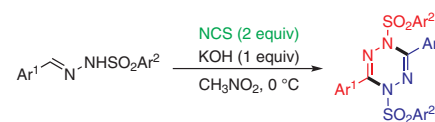


# Chlorination of Arylaldehyde-Derived Arylsulfonylhydrazones with *N*-Chlorosuccinimide Leading to 1,2,4,5-Tetrazine Derivatives

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- One-pot synthesis
- 16 examples
- Metal-free conditions
- Up to 93% yield

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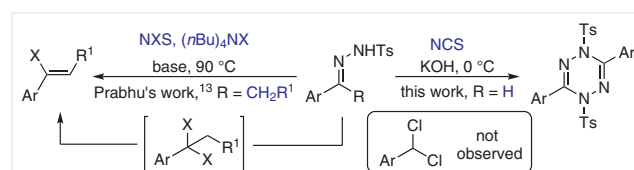
**Abstract** It has been reported previously that treatment of arylketone-derived arylsulfonylhydrazones with  $\text{NXS}/(n\text{Bu})_4\text{NX}$  affords exclusively vinyl halides. In contrast, we have found that treatment of arylaldehyde-derived arylsulfonylhydrazones with *N*-chlorosuccinimide in the presence of potassium hydroxide affords 1,2,4,5-tetrazine derivatives in good to excellent yields. The present reactions are carried out under metal-free and mild reaction conditions.

**Key words** 1,2,4,5-tetrazines, hydrazones, *N*-chlorosuccinimide, chlorination, metal-free

1,2,4,5-Tetrazine derivatives are versatile aromatic heterocycles<sup>1</sup> that have been applied in organic electronics [e.g., organic photovoltaic (OPV) devices, organic field-effect transistors (OFETs)],<sup>2</sup> energetic materials,<sup>3</sup> coordination chemistry,<sup>4</sup> electrofluorochromism,<sup>5</sup> and in the synthesis of biologically active molecules.<sup>6</sup> Recently, 1,2,4,5-tetrazines have also attracted a fair amount of attention in life sciences, with applications in cell imaging, DNA labelling, etc.<sup>7</sup> In general, 1,2,4,5-tetrazines are synthesized predominantly by the reaction of hydrazine with aromatic nitriles, followed by oxidation of the generated 1,2-dihydropyridazines.<sup>8</sup> In addition, further modification of 1,2,4,5-tetrazines has also emerged as a useful tool.<sup>9</sup>


On the other hand, arylsulfonylhydrazones are key building blocks in synthetic chemistry,<sup>10,11</sup> especially for the synthesis of nitrogen-containing heterocycles.<sup>12</sup> In 2015, Prabhu and Ojha<sup>13</sup> reported an elegant synthesis of vinyl halides from arylketone-derived *N*-tosylhydrazones using  $\text{NXS}/(n\text{Bu})_4\text{NX}$ , in which dihalides were the proposed reaction intermediates (Scheme 1). Herein, we report a facile synthesis of 1,2,4,5-tetrazine derivatives from arylaldehyde-derived arylsulfonylhydrazones in the presence of

*NCS* and *KOH* under metal-free conditions (Scheme 1). The discovery of this 1,2,4,5-tetrazine synthetic protocol was somewhat unexpected. It began with our attempts to synthesize dichlorides from arylaldehyde-derived arylsulfonylhydrazones using Prabhu's conditions. Regrettably, the chlorination reaction did not afford the desired dichlorides; instead, 1,2,4,5-tetrazines were unexpectedly obtained. Considering the importance of 1,2,4,5-tetrazine derivatives in chemical, biological, and environmental sciences,<sup>1–7</sup> we decided to study this process further by optimizing the reaction conditions for the synthesis of 1,2,4,5-tetrazines.



