Chemistry of an Unexplored Heterocyclic Ring System: Versatile Synthesis of 5-Aryl-2,3,4-benzothiadiazepine 2,2-dioxides

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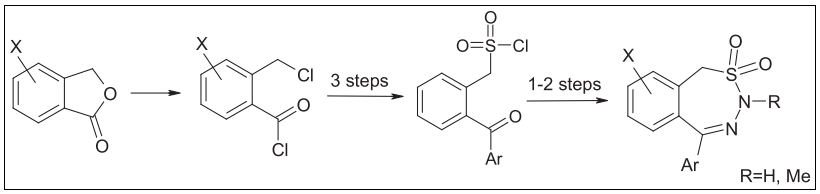

The article gives insight into the synthetic approach of a practically new heterocyclic ring system, 2,3,4-benzothiadiazepines. Starting from the easily available phthalides, an efficient synthesis of 5-aryl-2,3,4-benzothiadiazepine 2,2-dioxides is described here. Owing to their close structural similarity to 2,3-benzodiazepines and 2,3-benzodiazepine-4-ones, two well-known bioactive compound families, the new derivatives can be of importance in medicinal chemistry.

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INTRODUCTION

Biological efficacy of compounds bearing a phthalazine (**1**, Scheme 1), phthalazinone (**2**), or the homologous 2,3-benzodiazepine (**3**) and 2,3-benzodiazepine-4-one (**4**) skeleton is discussed in several papers and patent applications. Various pharmacological and therapeutic effects are described for these compounds ranging from poly(ADP-ribose) polymerase inhibition [1] and antagonism of chemoattractant receptor-homologous molecule expressed on T helper type 2 cells [2] to phosphodiesterase inhibition [3,4] and to the treatment of gastric disorders [5]. The biological importance of 2,3-benzodiazepines (**3**) is even better demonstrated by tofisopam [6], a well-known anxiolytic drug from this family, or the drug candidates girisopam [7], nerisopam [8], and talampanel [9], which reached the clinical development stage. Phthalazines **1** are known to be advanced intermediates for the preparation of tricyclic sydnonimine derivatives exhibiting an antihypertensive effect [10]. Representatives of the 1,2,3-benzothiadiazine 1,1-dioxide (**5**) family, structurally related to compounds **2**, also act as antagonists of the chemoattractant receptor-homologous molecule expressed on T helper type 2 cells [2] or as advanced intermediates for the preparation of disinfectants and herbicides [11].

The syntheses of phthalazines (**1**) [12], phthalazinones (**2**) [12], 2,3-benzodiazepines (**3**) [13–15], and 2,3-benzodiazepine-4-ones (**4**) [16] are well elaborated. However, while numerous 1,2,3-benzothiadiazine 1,1-dioxides (**5**) [17] have been synthesized, the only representative of the homologous 2,3,4-benzothiadiazepine 2,2-dioxide family described in the literature is the unsubstituted congener, that is, compound **6a** itself (Scheme 1) [18]. Moreover, it is noteworthy that apart from **6a**, there is no other compound described in the literature that corresponds to the general structure **6** (2,3,4-benzothiadiazepine and related compounds).

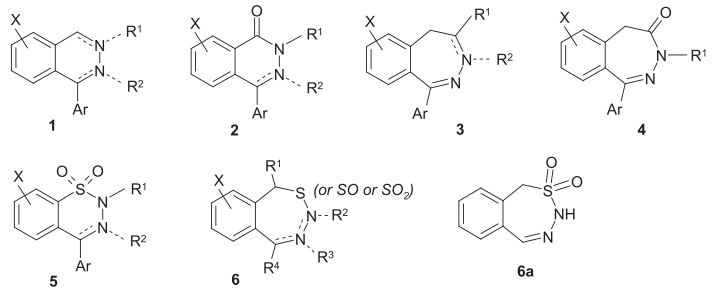
Compound **6a** was prepared more than 40 years ago with the aim of studying the chlorination reactions of "heterocyclic sulfonhydrazones." It was obtained by cyclization of (2-formylphenyl)methanesulfonyl chloride (**7**) with hydrazine (Scheme 2) [18]. Sulfonyl chloride **7** was produced by treatment of an aqueous suspension of 1,3-dihydro-benzo [*c*]thiophene (**8**) with chlorine.

RESULTS AND DISCUSSION

We aimed at elaborating an efficient synthesis of new 2,3,4-benzothiadiazepine 2,2-dioxides (**9**) exhibiting an aryl substituent at the 5-position and various substituents on the benzene ring, by ring closure of sulfonyl chlorides **10** with hydrazine (Scheme 3). Because the reaction conditions applied for the preparation of sulfonyl chloride **7** (Scheme 2) are not generally suitable for the synthesis of the related type **10** compounds, we decided to elaborate a new synthesis for these key intermediates.

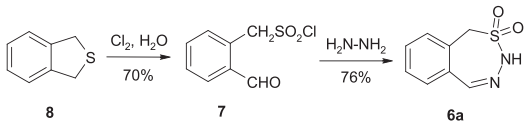
In recent publications, we have described the synthesis of phthalides **11**, which now serve as the starting compounds in our synthesis [19,20]. The reaction sequence starting from phthalides monosubstituted at the aromatic ring (**11a,b**) is depicted in Scheme 3, while that starting from the thiadiazolophthalide congener (5*H*,7*H*-furo[3,4-*f*][2,1,3]benzothiadiazol-5-one, **11c**) is shown in Scheme 4.

