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# Synthesis of 3-Amino-1,2,4-benzothiadiazine 1,1-Dioxides via a Tandem Aza-Wittig/Heterocumulene Annulation

Christopher Blackburn,* Abe Achab, Amy Elder, Shomir Ghosh, Jianping Guo, Geraldine Harriman, and Matthew Jones

*Department of Medicinal Chemistry, Millennium Pharmaceuticals, 35 Lansdowne Street, Cambridge, Massachusetts 02139*

*chris.blackburn@mpi.com*

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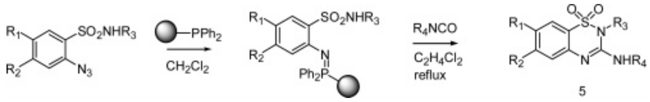

Reaction of *o*-azidobenzenesulfonamides with polymer-supported triphenylphosphine affords the corresponding iminophosphoranes. Subsequent reaction with isocyanates gives 3-amino-1,2,4-benzothiadiazine 1,1-dioxides in high yields and purities. The reaction has been successfully applied to the synthesis of derivatives with various substituents at the 2- and 3-positions and in the benzenoid ring.

3-Amino-1,2,4-benzothiadiazine 1,1-dioxides, which have been shown[1] to exist predominantly in the tautomeric form **1**, possess diverse biological activities including potassium[1−4] and calcium channel[5] modulation and adrenergic antagonism[6] effects. These compounds are typically prepared (Figure 1) by reaction of amines with thioethers **2** or their sulfone derivatives. The thioethers **2** are obtained either by cyclization of a chlorosulfonylthiourea or by reaction of *o*-aminobenzenesulfonamides **3** ($R_2$ = H) with $CS_2$ (or an equivalent reagent) followed by methylation.[4−6] 2-*N*-Alkyl derivatives **5** can only be accessed by this second route from **3** ($R_2$ = alkyl) because reaction of **2** with alkylating agents takes place at the 4-position.[3] Hence, analogues **5** are quite rare despite their isosteric relationship to the well studied quinazolinone system **6**.[7−12] The synthetic route to compound class **6** introduced by Molina[8] and subsequently used by Eguchi[9] entails a Staudinger reaction[13] of *o*-azidoarylcarboxamides with triphenyphosphine followed by reaction of the resultant iminophosphoranes with isocyanates in an aza-Wittig reaction[14] affording the desired **6** via cyclization of the diimide intermediate.

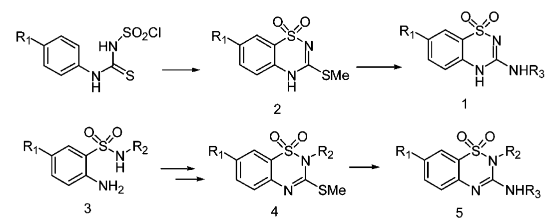

**FIGURE 1.** Typical syntheses of 3-amino-1,2,4-benzothiadiazine 1,1-dioxides.

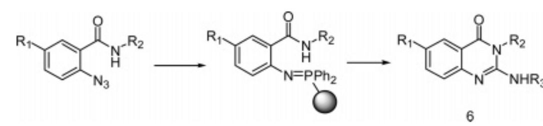

**FIGURE 2.** Synthesis of quinazolinones via intramolecular aza-Wittig reaction.

Recently, iminophosphoranes have been prepared from polymer-supported triphenylphosphine by reaction with an *o*-aminobenzamide[11] in the presence of $C_2Br_2Cl_4$ (Kirsanov conditions) or, in our own laboratories, by reaction with an *o*-azidobenzamide.[12] In each case, subsequent reaction with isocyanates at elevated temperatures released quinazolinones **6** into solution. The high yields we achieved in this reaction[12] (Figure 2) prompted us to investigate analogous transformations starting from the corresponding *o*-azidosulfonamides, which we report herein, leads to a short and high yield route to **5**. In addition, we show that primary sulfonamides undergo the same reaction opening up a new route to compounds of type **1**.

Sulfonamides bearing an *o*-azido group were prepared beginning with the diazotization of the appropriate orthanilic acid derivative followed by reaction with sodium azide to give sulfonic acids **7a**−**c**. Conversion to the corresponding sulfonyl chlorides **8a**−**c** by treatment with oxalyl chloride followed by reaction with the appropriate amines gave the requisite sulfonamides **9**−**11** (Scheme 1).[15] To simplify isolation, we investigated iminophosphorane formation using commercially avail-

* To whom correspondence should be addressed. Tel: +1-617-761-6811. Fax: +1-617-444-1483.

