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A one-pot, non-catalytic approach to 1,2,4-benzothiadiazine-1,1-dioxides

Artem Cherepakha [a], Vladimir O. Kovtunenko [a], Andrey Tolmachev [a,b], Oleg Lukin [a,b,*]

[a] National Taras Shevchenko University, ChemBioCenter, Volodymyrska St. 62, 01033 Kiev, Ukraine
[b] Enamine Ltd., A. Matrosova St. 23, 01103 Kiev, Ukraine

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ABSTRACT

Condensations of *o*-halo-substituted benzenesulfonyl chlorides with 2-aminopyridines and amidines may give the corresponding 1,2,4-benzothiadiazine-1,1-dioxides under mild, non-catalytic conditions in nearly quantitative yields. The successful one-pot cyclization depends on three factors: (i) the nature of the *o*-halogen, (ii) the electronic character of the benzene ring substituent, and (iii) the steric load around the amidine unit. *O*-Fluorobenzenesulfonyl chlorides bearing methylcarboxyl- or nitro-group and *o*-chloro- and *o*-bromobenzenesulfonyl chlorides bearing nitro-group are reactive enough to give the desired 1,2,4-benzothiadiazine-1,1-dioxides in a one-pot base-promoted reaction. In all other cases, open-chain sulfonylated amidine intermediates are isolated. The latter are converted to the title compounds either in the presence of potassium carbonate or upon the addition of a copper(I) catalyst.

1. Introduction

Benzothidiazine-1,1-dioxides are a remarkably important class of heterocycles in the pharmacological area because of their broad range of biological activities, such as antihypertensive,[1,2] antimicrobial,[3] and antiviral[4] ones. In this connection several synthetic routes to the benzothiadiazine ring system have been developed. These synthetic routes can roughly be divided into two common approaches. In the first, non-catalytic, approach the ring is constructed through reactions of *o*-aminoaryl-sulfonamides with orthoesters[5,6] or acylating reagents[7–9] and *o*-haloaryl-sulfonamides with lactim ethers.[10] Main disadvantages of this approach are considerably harsh reaction conditions (e.g., pyrolytic conditions in the case of acylating reagents[7]) causing the formation of byproducts and a somewhat limited availability of *o*-aminosulfonamides narrowing the chemical space for drug design. An alternative approach to the 1,2,4-benzothiadiazine-1,1-dioxide ring is based on metal catalyzed reactions, such as: Friedel–Crafts ring closure of Michael adducts of chlorosulfonyl isocyanate and aniline derivatives,[11] a Cu(I)-catalyzed coupling of *o*-bromobenzylsulfonyl azide with functionalized terminal acetylene and ammonium chloride,[12] a cyclization of *o*-haloarylsulfonyl amidines in the presence of a copper bronze powder,[13] and a Fe(III)-mediated cyclization of *o*-bromobenzenesulfonamide with amidines.[14] However, transition metal-based protocols, although successful, have some inherent limitations, such as moisture sensitivity and environmental toxicity. In addition, their separation from polar reaction products, which is of particular importance for the synthesis of pharmaceutical fine chemicals because of their residual toxicity in the target compounds, is a central issue to consider. Given the limitations of the mentioned above synthetic approaches the development of efficient non-catalytic synthetic routes to the benzothiadiazine-1,1-dioxide ring system is necessary. In this contribution an efficient base-promoted synthesis of 4*H*-1,2,4-benzothiadiazine-1,1-dioxides from *o*-halobenzenesulfonyl chlorides and amidines or 2-aminopyridines is described.

2. Results and discussion

The 1,2,4-benzothiadiazine-1,1-dioxide is converted retrosynthetically into an *o*-halobenzenesulfonyl chloride and an amidine. These two components can be combined to give rise to the desired benzothiadiazine-1,1-dioxide ring by a two-step procedure involving the sulfonylation of the amidine and the aromatic nucleophilic substitution of the *ortho*-halogen atom. As noted above the latter step was carried out via Fe(III)[14] or copper bronze powder[13] mediated reaction. However, there are examples in which the intermolecular nucleophilic substitution of a halogen atom in activated *o*-halobenzenesulfonamides with nitrogen nucleophiles, such as aliphatic and aromatic amines, takes place under ambient non-catalytic conditions.[15] Consequently, a combination of enhanced reactivity of the *ortho*-halogen under the sufonylation conditions with sufficient nucleophilicity of the remaining amidine amine moiety should afford target benzothiadiazine dioxides via a one-pot procedure that would not require metal catalyst.

* Corresponding author. E-mail address: oleg.lukin@univ.kiev.ua (O. Lukin).

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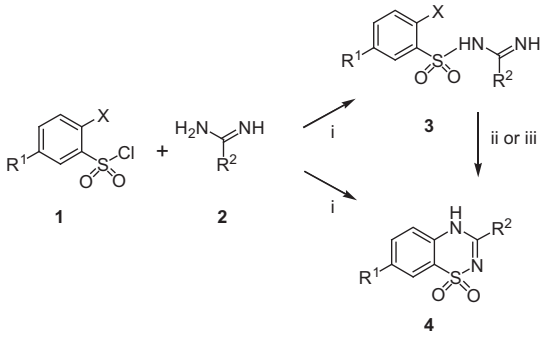
A systematic study of reactions of *o*-halobenzenesulfonyl chlorides **1** with amidines **2** and aminopyridines **5** (Schemes 1 and 2) revealed clear structural requirements to reagents to allow their clean and high-yielding one-pot conversion to the title compounds under non-catalytic conditions. Thus, reactions of sulfonyl chlorides **1a**–**f**, **1h**, and **1i** with amidines **2** (Scheme 1) resulted in open-chain sulfonylated products **3** in high yields. Isolated adducts **3a**, **3b**, **3e**, **3g**–**j**, **3n**, and **3l** are then nearly quantitatively converted to corresponding benzothiadiazine-1,1-dioxides **4** via nucleophilic substitution of the halogen in the presence of potassium carbonate in DMF. Bromine-substituted adducts **3c**, **3f**, **3k**, and **3m** require the addition of copper(I) iodide and *N*,*N*-dimethylethylenediamine (DMEDA) to complete the thiadiazine ring closure. It is interesting to note that the use of DMEDA instead of 1,10-phenanthroline as reported by Chang et al.[12] allowed us to achieve generally better conversions and a clean workup.



1a: X = F R^1 = H

1b: X = Cl R^1 = H

1c: X = Br R^1 = H

1d: X = F R^1 = CO_2Me

1e: X = Cl R^1 = CO_2Me

1f: X = Br R^1 = CO_2Me

1g: X = F R^1 = NO_2

1h: X = Cl R^1 = NO_2

1i: X = Br R^1 = NO_2

2a: R^2 = Me

2b: R^2 = Ph

3a: X = F R^1 = H, R^2 = Me

3b: X = Cl R^1 = H, R^2 = Me

3c: X = Br R^1 = H, R^2 = Me

3d: X = F R^1 = CO_2H, R_2 = Me

3e: X = Cl R^1 = CO_2Me, R^2 = Me

3f: X = Br R^1 = CO_2Me, R^2 = Me

3g: X = Cl R^1 = NO_2, R^2 = Me

3h: X = Br R^1 = NO_2, R^2 = Me

3i: X = F R^1 = H, R^2 = Ph

3j: X = Cl R^1 = H, R^2 = Ph

3k: X = Br R^1 = H, R^2 = Ph

3l: X = Cl R^1 = CO_2H, R^2 = Ph

3m: X = Br R^1 = CO_2Me, R^2 = Ph

3n: X = Cl R^1 = NO_2, R^2 = Ph

3o: X = Br R^1 = NO_2, R^2 = Ph

4a: R^1 = H, R^2 = Me

4b: R^1 = CO_2Me, R^2 = Me

4c: R^1 = NO_2, R^2 = Me

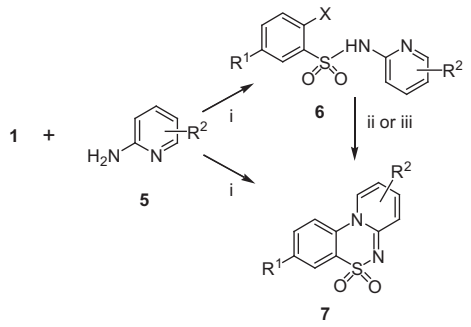
4d: R^1 = H, R^2 = Ph

4e: R^1 = CO_2Me, R^2 = Ph

4f: R^1 = NO_2, R^2 = Ph

4g: R^1 = CO_2H, R^2 = Ph

Scheme 1. Preparation of 1,2,4-benzothiadiazine-1,1-dioxides through the reaction of different *o*-halobenzenesulfonyl chlorides with amidines. Reagents and conditions: (i) CH_2Cl_2, aq NaOH, 0–10 °C; (ii) K_2CO_3, DMF, 100 °C; (iii) K_2CO_3, CuI, DMEDA, DMF, 100 °C.