Scheme 1



R^1, R^2, R^3, R^4: H, alkyl, aryl; X: various substituents

Scheme 2



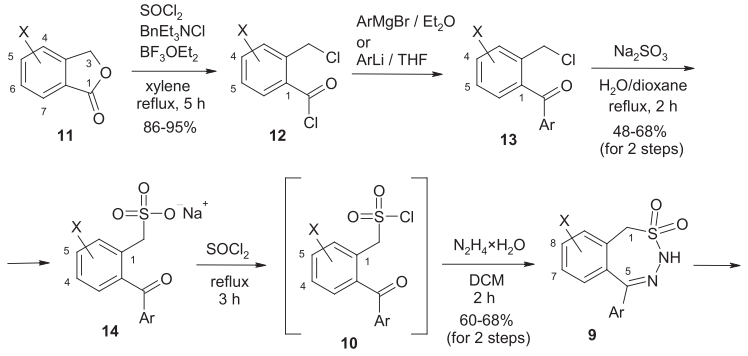
o-Chloromethyl benzoyl chlorides **12** were prepared as described in the literature [21], by the reaction of phthalides **11** with thionyl chloride in xylene in the presence of boron trifluoride diethyl etherate and benzyltriethylammonium chloride. Ketones **13a–c** were obtained by the reaction of compounds **12a,b** with an organomagnesium (**13a,c**) or organolithium (**13b**) reagent. It is remarkable that compound **13d** could not be prepared in a similar manner. It was obtained by treatment of benzoyl chloride **12c** with fluorobenzene under Friedel–Crafts conditions (Scheme 4).

o-Aroylbenzyl chlorides **13** were treated with sodium sulfite [22]. To our surprise, the products obtained after acidic workup were not the sulfonic acids but sodium methanesulfonates **14**, as indicated by the elementary analysis data and proven by gravimetric determination of the sodium content of **14a**. 2,3,4-Benzothiadiazepine 2,2-dioxides **9** were then prepared from methanesulfonates **14** in one-pot reaction with thionyl chloride furnished sulfonyl chlorides **10**, which were cyclized with hydrazine to give the target compounds **9**. The structure of **9d** has also been determined by single-crystal X-ray diffraction (see the Supporting Information).

Attempts to N-methylate benzothiadiazepine **9a** with methyl iodide in the presence of sodium hydrogen carbonate in refluxing acetonitrile resulted in only low yields (10–15%) of the required product **15a**, indicating the occurrence of a side reaction. Indeed, when refluxing compound **9a** with sodium hydrogen carbonate in the absence of a methylating agent, benzo[*c*]thiophene 2,2-dioxide **16** was obtained in 83% yield (Scheme 5). The structure of **16** has been proven by X-ray diffraction (see the Supporting information). A similar ring contraction was observed by King et al. when compound **6a** was heated at 175–180°C for 5 min [18].

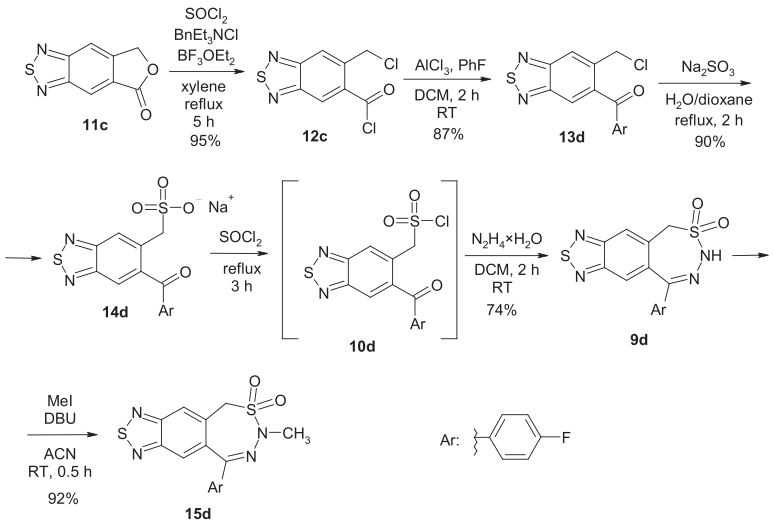
Finally, benzothiadiazepines **9** were successfully methylated to compounds **15** in high yield, using methyl iodide

Scheme 3

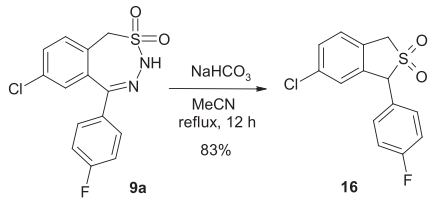


	X					Ar
	11	**12**	**13**	**10, 14**	**9, 15**	**9, 10, 13-15**
a	6-Cl	5-Cl	5-Cl	4-Cl	7-Cl	
b	5-F	4-F	5-Cl	4-Cl	7-Cl	
c	see Scheme 4	see Scheme 4	4-F	5-F	8-F	

Scheme 4



Scheme 5



in the presence of DBU in acetonitrile at ambient temperature (Schemes 3 and 4). It is important to note that the N-methylated derivative **15a** proved to be completely stable when refluxing for 15 h in acetonitrile in the presence of sodium hydrogen carbonate.