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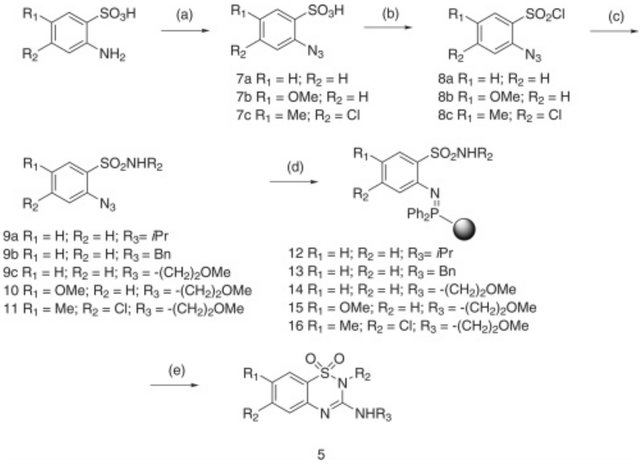
**SCHEME 1. Synthesis of 2-*N*-Alkyl-3-amino-1,2,4-benzothiadiazine 1,1-Dioxides[a]**




[a] Reagents and conditions: (a) (i) $NaNO_2$, $H_2SO_4$, 0 °C, (ii) $NaN_3$, 25 °C, 16 h; (b) $(COCl)_2$, DMF, $CH_2Cl_2$, reflux, 2 h; (c) $R_3NH_2$, DIEA, $CH_2Cl_2$, 25 °C; (d) PS-$PPh_2$, $CH_2Cl_2$, 25 °C, 16 h; (e) $R_3NCO$, $C_2H_4Cl_2$, 80 °C, 8 h.

able polymer-supported triphenylphosphine (loading 1.5 mmol/g). Treatment of *o*-azidosulfonamide **9a** with polymer-supported triphenylphosphine led to nitrogen evolution with formation of the corresponding polymer-bound iminophosphorane **12**.

Subsequent treatment with *n*-butylisocyanate in refluxing dichloroethane afforded **5a** in good yield (Table 1, entry 1) and analytical purity after filtration through a plug of silica gel. Somewhat lower yields of **5b** and **5c** were obtained by reaction of **12** with arylisocyanates (Table 1, entries 2 and 3) but the sulfonylisocyanate (entry 4) afforded **5d** in high yield and purity. Azides **9b** and **9c** derived from less hindered *N*-benzyl- and *N*-alkylsulfonamides also afforded polymer-supported iminophosphoranes **13** and **14**, respectively, which on treatment with the same isocyanates gave the corresponding heterocycles **5e**−**k** in generally higher yields than the isopropyl derivatives (Table 1, entries 5 to 10). Spectroscopic data for all compounds were in accord with structure **5** including the observation of coupling between the protons of the alpha methylene group and the NH of the 3-*n*-butylamino derivatives. Derivatives with substituents in the benzenoid ring could also be accessed. Thus, azides **10** and **11** readily formed supported iminophosphoranes **15** and **16** which afforded **5l**−**p** on reaction with isocyanates or sulfonyl isocyanates (Table 1).

This synthesis could also be adapted to the preparation of analogues that are unsubstituted at the 2-nitrogen atom (Scheme 2). Thus, azides **17**[16] bearing ortho primary sulfonamide groups formed the corresponding polymer-supported iminophosphoranes **18** on reaction with polymer supported triphenylphosphine; subsequent reaction with isocyanates afforded **1a**−**e** in good to moderate yields. This reaction contrasts that of the corresponding primary carboxamides which do not afford the quinazolinones but rather give nitriles arising from cyclization of the carbonyl oxygen onto the diimide followed by ring opening.[8]

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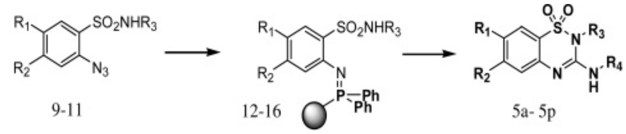
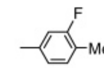
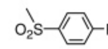
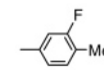
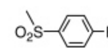
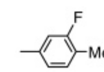
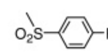
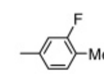
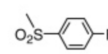
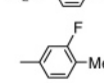
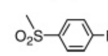
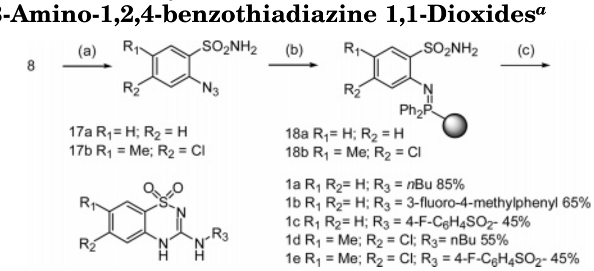
**TABLE 1. Synthesis of 3-*N*-Alkylamino-1,2,4-benzothiadiazine 1,1-Dioxides from Polymer-Supported Iminophosphoranes and Isocyanates**




