62 g, 17.7 mmol) the suspension was stirred for 30 h at room temperature. After filtration, the filtrate was washed with aqueous sodium hydrogen carbonate solution (5 w/w%, 50 mL) and water (50 mL), dried, and concentrated in vacuo to give pure **15b** (4.49 g, 88%) as yellow crystals, mp 53–54 °C (hexane). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.51 (1H, s), 7.79 (1H, d, J=8.2 Hz), 7.38 (1H, d, J=8.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 192.1, 147.2, 137.2, 136.9, 131.0, 130.0, 127.0. IR (KBr, cm^{-1}) 3392, 1705, 1373, 1178. Anal. Calcd for $C_7H_3Cl_3O_3S$ (273.52): C 30.74, H 1.11, Cl 38.88, S 11.72%. Found: C 30.93, H 1.19, Cl 38.78, S 11.99%.

4.13. 2-Chloro-6-formyl-3-methoxybenzenesulfonyl chloride (15c)

Butyllithium (10 mL of a 2.5 M solution in hexane, 25.0 mmol) was added to a solution of 2-(3-chloro-4-methoxyphenyl)-1,3-

dioxolane (**11c**, 4.50 g, 21.0 mmol) in THF (11 mL) under argon at −78 °C and the mixture was stirred for 2 h at this temperature. The resulting suspension was added to a stirred solution of sulfur dioxide (5.10 g, 80 mmol) in THF (9 mL) cooled to −78 °C. The mixture was stirred at ambient temperature for 2 h and the solid product was filtered to give lithium sulfinate **9c** (4.11 g, 69%) as colorless crystals. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.38 (1H, d, J=8.4 Hz), 7.33 (1H, s), 6.90 (1H, d, J=8.4 Hz), 3.86 (4H, m), 3.80 (3H, s).

Sulfuryl chloride (2.30 mL, 3.88 g, 28.8 mmol) in hexane (30 mL) was added dropwise over a period of 70 min to the suspension of the lithium sulfinate **9c** (4.11 g, 14.4 mmol) in hexane (5 mL) at −5 °C. After stirring for 15 min at 0 °C the solvent was evaporated, water (40 mL) was added, the mixture extracted with ethyl acetate (2×20 mL), dried, and concentrated in vacuo to give a mixture of **7c** and **15c** (ca. 3.0 g) as an oil.

To a suspension of Kieselgel (2.9 g) in chloroform (30 mL), concentrated sulfuric acid (1.6 mL) was added and stirred at room temperature for 10 min. After the addition of the mixture of **7c** and **15c** (3.0 g) obtained above, the suspension was stirred for 3 h at room temperature. After filtration, the filtrate was washed with aqueous sodium hydrogen carbonate solution (5 w/w%, 2×20 mL) and water (2×20 mL), dried, and concentrated in vacuo. The residue was crystallized from a 1:1 mixture of hexane and ethyl acetate to give **15c** (1.47 g, 38% calculated for **11c** as starting material) as colorless crystals, mp 106–109 °C (hexane–ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 10.62 (1H, s), 7.90 (1H, d, J=8.8 Hz), 7.32 (1H, d, J=8.8 Hz), 4.06 (3H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.7, 159.8, 142.7, 129.7, 116.4, 57.3. IR (KBr, cm^{-1}) 2946, 1683, 1578, 1470, 1182. Anal. calcd for $C_8H_6Cl_2O_4S$ (269.12): C 35.70, H 2.25, Cl 26.35, S 11.92%. Found: C 36.23, H 2.08, Cl 25.81, S 12.21%.

4.14. 2-Formyl-4-methoxybenzenesulfonyl chloride (15d)

To a suspension of Kieselgel (9.4 g) in chloroform (68 mL), concentrated sulfuric acid (1.15 mL) was added and stirred at room temperature for 10 min. After the addition of 2-(1,3-dioxolan-2-yl)-4-methoxybenzenesulfonyl chloride (**7d**, 2.37 g, 8.5 mmol) the suspension was stirred for 20 h at room temperature. After filtration, the filtrate was washed with aqueous sodium hydrogen carbonate solution (5 w/w%, 30 mL) and water (30 mL), dried, and concentrated in vacuo. The residue was crystallized from diethyl ether to give pure **15d** (1.30 g, 65%) as colorless crystals, mp 89–91 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.88 (1H, s), 7.79 (1H, d, J=8.5 Hz), 7.25 (1H, d, J=2.8 Hz), 7.16 (1H, dd, J=8.5, 2.8 Hz), 3.79 (3H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 193.5, 159.8, 142.9, 134.1, 129.1, 118.6, 110.8, 55.7. IR (KBr, cm^{-1}) 1713, 1566, 1407. Anal. Calcd for $C_8H_7ClO_4S$ (234.67): C 40.95, H 3.00, Cl 15.11, S 13.66%. Found: C 40.63, H 3.05, Cl 15.02, S 13.68%.