**Scheme 1** Synthetic applications of arylsulfonylhydrazones

4-Nitrobenzaldehyde *N*-tosylhydrazone (**1a**) was selected as a model substrate for optimizing the reaction conditions (Table 1). Following Prabhu's procedure [*NBS* (1.5 equiv),  $(n\text{Bu})_4\text{NBr}$  (3 equiv),  $\text{K}_2\text{CO}_3$  (3.0 equiv), 1,4-dioxane],<sup>13</sup> treatment of 4-nitrobenzaldehyde *N*-tosylhydrazone (**1a**) at 25 °C for 3 hours did not afford the corresponding benzyl dihalide. Instead, 3,6-bis(4-nitrophenyl)-1,4-ditosyl-1,4-dihydro-1,2,4,5-tetrazine (**2a**) was obtained, albeit in only 19% yield (entry 1). The reaction proceeded uneventfully in the absence of TBAB (entries 1 and 2). Promoters such as *N*-chlorosuccinimide (*NCS*), *N*-iodosuccinimide (*NIS*) and iodine ( $\text{I}_2$ ) could be used for this reaction, but *NCS* gave the best yield (entries 2–5). Various solvents including  $\text{CH}_3\text{NO}_2$ ,  $\text{CH}_3\text{CN}$ , THF,  $\text{CH}_2\text{Cl}_2$  and 1,4-dioxane were also investigated, among which  $\text{CH}_3\text{NO}_2$  was the best (entries 3

**Table 1** Optimization of the Reaction Conditions<sup>a</sup>


Entry	Promoter (equiv)	Solvent	Base (equiv)	Yield (%) <sup>b</sup>
1 <sup>c</sup>	NBS (1.5)	1,4-dioxane	K <sub>2</sub> CO <sub>3</sub> (3.0)	19
2	NBS (1.5)	1,4-dioxane	K <sub>2</sub> CO <sub>3</sub> (3.0)	19
3	NCS (1.5)	1,4-dioxane	K <sub>2</sub> CO <sub>3</sub> (3.0)	63
4	NIS (1.5)	1,4-dioxane	K <sub>2</sub> CO <sub>3</sub> (3.0)	10
5	I <sub>2</sub> (1.5)	1,4-dioxane	K <sub>2</sub> CO <sub>3</sub> (3.0)	25
6	NCS (1.5)	CH <sub>3</sub> CN	K <sub>2</sub> CO <sub>3</sub> (3.0)	40
7	NCS (1.5)	THF	K <sub>2</sub> CO <sub>3</sub> (3.0)	10
8	NCS (1.5)	CH <sub>2</sub> Cl <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub> (3.0)	25
9	NCS (1.5)	CH <sub>3</sub> NO <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub> (3.0)	65
10	none	CH <sub>3</sub> NO <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub> (3.0)	0
11	NCS (0.5)	CH <sub>3</sub> NO <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub> (3.0)	9
12	NCS (1.0)	CH <sub>3</sub> NO <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub> (3.0)	44
13	NCS (2.0)	CH <sub>3</sub> NO <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub> (3.0)	72
14	NCS (2.5)	CH <sub>3</sub> NO <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub> (3.0)	72
15	NCS (2.0)	CH <sub>3</sub> NO <sub>2</sub>	Na <sub>2</sub> CO <sub>3</sub> (3.0)	67
16	NCS (2.0)	CH <sub>3</sub> NO <sub>2</sub>	Cs <sub>2</sub> CO <sub>3</sub> (3.0)	69
17	NCS (2.0)	CH <sub>3</sub> NO <sub>2</sub>	Li <sub>2</sub> CO <sub>3</sub> (3.0)	44
18	NCS (2.0)	CH <sub>3</sub> NO <sub>2</sub>	KOH (3.0)	78
19	NCS (2.0)	CH <sub>3</sub> NO <sub>2</sub>	K <sub>3</sub> PO <sub>4</sub> (3.0)	50
20	NCS (2.0)	CH <sub>3</sub> NO <sub>2</sub>	Et <sub>3</sub> N (3.0)	0
21	NCS (2.0)	CH <sub>3</sub> NO <sub>2</sub>	DMAP (3.0)	0
22	NCS (2.0)	CH <sub>3</sub> NO <sub>2</sub>	none	31
23	NCS (2.0)	CH <sub>3</sub> NO <sub>2</sub>	KOH (0.5)	44
24	NCS (2.0)	CH <sub>3</sub> NO <sub>2</sub>	KOH (1.0)	78
25	NCS (2.0)	CH <sub>3</sub> NO <sub>2</sub>	KOH (2.0)	78
26 <sup>d</sup>	NCS (2.0)	CH <sub>3</sub> NO <sub>2</sub>	KOH (1.0)	88
27 <sup>d,e</sup>	NCS (2.0)	CH <sub>3</sub> NO <sub>2</sub>	KOH (1.0)	85

<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), promoter (0–0.5 mmol), base (0–0.6 mmol), solvent (1.0 mL), 25 °C, 3 h.

<sup>b</sup> Yield of isolated product.