| Entry | Product | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield(%)[a] |
|---|---|---|---|---|---|---|
| 1 | 5a | H | H | *i* Pr | *n* Bu | 65 |
| 2 | 5b | H | H | *i* Pr | Ph | 46 |
| 3 | 5c | H | H | *i* Pr |  | 40 |
| 4 | 5d | H | H | *i* Pr |  | 70 |
| 5 | 5e | H | H | Bn | *n* Bu | 76 |
| 6 | 5f | H | H | Bn |  | 63 |
| 7 | 5g | H | H | Bn |  | 75 |
| 8 | 5h | H | H | 2-MeO-ethyl | *n* Bu | 61 |
| 9 | 5i | H | H | 2-MeO-ethyl | Ph | 85 |
| 9 | 5j | H | H | 2-MeO-ethyl |  | 72 |
| 10 | 5k | H | H | 2-MeO-ethyl |  | 73 |
| 11 | 5l | OMe | H | 2-MeO-ethyl | *n* -Bu | 71 |
| 12 | 5m | OMe | H | 2-MeO-ethyl |  | 54 |
| 13 | 5n | OMe | H | 2-MeO-ethyl |  | 66 |
| 14 | 5o | Me | Cl | 2-MeO-ethyl |  | 45 |
| 15 | 5p | Me | Cl | 2-MeO-ethyl |  | 80 |

[a] Isolated yield of pure product calculated over two steps.

**SCHEME 2. Synthesis of 3-Amino-1,2,4-benzothiadiazine 1,1-Dioxides[a]**




[a] Reagents and conditions: (a) 2 M $NH_3$ in MeOH, $CH_2Cl_2$, 25 °C; (b) PS-$PPh_2$, $CH_2Cl_2$, THF, 25 °C, 24 h; (c) $R_3NCO$, THF, $C_2H_4Cl_2$, 80 °C, 16 h.

In summary, we have shown that reaction of *o*-azidobenzenesulfonamides with polymer-supported triphenylphosphine affords iminophosphoranes that undergo a tandem aza-Wittig heterocummulene annulation with isocyanates or sulfonylisocyanates releasing 3-amino-1,2,4-benzothiadiazine 1,1-dioxides into solution in good yields.

## Experimental Section:

**General Considerations and Synthesis of 2-Azidobenzenesulfonic Acids 7a−c.** See the Supporting Information.

**General Procedure for the Synthesis of 2-Azido-*N*-benzylbenzenesulfonamide (9b).** To a suspension of 2-azidobenzenesulfonic acid **7a** (0.225 g, 1.13 mmol) in dichloromethane (10 mL) were added 2 M oxalyl chloride in $CH_2Cl_2$ (2.83 mmol) and DMF (50 $\mu$L). The resulting mixture was heated under reflux for 3 h and then evaporated under reduced pressure. The residue (IR: $\nu_{max}$ 2125 $cm^{-1}$) was dissolved in dichloromethane (10 mL), treated with DIEA (0.39 mL, 2.26 mmol) and benzylamine (0.18 mL, 1.7 mmol, 1.5 equiv), and stirred at ambient temperature for 6 h and then washed with 1 N HCl followed by water and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue subjected to chromatography on silica gel eluting with a hexanes−ethyl acetate gradient from 15% ethyl acetate to 60% ethyl acetate to give **9b** 0.257 g (79%) as a light tan solid: mp 80−82 °C (lit.[15] mp 78−79 °C); IR (neat) $\nu_{max}$ 3290, 2107 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.00 (d, 1H), 7.55 (t, 1H), 7.30−7.14 (m, 7H), 5.26 (m, 1H), 4.11 (d, 2H); $^{13}$C NMR (100, MHz, $CDCl_3$) $\delta$ 138.2, 136.6, 134.6, 131.3, 130.6, 129.2, 128.6, 128.5, 125.5, 119.9, 48.3.

**2-Azido-*N*-isopropylbenzenesulfonamide (9a):** 90%; white solid; mp 106−109 °C; IR (neat) $\nu_{max}$ 3292, 2134, 2100 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.92 (d, $J$ = 9 Hz, 1H), 7.52 (dd, $J$ = 9 Hz, $J$ = 9 Hz, 1H), 7.20 (m, 2H), 4.82 (m, 1H), 3.37 (m, 1H), 1.02 (d, 6H); $^{13}$C NMR (100, MHz, $CDCl_3$) $\delta$ 138.1, 134.4, 131.9, 131.0, 125.5, 120.1, 47.1, 24.2; MS (ESI-) 239 (M − $H^+$).

