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### Solid-Phase Synthesis of 2-Arylamino-5-(4-hydroxyphenyl)-1,3,4-thiadiazole Derivatives Based on Resin-Bound Acylhydrazines

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## SOLID-PHASE SYNTHESIS OF 2-ARYLAMINO-5-(4-HYDROXYPHENYL)-1,3,4-THIADIAZOLE DERIVATIVES BASED ON RESIN-BOUND ACYLHYDRAZINES

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*A highly efficient, solid-phase synthesis of 2-arylamino-5-(4-hydroxy-phenyl)-1,3,4-thiadiazole derivatives under mild conditions has been developed. The 1,3,4-thiadiazole derivatives were synthesized from resin-bound acylhydrazines in several steps, which gave 78–88% overall yields and excellent purities of the products.*

**Keywords** Resin-bound acylhydrazine; solid phase synthesis; 1,3,4-thiadiazole

### INTRODUCTION

Five-membered ring heterocyclic compounds are commonly used scaffolds on which pharmacophores are arranged to provide potent and selective drugs, which serve as the core components of a large number of substances that possess a wide range of interesting biological activities. Among five-membered rings, 2,5-disubstituted 1,3,4-thiadiazoles and their derivatives appear pharmacologically relevant since they are found in many bioactive compounds.<sup>1</sup> 1,3,4-Thiadiazoles and related compounds have attracted significant interest in medicinal chemistry and many fields of technology. Thiadiazole derivatives are found to exhibit antitumor,<sup>2</sup> hypoglycemic,<sup>3</sup> anticonvulsant,<sup>4</sup> hypotensive,<sup>5</sup> antiproliferative,<sup>6</sup> and antitubercular<sup>7</sup> activities. Some of the technological applications involve dyes,<sup>8</sup> lubricating compositions,<sup>9</sup> optically active liquid crystals,<sup>10</sup> and photographic materials.<sup>11</sup>

There is a large number of methods for the synthesis of 2-amino-5-substituted 1,3,4-thiadiazoles with variations. The most universal one is a two-stage method consisting of acylation of a thiosemicarbazide using carboxylic acid chlorides and subsequent cyclization of the intermediate acylthiosemicarbazides. Various dehydrating agents are used in commonly applied methods: sulfuric acid, phosphorus oxychloride, benzoyl chloride, and acetyl chloride.<sup>12–17</sup> Acylthiosemicarbazides can be also obtained in the reaction of acylhydrazine with isothiocyanates. Ring closure to the thiadiazole occurs by heating with

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sulfuric or methanesulfonic acid.<sup>18, 19</sup> Oxidative cyclization of 1-thioaroylsemicarbazides with bromine or hydrogen peroxide<sup>20</sup> or of thiosemicarbazones with iron(III) chloride gave also the described compounds.<sup>21, 22</sup> For the synthesis of 1,3,4-thiadiazole rings substituted by other than amine groups, thiohydrazides<sup>23</sup> and thioacylamidrazones<sup>24</sup> are commonly applied. Sulfur-containing reagents are used for analogous cyclizations of amidrazones.<sup>25</sup> In the reaction of sulfinyl-bis(2,4-dihydroxythiobenzoyl) (STB) with *N*<sup>3</sup>-substituted amidrazones, the linear products, *N*<sup>1</sup>-thioacyl derivatives, and the cyclic products, 2,5-disubstituted 1,3,4-thiadiazoles, with a considerably higher fungistatic activity, were obtained.<sup>26, 27</sup> Many of the solution-phase methodologies described above possess important drawbacks such as long reaction times, poor yields, and exhaustive purification protocols.

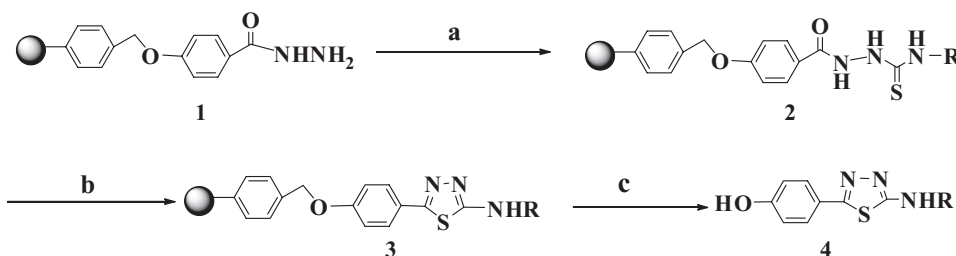
With the availability of automated techniques, the solid phase synthesis of small organic molecules is becoming a fundamental method for the rapid and easy preparation of libraries of organic compounds in order to accelerate the drug discovery process.<sup>28</sup> This approach facilitates the rapid synthesis of a large number of compounds in a short time frame and facilitates their use in high throughput screening. Solid-phase organic synthesis is another synthetic route to these compounds, which has been recently developed. Solid-phase syntheses of 5-acylamino-2-alkylamino-1,3,4-thiadiazoles are developed based on cyclization of resin-bound thiosemicarbazone using iron (III) chloride.<sup>29</sup> Hwang et al.<sup>30</sup> reported cyclodehydration of the acyldithiocarbazate resin, followed by oxidation and treatment with amines, to give the 5-amino-1,3,4-thiadiazoles.