5a: R^2 = H

5b: R^2 = 3-Me

5c: R^2 = 4-Me

5d: R^2 = 5-Me

5e: R^2 = 6-Me

6a: X = F R^1 = R^2 = H

6b: X = Cl R^1 = R^2 = H

6c: X = Br R^1 = R^2 = H

6d: X = Cl R^1 = CO_2Me, R^2 = H

6e: X = Br R^1 = CO_2Me, R^2 = H

6f: X = Cl R^1 = CO_2Me, R^2 = 4-Me

6g: X = Br CO_2Me, R^2 = 4-Me

6h: X = Cl R^1 = CO_2Me, R^2 = 5-Me

6i: X = Br R^1 = CO_2Me, R^2 = 5-Me

6j: X = Cl R^1 = CO_2Me, R^2 = 6-Me

6k: X = Br R^1 = CO_2Me, R^2 = 6-Me

7a: R^1 = R^2 = H

7b: R^1 = CO_2Me, R^2 = H

7c: R^1 = NO_2, R^2 = H

7d: R^1 = CO_2Me, R^2 = 4-Me

7e: R^1 = CO_2Me, R^2 = 5-Me

Scheme 2. Preparation of 1,2,4-benzothiadiazine-1,1-dioxides through the reaction of different *o*-halobenzenesulfonyl chlorides with 2-methylpyridine. Reagents and conditions: (i) pyridine, reflux, (ii) K_2CO_3, DMF, 80 °C, (iii) K_2CO_3, CuI, DMEDA, DMF, 80 °C.

Interestingly, the reaction of 4-fluoro-3-chlorosulfonyl-methylbenzoate **1d** with methylamidine **2a** readily gives open-chain sulfamoyl-4-fluoro-benzoic acid **3d**. A similar result was obtained in the case of the reaction of 4-chloro-3-chlorosulfonyl-methylbenzoate **1e** with phenylamidine **2b** giving rise to sulfamoyl-4-chlorobenzoic acid **3l**. Presumably this occurs on account of the good solubility of the intermediate sulfonylated amidines in aqueous NaOH in which the hydrolysis of the ester group takes place. All attempts to carry out cyclization reactions of acids **3d** and **3l** to yield the corresponding thiadiazine-1,1-dioxide rings were unsuccessful.

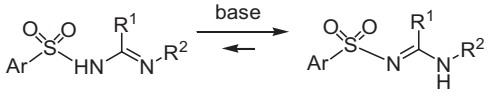
On the contrary, the reaction of **1d** with phenylamidine **2b** readily gives benzothiadiazine-1,1-dioxide carboxylic acid **4g**. This indicates that in the latter case the rate of aromatic nucleophilic substitution is faster than that of the hydrolysis. Finally, both the sulfonylation and cyclization steps proceed in one-pot in case of the reaction of fluoronitrobenzenesulfonyl chloride **1g** with **2a** and **2b** giving rise to benzothiadiazine-1,1-dioxides **4c** and **4f**, respectively. To our knowledge this constitutes the first example of a one-pot non-catalytic construction of the thiadiazine-1,1-dioxide ring. Additionally, this is a straightforward method for preparation of nitrobenzothiadiazine dioxides. The latter were formerly prepared by nitration of the parent benzothiadiazine dioxides.[16]

The versatility of the one-pot approach to the benzothiadiazine-1,1-dioxides could be possibly expanded by the use of stronger intramolecular nucleophiles, such as sulfonylated 2-aminopyridine derivatives. Indeed, the reactions of parent 2-aminopyridine

5a with halonitrobenzenesulfonyl chlorides **1g**–**i** (Scheme 2) readily afford the corresponding benzothiadiazine-1,1-dioxide **7c**. Moreover, the reaction of 4-fluoro-3-chlorosulfonyl-methylbenzoate **1d** with **5a** also proceeds in one-pot resulting in the benzothiadiazine-1,1-dioxide **7b**. Similar reactions of other halobenzenesulfonyl chlorides with aminopyridine **5a** yield open-chain sulfonamides **6a**–**e** (Scheme 2) of which compounds **6a**, **6b**, and **6d** undergo base-promoted cyclization to give corresponding benzothiadiazine-1,1-dioxides **7a** and **7b**.

To investigate the influence of the steric load around the amidine unit on the reaction outcome a series of isomeric methylpyridin-2-ylamines **5b**–**e** were reacted with methylcarboxyl-substituted *o*-halobenzenesulfonyl chlorides **1d**–**f** (Scheme 2). Reactions of the three sulfonyl chlorides with 4- and 5-methylpyridin-2-ylamines **5c** and **5d** proceed identically to those with parent 2-aminopyridine **5a**. Thus, the reaction of **1d** with either **5c** or **5d** is a one-pot process giving rise to benzothiadiazine-1,1-dioxides **7d** and **7e**, respectively. Similar reactions of **1e** and **1f** with **5c** or **5d** result in open-chain adducts **6f**–**i**. Chlorinated adducts **6f** and **6h** are easily cyclized in the presence of potassium carbonate to give thiadiazine-1,1-dioxides **7d** and **7e**, respectively. Brominated derivatives **6g** and **6i** undergo the cyclization step under copper(I) catalyzed conditions (Scheme 2). In the case of 3-methylpyridin-2-ylamine **5b** no reaction occurs irrespective of the *o*-halobenzenesulfonyl chloride used. Sulfonyl chlorides **1e** and **1f** react with 6-methylpyridin-2-ylamine **5e** to give open-chain sulfonylated amidines **6j** and **6k**, respectively. The latter, however, are not cyclized to the benzothiadiazine-1,1-dioxides under both base-promoted and copper(I) catalyzed conditions.

Interestingly, although the methyl group of **5b** situated next to the amino group sterically precludes the sulfonylation step there is no steric obstacle for aromatic nucleophilic substitution of the halogen. In the case of **5e** the aromatic nucleophilic substitution step is apparently prevented sterically. Therefore, only the sulfonylated amidine is capable of the nucleophilic displacement of the halogen under given conditions. A reasonable explanation for this fact shown in Scheme 3 is that in the presence of a base sulfonylated amidines tautomerize into a more favorable form in which the imine unit is conjugated with the sulfo-group.[17]



Scheme 3. A possible tautomerization of sulfonylated amidines.

3. Conclusions

The presented approach allows the straightforward preparation of 1,2,4-benzothiadiazine-1,1-dioxides from readily available *o*-halo-substituted benzenesulfonyl chlorides and 2-aminopyridines or amidines in the presence of a base in high yields. The presence of electron withdrawing groups in the benzene ring of the *o*-halobenzenesulfonyl chlorides is a prerequisite for the successful one-pot preparation of benzothiadiazine-1,1-dioxides. In the case of fluorine containing sulfonyl chlorides the presence of a relatively weak electron acceptor, such as methylcarboxyl-group, is sufficient for activating the halogen toward aromatic nucleophilic substitution under mild conditions. This is, however, not the case for the chlorine and bromine containing sulfonyl chlorides requiring the presence of the much stronger electron withdrawing nitro-group to react under given conditions. The combination of the high-yielding one-pot procedure allowing the multigram scale preparation of nitro-functionalized benzothiadiazine dioxides with the variety of functional group transformations the nitro-group can undergo opens a range of possibilities for the design and synthesis of biologically potent benzothiadiazine derivatives.

4. Experimental details

4.1. General

^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on Bruker Avance DRX 500 spectrometer with TMS as an internal standard. High-performance (HP) LC–MS analyses were done on an Agilent 1100 LCMSD SL instrument (APCI mode). Elemental analyses were carried out on a LECO CHN-900 analyzer. The values of elemental analyses reported herein are averages of three independent measurements. Melting points were measured with a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer Spectrum BX II (FT-IR).

Sulfonyl chlorides **1a**–**c** and **1d**–**i** were purchased from Acros and Enamine Ltd, respectively.

4.2. General procedure for preparation of sulfonylated amidines 3

To a stirred solution of equimolar amounts of *o*-halogenoarylsulfonyl chloride **1** (0.02 mol) and amidine hydrochloride **2** (0.02 mol) in dichloromethane (50 mL) a concentrated water solution of potassium hydroxide (5.6 g, 0.1 mol) was slowly added at 0 °C. The reaction mixture was allowed to stir overnight at room temperature and acidified to pH 1. The precipitated sulfonylated amidine was filtered, washed with water and dichloromethane and dried at ambient conditions. If necessary the product is recrystallized from ethanol/water mixture.

*4.2.1. N′-((2-Fluorophenyl)sulfonyl)ethanimidate (**3a**).* Colorless solid; yield 3.6 g (83%); mp 138–140 °C; [found: C, 44.48; H, 4.19; N, 12.95. $C_8H_9FN_2O_2S$ requires C, 44.44; H, 4.20; N, 12.96%]; δ_H (500 MHz, DMSO-d_6) 1.98 (3H, s, C*H*$_3$), 7.40–7.53 (2H, m, Ar*H*), 7.79 (1H, dd, *J* 14.0, 7.0 Hz, Ar*H*), 7.94 (1H, t, *J* 7.0 Hz, Ar*H*), 12.5 (1H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 23.6, 117.7 (d, *J* 20.0 Hz), 125.3 (d, *J* 2.5 Hz), 127.5 (d, *J* 13.8 Hz), 131.7, 137.0 (d, *J* 8.8 Hz), 158.7 (d, *J* 253.8 Hz), 169.4; δ_F (470 MHz, DMSO-d_6) −110.3.