**2-Azido-*N*-(2-methoxyethyl)benzenesulfonamide (9c):** 75%; oil; IR (neat) $\nu_{max}$ 3307, 2131, 2101 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.90 (d, $J$ = 9 Hz, 1H), 7.52 (dd, $J$ = 9 Hz, $J$ = 9 Hz, 1H), 7.20 (m, 2H), 5.42 (br, 1H), 3.30 (t, 2H), 3.20 (s, 3H), 3.02 (t, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 138.4, 134.6, 131.2, 130.6, 125.4, 120.0, 70.9, 59.5, 43.9; MS (ESI-) 255 (M − $H^+$).

**2-Azido-5-methoxy-*N*-(2-methoxyethyl)benzenesulfonamide (10):** 65%; oil; IR (neat) $\nu_{max}$ 3305, 2122 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.46 (d, $J$ = 3 Hz, 1H), 7.20 (d, $J$ = 9 Hz, 1H), 7.12 (d, $J$ = 9 Hz, 1H), 5.52 (t, 1H), 3.83 (s, 3H), 3.37 (t, 2H), 3.34 (s, 3H), 3.07 (t, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 157.1, 131.0, 130.3, 121.3, 120.8, 115.4, 70.8, 59.4, 56.6, 43.8; ESI-MS 285 (M − H)$^-$.

**2-Azido-4-chloro-*N*-(2-methoxyethyl)-5-methylbenzenesulfonamide (11):** 75%; white solid; mp 104−106 °C; IR (neat) $\nu_{max}$ 3299, 2133 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.82 (s, 1H), 7.30 (s, 1H), 5.42 (br, 1H), 3.40 (t, 2H), 3.29 (s, 3H), 3.07 (t, 2H), 2.39 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 140.5, 136.8, 133.9, 133.0, 128.8, 120.1, 70.9, 59.5, 43.9, 20.1; MS (ESI-) 303 (M − $H^+$).

**General Procedure for Synthesis of 2-*N*-Alkyl-3-amino-1,2,4-benzothiadiazine 1,1-Dioxides 5. 2-*N*-Isopropyl-3-*n*-butylamino-1,2,4-benzothiadiazine 1,1-Dioxide 5a.** Triphenylphosphine resin (220 mg, 0.33 mmol) was washed with several times with anhydrous THF followed by anhydrous dichloromethane and treated with a solution of **9a** (80 mg, 0.33 mmol) in dichloromethane (1.5 mL), resulting in evolution of nitrogen gas. The reaction mixture was shaken at ambient temperature for 16 h and then filtered and washed with dichloromethane and dichloroethane. The resin was then resuspended in dichloroethane (1.5 mL), treated with *n*-butyl isocyanate (30 mg, 34 uL, 0.30 mmol, 0.9 equiv), and heated in a sealed vial at 80 °C for 16 h. The solvent was decanted and the resin resuspended in dichloroethane and treated with further *n*-butyl isocyanate (0.3 equiv) at 80 °C for 8 h. This procedure improved the yield of the title compound while minimizing further reaction of the product with the isocyanate. The resin was filtered and washed thoroughly with dichloromethane (12 × 4 mL), and the combined filtrates were treated with polystyrene trisamine resin (3 equiv) and allowed to stand for 3 h at ambient temperature. The crude product was filtered over a plug of silica gel eluting with 50% ethyl acetate in hexane and the solvent evaporated to give **5a**: 63 mg (65%); colorless oil; IR (neat) $\nu_{max}$ 3371, 1613 $cm^{-1}$; $^1$H NMR (400 MHz, $CD_3OD$, 25 °C) $\delta$ 7.65 (dd, $J$ = 9 Hz, $J$ = 3 Hz, 1H), 7.53 (t, 1H) 7.24 (d, $J$ = 9 Hz, 1H), 7.18 (dd, $J$ = 9 Hz, $J$ = 3 Hz, 1H), 4.19 (m, 1H), 3.44 (m, 2H), 1.67 (m, 2H), 1.46 (m, 2H), 1.20 (d, $J$ = 7 Hz, 6H), 0.98 (t, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$, 25 °C) $\delta$ 152.9, 146.6, 134.5, 128.2, 126.4, 123.0, 122.6, 55.6, 42.6, 32.4, 22.2, 21.4, 14.2; HRMS (ESI+) calcd for $C_{14}H_{21}N_3O_2S$ + H, 296.1433, found 296.1443.