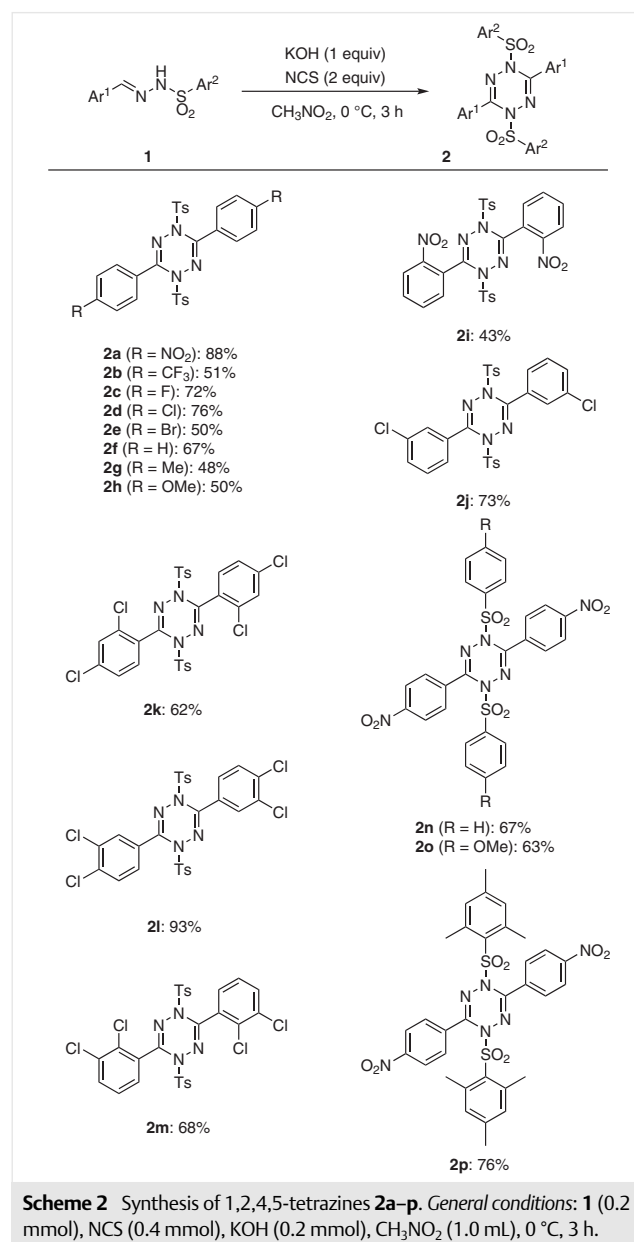
<sup>c</sup> (nBu)<sub>4</sub>NBr (0.6 mmol) was used.

<sup>d</sup> Reaction was performed at 0 °C.

<sup>e</sup> Reaction was carried out on a 1.28 g scale of **1a** (4.0 mmol).

and 6–9). The reaction did not work without NCS, and the reaction with *N*-tosylhydrazone **1a** afforded a higher yield when using the 2.0 equivalents of NCS (entries 9–14). The choice of base was also important for this reaction. The reaction could be achieved with various inorganic bases such as Na<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, Li<sub>2</sub>CO<sub>3</sub>, KOH and K<sub>3</sub>PO<sub>4</sub> (entries 15–19). However, KOH was selected for our further studies because it displayed the best efficiency (entries 13 and 15–19).

On using organic bases, such as Et<sub>3</sub>N and DMAP, no reaction occurred and the starting materials were recovered (Table 1, entries 20 and 21). The yield of 1,2,4,5-tetrazine **2a** decreased when the loading of KOH was less than 1.0 equivalent (entries 18 and 22–25). The effect of different temperatures was investigated and the reaction at 0 °C was found to give 1,2,4,5-tetrazine **2a** in a higher yield (entries 24 and 26). Furthermore, a large-scale reaction using 4-nitrobenzaldehyde *N*-tosylhydrazone (**1a**) (1.28 g) also gave an excellent yield of the corresponding 1,2,4,5-tetrazine **2a** (entry 27).