In continuation of our efforts to develop novel and efficient polymer-supported routes leading to heterocyclic derivatives with potentially attractive pharmacological properties, we have recently reported an easy method for the preparation of polymer-supported acylhydrazines on Merrifield resin.<sup>31a</sup> We have also reported the synthesis of 1,3,4-oxadiazoline-5-thiones,<sup>31a</sup> 1,2,3-thiadiazoles,<sup>31b</sup> and 4,5-disubstituted 1,2,4-triazol-3-one derivatives<sup>31c</sup> from resin-bound acylhydrazines. As the phenol scaffold has important biological activity, the presence of a 4-hydroxyphenyl substituent in the molecule is responsible first of all for its amphiphilic character, we wanted to prepare the 2-arylamino-5-(4-hydroxyphenyl)-1,3,4-thiadiazole derivatives based on resin-bound acylhydrazines.

## RESULTS AND DISCUSSION

In this article, we extend our chemistry to solid-phase synthesis of 2-arylamino-5-(4-hydroxyphenyl)-1,3,4-thiadiazole derivatives.

Scheme 1 shows the synthetic route of 2-arylamino-5-(4-hydroxy-phenyl)-1,3,4-thiadiazole derivatives. We have prepared resin-bound acylhydrazine **1** from the



**Scheme 1** (a) RNCS, EtOH, reflux, 6 h; (b) conc. H<sub>2</sub>SO<sub>4</sub>, r.t. 4 h; (c) TFA/CH<sub>2</sub>Cl<sub>2</sub>.

**Table I** Solid-phase synthesis of 2-arylamino-5-(4-hydroxyphenyl)-1,3,4-thiadiazole derivatives

Entry	Product	R	Yield <sup>a</sup> (%)	Purity <sup>b</sup> (%)
1	4a	4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>	84	95
2	4b	Ph	86.9	90
3	4c	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	88.5	92
4	4d	p-CF <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>	86	86
5	4e	2,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	79	88
6	4f	2-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	85.4	95
7	4g	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	80	92

<sup>a</sup>Yield of crude product based on the loading of acylhydrazine resin **1**.<sup>b</sup>Determined by HPLC analysis (area%).

Merrifield resin according to our previously reported method.<sup>31a</sup> The acylhydrazine resin **1** was reacted with excessive aryl/alkyl isothiocyanates in ethanol to give the corresponding resin-bound thiosemicarbazides **2**. After acid-catalyzed ring closures of the corresponding aroylthiosemicarbazides resin **2**, the resin **3** was obtained. The desired 2-arylamino-5-(4-hydroxyphenyl)-1,3,4-thiadiazole derivatives **4** were released at TFA/DCM cleavage for 4 h in high yield and purity, and were characterized by spectroscopic methods. The results are summarized in Table I.

The successful formation of resin **2** was supported by comparison of its FT-IR spectrum (KBr pellet) with resin **1**. The N-H stretching bands at 3429, 3318 cm<sup>-1</sup> shifted to 3298 and 3247 cm<sup>-1</sup> and a strong C=O stretching band at 1676 cm<sup>-1</sup> for aroylsemicarbazide resin **2** appeared, which is different from the C=O signal of acylhydrazine resins at 1630 cm<sup>-1</sup>. When the resin **2** was converted into the resin **3**, the strong carbonyl peak at 1676 cm<sup>-1</sup> disappeared, and the signal of N-H shifted to 3240 cm<sup>-1</sup>. When the resin **3** was cleaved by TFA/DCM, the product **4** was obtained in good yields and high purity.

Using this methodology, we have synthesized a representative set of 2-arylamino-5-(4-hydroxyphenyl)-1,3,4-thiadiazole derivatives **4** (Table I) in 79–89% overall yield, indicating a good yield for each step of the reaction.

In summary, we have studied and developed a new strategy for the preparation of 2-arylamino-5-(4-hydroxyphenyl)-1,3,4-thiadiazole derivatives on solid support. The use of resin-bound acylhydrazines in the reaction benefits the solid-phase synthetic route because it not only provides a short synthetic route to the desired products but its chemical versatility also adds to the diversity of the library. The 2-arylamino-5-(4-hydroxyphenyl)-1,3,4-thiadiazole derivatives were synthesized in several steps providing 79–88% overall yields and excellent purity. This synthetic methodology is ideally suitable for the high throughput synthesis of drug libraries for potential drug discovery because all the reactions were carried out under mild conditions. Further work is in progress on the solid-phase synthesis of heterocyclic compounds via the resin-bound acylhydrazines.