In conclusion, a high-yielding reaction sequence has been elaborated for the preparation of a novel compound family, 5-aryl-2,3,4-benzothiadiazepine 2,2-dioxides. Besides the target compounds described earlier (**9a–d** and **15a–d**), several other representatives of this family were synthesized at our laboratory, and preliminary *in vivo* animal experiments demonstrated their central nervous system pharmacological activity [23]. Nevertheless, thanks to the novel, versatile intermediates (**10** and **12–14**), the significance of the synthetic route described earlier goes beyond the synthesis of these particular compounds. Further efforts are in progress for the application of these intermediates for the synthesis of other new heterocyclic ring systems.

EXPERIMENTAL

All melting points were determined on a Büchi (Flawil, Switzerland) B-540 capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Bruker Vector 22 FT spectrometer (Billerica, MA) in KBr pellets or in neat. ^{1}H and ^{13}C NMR spectra were recorded at 303 K on a Varian Unity Inova 500 (Palo Alto, CA; 500 and 125 MHz for ^{1}H and ^{13}C NMR spectra, respectively) or a Varian Mercury Plus 200 (200 and 50 MHz for ^{1}H and ^{13}C NMR spectra, respectively), or a Bruker Avance III 400 (400 and 100 MHz for ^{1}H and ^{13}C spectra, respectively) spectrometer. DMSO-d_6 or $CDCl_3$ was used as the solvent and TMS as the 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 Vario EL III analyzer (Elementar Analysensysteme GmbH, Hanau, Germany). The reactions were followed by analytical thin layer chromatography on silica gel 60 F_{254} (Merck Millipore, Darmstadt, Germany). All reagents were purchased from commercial sources. Analytical samples of new compounds were obtained by recrystallization from the solvents given as follows.

5-Chloro-2-(chloromethyl)-benzoyl chloride (12a). To a suspension of **11a** (18.7 g, 0.111 mol) in xylene (100 mL), thionyl chloride (22 mL, 36.0 g, 0.303 mol), boron trifluoride diethyl etherate (1.6 mL, 1.84 g, 13 mmol), and benzyltriethylammonium chloride (2.30 g, 10 mmol) were added, and the mixture was refluxed for 5 h. The solvent was evaporated, and diethyl ether (100 mL) was added to the residue. After treatment with charcoal and evaporation of the solvent, the oily residue was distilled *in vacuo* (bp 118–121°C, 4×10^{-2} Hgmm) to give **12a** (22.9 g, 89%) as a colorless oil, which solidified in the refrigerator to give a colorless solid (mp 30–32°C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 4.85 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.5, 137.4, 134.8, 134.4, 133.5, 133.3, 132.3, 43.0 ppm. IR (KBr, cm^{-1}): 1766, 1560, 1479. Elemental analysis for $C_8H_5Cl_3O$ (223.49): Calcd C 43.00, H 2.26, Cl 47.59%; Found C 43.16, H 2.40, Cl 47.14%.

2-(Chloromethyl)-4-fluorobenzoyl chloride (12b). This compound was prepared according to the procedure described for the synthesis of **12a**, starting from **11b** (20.0 g, 0.132 mol) [19] to give after distillation **12b** (23.6 g, 86%) as a colorless oil (bp 120–122°C, 10^{-1} Hgmm). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.35 (dd, J = 8.9, 5.6 Hz, 1H), 7.42 (dd, J = 9.3, 2.4 Hz, 1H), 7.18 (td, J = 9.7, 2.6 Hz, 1H), 4.91 (s, 2H) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.4, 166.1 (d, J = 259.3 Hz), 143.2 (d, J = 9.3 Hz), 137.5 (d, J = 9.8 Hz), 127.8, 118.1 (d, J = 23.9 Hz), 115.7 (d, J = 21.6 Hz), 43.6 ppm. IR (KBr, cm^{-1}): 1768, 1607, 1583, 1220. Elemental analysis for $C_8H_5Cl_2FO$

(207.03): Calcd C 46.41, H 2.43, Cl 34.25%; Found C 46.48, H 2.48, Cl 34.10%.

6-(Chloromethyl)-2,1,3-benzothiadiazole-5-carbonyl chloride (12c). This compound was prepared according to the procedure described for the synthesis of compound **12a**, starting from **11c** (60.5 g, 0.315 mol) [20] to give after distillation **12c** (73.8 g, 95%) as a colorless oil (bp 110–115°C, 10^{-2} Hgmm), which solidified at ambient temperature (mp 45–47°C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.59 (s, 1H), 8.31 (s, 1H), 5.30 (s, 2H) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 167.4, 154.8, 153.3, 138.2, 132.3, 124.5, 123.0, 44.9 ppm. IR (KBr, cm^{-1}): 1749, 1145, 880. Elemental analysis for $C_8H_4Cl_2N_2OS$ (247.10): Calcd C 38.89, H 1.63, N 11.34, Cl 28.69, S 12.98%; Found C 39.22, H 1.61, N 11.38, Cl 28.41, S 12.77%.