Having optimized the reaction conditions, the scope of the reaction with arylaldehyde-derived arylsulfonylhydrazones was subsequently explored and the results are compiled in Scheme 2. A wide range of *N*-tosylhydrazones, with either hydrogen atoms, electron-withdrawing groups or electron-donating groups at the *ortho*, *meta* or *para* positions of their aromatic rings, reacted smoothly in the presence of NCS (2.0 equiv) and KOH (1.0 equiv) at 0 °C to afford 1,2,4,5-tetrazines **2a–m** in moderate to excellent yields within 3 hours. Arylsulfonylhydrazones derived from methoxy- and methyl-substituted benzenesulfonyl hydrazides reacted under the optimized conditions to generate 1,2,4,5-tetrazines **2n–p** in good yields. The structures of these 1,2,4,5-tetrazines were determined from their NMR spectra and by X-ray crystallographic analysis of 1,2,4,5-tetrazines **2c** and **2e** (Figure 1).<sup>14</sup>

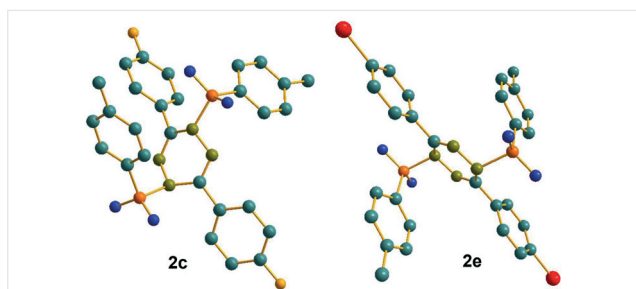
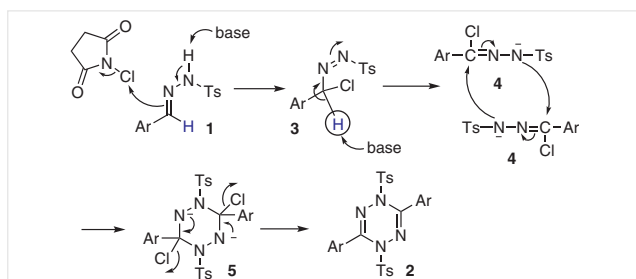


Figure 1 X-ray crystal structures of 1,2,4,5-tetrazines **2c** and **2e**<sup>14</sup>

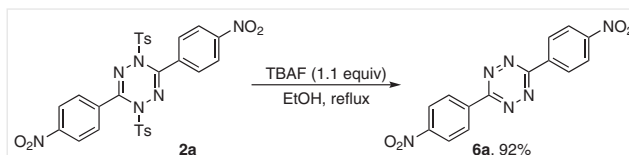
A possible reaction mechanism for the NCS-mediated chlorination of *N*-tosylhydrazones **1** is illustrated in Scheme 3. Initially, the NCS-mediated chlorination of arylaldehyde-derived *N*-tosylhydrazones **1** could lead to compounds **3**. The three electron-withdrawing functionalities, i.e., the N=N double bond, the chlorine and the aromatic substituents, make the hydrogen on the  $\alpha$ -carbon very acidic. Therefore, removal of this hydrogen from **3** in the presence of the base KOH would take place to provide the anions **4**, and thereby obviating the formation of dichlorides via the reaction of **3** with a chlorine anion. The double intermolecular azacyclization reaction of **4** may subsequently lead to



Scheme 3 Proposed mechanism involving the chlorination of *N*-tosylhydrazones **1** and the formation of 1,2,4,5-tetrazines **2**

dianions **5**. Finally, removal of the two chlorine anions from intermediate **5** affords the corresponding 1,2,4,5-tetrazines **2**.

According to the literature,<sup>9d</sup> 3,6-disubstituted-1,2,4,5-tetrazines **6** can be synthesized via deprotection and aromatization of 1,4-dihydro-3,6-disubstituted-1,4-bis(arylsulfonyl)-1,2,4,5-tetrazines **2**. For example, following Wei's procedure [TBAF (1.1 equiv), EtOH, reflux],<sup>9d</sup> the reaction of 3,6-bis(4-nitrophenyl)-1,4-ditosyl-1,4-dihydro-1,2,4,5-tetrazine (**2a**) afforded 3,6-bis(4-nitrophenyl)-1,2,4,5-tetrazine (**6a**) in 92% yield (Scheme 4).



Scheme 4 Deprotection/aromatization of 3,6-bis(4-nitrophenyl)-1,4-ditosyl-1,4-dihydro-1,2,4,5-tetrazine (**2a**)

In summary, we have developed a facile method for the synthesis of 1,2,4,5-tetrazines which proceeds via NCS-mediated chlorination of arylaldehyde-derived *N*-tosylhydrazones. The reactions take place under metal-free conditions and tolerate a wide range of hydrazone substrates to afford the corresponding 1,2,4,5-tetrazines in good to excellent isolated yields. Furthermore, the reported procedure for the preparation of 1,2,4,5-tetrazines and the synthesis of vinyl halides described by Prabhu<sup>13</sup> enrich the reaction diversity. Studies on the further applications of this method are ongoing in our laboratory.