**2-*N*-Isopropyl-3-phenylamino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (5b)** was purified by preparative TLC on neutral alumina eluting with 20% ethyl acetate in hexane. The major UV-active band was extracted with ethyl acetate and the solvent evaporated to give **5b**: 46%; white solid; mp 119−122 °C; IR (neat) $\nu_{max}$ 3363, 2924, 1608 $cm^{-1}$; $^1$H NMR (400 MHz, $CD_3OD$, 25 °C) $\delta$ 7.75 (d, $J$ = 8 Hz, 1H), 7.66 (m, 3H), 7.40−7.32 (m, 4H), 7.22 (t, 1H), 4.29 (m, 1H), 1.25 (d, $J$ = 7 Hz, 6H); $^{13}$C NMR (100 MHz, $CD_3OD$, 25 °C) $\delta$ 150.5 (br), 145.3 (br), 140.5 (br), 134.8, 130.5 (br), 130.1, 126.8 (br), 125.4, 125.1, 122.7, 122.2, 56.9, 22.2; HRMS calcd for $C_{16}H_{17}N_3O_2S$ + H, 316.1120, found 316.1131.

**2-*N*-Isopropyl-3-(3-fluoro-4-methylphenylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (5c)** was purified as described for **5b**: 40%; white solid; mp 111−114 °C; $^1$H NMR (400 MHz, $CD_3OD$, 25 °C) $\delta$ 7.74 (d, 1H), 7.62 (m, 2H), 7.39−7.29 (m, 3H), 7.19 (1H, t), 4.23 (1H, m), 2.24 (3H, s), 1.22 (6H, d); $^{13}$C NMR (100 MHz, $CD_3OD$, 25 °C) $\delta$ 162.5, 150.1, 145.4, 134.8, 132.5, 130.3, 127.0, 125.6, 122.8, 121.0, 117.2, 108.7, 57.0, 22.2, 14.0; HRMS calcd for $C_{17}H_{18}FN_3O_2S$ + H 348.1182, found 348.1196.

**2-*N*-Isopropyl-3-(4-fluorophenylsulfonylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (5d)** was purified as described for **5a**: 70%; white solid; mp 128−130 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C) $\delta$ 10.76 (br, 1H), 7.95 (m, 2H), 7.81 (d, 1H), 7.69 (t, 1H), 7.36 (t, 1H), 7.20 (m, 3H), 4.95 (m, 1H), 1.47 (d, $J$ = 7 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 165.7, 149.5, 138.6, 135.3, 134.0, 129.6, 125.9, 125.7, 123.0, 118.6, 117.0, 116.8, 51.8, 50.3; HRMS calcd for $C_{16}H_{16}FN_3O_4S_2$ + H 398.0645, found 398.0661.

**2-*N*-Benzyl-3-*n*-butylamino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (5e)** was purified as described for **5a**: 76%; white solid;, mp 87−88 °C; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 7.79 (dd, 1H), 7.52 (dd, 1H), 7.36 (m, 5H), 7.32 (d, 1H), 7.18, (t, 1H), 4.94, (s, 2H), 4.61 (br, 1H), 3.34 (br, 2H), 1.37 (m, 2H), 1.15 (m, 2H), 0.82 (t, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 149.9, 145.0, 136.1, 134.1, 130.0, 129.1, 127.9, 126.7, 126.6, 123.4, 121.9, 49.5, 42.2, 31.6, 20.5, 14.3; HRMS calcd for $C_{18}H_{21}N_3O_2S$ + H 344.1433, found 344.1435.

**2-*N*-Benzyl-3-(3-fluoro-4-methylphenylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (5f)** was purified as described for **5b**: 63%; white solid; mp 137−138 °C; $^1$H NMR (400 MHz, $CD_3OD$, 25 °C) $\delta$ 7.76 (d, $J$ = 9 Hz, 1H), 7.53 (t, 1H), 7.44−7.00 (m, 8H), 6.83 (m, 2H), 5.12 (m, 2H), 2.18 (s, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$, 25 °C) 162.4, 148.7, 144.7, 139.7, 136.0, 134.6, 132.6, 129.7, 129.5, 129.2, 129.0, 127.0, 125.4, 122.3, 120.8, 117.0, 108.6, 108.3, 51.7, 14.0; HRMS calcd for $C_{21}H_{18}FN_3O_2S$ + H 396.1182, found 396.1193.