[5-Chloro-2-(chloromethyl)phenyl](4-fluorophenyl)methanone (13a). To a solution of **12a** (56.7 g, 0.254 mol) in toluene (500 mL) was added an ethereal solution of 4-fluorophenylmagnesium bromide [prepared from 4-bromofluorobenzene (31 mL, 49.4 g, 0.282 mol) and magnesium (7.0 g, 0.288 mol) in diethyl ether (250 mL)] dropwise under vigorous stirring at −20°C. The cooling bath was removed, and the mixture was stirred for 2 h, while the temperature rose to 0°C. An aqueous HCl solution (1.0*M*, 110 mL, 0.11 mol) was added, the mixture was stirred for 5 min, and then the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 200 mL), the combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (100 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated to give crude **13a** (72.0 g) as a yellow oil, which was used in the next reaction step without further purification. An analytical sample of compound **13a** was prepared by flash chromatography (eluent:hexane/EtOAc = 98:2), to give a colorless solid, mp 100–101°C (hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 (dd, *J* = 9.0, 5.5 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.47 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.32 (d, *J* = 2.1 Hz, 1H), 7.16 (t, *J* = 8.7 Hz, 2H), 4.68 (s, 2H) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 194.3, 166.2 (d, *J* = 256.4 Hz), 139.6, 135.4, 134.0, 133.1 (d, *J* = 3.0 Hz), 133.0 (d, *J* = 9.3 Hz), 132.0, 130.8, 128.8, 115.9 (d, *J* = 22.5 Hz), 42.4 ppm. IR (KBr, cm^{-1}): 1668, 1597, 1504. Elemental analysis for $C_{14}H_9Cl_2FO$ (283.13): Calcd C 59.39, H 3.20, Cl 25.04%; Found C 58.35, H 3.13, Cl 24.35%.

1-Benzothiophen-2-yl[5-chloro-2-(chloromethyl)phenyl] methanone (13b). To a solution of **12a** (16.0 g, 72 mmol) in THF (300 mL) was added a solution of 2-benzo[*b*]thienyllithium [prepared by lithiation of a solution of benzo[*b*]thiophene (8.1 g, 60 mmol) in THF (200 mL) with butyllithium (31.2 mL of a 2.5*M* solution in hexane, 78 mmol) at −78°C] dropwise at −78°C. The mixture was allowed to warm to −20°C over a period of 3 h. A saturated aqueous solution of NH_4Cl (280 mL) and ethyl acetate (240 mL) was added. After separation, the organic layer was washed with saturated aqueous $NaHCO_3$ solution (200 mL) and brine (200 mL), dried ($MgSO_4$), and evaporated to give crude **13b** (20.2 g) as a pale yellow oil, which was used in the next reaction step without further purification. An analytical sample of compound **13b** was prepared by flash chromatography (eluent: hexane/EtOAc = 98:2) as pale yellow crystals, mp 94–96°C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.12 (d, *J* = 8.2 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.96 (s, 1H), 7.82 (s, 1H), 7.72 (m, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 4.83 (s, 2H) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 188.9, 142.7, 142.5, 139.3, 139.1, 135.1, 134.9, 133.3, 133.0, 131.2, 128.8, 128.5, 127.2, 125.5, 123.3, 42.5 ppm. IR (KBr, cm^{-1}): 1637, 1511, 1294, 1184. Elemental analysis for $C_{16}H_{10}Cl_2OS$ (321.23): Calcd C 59.83, H 3.14, Cl 22.07, S 9.98%; Found C 59.60, H 3.15, Cl 22.14, S 9.87%.

[2-(Chloromethyl)-4-fluorophenyl](4-fluorophenyl)methanone (13c). This compound was prepared according to the procedure described for the synthesis of compound **13a**, starting from **12b** (8.0 g 38.6 mmol) to give crude **3c** (10.2 g) as a pale green oil, which was used in the next reaction step without further purification. An analytical sample of compound **13c** was prepared by flash chromatography (eluent:hexane/EtOAc = 95:5), to give colorless crystals, mp 62–63°C (after trituration with pentane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (dd, *J* = 9.0, 5.5 Hz, 2H), 7.38 (dd, *J* = 8.4, 5.5 Hz, 1H), 7.33 (dd, *J* = 9.3, 2.4 Hz, 1H), 7.14 (t, *J* = 9.0 Hz, 2H), 7.06 (td, *J* = 8.2, 2.6 Hz, 1H), 4.75 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.6, 165.9 (d, *J* = 255.9 Hz), 163.6 (d, *J* = 252.9 Hz), 140.5 (d, *J* = 8.3 Hz), 133.7 (d, *J* = 2.9 Hz), 133.7 (d, *J* = 2.9 Hz), 132.9 (d, *J* = 9.3 Hz), 131.7 (d, *J* = 9.3 Hz), 117.7 (d, *J* = 22.5 Hz), 115.7 (d, *J* = 22.0 Hz), 114.5 (d, *J* = 21.5 Hz), 42.6 (d, *J* = 1.5 Hz) ppm. IR (KBr, cm^{-1}): 1652, 1593, 1411, 1282. Elemental analysis for $C_{14}H_9ClF_2O$ (266.68): Calcd C 63.06, H 3.40, Cl 13.29%; Found C 63.04, H 3.36, Cl 13.16%.