Reagents and solvents were obtained from commercial sources and no further purification was required. The products were purified by column chromatography on Yantai Xinnuo silica gel (200–300 meshes). Melting points were recorded on a Gongyi X-5 microscopy digital melting point apparatus and are uncorrected. IR spectra were measured on an Electrothermal Nicolet 380 spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance III 400 MHz NMR spectrometer. All signals for protons are recorded in ppm using the residual NMR solvent signal as an internal reference (CDCl<sub>3</sub>, 7.26 ppm). All signals for carbon resonances are recorded in ppm using the residual NMR solvent signal as an internal reference (CDCl<sub>3</sub>, 77.0 ppm). High-resolution mass spectrometry (HRMS) were performed using an Electrothermal LTQ-Orbitrap mass spectrometer.

#### 1,2,4,5-Tetrazines; General Procedure

A mixture of arylaldehyde-derived arylsulfonylhydrazone **1** (1 equiv, 0.2 mmol), NCS (2 equiv, 0.4 mmol) and KOH (1 equiv, 0.2 mmol) in CH<sub>3</sub>NO<sub>2</sub> (1.0 mL) was stirred at 0 °C for 3 h. After completion of the reaction, H<sub>2</sub>O (5 mL) and EtOAc (10 mL) were added and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. Purification of the crude residue by flash chromatography on silica gel gave the corresponding 1,2,4,5-tetrazine **2**.

**3,6-Bis(4-nitrophenyl)-1,4-ditosyl-1,4-dihydro-1,2,4,5-tetrazine (2a)**

Yield: 55.8 mg (88%); yellow solid; mp 101–103 °C.

IR (film): 2925, 2854, 1595, 1525, 2332, 1174, 855, 605 cm<sup>-1</sup>.<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.27 (d, *J* = 8.7 Hz, 4 H), 7.75 (d, *J* = 8.3 Hz, 4 H), 7.66 (d, *J* = 8.7 Hz, 4 H), 7.42 (d, *J* = 8.2 Hz, 4 H), 2.51 (s, 6 H).<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 152.2, 149.6, 146.5, 135.6, 133.5, 130.0, 129.7, 128.6, 123.5, 21.8.HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>28</sub>H<sub>23</sub>N<sub>6</sub>O<sub>8</sub>S<sub>2</sub>: 635.1013; found: 635.1017.**1,4-Ditosyl-3,6-bis[4-(trifluoromethyl)phenyl]-1,4-dihydro-1,2,4,5-tetrazine (2b)**

Yield: 34.7 mg (51%); white solid; mp 103–105 °C.

IR (film): 2854, 1595, 1409, 1321, 1175, 843, 597 cm<sup>-1</sup>.<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.74 (d, *J* = 8.2 Hz, 4 H), 7.68 (d, *J* = 8.3 Hz, 4 H), 7.61 (d, *J* = 8.2 Hz, 4 H), 7.39 (d, *J* = 8.1 Hz, 4 H), 2.50 (s, 6 H).<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 153.1, 146.2, 133.9, 133.4 (q, *J*<sub>C-F</sub> = 33.3 Hz, 2 C), 133.2, 129.9, 129.2, 128.6, 125.3 (q, *J*<sub>C-F</sub> = 3.5 Hz, 2 C), 123.6 (q, *J*<sub>C-F</sub> = 272.7 Hz, 2 C), 21.8.HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>30</sub>H<sub>23</sub>F<sub>6</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: 681.1059; found: 681.1066.**3,6-Bis(4-fluorophenyl)-1,4-ditosyl-1,4-dihydro-1,2,4,5-tetrazine (2c)**

Yield: 41.8 mg (72%); yellow solid; mp 99–101 °C.