**2-*N*-Benzyl-3-(4-fluorophenylsulfonylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (5g)** was purified as described for **5b**: 75%; white solid; mp 183−185 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C) $\delta$ 10.76 (s, 1H), 7.94 (d, 1H), 7.70 (m, 2H), 7.40 (t, 1H), 7.15 (m, 9H), 5.14 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) 165.6, 149.3, 138.2, 135.7, 135.6, 133.6, 131.5, 129.6, 129.5, 129.1, 129.0, 128.6, 126.1, 124.6, 123.5, 118.7, 116.80, 116.6, 46.3; HRMS calcd for $C_{20}H_{16}FN_3O_4S_2$ + H 446.0639, found 446.0633.

**2-*N*-(2-Methoxyethyl)-3-*n*-butylamino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (5h)** was prepared and purified as described for **5a**: 61%; colorless oil; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C) $\delta$ 7.70 (d, 1H), 7.50 (t, 1H), 7.40 (d, 1H), 7.16 (t, 1H), 6.92 (br, 1H), 3.96 (t, 2H), 3.80 (t, 2H), 3.50 (m, 5H), 1.60 (m, 2H), 1.42 (m, 2H), 0.96 (t, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 134.5, 126.7, 125.3, 124.2, 121.6, 74.1, 60.1, 48.0, 43.3, 31.7, 20.6, 14.4; HRMS calcd for $C_{14}H_{21}N_3O_3S$ + H 312.1376, found 312.1367.

**2-*N*-(2-methoxyethyl)-3-phenylamino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (5i)** was prepared and purified as described for **5b**: 85%; white solid; mp 108−110 °C; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.80 (d, 1H), 7.64−7.26 (m, 7H), 7.15 (t, 1H), 4.02 (t, 2H), 3.82 (t, 2H), 3.56 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) δ 148.4, 143.5, 138.6, 134.3, 129.9, 129.9, 127.6, 125.9, 125.9, 125.0, 124.8, 121.7, 121.0, 73.6, 60.1, 48.1; HRMS calcd for $C_{16}H_{17}N_3O_3S$ + H 332.1069, found 332.1081.

**2-*N*-(2-methoxyethyl)-3-(3-fluoro-4-methylphenylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (5j)** was purified as described for **5b**: 72%; white solid; mp 117−119 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C) δ 9.05 (br, 1H), 7.78 (d, 1H), 7.60 (m, 2H), 7.48 (d, 1H), 7.27 (t, 1H), 7.12 (m, 2H), 4.00 (t, 2H), 3.86 (t, 2H), 3.60 (s, 3H), 2.24 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) δ 161.8 (d, $J$ = 234 Hz), 146.9, 144.4, 138.4, 134.1, 131.9, 127.7, 127.1, 124.4, 121.5, 120.3, 115.6, 107.9, 74.5, 60.3, 47.9, 14.7; HRMS calcd for $C_{17}H_{18}FN_3O_3S$ + H 364.1131, found 364.1146.

**2-*N*-(2-Methoxyethyl)-3-(4-fluorophenylsulfonylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (5k)** was purified as described for **5a**: 73%; white solid; mp 133−134 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C) δ 10.80 (s, 1H), 7.98 (m, 2H), 7.86 (d, 1H), 7.70 (t, 1H), 7.42 (t, 1H), 7.20 (m, 3H), 4.16 (t, 2H), 3.56 (t, 2H), 3.22 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) δ 165.7, 149.9, 138.4, 135.4, 133.8, 129.7, 126.1, 124.9, 123.2, 118.8, 117.0, 116.7, 70.0, 59.3, 43.0; HRMS calcd for $C_{16}H_{16}FN_3O_5S_2$ + H 414.0588, found 414.0586.

**2-*N*-(2-Methoxyethyl)-3-*n*-butylamino-7-methoxy-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (5l)** was purified as described for **5a**: 71%; white solid; mp 86−89 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.23 (d, $J$ = 10 Hz, 1H), 7.08 (dd, $J$ = 10 Hz, 3 Hz, 1H), 6.61 (br, 1H), 3.91 (t, 3H), 3.82 (s, 2H), 3.78 (t, 3H), 3.48 (s, 3H), 3.40 (d of t, 2H), 1.60 (m, 2H), 1.42 (m, 2H), 0.96 (t, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) δ 155.6, 149.4, 139.3, 127.9, 126.7, 122.4, 103.7, 74.5, 60.0, 56.5, 47.4, 42.0, 31.9, 20.7, 14.5; HRMS calcd for $C_{15}H_{23}FN_3O_4S$ + H 342.1482, found 342.1480.