*4.2.2. N′-[(2-Chlorophenyl)sulfonyl]ethanimidamide (**3b**).* Colorless solid; yield 3.94 g (85%); mp 156–158 °C; [found: C, 41.31; H, 3.89; Cl, 15.20; N, 12.06. $C_8H_9ClN_2O_2S$ requires C, 41.29; H, 3.90; Cl, 15.24; N, 12.04%]; δ_H (500 MHz, DMSO-d_6) 2.13 (3H, s, C*H*$_3$), 7.52 (1H, t, *J* 7.0 Hz, Ar*H*), 7.55–7.68 (2H, m, Ar*H*), 8.05 (1H, d, *J* 7.0 Hz, Ar*H*), 8.17 (1H, br s, N*H*), 8.56 (1H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 22.1, 127.5, 129.5, 131.6, 132.0, 133.7, 140.9, 168.8.

*4.2.3. N′-[(2-Bromophenyl)sulfonyl]ethanimidamide (**3c**).* Colorless solid; yield 5.28 g (95%); mp 177–179 °C; [found: C, 34.62; H, 3.21; Br, 23.75; N, 10.19. $C_8H_9BrN_2O_2S$ requires C, 34.67; H, 3.27; Br, 23.83; N, 10.11%]; ν_{max} (ATP) 3409, 3324, 3242 (NH), 1637 (NH_2), 1541 (C=N), 1288, 1146 (SO_2) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.12 (3H, s, C*H*$_3$), 7.48 (1H, t, *J* 7.0 Hz, Ar*H*), 7.55 (1H, t, *J* 7.0 Hz, Ar*H*), 7.81 (1H, d, *J* 7.0 Hz, Ar*H*), 8.06 (1H, d, *J* 7.0 Hz, Ar*H*), 8.13 (1H, br s, N*H*), 8.56 (1H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 22.2, 120.2, 128.2, 129.6, 133.6, 135.5, 142.5, 168.8.

*4.2.4. 3-((1-Aminoethylidene)sulfamoyl)-4-fluoro-benzoic acid (**3d**).* Colorless solid; yield 4.36 g (84%); mp 232–234 °C; [found:

C, 41.52; H, 3.48; N, 10.78. $C_9H_9FN_2O_4S$ requires C, 41.54; H, 3.49; N, 10.76%]; δ_H (500 MHz, DMSO-d_6) 1.99 (3H, s, CH_3), 7.62 (1H, t, *J* 9.0 Hz, Ar*H*), 8.30 (1H, br s, Ar*H*), 8.43 (1H, d, *J* 2.0 Hz, Ar*H*), 12.66 (1H, br s, CO_2H); δ_C (125 MHz, DMSO-d_6) 23.7, 118.5 (d, *J* 21.3 Hz), 127.7 (d, *J* 13.8), 128.1, 132.9, 137.9 (d, *J* 11.3), 162.2 (d, *J* 261.3), 165.6, 169.6; δ_F (470 MHz, DMSO-d_6) −105.38.

*4.2.5. Methyl-3-((1-aminoethylidene)sulfamoyl)-4-chlorobenzoate (**3e**).* Colorless solid; yield 5.34 g (92%); mp 178–180 °C; [found: C, 41.35; H, 3.80; Cl, 12.23; N, 9.64. $C_{10}H_{11}ClN_2O_4S$ requires C, 41.31; H, 3.81; Cl, 12.19; N, 9.64%]; δ_H (500 MHz, DMSO-d_6) 2.14 (3H, s, CH_3), 3.91 (3H, s, CO_2CH_3), 7.78 (1H, d, *J* 8.0 Hz, Ar*H*), 8.09 (1H, d, *J* 8.0 Hz, Ar*H*), 8.29 (1H, br s, N*H*), 8.53 (1H, s, Ar*H*), 8.71 (1H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 22.0, 53.2, 129.1, 129.8, 132.9, 133.8, 136.5, 141.2, 165.1, 169.2.

*4.2.6. Methyl-3-((1-aminoethylidene)sulfamoyl)-4-bromobenzoate (**3f**).* Colorless solid; yield 5.7 g (85%); mp 193–195 °C; [found: C, 35.75; H, 3.22; Br, 23.67; N, 8.15. $C_{10}H_{11}BrN_2O_4S$ requires C, 35.84; H, 3.31; Br, 23.84; N, 8.36%]; ν_{max} (ATP) 3331, 3131 (NH), 1590 (NH_2), 1537 (C=N), 1292, 1130 (SO_2) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.15 (3H, s, CH_3), 3.90 (3H, s, CO_2CH_3), 7.97 (2H, s, Ar*H*), 8.54 (1H, s, Ar*H*), 9.12 (2H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 22.1, 53.2, 125.8, 129.5, 129.7, 133.6, 136.4, 143.2, 165.3, 169.2.

*4.2.7. N′-[(2-Chloro-5-nitrophenyl)sulfonyl]ethanimidamide (**3g**).* Yellowish solid; yield 4.72 g (85%); mp 203–204 °C (dec); [found: C, 34.55; H, 2.90; N, 15.15. $C_8H_8ClN_3O_2S$ requires C, 34.60; H, 2.90; N, 15.13%]; δ_H (500 MHz, DMSO-d_6) 2.18 (3H, s, CH_3), 7.94 (1H, s, Ar*H*), 8.40 (2H, br s, NH_2), 8.72 (2H, d, *J* 7.0 Hz, Ar*H*); δ_C (125 MHz, DMSO-d_6) 22.1, 124.2, 128.1, 133.8, 138.3, 142.1, 146.4, 169.6.

*4.2.8. N′-[(2-Bromo-5-nitrophenyl)sulfonyl]ethanimidamide (**3h**).* Yellowish solid; yield 5.86 g (91%); mp 235–237 °C (dec); [found: C, 29.80; H, 2.51; Br, 25.00; N, 12.99. $C_8H_8BrN_3O_4S$ requires C, 29.83; H, 2.50; Br, 24.80; N, 13.04%]; δ_H (500 MHz, DMSO-d_6) 2.19 (3H, s, CH_3), 8.12 (1H, s, Ar*H*), 8.31(2H, br s, NH_2), 8.73 (2H, s, Ar*H*); δ_C (125 MHz, DMSO-d_6) 22.2, 124.1, 127.8, 137.3, 144.0, 147.0, 169.6.

*4.2.9. N′-((2-Fluorophenyl)sulfonyl)benzenecarboximidamide (**3i**).* Colorless solid; yield 5.06 g (91%); mp 105–106 °C; [found: C, 56.08; H, 4.00; N, 10.05. $C_{13}H_{11}FN_2O_2S$ requires C, 56.11; H, 3.98; N, 10.07%]; δ_H (500 MHz, DMSO-d_6) 7.34–7.46 (2H, m, Ar*H*), 7.50 (1H, t, *J* 8.0 Hz, Ar*H*), 7.61 (1H, t, *J* 8.0 Hz, Ar*H*), 7.65–7.75 (1H, m, Ar*H*), 7.88 (2H, d, *J* 8.0 Hz, Ar*H*), 7.99 (1H, t, *J* 8.0 Hz, Ar*H*), 8.77 (2H, br s, Ar*H*); δ_C (125 MHz, DMSO-d_6) 117.6 (d, *J* 21.3 Hz), 125.0 (d, *J* 3.8 Hz), 128.4, 129.0, 129.2, 130.6 (d, *J* 13.8 Hz), 133.1, 133.6, 135.3 (d, *J* 8.8 Hz), 159.0 (d, *J* 252.5 Hz), 163.7; δ_F (470 MHz, DMSO-d_6) −110.6, −75.8.

*4.2.10. N′-((2-Chlorophenyl)sulfonyl)benzenecarboximidamide (**3j**).* Colorless solid; yield 5.3 g (90%); mp 125–127 °C; [found: C, 53.01; H, 3.74; Cl, 12.00; N, 9.49. $C_{13}H_{11}ClN_2O_2S$ requires C, 52.97; H, 3.76; Cl, 12.03; N, 9.50%]; δ_H (500 MHz, DMSO-d_6) 7.39–7.78 (5H, m, Ar*H*), 7.90 (2H, d, *J* 7.0 Hz, Ar*H*), 8.17 (1H, d, *J* 7.0 Hz, Ar*H*), 8.81 (2H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 127.4, 128.5, 129.0, 129.8, 131.8, 132.2, 133.0, 133.7, 134.1, 140.2, 163.8.

*4.2.11. N′-((2-Bromophenyl)sulfonyl)benzenecarboximidamide (**3k**).* Colorless solid; yield 6.5 g (96%); mp132–134 °C; [found: C, 45.99; H, 3.28; N 8.23. $C_{13}H_{11}BrN_2O_2S$ requires C, 46.03; H, 3.27; N, 8.26%]; δ_H (500 MHz, DMSO-d_6) 7.43–7.58 (3H, m, Ar*H*), 7.58–7.66 (2H, m, Ar*H*), 7.83 (1H, d, *J* 7.0 Hz, Ar*H*), 7.90 (2H, d, *J* 7.0 Hz, Ar*H*), 8.18 (1H, d, *J* 7.0 Hz, Ar*H*), 8.62 (2H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 120.4, 128.3, 129.0, 133.0, 133.8, 134.1, 135.6, 141.8, 163.8.