[6-(Chloromethyl)-2,1,3-benzothiadiazol-5-yl](4-fluorophenyl) methanone (13d). To a solution of **12c** (12.3 g, 50 mmol) and fluorobenzene (45 mL, 72.0 g, 411 mmol) in dichloromethane (45 mL) was added $AlCl_3$ (13.8 g, 104 mmol) at 0°C in small portions, under stirring. The resulting mixture was stirred for further 2 h at ambient temperature. It was poured on ice, concentrated aqueous HCl (10 mL) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layer was dried ($MgSO_4$) and evaporated. The residue was triturated with cold (−20°C) methanol (20 mL) to give **13d** (13.4 g, 87%) as colorless crystals, mp 106–107°C (hexane–EtOAc). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.15 (q, *J* = 0.7 Hz, 1H), 8.01 (s, 1H), 7.97 (dd, *J* = 9.2, 5.5 Hz, 2H), 7.19 (t, *J* = 8.6 Hz, 2H), 4.97 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ 194.3, 166.2, (d, *J* = 256.8 Hz), 154.7, 153.2, 138.9, 138.4, 133.2 (d, *J* = 9.5 Hz), 123.0, 122.9, 115.9 (d, *J* = 22.1 Hz), 43.8 ppm. IR (KBr, cm^{-1}): 1660, 1592, 1504. Elemental analysis for $C_{14}H_8ClFN_2OS$ (306.75): Calcd C 54.82, H 2.63, N 9.13, Cl 11.56, S 10.45%; Found C 54.99, H 2.66, N 9.19, Cl 11.48, S 10.35%.

Sodium {4-chloro-2-[(4-fluorophenyl)carbonyl]phenyl} methanesulfonate (14a). A mixture of crude **13a** (32 g, an aliquot portion of the 72 g crude **13a** described earlier), sodium sulfite (30.0 g, 238 mmol), dioxane (420 mL), and water (620 mL) was refluxed for 2 h and evaporated to dryness. *tert*-Butyl methyl ether (30 mL) was added, the mixture was stirred for 5 min, and the solvent was decanted. Concentrated aqueous HCl (50 mL, 60 g, 0.61 mol) was added at a temperature of 0–5°C. The suspension obtained was filtered, and the crystalline product was washed with cold (ca. 5°C) water (2 × 20 mL) and dried to give **14a** (23.8 g, 60%, calculated for **12a**) as a colorless solid, mp 254–256°C (water). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.80 (dd, *J* = 8.8, 5.7 Hz, 2H), 7.55 (m, 2H), 7.35 (t, *J* = 8.8 Hz, 2H), 7.23 (m, 1H), 3.98 (s, 2H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 194.9, 165.1 (d, *J* = 251.5 Hz), 141.0, 134.6, 134.0 (d, *J* = 2.9 Hz), 133.6, 133.4 (d, *J* = 9.3 Hz), 130.8, 129.9, 127.9, 115.5 (d, *J* = 22.0 Hz), 53.0 ppm. IR (KBr, cm^{-1}): 1667, 1598, 1412. Elemental analysis for $C_{14}H_9ClFO_4SNa$ (350.73): Calcd C 47.94, H 2.59, Cl 10.11, S 9.14%; Found C 47.56, H 2.77, Cl 10.00, S 9.06%. Sodium content (gravimetric): Calcd 6.55%, Found 6.22%.

Sodium [2-(1-benzothiophen-2-ylcarbonyl)-4-chlorophenyl] methanesulfonate (14b). This compound was prepared according to the procedure described for the synthesis of compound **14a**, starting from crude **13b** (20.2 g, 63 mmol) to give the title compound **14b** (13.4 g, 48%, calculated for **12a**) as a colorless solid, mp 313–315°C (water). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 8.09 (m, 1H), 8.05 (m, 1H), 7.82 (d, J = 0.4 Hz, 1H), 7.58 (m, 3H), 7.55 (m, 1H), 7.46 (m, 1H), 3.94 (s, 2H) ppm. ^{13}C NMR (DMSO-d_6, 50 MHz): δ 189.7, 143.3, 142.1, 140.1, 139.2, 134.5, 134.1, 133.6, 130.8, 129.9, 128.0, 127.9, 126.9, 125.3, 123.2, 53.0 ppm. IR (KBr, cm^{-1}): 1650, 1512, 1300, 1182, 1040. Elemental analysis for $C_{16}H_{10}ClO_4S_2Na$ (388.83): Calcd C 49.43, H 2.59, S 16.49, Cl 9.12%; Found C 48.93, H 2.61, S 16.27, Cl 8.92%.