IR (film): 3071, 2924, 2852, 1602, 1508, 1375, 1175, 841, 667, 586 cm<sup>-1</sup>.<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.76 (d, *J* = 8.2 Hz, 4 H), 7.52 (dd, *J* = 8.6 Hz, 5.3 Hz, 4 H), 7.38 (d, *J* = 8.2 Hz, 4 H), 7.10 (t, *J* = 8.5 Hz, 4 H), 2.48 (s, 6 H).<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 164.7 (d, *J*<sub>C-F</sub> = 253.1 Hz, 2 C), 153.9, 145.8, 134.2, 131.0 (d, *J*<sub>C-F</sub> = 8.9 Hz, 2 C), 129.7, 128.4, 125.7 (d, *J*<sub>C-F</sub> = 3.2 Hz, 2 C), 115.5 (d, *J*<sub>C-F</sub> = 22.2 Hz, 2 C), 21.6.HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>28</sub>H<sub>23</sub>F<sub>2</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: 581.1123; found: 581.1127.**3,6-Bis(4-chlorophenyl)-1,4-ditosyl-1,4-dihydro-1,2,4,5-tetrazine (2d)**

Yield: 46.5 mg (76%); yellow solid; mp 95–97 °C.

IR (film): 2921, 2850, 2360, 1595, 1375, 1172, 1092, 1013, 833, 661, 560 cm<sup>-1</sup>.<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.74 (d, *J* = 8.3 Hz, 4 H), 7.43 (d, *J* = 8.6 Hz, 4 H), 7.38 (d, *J* = 8.7 Hz, 8 H), 2.48 (s, 6 H).<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 153.8, 145.9, 138.0, 134.1, 130.1, 129.8, 128.6, 128.5, 128.1, 21.7.HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>28</sub>H<sub>23</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: 613.0532; found: 613.0536.**3,6-Bis(4-bromophenyl)-1,4-ditosyl-1,4-dihydro-1,2,4,5-tetrazine (2e)**

Yield: 35.0 mg (50%); white solid; mp 104–106 °C.

IR (film): 2923, 2852, 1592, 1375, 1173, 1074, 1010, 628, 521 cm<sup>-1</sup>.<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.74 (d, *J* = 8.2 Hz, 4 H), 7.54 (d, *J* = 8.4 Hz, 4 H), 7.36 (t, *J* = 8.0 Hz, 8 H), 2.48 (s, 6 H).<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 153.8, 145.9, 134.1, 131.6, 130.2, 129.8, 128.6, 128.5, 126.4, 21.7.HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>28</sub>H<sub>23</sub>Br<sub>2</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: 700.9522; found: 700.9526.**3,6-Diphenyl-1,4-ditosyl-1,4-dihydro-1,2,4,5-tetrazine (2f)**

Yield: 36.5 mg (67%); yellow solid; mp 103–105 °C.

IR (film): 2922, 2850, 1595, 1374, 1331, 1174, 597, 559 cm<sup>-1</sup>.<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.76 (d, *J* = 8.2 Hz, 4 H), 7.53–7.49 (m, 6 H), 7.41 (d, *J* = 7.2 Hz, 4 H), 7.36 (d, *J* = 8.2 Hz, 4 H), 2.48 (s, 6 H).<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 154.6, 149.1, 145.5, 134.4, 131.5, 129.7, 128.8, 128.6, 128.2, 21.7.HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>28</sub>H<sub>25</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: 545.1312; found: 545.1318.**3,6-Di-*p*-tolyl-1,4-ditosyl-1,4-dihydro-1,2,4,5-tetrazine (2g)**

Yield: 27.5 mg (48%); yellow solid; mp 166–168 °C.

IR (film): 2923, 2854, 1596, 1370, 1335, 1174, 817, 668, 589 cm<sup>-1</sup>.<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.78 (d, *J* = 8.3 Hz, 4 H), 7.42 (d, *J* = 8.0 Hz, 4 H), 7.37 (d, *J* = 8.1 Hz, 4 H), 7.21 (d, *J* = 8.0 Hz, 4 H), 2.47 (s, 6 H), 2.41 (s, 6 H).<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 154.9, 145.4, 142.0, 134.5, 129.6, 128.9, 128.7, 128.5, 126.8, 21.6, 21.5.HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>30</sub>H<sub>29</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: 573.1625; found: 573.1629.**3,6-Bis(4-methoxyphenyl)-1,4-ditosyl-1,4-dihydro-1,2,4,5-tetrazine (2h)**

Yield: 30.2 mg (50%); yellow solid; mp 153–155 °C.