*4.2.12. 3-((Amino(phenyl)methylidene)sulfamoyl)-4-chlorobenzoic acid (**3l**).* Colorless solid; yield 5.55 g (82%); mp 229–231 °C; [found: C, 49.51; H, 3.29; Cl, 10.48; N, 8.27. $C_{14}H_{11}ClN_2O_4S$ requires C, 49.64; H, 3.27; Cl, 10.47; N, 8.27%]; δ_C (500 MHz, DMSO-d_6) 7.50 (2H, t, *J* 7.0 Hz, Ar*H*), 7.61 (1H, t, *J* 7.0 Hz, Ar*H*), 7.71 (2H, s, Ar*H*), 7.88 (2H, d, *J* 7.0 Hz, Ar*H*), 8.15 (1H, s, Ar*H*), 8.85 (2H, br s, NH_2); δ_C (125 MHz, DMSO-d_6) 128.6, 129.0, 129.4, 130.5, 132.4, 133.1, 133.6, 133.8, 133.9, 141.7, 164.2.

*4.2.13. Methyl-3-((amino(phenyl)methylidene)sulfamoyl)-4-bromobenzoate (**3m**).* Colorless solid; yield 7.3 g (92%); mp 191–193 °C; [found: C, 45.02; H, 3.37; Br 19.89; N, 6.92. $C_{15}H_{13}BrN_2O_4S$ requires C, 45.35; H, 3.30; Br, 20.11; N, 7.05%]; ν_{max} (ATP) 3335, 3177 (NH), 1586 (NH_2), 1482(C=N), 1297, 1174 (SO_2) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.90 (3H, s, CO_2CH_3), 7.49 (2H, t, *J* 8.0 Hz, Ar*H*), 7.60 (1H, t, *J* 8.0 Hz, Ar*H*), 7.91 (2H, t, *J* 8.0 Hz, Ar*H*), 8.00 (2H, s, Ar*H*), 8.41 (1H, br s, N*H*), 8.54 (1H, s, Ar*H*), 9.33 (1H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 52.8, 125.8, 128.6, 128.6, 128.7, 129.5, 130.0, 130.9, 134.3, 135.1, 147.7, 166.0, 166.1.

*4.2.14. N′-[(2-Chloro-5-nitrophenyl)sulfonyl]benzenecarboximidamide (**3n**).* Yellow solid; yield 6.38 g (94%); mp 162–164 °C; [found: C, 45.94; H, 2.98; Cl, 10.49; N, 12.35. $C_{13}H_{10}ClN_3O_4S$ requires C, 45.96; H, 2.97; Cl, 10.43; N, 12.37%]; δ_H (500 MHz, DMSO-d_6) 7.51 (2H, t, *J* 7.0 Hz, Ar*H*), 7.62 (1H, t, *J* 7.0 Hz, Ar*H*), 7.90 (2H, d, *J* 7.0 Hz, Ar*H*), 7.96 (1H, d, *J* 8.0 Hz, Ar*H*), 8.42 (1H, d, *J* 8.0 Hz, Ar*H*), 8.47 (1H, br s, N*H*), 8.83 (1H, s, Ar*H*), 9.31 (1H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 124.6, 128.4, 128.6, 129.0, 133.2, 133.4, 133.9, 138.4, 141.5, 146.5, 164.3.

*4.2.15. N′-[(2-Bromo-5-nitrophenyl)sulfonyl]benzenecarboximidamide (**3o**).* Yellowish solid; yield 7.3 g (95%); mp 186–188 °C; [found: C, 40.61; H, 2.63; Br, 20.83; N, 10.94. $C_{13}H_{10}BrN_3O_4S$ requires C, 40.64; H, 2.62; Br, 20.80; N, 10.94%]; δ_H (500 MHz, DMSO-d_6) 7.50 (2H, t, *J* 7.0 Hz, Ar*H*), 7.62 (1H, t, *J* 7.0 Hz, Ar*H*), 7.90 (2H, d, *J* 7.0 Hz, Ar*H*), 8.14 (1H, d, *J* 8.5 Hz, ArH), 8.31 (1H, d, *J* 8.5 Hz, Ar*H*), 8.49 (1H, br s, N*H*), 8.3 (1H, s, Ar*H*), 9.34 (1H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 124.5, 127.8, 128.1, 128.6, 129.0, 133.2, 133.4, 137.4, 143.3, 147.0, 164.3.

4.3. General non-catalytic procedure for the preparation of 4*H*-1,2,4-benzothiadiazine-1,1-dioxides 4 from sulfonylated amidines 3

A stirred solution of sulfonylated amidine (0.015 mol) and potassium carbonate (4.5 g, 0.035 mol) in dry DMF (100 mL) was heated at 80 °C for 8 h. Then the solvent was removed under reduced pressure. The residue was triturated with water (200 mL) and acidified with hydrochloric acid to pH 1. The solid precipitate was filtered, washed with water, and dried under vacuum.

4.4. One-pot procedure for the preparation of 4*H*-1,2,4-benzothiadiazine-1,1-dioxides 4c, 4f, and 4g from *o*-fluoronitrobenzenesulfonyl chlorides 1d, 1g and amidines 2

To a stirred solution of equimolar amounts of *o*-halogenoarylsulfonyl chloride **1** (0.015 mol) and amidine **2** hydrochloride (0.015 mol) in dichloromethane (37 mL) a concentrated water solution of potassium hydroxide (4.2 g, 0.075 mol) was slowly added at 0 °C. The reaction mixture was allowed to stir overnight at room temperature and then acidified with hydrochloric acid to pH 1. The precipitated 4*H*-1,2,4-benzothiadiazine-1,1-dioxide was filtered,

washed with water and dichloromethane, and dried under ambient conditions.

4.5. General catalytic procedure for the preparation of 4*H*-1,2,4-benzothiadiazine-1,1-dioxides 4 from *o*-bromoarylsulfonyl amidines 3

Potassium carbonate (4.08 g, 0.03 mol), copper(I) iodide (0.14 g, 0.75 mmol, 5 mol %), and 0.13 g (0.0015 mol, 10 mol %) of DMEDA were added to a solution of sulfonylated amidine **2** (0.015 mol) in DMF (100 mL) under argon. The reaction mixture was stirred under argon at 80 °C for 8 h. Then the solvent was removed under reduced pressure. The residue was dissolved in water and acidified with hydrochloric acid to pH 1. Solid precipitate was filtered, washed with water, and dried under ambient condition.

*4.5.1. 3-Methyl-4H-1,2,4-benzothiadiazine-1,1-dioxide (**4a**).* Colorless solid; yield 2.76 g (96%) (from **3a**), 2.73 g (93%) (from **3b**), 2.88 g (98%) (from **3c**); mp 253–255 °C (lit. 254–255 °C[12]); [found: C, 48.75; H, 4.05; N, 14.53. $C_8H_8N_2O_2S$ requires C, 48.97; H, 4.11; N 14.28%]; δ_H (500 MHz, DMSO-d_6) 2.31 (3H, s, CH_3), 7.30 (1H, d, *J* 8.0 Hz, Ar*H*), 7.43 (1H, t, *J* 8.0 Hz, Ar*H*), 7.67 (1H, t, *J* 8.0 Hz, Ar*H*), 7.79 (1H, d, *J* 8.0 Hz, Ar*H*), 12.03 (1H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 23.2, 120.1, 120.5, 126.2, 126.3, 129.6, 137.0, 158.0.

*4.5.2. Methyl-1,1-dioxo-3-methyl-4H-1,2,4-benzothiadiazine-7-carboxylate (**4b**).* Colorless solid; yield 3.54 g (93%) (from **3e**), 3.71 g (95%) (from **3f**); mp 263–265 °C; [found: C, 47.02; H, 3.92; N, 11.15. $C_{10}H_{10}N_2O_4S$ requires C, 47.24; H, 3.96; N, 11.02%]; ν_{max} (ATP) 1244, 1133 (SO_2) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.34 (3H, s, CH_3), 3.90 (3H, s, CO_2CH_3), 7.43 (1H, d, *J* 9.0 Hz, Ar*H*), 8.18 (1H, dd, *J* 9.0, 2.0 Hz, Ar*H*), 8.25 (1H, d, *J* 2.0 Hz, Ar*H*), 12.43 (1H, br s, NH); δ_C (125 MHz, DMSO-d_6) 23.2, 53.0, 118.5, 121.2, 125.5, 127.4, 133.7, 139.1, 158.5, 164.9.