## EXPERIMENTAL

Starting materials were obtained from commercial suppliers and were used without further purification. Solvents were distilled before use; CH<sub>2</sub>Cl<sub>2</sub> was distilled from CaH<sub>2</sub>. Merrifield resin (100–200 mesh, cross-linked with 1% divinylbenzene, loading

1.95 mmol/g Cl) was purchased from commercial sources (Nankai University). Acylhydrazine resin **1** was prepared from the Merrifield resin according to our previously reported method.<sup>31a</sup>

<sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) spectra were recorded on a Bruker Avance (400 MHz) spectrometer, using DMSO-*d*<sub>6</sub> as the solvent and TMS as internal standard. MS spectra (EI, 70 eV) were recorded on a HP5989B mass spectrometer. IR spectra were recorded on a Bruker Vector 22 spectrophotometer. Elemental analyses were performed on a Flash EA1112 instrument. High-performance liquid chromatography (HPLC) was performed on an Agilent 1100 [column, Eclipse XDB-C18 5  $\mu$ m, 4.6–150 mm; mobile phase, MeOH/H<sub>2</sub>O, 80/20 (v/v); flow rate, 1.0 mL/min; detector, UV 254 nm]. The samples were further purified by preparative thin-layer chromatography (PTLC) for <sup>13</sup>C NMR and microanalyses.

### General Procedure for the Synthesis of 2-Arylamino-5-(4-hydroxyphenyl)-1,3,4-thiadiazole Derivatives

To the mixture of the acylhydrazine resin **1** (0.5 g, loading 1.59 mmol/g, based on N microanalysis) in absolute EtOH (5 mL), phenyl isothiocyanate (0.324 g, 2.4 mmol) was added. Then the mixture was stirred and refluxed for 6 h. The resin was filtered and washed with EtOH (3  $\times$  5 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  5 mL) to remove contaminated species and then dried to afford the resin **2**.

Resin **2** was added to 3 mL concentrated H<sub>2</sub>SO<sub>4</sub> (98%). The mixture was stirred at room temperature for 4 h. Then it was poured into ice-water and filtered, and the resin was washed with H<sub>2</sub>O (3  $\times$  10 mL), EtOH (3  $\times$  5 mL), and CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  5 mL) and dried to afford the resin **3**.

The resin **3** was well swollen in 3 mL CH<sub>2</sub>Cl<sub>2</sub>, and then 0.5 mL TFA was added. The mixture was stirred at room temperature for 4 h and then filtered. The resin was washed completely with EtOH (3  $\times$  5 mL) and acetone (3  $\times$  5 mL). The filtrate was combined to afford the crude product **4** by evaporation.

All compounds gave satisfactory <sup>1</sup>H NMR (400 MHz), <sup>13</sup>CNMR (100 MHz), IR, and MS spectra.

#### 5-(4-Hydroxyphenyl)-2-(4-methoxyphenylamino)-1,3,4-thiadiazole (4a)

Mp 208–210°C. <sup>1</sup>H NMR:  $\delta$  3.73 (s, 3H), 6.86 (d, 2H, *J* = 8.8 Hz), 6.93 (d, 2H, *J* = 8.8 Hz), 7.53 (d, 2H, *J* = 8.8 Hz), 7.64 (d, 2H, *J* = 8.8 Hz), 10.01 (s, 1H), 10.20 (s, 1H). <sup>13</sup>C NMR:  $\delta$  59.73, 118.80, 120.43, 123.69, 125.98, 132.83, 138.72, 159.00, 161.62, 163.73, 168.23. MS (*m/e* %): 299 (100), 284 (25), 165 (17). IR: 3186, 3063, 2947, 1606, 1574, 1511, 1464, 1435, 1280, 1247 cm<sup>-1</sup>. Calcd. for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>S: C, 60.18; H, 4.38; N, 14.04; S, 10.71; Found: C, 60.45; H, 4.51; N, 13.73.

#### 5-(4-Hydroxyphenyl)-2-phenylamino-1,3,4-thiadiazole (4b)

Mp 246–248°C. <sup>1</sup>H NMR:  $\delta$  6.85 (d, 2H, *J* = 8.0 Hz), 7.14 (d, 2H, *J* = 8.0 Hz), 7.52 (m, 3H), 7.88 (m, 2H), 10.05 (s, 1H), 10.45 (s, 1H). <sup>13</sup>C NMR:  $\delta$  120.50, 120.93, 125.64, 131.14, 133.02, 145.27, 145.97, 162.67, 164.01, 167.50. MS (*m/e* %): 269 (100),

150 (53), 134 (59), 91 (44). IR: 3252, 3132, 3065, 1602, 1555, 1500, 1484  $\text{cm}^{-1}$ . Calcd. for  $\text{C}_{14}\text{H}_{11}\text{N}_3\text{OS}$ : C, 62.43; H, 4.12; N, 15.60; S, 11.91; Found: C, 62.71; H, 4.36; N, 15.78.