4.15. 2*H*-1,2,3-Benzothiadiazine 1,1-dioxide (5a)[13b,13c,17]

2-Formylbenzenesulfonylchloride (**15a**, 2.15 g, 10.5 mmol) was dissolved in THF (35 mL) and hydrazine monohydrate (3.1 mL, 3.17 g, 63.4 mmol) was added dropwise to the solution. The reaction stirred at room temperature for 1 h. Thereafter the mixture was poured into ice-water (150 mL), acidified with aqueous HCl (10 w/w %, 15 mL) and the precipitate was filtered to give **5a** (1.70 g, 89%) as yellow crystals, mp 143–146 °C (lit.[13b] mp 142–143 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.43 (1H, br s), 8.31 (1H, s), 7.98 (1H, m), 7.87 (3H, m). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 142.2, 133.1, 132.7, 128.0, 127.5, 119.9. IR (KBr, cm^{-1}) 3243, 1322, 1178. Anal. Calcd for $C_7H_6N_2O_2S$ (180.20): C 46.15, H 3.32, N 15.35, S 17.60%. Found: C 46.41, H 3.43, N 15.16, S 17.48%.

4.16. 7,8-Dichloro-2*H*-1,2,3-benzothiadiazine 1,1-dioxide (5b)[17]

4.16.1. Route E. *N′*-{[2,3-Dichloro-6-(1,3-dioxolan-2-yl)phenyl]sulfonyl}acetohydrazide (**14b**, 67.5 g, 0.19 mol) was refluxed with aqueous HCl (10 w/w%, 400 mL) for 2.5 h and filtered to give **5b** (41.52 g, 87%) as colorless crystals, mp 183–185 °C (2-propanol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.46 (1H, br s), 7.94 (1H, s), 7.83 (1H, d, J=8.4 Hz), 7.45 (1H, d, J=8.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 141.8, 136.2, 134.4, 132.9, 129.0, 128.2, 124.9. IR (KBr, cm^{-1}) 3242, 1361, 1175. Anal. Calcd for $C_7H_4Cl_2N_2O_2S$ (251.09): C 33.48, H 1.61, Cl 28.24, N 11.16, S 12.77%. Found: C 33.88, H 1.64, Cl 27.98, N 11.06, S 12.63%.

4.16.2. Route F. 2,3-Dichloro-6-formylbenzenesulfonyl chloride (**15b**, 4.04 g, 14.0 mmol) was dissolved in THF (32 mL) and hydrazine monohydrate (1.4 mL, 1.44 g, 28.8 mmol) was added dropwise to the solution. The reaction mixture was refluxed for 1 h. Thereafter the mixture was poured into water, acidified with aqueous HCl (10 w/w%, 1 mL) and the precipitate was filtered to give **5b** (0.70 g, 20%) as colorless crystals, mp 184–186 °C identical with compound obtained via *Route E*.

4.17. 8-Chloro-7-methoxy-2*H*-1,2,3-benzothiadiazine 1,1-dioxide (5c)

2-Chloro-6-formyl-3-methoxybenzenesulfonyl chloride (**15c**, 2.69 g, 0.01 mol) was dissolved in THF (28 mL) and hydrazine monohydrate (2.45 mL, 2.50 g, 0.05 mol) was added dropwise to the solution. The reaction mixture was refluxed for 2 h. It was poured into water (15 mL) and acidified with aqueous HCl (10 w/w%, 10 mL). The mixture was extracted with ethyl acetate (20 mL) and the solvent was evaporated in vacuo. The residue was stirred with hexane (10 mL) and the crystals formed were filtered to give **5c** (2.0 g, 77%) as yellow crystals, mp 189–191 °C (ethyl acetate). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 12.29 (1H, br s), 8.19 (1H, s), 7.84 (1H, d, J=8.8 Hz), 7.65 (1H, d, J=8.8 Hz), 3.35 (3H, s). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 157.4, 142.5, 133.1, 129.5, 121.9, 116.7, 114.4, 57.4. IR (KBr, cm^{-1}): 3292, 1481, 1282. Anal. Calcd for $C_8H_7ClN_2O_3S$ (246.67): C 38.95, H 2.86, Cl 14.37, N 11.36, S 13.00%. Found: C 39.23, H 2.80, Cl 14.38, N 11.13, S 13.04%.