*4.5.3. 3-Methyl-7-nitro-4H-1,2,4-benzothiadiazine-1,1-dioxide (**4c**).* Yellow solid; yield 3.4 g (94%) (one-pot from **4g**), 3.4 g (94%) (from **3g**), 3.33 g (92%) (from **3h**); mp 264–266 °C (lit. 264–265 °C[16]); [found: C, 39.85; H, 2.90; N, 17.43. $C_8H_7N_3O_4S$ requires C, 39.83; H, 2.92; N, 17.42%]; δ_C (500 MHz, DMSO-d_6) 2.38 (3H, s, CH_3), 7.51 (1H, d, *J* 9.0 Hz, Ar*H*), 8.45 (1H, dd, *J* 9.0, 2.0 Hz, Ar*H*), 8.50 (1H, d, *J* 2.0 Hz, Ar*H*); δ_C (125 MHz, DMSO-d_6) 23.3, 119.6, 120.5, 121.1, 128.3, 140.5, 144.6, 159.0.

*4.5.4. 3-Phenyl-4H-1,2,4-benzothiadiazine-1,1-dioxide (**4d**).* Colorless solid; yield 3.68 g (95%) (from **3i**), 3.75 g (97%) (from **3j**), 3.72 g (96%) (from **3k**); mp 307–309 °C (lit. 307–308 °C[1]); [found: C, 60.43; H, 3.91; N, 10.81. $C_{13}H_{10}N_2O_2S$ requires C, 60.45; H, 3.90; N, 10.85%]; δ_H (500 MHz, DMSO-d_6) 7.53 (1H, t, *J* 8.0 Hz, Ar*H*), 7.60–7.69 (3H, m, Ar*H*), 7.69–7.80 (2H, m, Ar*H*), 7.88 (1H, d, *J* 8.0 Hz, Ar*H*), 8.07 (2H, d, *J* 8.0 Hz, Ar*H*); δ_C (125 MHz, DMSO-d_6) 119.0, 122.0, 123.8, 127.2, 128.8, 129.3, 132.4, 133.3, 133.6, 136.1, 155.3.

*4.5.5. Methyl-1,1-dioxo-3-phenyl-4H-1,2,4-benzothiadiazine-7-carboxylate (**4e**).* Colorless solid; yield 4.6 g (97%) (from **3m**); mp 302–304 °C; [found: C, 56.72; H, 3.85; N, 8.78. $C_{15}H_{12}N_2O_4S$ requires C, 56.95; H, 3.82; N, 8.86%]; ν_{max} (ATP) 1246, 1123 (SO_2) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.90 (3H, s, CO_2CH_3), 7.6–7.68 (2H, m, Ar*H*), 7.69–7.82 (2H, m, Ar*H*), 8.0–8.1 (2H, m, Ar*H*), 8.25 (1H, d, *J* 7.5 Hz, Ar*H*), 8.32 (1H, s, Ar*H*), 12.55 (1H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 53.1, 119.7, 121.6, 125.3, 128.0, 128.9, 129.5, 131.9, 133.8, 133.8, 139.4, 156.0, 165.0.

*4.5.6. 7-Nitro-3-phenyl-4H-1,2,4-benzothiadiazine-1,1-dioxide (**4f**).* Yellowish solid; yield 4.41 g (97%) (one-pot from **1g**), 4.18 g (92%) (from **3n**), 4.1 g (90%) (from **3o**); mp 310–312 °C; [found: C, 51.50; H, 2.98; N, 13.87. $C_{13}H_9N_3O_4S$ requires C, 51.48; H, 2.99; N, 13.85%]; δ_H (500 MHz, DMSO-d_6) 7.67 (2H, t, *J* 7.0 Hz, Ar*H*), 7.75 (1H, t, *J* 7.0 Hz, Ar*H*), 7.90 (1H, d, *J* 9.0 Hz, Ar*H*), 8.11 (2H, d, *J* 7.0 Hz, Ar*H*), 8.53 (1H, d, *J* 9.0 Hz, Ar*H*), 8.58 (1H, s, Ar*H*), 12.58 (1H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 120.4, 120.9, 121.6, 128.3, 129.0, 129.4, 131.7, 133.9, 140.8, 145.0, 156.0.

*4.5.7. 3-Phenyl-4H-1,2,4-benzothiadiazine-7-carboxylic acid 1,1-dioxide (**4g**).* Colorless solid; yield 3.85 g (85%) (from **1d**); mp 340–343 °C; [found: C, 55.60; H, 3.32; N, 9.29. $C_{14}H_{10}N_2O_4S$ requires C, 55.62; H, 3.33; N, 9.27]; δ_H (500 MHz, DMSO-d_6) 7.66 (2H, t, *J* 7.0 Hz, Ar*H*), 7.70–7.83 (2H, m, Ar*H*), 8.09 (2H, d, *J* 7.0 Hz, Ar*H*), 8.26 (1H, d, *J* 8.0 Hz, Ar*H*), 8.34 (1H, s, ArH), 12.50 (1H, br s, N*H*), 13.47 (1H, br s, CO_2H); δ_C (125 MHz, DMSO-d_6) 119.6, 121.7, 125.4, 128.9, 129.2, 129.4, 132.1, 133.6, 134.0, 139.2, 155.8, 165.9.

4.6. General procedure for preparation of sulfonamides 6

To a stirred solution of 2-aminopyridine derivative **5** (0.025 mol) in dry pyridine (25 mL) 2-halobenzenesulfonyl chloride **1** (0.025 mol) was added. The reaction mixture was stirred at reflux for 4 h. Then the solvent was removed under reduced pressure and the residue triturated with deionized water (50 mL). The resulting solid precipitate was filtered, washed with water (2×15 mL), methanol (3×10 mL), and dried in vacuum. The product can additionally be purified by recrystallization from methanol.

*4.6.1. 2-Fluoro-N-(pyridin-2-yl)benzenesulfonamide (**6a**).* Colorless solid; yield 5.77 g (92%); mp 202–205 °C; [found: C, 52.35; H, 3.61; N, 11.05. $C_{11}H_9FN_2O_2S$ requires C, 52.37; H, 3.60; N, 11.10%]; ν_{max} (ATP) 3215 (NH), 1600 (C=N), 1294, 1146 (SO_2) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 6.83–6.89 (1H, m, Ar*H*), 7.26 (1H, d, *J* 9.0 Hz, Ar*H*), 7.30–7.37 (2H, m, Ar*H*), 7.59–7.65 (1H, m, Ar*H*), 7.79 (1H, t, *J* 7.0 Hz, Ar*H*), 7.92–7.95 (2H, m, Ar*H*), 12.62 (1H, br s, N*H*); δ_H (500 MHz, CF_3CO_2D) 7.34 (1H, t, *J* 10.0 Hz, Ar*H*), 7.49 (1H, t, *J* 6.5 Hz, Ar*H*), 7.67–7.74 (2H, m, Ar*H*), 7.84 (1H, d, *J* 4.5 Hz, Ar*H*), 8.10 (1H, t, *J* 6.0 Hz, Ar*H*), 8.48 (1H, t, *J* 8.5 Hz, Ar*H*), 8.52 (1H, d, *J* 5.0 Hz, Ar*H*); δ_C (125 MHz, DMSO-d_6) 114.5, 115.5, 117.5 (d, *J* 21.3 Hz), 124.9, 130.1, 130.9 (d, *J* 7.5 Hz), 134.8 (d, *J* 7.5 Hz), 140.9, 142.2, 154.6, 158.8 (d, *J* 251.3 Hz); δ_C (125 MHz, CF_3CO_2D) 116.6, 176.0 (d, *J* 18.8 Hz), 120.9, 125.0 (d, *J* 12.5 Hz), 125.3, 129.8, 138.1, 138.2 (d, *J* 8.8 Hz), 146.5, 148.5 (d, *J* 253.8 Hz); δ_F (470 MHz, DMSO-d_6) −111.5; δ_F (470 MHz, CF_3CO_2D) −79.5.

*4.6.2. 2-Chloro-N-(pyridin-2-yl)benzenesulfonamide (**6b**).* Colorless solid; yield 6.04 g (90%); mp 215–217 °C; [found: C, 49.23; H, 3.35; Cl, 13.21; N, 10.40. $C_{11}H_9ClN_2O_2S$ requires C, 49.17; H, 3.38; Cl, 13.19; N, 10.42%]; ν_{max} (ATP) 1600 (C=N), 1292, 1145 (SO2) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 6.84 (1H, t, *J* 6.0 Hz, Ar*H*), 7.20 (1H, d, *J* 8.5 Hz, Ar*H*), 7.50–7.55 (1H, m, Ar*H*), 7.55–7.59 (2H, m, Ar*H*), 7.77 (1H, t, *J* 8.0 Hz, Ar*H*), 7.92 (1H, d, *J* 4.5 Hz, Ar*H*), 8.13 (1H, d, *J* 7.5 Hz, Ar*H*), 12.71 (1H, br s, N*H*); δ_H (500 MHz, CF_3CO_2D) 7.68–7.74 (3H, m, Ar*H*), 7.74–7.81 (2H, m, Ar*H*), 8.34 (1H, d, *J* 8.0 Hz, Ar*H*), 8.49 (1H, t, *J* 8.0 Hz, Ar*H*), 8.54 (1H, d, *J* 5.5 Hz, Ar*H*); δ_C (125 MHz, DMSO-d_6) 115.6, 127.7, 130.8, 131.3, 132.0, 133.7, 140.6, 142.0, 154.5; δ_C (125 MHz, CF_3CO_2D) 116.5, 120.8, 127.8, 131.5, 132.4, 134.3, 136.6, 138.2, 146.7, 148.5.