Sodium {5-fluoro-2-[(4-fluorophenyl)carbonyl]phenyl} methanesulfonate (14c). This compound was prepared according to the procedure described for the synthesis of compound **14a**, starting from crude **13c** (5.0 g, 18.7 mmol, an aliquot portion of the 10.2 g crude **13a** described earlier) to give the title compound **14c** (4.30 g, 68%, calculated for **12b**) as a colorless solid, mp 286–288°C (water). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.75 (m, 2H), 7.33 (t, J = 8.2 Hz, 2H), 7.32 (m, 1H), 7.25 (dd, J = 7.2, 6.2 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 3.99 (s, 2H) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 195.4, 164.9 (d, J = 249.6 Hz), 162.4 (d, J = 244.7 Hz), 138.3 (d, J = 9.0 Hz), 135.8 (d, J = 2.9 Hz), 134.6 (d, J = 2.6 Hz), 133.2 (d, J = 9.5 Hz), 131.0 (d, J = 8.9 Hz), 119.1 (d, J = 21.8 Hz), 115.3 (d, J = 22.0 Hz), 112.6 (d, J = 21.4 Hz), 53.3 ppm. IR (KBr, cm^{-1}): 1766, 1665, 1598, 1504, 1411, 1233, 1049. Elemental analysis for $C_{14}H_9F_2O_4SNa$ (334.28): Calcd C 50.30, H 2.71, S 9.59%; Found C 50.17, H 2.65, S 9.69%.

Sodium {6-[(4-fluorophenyl)carbonyl]-2,1,3-benzothiadiazol-5-yl}methanesulfonate (14d). This compound was prepared according to the procedure described for the synthesis of compound **14a**, starting from compound **13d** (20.0 g, 65.2 mmol) to give the title compound **14d** (22.0 g, 90%) as a pale yellow powder, mp 320–323°C (water, dec.). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.09 (d, J = 0.6 Hz, 1H), 7.91 (d, J = 0.6 Hz, 1H), 7.90 (dd, J = 8.8, 5.5 Hz, 2H), 7.36 (t, J = 8.9 Hz, 2H), 4.21 (s, 2H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 194.9, 165.1 (d, J = 251.5 Hz), 154.6, 152.4, 141.2, 136.5, 134.0 (d, J = 2.9 Hz), 133.8 (d, J = 9.3 Hz), 124.1, 121.5, 115.3 (d, J = 22.0 Hz), 53.7 ppm. IR (KBr, cm^{-1}): 1657, 1600, 1207. Elemental analysis for $C_{14}H_8FN_2O_4S_2Na$ (374.35): Calcd C 44.92, H 2.15, N 7.48%; Found C 44.59, H 2.16, N 7.23%.

7-Chloro-5-(4-fluorophenyl)-1,3-dihydro-2,3,4-benzothiadiazepine 2,2-dioxide (9a). A mixture of methanesulfonate **14a** (9.50 g, 27 mmol) and thionyl chloride (30 mL, 49.2 g, 413 mmol) was refluxed for 3 h. The excess of thionyl chloride was removed *in vacuo*. Toluene (60 mL) was added, and the solution evaporated to dryness. The oily residue (compound **10a**) was dissolved in dichloromethane (50 mL), and the solution was added dropwise to a stirred mixture of hydrazine monohydrate (16.5 mL, 17.0 g, 340 mmol) and dichloromethane (140 mL) at 0°C. It was stirred for 2 h at ambient temperature, and concentrated aqueous HCl (80 mL) and water (60 mL) were added. After separation, the aqueous layer was extracted with dichloromethane (2 × 20 mL), and the combined organic layer was dried ($MgSO_4$), treated with charcoal, and evaporated to dryness. The residue was triturated with cold (−20°C) ethanol (10 mL) to give compound **9a** (6.0 g, 68%) as colorless crystals, mp 195–198°C (methanol). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70 (dd, J = 5.3, 2.2 Hz, 2H), 7.57 (dd, J = 8.2, 2.1 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.25 (d, J = 2.2 Hz, 1H), 7.15 (t, J = 8.6 Hz, 2H), 7.08 (br s, 1H), 4.39 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.2, 165.1 (d, J = 254.4 Hz), 135.3, 135.0, 131.7 (d, J = 8.8 Hz), 131.7, 131.0 (d, J = 2.9 Hz), 130.7, 129.5, 129.2, 116.0 (d, J = 22.0 Hz), 55.7. IR (KBr, cm^{-1}): 3222, 1602, 1508, 1329. Elemental analysis for $C_{14}H_{10}ClFN_2O_2S$ (324.76): Calcd C 51.78, H 3.10, N 8.63%; Found C 51.87, H 3.13, N 8.51%.

5-(1-Benzothiophen-2-yl)-7-chloro-1,3-dihydro-2,3,4-benzothiadiazepine 2,2-dioxide (9b). This compound was prepared analogously to **9a** starting from **14b** (13.2 g, 33.9 mmol) to give **9b** (7.38 g, 60%) as colorless crystals, mp 194–195°C (ethanol). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 10.52 (s, 1H), 8.02 (t, J = 7.0 Hz, 1H), 7.94 (d, J = 1.5 Hz, 1H), 7.78–7.64 (m, 3H), 7.62 (s, 1H), 7.55–7.36 (m, 2H), 4.76 (s, 2H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 166.3, 140.5, 139.7, 139.2, 134.6, 133.2, 131.5, 131.4 130.8, 128.7, 127.1, 125.6, 125.0, 122.7, 122.6, 54.6 ppm. IR (KBr, cm^{-1}): 3200, 1322, 1158. Elemental analysis for $C_{16}H_{11}ClN_2O_2S_2$ (362.86): Calcd C 52.96, H 3.06, N 7.72, Cl 9.77%; Found C 52.74, H 3.18, N 7.66, Cl 9.88%.