**2-*N*-(2-Methoxyethyl)-3-(3-fluoro-4-methylphenyl)-7-methoxy-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (5m)** was purified as described for **5b**: 54%; white solid; mp 128 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C) δ 9.00 (br, 1H), 7.62 (d, 1H), 7.42 (d, 1H), 7.23−7.05 (m, 4H), 4.00 (t, 2H), 3.89 (t, 3H), 3.88 (s, 3H), 3.65 (s, 3H), 2.24 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) δ 161.9 (d, $J$ = 242 Hz), 156.8, 145.7, 138.7, 137.8, 131.9, 128.5, 127.7, 122.3, 119.9 (d, $J$ = 17 Hz), 115.4, 107.4 (d, $J$ = 27 Hz), 103.9, 74.5, 60.3, 56.6, 47.9, 14.7; HRMS calcd for $C_{18}H_{20}FN_3O_4S$ + H 394.1237, found 394.1249.

**2-*N*-(2-Methoxyethyl)-3-(4-fluorophenylsulfonyl)-7-methoxy-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (5n)** was purified as described for **5a**: 66%; white solid; mp 196−198 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C) δ 10.64 (s, 1H), 7.96 (d, 1H), 7.30−7.16 (m, 6H), 4.14 (t, 2H), 3.92 (s, 3H), 3.56 (t, 2H), 3.22 (s, 3H); $^{13}$C NMR (100 Hz, $CDCl_3$, 25 °C) δ 165.5 (d, $J$ = 253 Hz), 157.7, 149.7, 138.6, 129.6, 127.0, 125.5, 123.3, 120.3, 116.9, 105.7, 70.1, 59.4, 56.8, 43.0; HRMS calcd for $C_{17}H_{18}FN_3O_6S_2$ + H 444.0699, found 444.0709.

**2-*N*-(2-Methoxyethyl)-3-(3-fluoro-4-methylphenyl)-6-chloro-7-methyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (5o)** was purified as described for **5b**: 45%; white solid; mp 190−191 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C) δ 9.10 (br, 1H), 7.62 (m, 2H), 7.58 (s, 1H), 7.10 (m, 2H), 4.00 (t, 2H), 3.86 (t, 2H), 3.62 (s, 3H), 2.43 (s, 3H), 2.27 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) δ 161.8 (d, $J$ = 234 Hz), 147.9, 142.9, 140.5, 133.2, 132.2, 132.1, 126.8, 126.0, 123.0, 120.6, 120.2, 115.8, 107.9 (d, $J$ = 28 Hz), 74.2, 60.3, 48.1, 20.4, 14.8; HRMS calcd for $C_{18}H_{19}ClFN_3O_3S$ + H 412.0898, found 412.0901.

**2-*N*-(2-methoxyethyl)-3-(4-fluorophenylsulfonyl)-6-chloro-7-methyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (5p)** was purified as described for **5a**: 80%; white solid; mp 160−165 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C) δ 10.70 (br, 1H), 7.96 (m, 2H), 7.69 (s, 1H), 7.32 (s, 1H), 7.20 (m, 2H), 5.11 (m, br, 1H), 4.09 (t, 2H), 3.50 (t, 2H), 3.20 (s, 3H), 2.43 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) δ 165.8 (d, $J$ = 255 Hz), 149.7, 141.9, 138.8, 138.2, 135.0, 132.4, 129.8, 124.6, 123.2, 119.3, 117.0, 69.9, 59.3, 43.1, 20.4; HRMS calcd for $C_{17}H_{17}ClFN_3O_5S_2$ + H 462.0360, found 462.0370.

**2-Azidobenzenesulfonamide 17a.**[16] 2-Azidobenzenesulfonyl chloride (0.65 g, 3 mmol) in dichloromethane (20 mL) was treated dropwise with 0.5 M $NH_3$ in dioxane (20 mL) and stirred at ambient temperature for 3 h. The mixture was evaporated to dryness, dissolved in ethyl acetate, and filtered through a short silica gel column washing with ethyl acetate. Evaporation of the solvent afforded **19a** (0.54 g, 81%) as a white solid: mp 175−177 °C dec; $^1$H NMR (300 MHz, $CD_3OD$) δ: 7.93 (d, 1H), 7.64 (t, 1H), 7.46 (d, 1H), 7.29 (t, 1H), 4.88 (s, 2H).

**2-Azido-4-chloro-5-methylbenzenesulfonamide 17b** was prepared from **8c** and purified as described for **17a**: 75%; white solid; mp 180−182 °C dec; IR (neat) $\nu$max 3270, 2125 cm$^{-1}$; $^1$H NMR (400 MHz, $CD_3OD$) δ: 7.82 (s, 1H), 7.47 (s, 1H), 2.39 (s, 3H); MS (ESI-) 245 (M − H$^+$).