*4.6.3. 2-Bromo-N-(pyridin-2-yl)benzenesulfonamide (**6c**).* Colorless solid; yield 7.35 g (94%); mp 217–219 °C; [found: C, 42.07; H, 2.87; Br, 25.57; N, 8.93. $C_{11}H_9BrN_2O_2S$ requires C, 42.19; H, 2.90; Br, 25.51; N, 8.94%]; ν_{max} (ATP) 1601 (C=N), 1294, 1146 (SO_2)

cm^{-1}; δ_H (500 MHz, DMSO-d_6) 6.83 (1H, t, *J* 8.0 Hz, Ar*H*), 7.19 (1H, d, *J* 9.0 Hz, Ar*H*), 7.47 (1H, t, *J* 8.0 Hz, Ar*H*), 7.56 (1H, t, *J* 7.5 Hz, Ar*H*), 7.77 (2H, d, *J* 8.0 Hz, Ar*H*), 7.92 (1H, d, *J* 4.5 Hz, Ar*H*), 8.15 (1H, d, *J* 7.5 Hz, Ar*H*), 12.82 (1H, br s, N*H*); δ_H (500 MHz, CF_3CO_2D) 7.71–7.73 (3H, m, Ar*H*), 7.76 (1H, d, *J* 9.0 Hz, Ar*H*), 7.94 (1H, d, *J* 9.0 Hz, ArH), 8.39 (1H, d, *J* 9.0 Hz, ArH), 8.49 (1H, t, *J* 8.0 Hz, Ar*H*), 8.55 (1H, d, *J* 6.0 Hz, Ar*H*); δ_C (125 MHz, DMSO-d_6) 114.2, 115.8, 119.9, 128.3, 130.9, 133.6, 135.5, 140.5, 142.3, 154.7; δ_C (125 MHz, CF_3CO_2D) 116.4, 120.0, 120.8, 128.3, 132.0, 135.9, 136.1, 136.4, 138.2, 146.7, 148.4.

*4.6.4. Methyl-4-chloro-3-[(pyridine-2-ylamino)sulfonyl]benzoate (**6d**).* Colorless solid; yield 7.51 g (92%); mp 226–228 °C; [found: C, 47.75; H, 3.39; Cl, 10.87; N, 8.52. $C_{13}H_{11}ClN_2O_4S$ requires C, 47.79; H, 3.39; Cl, 10.85; N, 8.57%]; ν_{max} (ATP) 1604 (C=N), 1287, 1167 (SO_2) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.98 (3H, s, CO_2CH_3), 6.83–6.88 (1H, m, Ar*H*), 7.25 (1H, d, *J* 8.5 Hz, Ar*H*), 7.74 (1H, d, *J* 8.0 Hz, Ar*H*), 7.82 (1H, t, *J* 7.5 Hz, Ar*H*), 7.92 (1H, d, *J* 2.0 Hz, Ar*H*), 8.07 (1H, d, *J* 8.0 Hz, Ar*H*), 8.64 (1H, s, Ar*H*), 13.03 (1H, br s, N*H*); δ_H (500 MHz, CF_3CO_2D) 4.32 (3H, s, CO_2CH_3), 7.76–7.88 (1H, m, Ar*H*), 7.88–8.03 (2H, m, Ar*H*), 8.56 (1H, t, *J* 8.5 Hz, Ar*H*), 8.60–8.67 (2H, m, Ar*H*), 9.16 (1H, s, Ar*H*); δ_C (125 MHz, DMSO-d_6) 53.2, 116.0, 125.4, 129.0, 130.8, 132.8, 133.7, 136.3, 141.6, 143.0, 154.9, 165.2; δ_C (125 MHz, CF_3CO_2D) 53.5, 116.7, 121.2, 129.4, 132.9, 133.2, 135.7, 136.9, 138.1, 138.5, 146.4, 148.7, 167.4.

*4.6.5. Methyl-4-bromo-3-[(pyridine-2-ylamino)sulfonyl]benzoate (**6e**).* Colorless solid; yield 8.63 g (93%); mp 243–245 °C; [found: C, 42.00; H, 3.01; Br, 21.57; N, 7.68. $C_{13}H_{11}BrN_2O_4S$ requires C, 42.06; H, 2.99; Br, 21.53; N, 7.55%]; ν_{max} (ATP) 1605 (C=N), 1280, 1147 (SO_2)cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.91 (3H, s, CO_2CH_3), 6,84 (1H, t, *J* 7.0 Hz, Ar*H*), 7.21 (1H, d, *J* 8.0 Hz, Ar*H*), 7.82 (1H, t, *J* 8.0 Hz, Ar*H*), 7.90–7.95 (3H, m, Ar*H*), 8.63 (1H, s, Ar*H*), 13.30 (1H, br s, N*H*); δ_H (500 MHz, CF_3CO_2D) 4.31 (3H, s, CO_2CH_3), 7.81 (1H, t, *J* 6.0 Hz, Ar*H*), 7.92 (1H, d, *J* 8.5 Hz, Ar*H*), 8.18 (1H, d, *J* 8.5 Hz, Ar*H*), 8.45 (1H, d, *J* 6.0 Hz, Ar*H*), 8.59–8.67 (2H, m, Ar*H*), 9.18 (1H, s, ArH); δ_C (125 MHz, DMSO-d_6) 53.2, 113.5, 116.3, 125.5, 129.5, 130.7, 133.4, 136.4, 143.3, 154.9, 165.4; δ_C (125 MHz, CF_3CO_2H) 53.5, 116.7, 121.2, 126.4, 129.9, 133.1, 136.6, 136.9, 137.5, 138.5, 146.4, 148.7, 167.6.

*4.6.6. Methyl-4-chloro-3-{[(4-methylpyridine-2-yl)amino]sulfonyl} benzoate (**6f**).* Colorless solid; yield 7.75 g (91%); mp 236–237 °C; [found: C, 49.36; H, 3.79; Cl, 10.45; N, 8.21. $C_{14}H_{13}ClN_2O_4S$ requires C, 49.34; H, 3.85; Cl, 10.40; N, 8.22%]; ν_{max} (ATP) 1612 (C=N), 1287, 1128 (SO_2) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.82 (3H, s, CH_3), 3.92 (3H, s, CO_2CH_3), 6.71 (1H, d, *J* 7.0 Hz, Ar*H*), 7.08 (1H, s, Ar*H*), 7.74 (1H, d, *J* 8.0 Hz, ArH), 7.78 (1H, d, *J* 7.0 Hz, Ar*H*), 8.07 (1H, dd, *J* 8.0, 2.0 Hz, Ar*H*), 8.62 (1H, d, *J* 2.0 Hz, Ar*H*), 12.98 (1H, br s, N*H*); δ_H (500 MHz, CF_3CO_2D) 2.84 (3H, s, CH_3), 4.34 (3H, s, CO_2CH_3), 7.66–7.73 (1H, m, Ar*H*), 7.73–7.76 (1H, m, Ar*H*), 7.98 (1H, d, *J* 8.0 Hz, Ar*H*), 8.49 (1H, m, ArH), 8.58 (1H, m, ArH), 9.17 (1H, s, ArH); δ_C (125 MHz, DMSO-d_6) 22.0, 53.2, 115.8, 126.8, 127.0, 130.5, 132.8, 133.4, 136.3, 165.3; δ_C (125 MHz, CF_3CO_2D) 21.3, 53.5, 116.6, 122.8, 129.5, 132.9, 133.3, 135.9, 137.0, 137.5, 138.1, 145.5, 164.8, 167.5.

*4.6.7. Methyl-4-bromo-3-{[(4-methylpyridine-2-yl)amino]sulfonyl} benzoate (**6g**).* Colorless solid; yield 8.95 g (93%); mp 227–229 °C; [found: C, 43.62; H, 3.43; Br, 20.81; N, 7.25. $C_{14}H_{13}BrN_2O_4S$ requires C, 43.65; H, 3.40; Br, 20.74; N, 7.27%]; ν_{max} (ATP) 1628 (C=N), 1296, 1149 (SO_2) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.29 (3H, s, CH_3), 3.92 (3H, s, CO_2CH_3), 6.70 (1H, d, *J* 6.0 Hz, Ar*H*), 7.09 (1H, s, Ar*H*), 7.76 (1H, d, *J* 6.0 Hz, Ar*H*), 7.9–7.97 (2H, m, Ar*H*), 8.66 (1H, s, Ar*H*), 12.73 (1H, br s, N*H*); δ_H (500 MHz, CF_3CO_2D) 2.85 (3H, s, CH_3), 4.35 (3H, s, CO_2CH_3), 7.59–7.67 (1H, m, Ar*H*), 7.67–7.76 (1H, m, Ar*H*), 8.22 (1H, d, *J* 8.0 Hz, Ar*H*), 8.47–8.52 (2H, m, Ar*H*), 9.20 (1H, s, Ar*H*); δ_C (125 MHz, DMSO-d_6) 22.0, 53.2, 115.2, 115.9, 124.8, 125.6, 129.4, 130.4, 133.2, 136.3, 138.0, 143.8, 149.1, 154.9, 155.1, 165.4; δ_C (125 MHz, CF_3CO_2D) 21.2, 53.5, 116.5, 122.7, 126.3, 129.9, 133.1, 136.6, 137.0, 137.4, 137.7, 145.5, 164.7, 167.6.