4.18. 6-Methoxy-2*H*-1,2,3-benzothiadiazine 1,1-dioxide (5d)[17]

4.18.1. Route E. *N′*-{[2-(1,3-Dioxolan-2-yl)-4-methoxyphenyl]sulfonyl}acetohydrazide (**14d**, 6.33 g, 0.02 mol) was refluxed with aqueous HCl (10 w/w%, 60 mL) for 3 h and filtered to give **5d** (2.37 g, 56%) as colorless crystals. An analytical sample was recrystallized from ethanol to give pure **5d**, mp 163–164 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.20 (1H, s), 8.21 (1H, s), 7.89 (1H, d, J=8.6 Hz), 7.41 (1H, d, J=2.6 Hz), 7.38 (1H, dd, J=8.7, 2.6 Hz), 3.90 (3H, s). ^{13}C NMR (DMSO-d_6, 100 MHz): 162.3, 141.6, 129.6, 126.0, 122.3, 119.3, 111.6, 56.2. IR (KBr, cm^{-1}): 3215, 1311, 1141. Anal. Calcd for $C_8H_8N_2O_3S$ (212.23): C 45.28, H 3.80, N 13.20, S 15.11%. Found: C 45.36, H 3.84, N 12.94, S 14.96%.

4.18.2. Route F. 2-Formyl-4-methoxybenzenesulfonyl chloride (**15d**, 1.64 g, 7.0 mmol) was dissolved in THF (13 mL) and hydrazine monohydrate (0.70 mL, 0.70 g, 14.0 mmol) was added dropwise to the solution. The reaction mixture was stirred at room temperature for 1 h. Thereafter the mixture was poured into ice-water, acidified with aqueous HCl (10 w/w%, 5 mL) and the precipitate was filtered to give **5d** (1.10 g, 74%) as colorless crystals, mp 164–166 °C, identical with compound obtained via *Route E*.

4.19. 7-Chloro-2*H*-1,2,3-benzothiadiazine 1,1-dioxide (5e)[17]

7,8-Dichloro-2*H*-1,2,3-benzothiadiazine 1,1-dioxide (**5b**, 8.03 g, 0.032 mol) was dissolved in THF (140 mL) and the solution was cooled to −78 °C. At this temperature, a solution of butyllithium in hexane (2.5 M, 40 mL, 0.10 mol) was added dropwise. The reaction mixture was stirred at −78 °C for 4 h, thereafter it was poured into the mixture of ice and water (160 g). The mixture was extracted with diethyl ether (2×100 mL). The aqueous layer was acidified with aqueous HCl (10 w/w%, 50 mL) and the precipitate was filtered to give crude **5e** (6.44 g, 93%). It was recrystallized from ethanol (150 mL) to give pure **5e** (4.80 g, 69%) as colorless crystals, mp 221–223 °C (ethanol). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 12.63 (1H, br s), 8.35 (1H, s), 8.07 (1H, d, J=2.1 Hz), 7.89 (1H, dd, J=8.3, 2.1 Hz), 7.91 (1H, d, J=8.3 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 141.7, 136.9, 134.3, 133.4, 130.4, 126.3, 119.9. IR (KBr, cm^{-1}): 3230, 1331, 1170. Anal. Calcd for $C_7H_5ClN_2O_2S$ (216.65): C 38.80, H 2.33, Cl 16.37, N 12.93, S 14.80%. Found: C 39.16, H 2.28, Cl 16.29, N 12.69, S 14.52%.

4.20. 7-Chloro-2*H*-1,2,3-benzothiadiazine-8-carboxylic acid 1,1-dioxide (5f)