**3-*n*-Butylamino-1,2,4-benzothiadiazine 1,1-dioxide (1a)** was prepared as described for **5a** except that the resin capture and aza-Wittig reactions were conducted in dichloromethane−THF (1:4) and dichloroethane−THF (1:1), respectively. The reaction solvent was evaporated and the product triturated with ether to give **1a**: 85%; white solid; mp 175−176 °C; IR (neat) $\nu_{max}$ 3298, 3184, 3114, 1626 cm$^{-1}$; $^1$H NMR (400 MHz, $CD_3OD$, 25 °C) δ 7.74 (dd, 1H), 7.54 (t, 1H), 7.27 (t, 1H), 7.10 (d, 1H), 3.34 (dt, 2H), 1.59 (m, 2H), 0.96 (t, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$, 25 °C) δ 153.1, 137.4, 133.9, 125.2, 124.3, 123.5, 117.4, 41.9, 32.5, 21.0, 14.1; HRMS calcd for $C_{11}H_{15}N_3O_2S$ + H 254.0963, found 254.0976.

**3-(3-Fluoro-4-methylphenylamino)-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (1b).** Following the solid-supported aza-Wittig reaction, the reaction mixture was filtered and the white solid occluded in the resin was dissolved in DMSO and subjected to preparative reverse-phase chromatography (see the Supporting Information) to give **1b** (65%): white solid; mp 325−330 °C; $^1$H NMR (400 MHz, DMSO-$d_6$, 25 °C) δ 9.50 (br, 1H), 7.70 (d, 1H), 7.59 (t, 1H), 7.40 (dd, 1H), 7.32−7.23 (m, 3H), 7.15 (dd, 1H), 2.20 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$, 25 °C) δ 160.2, (d, $J$ = 240 Hz), 148.0, 137.0, 135.8, 132.6, 131.6, 131.5, 124.2, 122.9, 122.5, 119.2, 117.4, 116.7, 107.8, (d, $J$ = 26 Hz), 13.7; HRMS calcd for $C_{14}H_{12}FN_3O_2S$ + H 306.0713, found 306.0723.

**3-(4-Fluorophenylsulfonylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (1c)** was prepared as described for **1a** and purified by chromatography on silica gel eluting with ethyl acetate: 45%; white solid; mp 264−266 °C; $^1$H NMR (THF-$d_8$) δ 9.88 (br, 1H), 8.08 (dd, 2H), 7.70 (d, 1H), 7.39 (t, 1H), 7.10 (m, 4H); $^{13}$C NMR (100 MHz, THF-$d_8$, 25 °C) δ 164.0 (d, $J$ = 248 Hz), 153.1, 141.2, 137.3, 131.6, 129.5, 123.1, 122.2 (d, $J$ = 8 Hz), 115.8, 114.4 (d, $J$ = 22 Hz); HRMS calcd for $C_{13}H_{10}FN_3O_4S_2$ + H 356.0175, found 356.0188.

**3-*n*-Butylamino-6-chloro-7-methyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (1d)** was prepared and purified as described for **1a**: 55%; white solid; mp 274−275 °C; $^1$H NMR (DMSO-$d_6$) δ 10.49 (br, 1H), 7.67 (s, 1H), 7.25 (br, 2H), 3.20 (m, 2H), 2.32 (s, 3H), 1.49 (m, 2H), 1.32 (m, 2H), 0.92 (t, 6H); $^{13}$C NMR (100 MHz, DMSO-$d_6$, 25 °C) δ 150.9, 136.8, 134.8, 131.1, 124.8, 121.5, 116.4, 40.0, 30.8, 19.4, 18.8, 13.6; HRMS calcd for $C_{12}H_{16}ClN_3O_2S$ + H 302.0730, found 302.0271.

**6-Chloro-7-methyl-3-(4-fluorophenylsulfonylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (1e)** was prepared as described for **1a** and purified by chromatography on silica gel eluting with ethyl acetate: 45%; white solid; mp 281−283 °C; $^1$H NMR (400 MHz, $CD_3OD$, 25 °C) δ 8.01 (m, 2H), 7.54 (s, 1H), 7.15 (m, 3H), 2.34 (s, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$, 25 °C) δ 165.7, (d, $J$ = 249 Hz), 154.4, 141.2, 139.4, 137.4, 132.4, 131.3, (d, $J$ = 9 Hz), 125.9, 121.4, 117.3, 115.9 ($J$ = 22 Hz), 19.5; HRMS calcd for $C_{14}H_{11}ClFN_3O_4S_2$ + H 403.9942, found 403.9951.

**Supporting Information Available:** $^1$H NMR and $^{13}$C NMR spectra of compounds **9−11**, **5a−p**, and **1a−e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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