IR (film): 2921, 2850, 1607, 1257, 1173, 667, 555 cm<sup>-1</sup>.<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.78 (d, *J* = 8.3 Hz, 4 H), 7.48 (d, *J* = 8.8 Hz, 4 H), 7.36 (d, *J* = 8.1 Hz, 4 H), 6.90 (d, *J* = 8.8 Hz, 4 H), 3.85 (s, 6 H), 2.47 (s, 6 H).<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 162.3, 155.1, 145.4, 134.7, 130.5, 129.6, 128.5, 121.8, 113.7, 55.3, 21.7.HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>30</sub>H<sub>29</sub>N<sub>4</sub>O<sub>6</sub>S<sub>2</sub>: 605.1523; found: 605.1526.**3,6-Bis(2-nitrophenyl)-1,4-ditosyl-1,4-dihydro-1,2,4,5-tetrazine (2i)**

Yield: 27.3 mg (43%); yellow solid; mp 103–105 °C.

IR (film): 2922, 2851, 1789, 1380, 1176, 761, 673, 563 cm<sup>-1</sup>.<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.89 (d, *J* = 8.3 Hz, 2 H), 7.79 (t, *J* = 7.8 Hz, 2 H), 7.66 (d, *J* = 7.8 Hz, 2 H), 7.54 (d, *J* = 8.0 Hz, 4 H), 7.42 (t, *J* = 7.5 Hz, 2 H), 7.18 (d, *J* = 8.0 Hz, 4 H), 2.35 (s, 6 H).<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 165.6, 149.6, 146.8, 135.8, 129.8, 129.4, 127.6, 125.8, 116.8, 114.6, 21.7.HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>28</sub>H<sub>23</sub>N<sub>6</sub>O<sub>8</sub>S<sub>2</sub>: 635.1013; found: 635.1019.**3,6-Bis(3-chlorophenyl)-1,4-ditosyl-1,4-dihydro-1,2,4,5-tetrazine (2j)**

Yield: 44.7 mg (73%); white solid; mp 98–100 °C.

IR (film): 2922, 2851, 2361, 1377, 1328, 1176, 1089, 797, 666, 597, 560 cm<sup>-1</sup>.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.74 (d,  $J$  = 8.2 Hz, 4 H), 7.48 (d,  $J$  = 7.8 Hz, 2 H), 7.43–7.35 (m, 10 H), 2.49 (s, 6 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 153.2, 146.0, 134.2, 134.0, 131.6, 131.2, 129.9, 129.6, 128.6, 128.5, 127.1, 21.7.

HRMS (ESI):  $m/z$  [ $M + H$ ] $^+$  calcd  $\text{C}_{28}\text{H}_{23}\text{Cl}_2\text{N}_4\text{O}_4\text{S}_2$ : 613.0532; found: 613.0539.

### 3,6-Bis(2,4-dichlorophenyl)-1,4-ditosyl-1,4-dihydro-1,2,4,5-tetrazine (2k)

Yield: 42.2 mg (62%); white solid; mp 172–174 °C.

IR (film): 3094, 2924, 1596, 1585, 1381, 1175, 1096, 814, 660, 567  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.51 (d,  $J$  = 7.8 Hz, 4 H), 7.41–7.34 (m, 6 H), 7.25 (d,  $J$  = 7.7 Hz, 4 H), 2.45 (s, 6 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 147.1, 145.6, 137.4, 134.8, 133.5, 133.3, 129.4, 129.3, 128.6, 126.9, 126.6, 21.6.

HRMS (ESI):  $m/z$  [ $M + H$ ] $^+$  calcd for  $\text{C}_{28}\text{H}_{21}\text{Cl}_4\text{N}_4\text{O}_4\text{S}_2$ : 680.9753; found: 680.9759.

### 3,6-Bis(3,4-dichlorophenyl)-1,4-ditosyl-1,4-dihydro-1,2,4,5-tetrazine (2l)

Yield: 63.3 mg (93%); yellow solid; mp 159–161 °C.

IR (film): 2921, 2850, 1382, 1329, 1174, 814, 662, 565  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.74 (d,  $J$  = 7.8 Hz, 4 H), 7.50 (d,  $J$  = 8.3 Hz, 2 H), 7.44–7.35 (m, 8 H), 2.49 (s, 6 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 152.6, 146.2, 136.2, 133.8, 132.7, 130.46, 130.40, 130.0, 129.3, 128.5, 127.9, 21.7.

HRMS (ESI):  $m/z$  [ $M + H$ ] $^+$  calcd for  $\text{C}_{28}\text{H}_{21}\text{Cl}_4\text{N}_4\text{O}_4\text{S}_2$ : 680.9753; found: 680.9757.