7,8-Dichloro-2*H*-1,2,3-benzothiadiazine 1,1-dioxide (**5b**, 5.02 g, 20.0 mmol) was dissolved in THF (87.5 mL) and the solution cooled to −78 °C. At this temperature, a solution of butyllithium in hexane (2.5 M, 25 mL, 62.5 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 5 h, thereafter it was poured into dry ice (ca. 300 g) and it was left at room temperature overnight. The mixture was diluted with water (100 mL) and extracted with diethyl ether (2×30 mL). To the aqueous layer was added aqueous HCl solution (10 w/w%, 20 mL), it was extracted with ethyl acetate (3×40 mL), dried and evaporated in vacuo. The crystalline residue was stirred with hexane (20 mL) and filtered to give crude **5f** (4.30 g), which furnished after recrystallization from a mixture ethyl acetate and hexane (1:3) pure **5f** (3.13 g, 60%) as colorless crystals, mp 283–284 °C (hexane–ethyl acetate). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 12.73 (1H, br s), 8.37 (1H, s), 8.06 (1H, d, J=8.6 Hz), 7.94 (1H, d, J=8.6 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 164.4, 142.2, 133.9, 132.7, 130.7, 130.5, 128.4, 126.7. IR (KBr, cm^{-1}): 3297, 1763, 1452, 1178. Anal. Calcd for $C_8H_5ClN_2O_4S$ (260.66): C 36.86, H 1.93, Cl 13.60, N 10.75, S 12.30%. Found: C 36.81, H 1.89, Cl 13.53, N 10.64, S 12.10%.

4.21. 7-Methoxy-2*H*-1,2,3-benzothiadiazine 1,1-dioxide hemihydrate (5g)

8-Chloro-7-methoxy-2*H*-1,2,3-benzothiadiazine 1,1-dioxide (**5c**, 0.50 g, 2.0 mmol) was dissolved in THF (10 mL) and the solution was cooled to −78 °C. At this temperature, a solution of butyllithium in hexane (2.5 M, 4.0 mL, 10.0 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 5 h, thereafter it was poured into the mixture of ice and water (20 g). The mixture was extracted with diethyl ether (2×20 mL). The aqueous layer was acidified with aqueous HCl (10 w/w%, 10 mL). The crystals separated by filtration after stirring at 0 °C for 30 min were identified as starting material (0.30 g, 60% recovered) containing traces of the product (**5g**) and 4-butyl substituted by-product (**16a**). The filtrate was extracted with ethyl acetate and dried. The solvent evaporated in vacuo, and the residue was crystallized from ethanol (1.5 mL) to give **5g** (0.10 g, 24%) as colorless crystals, mp 153–155 °C (ethanol). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 12.20 (1H, br s), 8.20 (1H, s), 7.81 (1H, d, J=8.5 Hz), 7.42 (1H, dd, J=8.5, 2.4 Hz), 7.40 (1H, d, J=2.4 Hz), 3.94 (3H, s). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 162.0, 142.2, 135.2, 130.4, 120.8, 120.2, 103.3, 56.4. IR (KBr, cm^{-1}): 3266, 1313, 1168. Anal. Calcd for $C_8H_8N_2O_3S\cdot0.5H_2O$ (220.23): C 43.43, H 4.10, N 12.66, S 14.49%. Found: C 43.58, H 4.08, N 12.47, S 14.00%.

4.22. 4-Butyl-8-chloro-7-methoxy-3,4-dihydro-1,2,3-benzothiadiazine 1,1-dioxide (16a)

8-Chloro-7-methoxy-2*H*-1,2,3-benzothiadiazine 1,1-dioxide (**5c**, 0.50 g, 2.0 mmol) was dissolved in THF (10 mL) and the solution was cooled to −78 °C. At this temperature, a solution of butyllithium in hexane (2.5 M, 4.0 mL, 10.0 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, thereafter it was poured into the mixture of ice and water (20 g). The mixture was extracted with diethyl ether (2×20 mL). The aqueous layer was acidified with aqueous HCl (10 w/w%, 10 mL), extracted with ethyl acetate and dried. The solvent was evaporated in vacuo, the residue (0.37 g, 60%) was crystallized from ethanol (4 mL) to give **16a** (0.05 g, 8%) as colorless crystals, mp 209–211 °C (ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.57 (1H, br s), 7.37 (1H, d, J=8.8 Hz), 7.33 (1H, d, J=8.8 Hz), 5.92 (1H, br s), 4.03 (1H, br s), 3.89 (3H, s), 1.84 (1H, br s), 1.67 (1H, br s), 1.28 (4H, m), 0.86 (3H, t, J=6.6 Hz), ^{13}C NMR (DMSO-d_6, 125 MHz): δ 153.7, 136.0, 134.7, 127.1, 117.9, 115.7, 56.9, 55.7, 32.9, 27.2, 22.2, 14.1. IR (KBr, cm^{-1}): 3294, 3189, 1289, 1192, 1173. Anal. Calcd for $C_{12}H_{17}N_2O_3S$ (304.80): C 47.29, H 5.62, Cl 11.63, N 9.19, S 10.52%. Found: C 46.93, H 5.39, Cl 11.36, N 9.36, S 10.52%.

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