8-Fluoro-5-(4-fluorophenyl)-1,3-dihydro-2,3,4-benzothiadiazepine 2,2-dioxide (9c). This compound was prepared analogously to **9a** starting from **14c** (4.3 g, 12.9 mmol) to give **9c** (2.38 g, 60%) as colorless crystals, mp 229–230°C (ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.31 (s, 1H), 7.66 (dd, J = 8.9, 5.6 Hz, 2H), 7.55 (dd, J = 9.3, 2.5 Hz, 1H), 7.33 (t, J = 8.8 Hz, 2H), 7.33 (td, J = 8.5, 2.0 Hz, 1H), 7.26 (dd, J = 8.6, 5.7 Hz, 1H), 4.73 (s, 2H) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 170.7, 164.1 (d, J = 249.5 Hz), 163.1 (d, J = 249.0 Hz), 135.1 (d, J = 9.3 Hz), 132.5 (d, J = 2.9 Hz), 131.9 (d, J = 8.8 Hz), 131.7 (d, J = 9.3 Hz), 130.7 (d, J = 2.9 Hz), 116.4 (d, J = 23.0 Hz), 115.7 (d, J = 22.0 Hz), 115.3 (d, J = 22.0 Hz), 55.0 ppm. IR (KBr, cm^{-1}): 3098, 1610, 1511, 1327. Elemental analysis for $C_{14}H_{10}F_2N_2O_2S$ (308.31): Calcd C 54.54, H 3.27, N 9.09, S 10.40%; Found C 54.62, H 3.28, N 9.07, S 10.33%.

9-(4-Fluorophenyl)-5*H*,7*H*-[1,2,5]thiadiazolo[3,4-*h*][2,3,4] benzothiadiazepine 6,6-dioxide (9d). This compound was prepared analogously to **9a** starting from **14d** (23.1 g, 61.8 mmol) with a favorable change in the final workup. After addition of concentrated aqueous HCl (200 mL) and water (200 mL) to the reaction mixture, a suspension was formed. The crystalline precipitation was filtered, washed with cold (−20°C) ethanol (25 mL) to give **9d** (15.9 g, 74%) as colorless crystals, mp 222–225°C (ethanol–DMF). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.34 (s, 1H), 8.38 (s, 1H), 8.02 (s, 1H), 7.80 (dd, J = 8.7, 5.5 Hz, 2H), 7.36 (t, J = 8.9 Hz, 2H), 4.96 (s, 2H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 172.0, 164.3 (d, J = 250.0 Hz), 154.4, 153.0, 136.3, 133.1, 132.4 (d, J = 2.9 Hz), 132.2 (d, J = 8.7 Hz), 122.6, 121.5, 115.8 (d, J = 22.0 Hz), 55.1 ppm. IR (KBr, cm^{-1}): 1569, 1508, 1326. Elemental analysis for $C_{14}H_9FN_4O_2S_2$ (348.38): Calcd C 48.27, H 2.60, N 16.08, S 18.41%; Found C 48.30, H 2.55, N 16.17, S 18.43%.

7-Chloro-5-(4-fluorophenyl)-3-methyl-1,3-dihydro-2,3,4-benzothiadiazepine 2,2-dioxide (15a). DBU (0.5 mL, 0.51 g, 3.3 mmol) and methyl iodide (0.21 mL, 0.48 g, 3.3 mmol) was added to a solution of **9a** in acetonitrile (30 mL) at ambient temperature. After stirring for 30 min at ambient temperature, the solvent was evaporated; then dichloromethane (40 mL) and water (10 mL) were added to the residue. After separation, the organic layer was washed with water (2 × 10 mL), dried ($MgSO_4$), and evaporated. The residue was triturated with methanol (3 mL), and

the crystalline product was filtered to give **15a** (0.91 g, 90%) as colorless crystals, mp 218–219°C (2-propanol). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.71 (dd, J = 8.9, 5.4 Hz, 2H), 7.55 (dd, J = 8.2, 2.2 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.24 (d, J = 2.2 Hz, 1H), 7.14 (t, J = 8.4 Hz, 2H), 4.35 (s, 2H), 3.14 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.8, 165.0 (d, J = 253.9 Hz), 135.7, 134.8, 131.7 (d, J = 8.8 Hz), 131.6, 130.9 (d, J = 3.4 Hz), 130.4, 128.9, 128.6, 115.9 (d, J = 22.0 Hz), 55.2, 35.3 ppm. IR (KBr, cm^{-1}): 1323, 1135, 842. Elemental analysis for $C_{15}H_{12}ClFN_2O_2S$ (338.79): Calcd C 53.18, H 3.57, N 8.27, S 9.46, Cl 10.46%; Found C 52.96, H 3.56, N 8.23, S 9.55, Cl 10.53%.