*4.6.8. Methyl-4-chloro-3-{[(5-methylpyridine-2-yl)amino]sulfonyl} benzoate (**6h**).* Colorless solid; yield 7.91 g (93%); mp 216–218 °C; [found: C, 49.37; H, 3.83; Cl, 10.46; N, 8.20. $C_{14}H_{13}ClN_2O_4S$ requires C, 49.34; H, 3.85; Cl, 10.40; N, 8.22%]; ν_{max} (ATP) 1593 (C=N), 1281, 1133 (SO_2) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.13 (3H, s, CH_3), 3.91 (3H, s, CO_2CH_3), 7.16 (1H, d, *J* 8.0 Hz, Ar*H*), 7.67 (1H, d, *J* 8.0 Hz, Ar*H*), 7.72 (1H, d, *J* 4.0 Hz, Ar*H*), 7.76 (1H, s, Ar*H*), 8.06 (1H, d, *J* 8.0 Hz, Ar*H*), 8.62 (1H, s, Ar*H*), 12.89 (1H, br s, N*H*); δ_H (500 MHz, CF_3CO_2D) 2.66 (3H, s, CH_3), 4.30 (3H, s, CO_2CH_3), 7.80 (1H, d, *J* 6.0 Hz, Ar*H*), 7.95 (1H, s, *J* 5.0 Hz, Ar*H*), 8.39–8.50 (2H, m, Ar*H*), 8.55 (1H, d, *J* 5.0 Hz, Ar*H*), 9.12 (1H, s, Ar*H*); δ_C (125 MHz, DMSO-d_6) 17.0, 53.2, 115.5, 124.0, 129.0, 130.9, 132.8, 133.6, 136.3, 138.9, 141.6, 144.1, 152.9, 165.2; δ_C (125 MHz, CF_3CO_2D) 15.9, 53.5, 116.6, 129.3, 132.8, 133.2, 133.9, 135.7, 136.8, 137.2, 138.0, 143.9, 150.1, 167.4.

*4.6.9. Methyl-4-bromo-3-{[(5-methylpyridine-2-yl)amino]sulfonyl} benzoate (**6i**).* Colorless solid; yield 8.76 g (91%); mp 111–113 °C; [found: C, 43.68; H, 3.38; Br, 20.64; N, 7.31. $C_{14}H_{13}BrN_2O_4S$ requires C, 43.65; H, 3.40; Br, 20.74; N, 7.27%]; ν_{max} (ATP) 1602 (C=N), 1296, 1130 (SO_2) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.14 (3H, s, CH_3), 3.91 (3H, s, CO_2CH_3), 7.15 (1H, d, *J* 8.5 Hz, Ar*H*), 7.67 (1H, d, *J* 8.5 Hz, Ar*H*), 7.76 (1H, s, Ar*H*), 7.90–8.00 (2H, m, Ar*H*), 8.64 (1H, s, Ar*H*), 12.83 (1H, br s, N*H*); δ_H (500 MHz, CF_3CO_2D) 2.78 (3H, s, CH_3), 4.42 (3H, s, CO_2CH_3), 7.94 (1H, d, *J* 7.5 Hz, Ar*H*), 8.30 (1H, d, *J* 7.5 Hz, Ar*H*), 8.51–8.64 (2H, m, Ar*H*), 9.27 (1H, s, Ar*H*); δ_C (125 MHz, DMSO-d_6) 17.0, 53.2, 115.7, 123.7, 125.4, 129.6, 130.9, 133.4, 136.3, 138.6, 143.4, 144.2, 153.0, 165.4; δ (125 MHz, CF_3CO_2D) 16.0, 53.6, 116.7, 126.4, 129.9, 133.2, 134.0, 136.6, 137.0, 137.3, 137.6, 144.0, 150.1, 167.7.

*4.6.10. Methyl-4-chloro-3-{[(6-methylpyridine-2-yl)amino]sulfonyl} benzoate (**6j**).* Colorless solid; yield 7.58 g (89%); mp 233–235 °C; [found: C, 49.39; H, 3.82; Cl, 10.43; N, 8.21. $C_{14}H_{13}ClN_2O_4S$ requires C, 49.34; H, 3.85; Cl, 10.40; N, 8.22%]; ν_{max} (ATP) 1590 (C=N), 1280, 1118 (SO_2) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.33 (3H, s, CH_3), 3.92 (3H, s, CO_2CH_3), 6.68 (1H, d, *J* 7.0 Hz, Ar*H*), 7.04 (1H, d, *J* 7.5 Hz, Ar*H*), 7.68–7.76 (2H, m, Ar*H*), 8.06 (1H, dd, *J* 8.0, 1.5 Hz, Ar*H*), 8.64 (1H, s, Ar*H*), 13.20 (1H, br s, N*H*); δ_H (500 MHz, CF_3CO_2D) 3.19 (3H, s, CH_3), 4.52 (3H, s, CO_2CH_3), 7.84 (1H, d, *J* 7.0 Hz, Ar*H*), 8.01 (1H, d, *J* 8.0 Hz, Ar*H*), 8.17 (1H, d, *J* 8.0 Hz, Ar*H*), 8.67 (1H, t, *J* 8.0 Hz, Ar*H*), 8.77 (1H, d, *J* 7.0 Hz, Ar*H*), 9.32 (1H, s, Ar*H*); δ_C (125 MHz, DMSO-d_6) 19.5, 53.2, 112.5, 126.6, 128.9, 130.9, 132.8, 133.5, 136.4, 143.5, 165.3; δ_C (125 MHz, DMSO-d_6) 18.6, 53.6, 113.8, 121.9, 129.5, 133.0, 133.4, 135.9, 137.0, 138.2, 146.1, 148.7, 152.6, 167.6.

*4.6.11. Methyl-4-bromo-3-{[(6-methylpyridine-2-yl)amino]sulfonyl} benzoate (**6k**).* Colorless solid; yield 8.37 g (87%); mp 228–230 °C; [found: C, 43.69; H, 3.38; Br, 20.69; N, 7.29. $C_{14}H_{13}BrN_2O_4S$ requires C, 43.65; H, 3.40; Br, 20.74; N, 7.27%]; ν_{max} (ATP) 3228 (NH), 1609 (C=N), 1283, 1119 (SO_2) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.34 (3H, s, CH_3), 3.92 (3H, s, CO_2CH_3), 6.67 (1H, d, *J* 7.0 Hz, Ar*H*), 7.05 (1H, s, Ar*H*), 7.70 (1H, t, *J* 7.0 Hz, Ar*H*), 7.86–8.00 (2H, m, Ar*H*), 8.66 (1H, s, Ar*H*), 13.37 (1H, br s, N*H*); δ_H (500 MHz, CF_3CO_2D) 3.06 (3H, s, CH_3), 4.39 (3H, s, CO_2CH_3), 7.70 (1H, d, *J* 7.0 Hz, Ar*H*), 7.87 (1H, d, *J* 8.0 Hz, Ar*H*), 8.26 (1H, d, *J* 8.0 Hz, Ar*H*), 8.50–8.56 (2H, m, Ar*H*), 9.21 (1H, s, Ar*H*); δ_C (125 MHz, DMSO-d_6) 19.2, 53.2, 112.9, 125.6, 129.4, 130.7, 133.2, 136.3, 143.7, 165.4; δ_C (125 MHz, CF_3CO_2D) 18.5,

53.5, 113.7, 121.8, 126.4, 130.0, 133.1, 136.5, 137.0, 137.6, 146.0, 148.5, 152.5, 167.7.

4.7. One-pot procedure for the preparation of pyrido[2,1-*c*][1,2,4]benzothiazine-5,5-dioxides 7 from selected sulfonyl chlorides 1 and 2-aminopyridines 5

The procedure is identical to the *General procedure for the preparation of sulfonamides* **6** above.

4.8. General non-catalytic procedure for the preparation of pyrido[2,1-*c*][1,2,4]benzothiazine-5,5-dioxides 7 from 2-halobenzenesulfonamides 6

A stirred solution of 2-halo-*N*-(pyridine-2yl)benzenesulfonamide (0.015 mol) and potassium carbonate (4.5 g, 0.0326 mol) in dry DMF (100 mL) was heated at 80–90 °C for 8 h. Then the solvent was removed under reduced pressure and the residue triturated with deionized water (250 mL). The precipitated crude product was filtered, washed with water, and dried under vacuum.

4.9. General catalytic procedure for the preparation of pyrido [2,1-*c*][1,2,4]benzothiazine-5,5-dioxides 7 from 2-halobenzenesulfonamides

To a degassed stirred solution of 2-halo-*N*-(pyridin-2-yl)benzenesulfonamide (0.015 mol) in DMF (100 mL) potassium carbonate (4.5 g, 0.0326 mol), copper(I) iodide (0.14 g, 0.75 mmol), and DMEDA (0.13 g, 0.015 mol) were added under argon flow. The stirred reaction mixture was heated at 80–90 °C for 8 h under argon. Then the reaction mixture was filtered through a Celite pad. The solvent was removed under reduced pressure and the residue was triturated with deionized water (250 mL). The solid precipitate was filtered, washed with water, and dried in vacuum.