### 3,6-Bis(2,3-dichlorophenyl)-1,4-ditosyl-1,4-dihydro-1,2,4,5-tetrazine (2m)

Yield: 46.3 mg (68%); white solid; mp 202–204 °C.

IR (film): 2924, 2853, 1597, 1381, 1177, 1135, 602, 564  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.59 (d,  $J$  = 8.0 Hz, 2 H), 7.50 (d,  $J$  = 7.6 Hz, 2 H), 7.36 (d,  $J$  = 7.9 Hz, 2 H), 7.32 (d,  $J$  = 8.4 Hz, 4 H), 7.16 (d,  $J$  = 7.9 Hz, 4 H), 2.41 (s, 6 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 146.7, 145.6, 133.2, 132.9, 132.5, 132.3, 131.8, 129.5, 129.3, 128.4, 127.2, 21.6.

HRMS (ESI):  $m/z$  [ $M + H$ ] $^+$  calcd for  $\text{C}_{28}\text{H}_{21}\text{Cl}_4\text{N}_4\text{O}_4\text{S}_2$ : 680.9753; found: 680.9756.

### 3,6-Bis(4-nitrophenyl)-1,4-bis(phenylsulfonyl)-1,4-dihydro-1,2,4,5-tetrazine (2n)

Yield: 40.6 mg (67%); yellow solid; mp 102–104 °C.

IR (film): 2919, 2849, 1523, 1332, 1185, 1175, 855, 608  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 8.34 (d,  $J$  = 8.3 Hz, 4 H), 7.91 (t,  $J$  = 6.9 Hz, 2 H), 7.80–7.73 (m, 12 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 151.4, 149.2, 135.5, 135.3, 135.1, 129.9, 129.8, 128.1, 123.5.

HRMS (ESI):  $m/z$  [ $M + H$ ] $^+$  calcd for  $\text{C}_{26}\text{H}_{19}\text{N}_6\text{O}_8\text{S}_2$ : 607.0700; found: 607.0704.

### 1,4-Bis[(4-methoxyphenyl)sulfonyl]-3,6-bis(4-nitrophenyl)-1,4-dihydro-1,2,4,5-tetrazine (2o)

Yield: 42.0 mg (63%); yellow solid; mp 152–154 °C.

IR (film): 2919, 2850, 2361, 1167, 855, 600, 560  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 8.35 (d,  $J$  = 8.8 Hz, 4 H), 7.73 (t,  $J$  = 9.3 Hz, 8 H), 7.25 (d,  $J$  = 9.0 Hz, 4 H), 3.91 (s, 6 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 164.5, 151.3, 149.1, 135.4, 130.7, 129.8, 126.3, 123.5, 115.1, 56.0.

HRMS (ESI):  $m/z$  [ $M + H$ ] $^+$  calcd for  $\text{C}_{28}\text{H}_{23}\text{N}_6\text{O}_{10}\text{S}_2$ : 667.0912; found: 667.0916.

### 1,4-Bis(mesitylsulfonyl)-3,6-bis(4-nitrophenyl)-1,4-dihydro-1,2,4,5-tetrazine (2p)

Yield: 52.4 mg (76%); yellow solid; mp 79–81 °C.

IR (film): 2978, 2940, 1600, 1525, 1348, 1333, 1173, 855, 606  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.25 (d,  $J$  = 8.6 Hz, 4 H), 7.58 (d,  $J$  = 8.6 Hz, 4 H), 7.09 (s, 4 H), 2.51 (s, 12 H), 2.42 (s, 6 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 149.9, 149.4, 145.2, 141.5, 135.6, 132.1, 130.6, 129.8, 123.5, 26.8, 23.1, 21.2.

HRMS (ESI):  $m/z$  [ $M + H$ ] $^+$  calcd for  $\text{C}_{32}\text{H}_{31}\text{N}_6\text{O}_8\text{S}_2$ : 691.1639; found: 691.1643.

### 3,6-Bis(4-nitrophenyl)-1,2,4,5-tetrazine (6a)

Yield: 59.6 mg (92%); purple solid; mp 234–236 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.90 (d,  $J$  = 8.6 Hz, 4 H), 8.50 (d,  $J$  = 8.6 Hz, 4 H).

The data for this product correspond with the published data.<sup>9d</sup>

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## Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0039-1690712>.

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- (14) CCDC 1939331 (**2c**) and CCDC 1939330 (**2e**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/getstructures](http://www.ccdc.cam.ac.uk/getstructures).