5-(1-Benzothiophen-2-yl)-7-chloro-3-methyl-1,3-dihydro-2,3,4-benzothiadiazepine 2,2-dioxide (15b). This compound was prepared analogously to **15a** starting from **9b** (1.09 g, 3.0 mmol) to give **15b** (0.90 g, 80%) as colorless crystals, mp 249–251°C (acetonitrile). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.03 (d, J = 7.9 Hz, 1H), 7.97 (d, J = 7.9 Hz, 1H), 7.78 (dd, J = 8.3, 2.3 Hz, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.65 (s, 1H), 7.50 (t, J = 6.9 Hz, 1H), 7.42 (t, J = 6.9 Hz, 1H), 4.89 (br s, 2H), 2.99 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 165.8, 140.8, 139.2, 139.0, 134.8, 133.5, 132.2, 131.7, 131.4, 129.8, 128.5, 127.3, 125.7, 125.1, 122.8, 53.8, 35.0 ppm. IR (KBr, cm^{-1}): 1317, 1191, 1159, 1135. Elemental analysis for $C_{17}H_{13}ClN_2O_2S_2$ (376.89): Calcd C 54.18, H 3.48, N 7.43, Cl 9.41, S 17.02%; Found C 54.01, H 3.51, N 7.44, Cl 9.40, S 17.01%.

8-Fluoro-5-(4-fluorophenyl)-3-methyl-1,3-dihydro-2,3,4-benzothiadiazepine 2,2-dioxide (15c). This compound was prepared analogously to **15a** starting from **9c** (0.92 g, 3.0 mmol) to give **15c** (0.85 g, 88%) as colorless crystals, mp 205–206°C (methanol). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70 (dd, J = 8.4, 5.4 Hz, 2H), 7.25 (m, 2H), 7.18 (dt, J = 8.3, 2.4 Hz, 1H), 7.12 (t, J = 8.4 Hz, 2H), 4.35 (s, 2H), 3.14 (d, J = 0.6 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.3, 165.0 (d, J = 253.4 Hz), 163.9 (d, J = 253.9 Hz), 132.9 (d, J = 8.8 Hz), 131.7 (d, J = 8.8 Hz), 131.3 (d, J = 3.4 Hz), 131.1 (d, J = 9.3 Hz), 130.4 (d, J = 3.4 Hz), 116.5 (d, J = 22.9 Hz), 115.9 (d, J = 22.0 Hz), 115.8 (d, J = 22.0 Hz), 55.5 (d, J = 2.0 Hz), 35.3 ppm. IR (KBr, cm^{-1}): 1601, 1555, 1493, 1326, 1263, 1231. Elemental analysis for $C_{15}H_{12}F_2N_2O_2S$ (322.34): Calcd C 55.89, H 3.75, S 9.95, N 8.69%; Found C 55.98, H 3.57, S 9.98, N 8.79%.

9-(4-Fluorophenyl)-7-methyl-5*H*,7*H*-[1,2,5]thiadiazolo[3,4-*h*][2,3,4]benzothiadiazepine 6,6-dioxide (15d). This compound was prepared analogously to **15a** starting from **9d** (4.98 g, 14.3 mmol) to give **15d** (4.80 g, 92%) as colorless crystals, mp 273–275°C (2-propanol–DMF). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.41 (s, 1H), 8.04 (s, 1H), 7.83 (dd, J = 8.9, 5.5 Hz, 2H), 7.36 (t, J = 8.9 Hz, 2H), 5.10 (s, 2H), 2.98 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 171.1, 164.5 (d, J = 251.0 Hz), 154.5, 153.0, 136.0, 132.5 (d, J = 8.8 Hz), 132.1, 131.8 (d, J = 2.9 Hz), 122.3, 121.6, 115.8 (d, J = 22.0 Hz), 54.4, 34.6 ppm. IR (KBr, cm^{-1}): 1604, 1509, 1319, 1146. Elemental analysis for $C_{15}H_{11}FN_4O_2S_2$ (362.41): Calcd C 49.71, H 3.06, N 15.46, S 17.70%; Found C 49.50, H 3.08, N 15.41, S 17.53%.

6-Chloro-1-(4-fluorophenyl)-1,3-dihydro-2-benzothiophene 2,2-dioxide (16). A suspension of **9a** (0.20 g, 0.62 mmol) and $NaHCO_3$ (0.50 g, 6.0 mmol) in acetonitrile (20 mL) was refluxed for 12 h. It was evaporated to dryness, and then water (10 mL) and dichloromethane (10 mL) were added. After separation, the organic layer was dried ($MgSO_4$) and evaporated. The residue was triturated with diethyl ether (5 mL) to give **16** (0.15 g, 83%) as colorless crystals, mp 112–114°C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.54 (m, 2H), 7.30 (m, 4H), 7.10 (s, 1H), 5.93 (s, 1H), 4.70 (d, J = 16 Hz, 1H), 4.63 (d, J = 16 Hz, 1H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 162.8, 138.5, 133.2, 132.7, 131.1, 129.0, 128.2, 126.7, 125.8, 116.0, 69.4, 54.1 ppm. IR (KBr, cm^{-1}): 1510, 1316, 1140. Elemental analysis for $C_{14}H_{10}ClFO_2S$ (296.74): Calcd C 56.67, H 3.40, Cl 11.95, S 10.81%; found C 56.61, H 3.27, Cl 11.77, S 11.15%.

The ORTEP drawings of **9d** and **16**, CIF structure files (atomic coordinates, bond lengths, bond angles, and torsion angles), and conditions of the single-crystal X-ray measurements are available free of charge via the Internet.

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