*4.9.1. Pyrido[2,1-c][1,2,4]benzothiadiazine 5,5-dioxide (**7a**).* Colorless solid; yield 3.41 g (98%) (from **6a**), 1.84 g (53%) (from **6b**), 2.96 g (85%) (from **6c**); mp 235–237 °C; [found: C, 55.82; H, 3.49; N, 12.02. $C_{11}H_8N_2O_2S$ requires C, 56.89; H, 3.47; N, 12.06%]; ν_{max} (ATP) 1641 (C=N), 1297, 1116 (SO_2)cm^{-1}; δ_H (500 MHz, DMSO-d_6) 7.00–7.06 (1H, m, Ar*H*), 7.12 (1H, d, *J* 8.0 Hz, Ar*H*), 7.75–7.90 (2H, m, Ar*H*), 7.92 (1H, t, *J* 8.0 Hz, Ar*H*), 8.01 (1H, d, *J* 5.0 Hz, Ar*H*), 8.16 (1H, d, *J* 6.5 Hz, ArH), 8.83 (1H, s, Ar*H*); δ_H (500 MHz, CF_3CO_2D) 7.89–7.93 (2H, m, Ar*H*), 8.09 (1H, t, *J* 6.5 Hz, Ar*H*), 8.14–8.25 (2H, m, ArH), 8.31 (1H, d, *J* 7.0 Hz, Ar*H*), 8.56 (1H, t, *J* 6.5 Hz, Ar*H*), 9.22 (1H, d, *J* 5.0 Hz, ArH); δ_C (125 MHz, DMSO-d_6) 113.5, 120.7, 123.9, 124.0, 127.7, 130.3, 133.1, 133.6, 135.7, 140.7, 152.7; δ_C (125 MHz, CF_3CO_2D) 120.2, 121.7, 122.1, 123.6, 130.1, 132.6, 134.6, 135.9, 136.4, 147.4.

*4.9.2. Methyl-pyrido[2,1-c][1,2,4]benzothiadiazine-3-carboxylate 5,5-dioxide (**7b**).* Colorless solid; yield 6.3 g (87%) (one-pot from **1a** and **5a**), 3.91 g (90%) (from **6d**), 4 g (92%) (from **6e**); mp 237–239 °C; [found: C, 53.70; H, 3.48; N, 9.61. $C_{13}H_{10}N_2O_4S$ requires C, 53.79; H, 3.47; N, 9.65%]; ν_{max} (ATP) 1655 (C=N), 1290, 1126 (SO_2)cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.96 (3H, s, CO_2CH_3), 7.08 (1H, t, *J* 7.0 Hz, Ar*H*), 7.16 (1H, d, *J* 8.0 Hz, Ar*H*), 7.89 (1H, t, *J* 7.0 Hz, Ar*H*), 8.24–8.47 (3H, m, ArH), 8.89 (1H, d, *J* 7.0 Hz, Ar*H*); δ_H (500 MHz, CF_3CO_2D) 4.37 (3H, s, CO_2CH_3), 7.89 (1H, t, *J* 7.0 Hz, Ar*H*), 7.96 (1H, d, *J* 8.0 Hz, Ar*H*), 8.45 (1H, d, *J* 8.0 Hz, Ar*H*), 8.59 (1H, t, *J* 8.0 Hz, Ar*H*), 8.93 (1H, d, *J* 8.0 Hz, Ar*H*), 9.10 (1H, s, Ar*H*), 9.22 (1H, d, *J* 7.0 Hz, Ar*H*); δ_C (125 MHz, DMSO-d_6) 53.3, 113.8, 121.7, 124.2, 124.7, 127.4, 130.8, 132.2, 133.4, 138.8, 141.3, 152.8, 164.7; δ_C (125 MHz, CF_3CO_2D) 53.8, 120.3, 121.5, 122.5, 125.6, 129.7, 133.0, 135.4, 136.1, 138.4, 146.8, 150.5, 166.6.

*4.9.3. 3-Nitro[2,1-c][1,2,4]benzothiadiazine 5,5-dioxide (**7c**).* Yellow solid; yield 6.5 g (94%) (from **1g**), 6.37 g (92%) (from **1h**), 6.37 g (92%) (from **1i**); mp 317–319 °C; [found: C, 47.59; H, 2.53; N, 15.18. $C_{11}H_7N_3O_4S$ requires C, 47.65; H, 2.54; N, 15.16%]; ν_{max} (ATP) 1646 (C=N), 1508, 1348 (NO_2), 1295, 1126 (SO_2)cm^{-1}; δ_H (500 MHz, DMSO-d_6)= 7.12 (1H, t, *J* 7.0 Hz, Ar*H*), 7.20 (1H, d, *J* 9.0 Hz, Ar*H*), 7.92 (1H, t, *J* 8.0 Hz, Ar*H*), 8.45 (1H, d, *J* 9.5 Hz, ArH), 8.61 (1H, s, Ar*H*), 8.67 (1H, d, *J* 9.0 Hz, Ar*H*), 8.93 (1H, d, *J* 7.0 Hz, ArH); δ_C (125 MHz, DMSO-d_6) 114.2, 119.5, 123.3, 124.2, 127.5, 127.8, 133.6, 139.9, 141.8, 147.4, 153.0.

*4.9.4. Methyl-8-methylpyrido[2,1-c][1,2,4]benzothiadiazine-3-carboxylate 5,5-dioxide (**7d**).* Colorless solid; yield 7.07 g (93%) (one-pot from **1d**), 4.15 g (91%) (from **6f**), 4.24 g (93%) (from **6g**); mp 240–242 °C; [found: C, 55.24; H, 3.98; N, 9.24. $C_{14}H_{12}N_2O_4S$ requires C, 55.26; H, 3.97; N, 9.21%]; ν_{max} (ATP) 1645 (C=N), 1290, 1124 (SO_2) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.40 (3H, s, CH_3), 3.96 (3H, s, CO_2CH_3), 6.97–7.15 (2H, m, ArH), 8.30 (1H, d, *J* 8.5 Hz, Ar*H*), 8.36–8.39 (2H, m, Ar*H*), 8.81 (1H, d, *J* 6.5 Hz, Ar*H*); δ_H (500 MHz, CF_3CO_2D) 3.00 (3H, s, CH_3), 4.43 (3H, s, CO_2CH_3), 7.78–8.00 (2H, m, Ar*H*), 8.52 (1H, d, *J* 8.5 Hz, Ar*H*), 9.00 (1H, d, *J* 8.5 Hz, Ar*H*), 9.14 (1H, s, Ar*H*), 9.25 (1H, d, *J* 6.0 Hz, Ar*H*); δ_C (125 MHz, DMSO-d_6) 21.4, 53.3, 116.4, 121.4, 122.0, 124.7, 127.5, 130.6, 132.4, 133.3, 138.7, 152.6, 153.8, 164.8; δ_C (125 MHz, CF_3CO_2D) 21.2, 53.8, 119.6, 122.6, 123.5, 125.7, 130.5, 133.0, 135.4, 136.4, 137.9, 148.1, 164.8, 166.4.

*4.9.5. Methyl-9-methylpyrido[2,1-c][1,2,4]benzothiadiazine-3-carboxylate 5,5-dioxide (**7e**).* Colorless solid; yield 6.92 g (91%) (one-pot from **1d**), 4.2 g (92%) (from **6h**), 4.2 g (92%) (from **6i**); mp 158–160 °C; [found: C, 55.30; H, 3.95; N, 9.24. $C_{14}H_{12}N_2O_4S$ requires C, 55.26; H, 3.97; N, 9.21%] ν_{max} (ATP) 1653 (C=N), 1291, 1129 (SO_2) cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.30 (3H, s, CH_3), 3.95 (3H, s, CO_2CH_3), 7.10 (1H, d, *J* 8.0 Hz, Ar*H*), 7.78 (1H, d, *J* 8.0 Hz, Ar*H*), 8.26–8.43 (2H, m, Ar*H*), 8.69 (1H, s, Ar*H*); δ_H (500 MHz, CF_3CO_2D) 2.95 (3H, s, CH_3), 4.49 (3H, s, CO_2CH_3), 8.09 (1H, d, *J* 8.0 Hz, ArH), 8.62–8.75 (2H, m, Ar*H*), 9.09 (1H, d, *J* 7.0 Hz, Ar*H*), 9.22(1H, s, Ar*H*), 9.26 (1H, s, Ar*H*); δ_C (125 MHz, DMSO-d_6) 17.4, 53.3, 121.7, 123.7, 124.7, 127.3, 130.3, 130.7, 133.3, 138.8, 144.0, 151.9, 164.7; δ_C (125 MHz, CF_3CO_2D) 16.5, 53.9, 120.3, 123.2, 125.8, 130.6, 132.6, 133.2, 134.6, 134.7, 136.7, 138.5, 150.0, 168.3.

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