#### 5-(4-Hydroxyphenyl)-2-(4-methylphenylamino)-1,3,4-thiadiazole (4c)

Mp 168–170°C.  $^1\text{H}$  NMR:  $\delta$  2.27 (s, 3H), 6.86 (d, 2H,  $J = 7.6$  Hz), 7.14 (d, 2H,  $J = 7.6$  Hz), 7.50 (d, 2H,  $J = 8.0$  Hz), 7.65 (d, 2H,  $J = 8.0$  Hz), 9.97 (s, 2H), 10.302 (s, 1H).  $^{13}\text{C}$  NMR:  $\delta$  24.85, 120.45, 122.02, 125.88, 132.87, 133.98, 135.33, 142.78, 161.98, 163.80, 167.84. MS (m/e%): 283 (63), 164 (38), 134 (100). IR: 3250, 3210, 1620, 685  $\text{cm}^{-1}$ . Calcd. for  $\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS}$ : C, 63.58; H, 4.62; N, 14.83; S, 11.32; Found: C, 63.39; H, 4.54; N, 14.67.

#### 5-(4-Hydroxyphenyl)-2-(4-trifluoromethoxyphenylamino)-1,3,4-thiadiazole (4d)

Mp 206–208°C.  $^1\text{H}$  NMR:  $\delta$  6.88 (d, 2H,  $J = 8.0$  Hz), 7.36 (d, 2H,  $J = 8.0$  Hz), 7.65 (d, 2H,  $J = 8.0$  Hz), 7.81 (d, 2H,  $J = 8.0$  Hz), 10.34 (s, 2H), 11.0 (s, 1H).  $^{13}\text{C}$  NMR:  $\delta$  120.54, 122.96, 123.45, 125.66, 125.99, 126.45, 132.93, 144.53, 146.80, 162.94, 164.15, 167.20. MS (m/e%): 353 (100). IR: 3421, 3216, 2925, 1610, 1546, 1510, 1461, 1433, 1384, 1264  $\text{cm}^{-1}$ . Calcd. for  $\text{C}_{15}\text{H}_{10}\text{F}_3\text{N}_3\text{O}_2\text{S}$ : C, 50.99; H, 2.85; F, 16.13; N, 11.89; S, 9.08; Found: C, 50.78; H, 2.66; N, 11.83.

#### 5-(4-Hydroxyphenyl)-2-(2,4-difluorophenylamino)-1,3,4-thiadiazole (4e)

Mp 214–216°C.  $^1\text{H}$  NMR:  $\delta$  6.86 (d, 2H,  $J = 8.0$  Hz), 7.14 (m, 1H), 7.32 (m, 1H), 7.63 (d, 2H,  $J = 8.0$  Hz), 8.32 (m, 1H), 9.89 (s, 1H), 10.29 (s, 1H).  $^{13}\text{C}$  NMR: 108.26, 108.50, 115.50, 115.74, 120.51, 125.49, 126.07, 130.05, 132.80, 163.37, 164.29, 167.85. MS (m/e%): 305 (100), 286 (32), 246 (17), 134 (53). IR: 3419, 3250, 2925, 1607, 1544, 1510, 1466, 1383, 1308  $\text{cm}^{-1}$ . Calcd. for  $\text{C}_{14}\text{H}_9\text{F}_2\text{N}_3\text{OS}$ : C, 55.08; H, 2.97; N, 13.76; S, 10.50; Found: C, 54.82; H, 3.12; N, 13.65.

#### 5-(4-Hydroxyphenyl)-2-(2-methylphenylamino)-1,3,4-thiadiazole (4f)

Mp 232–234°C.  $^1\text{H}$  NMR:  $\delta$  2.28 (s, 3H), 6.85 (d, 2H,  $J = 8.4$  Hz), 7.02 (m, 1H), 7.21 (m, 1H), 7.61 (d, 2H,  $J = 8.4$  Hz), 7.86 (m, 2H,  $J = 7.6$  Hz), 9.59 (s, 1H), 10.31 (s, 1H).  $^{13}\text{C}$  NMR:  $\delta$  22.69, 120.49, 125.76, 125.87, 128.35, 131.14, 132.75, 133.59, 135.19, 143.82, 162.34, 164.00, 169.71. MS (m/e%): 283 (69), 164 (100), 149 (78), 131 (54), 121 (60). IR: 3188, 3065, 2952, 1607, 1586, 1558, 1413, 1382, 1278  $\text{cm}^{-1}$ . Calcd. for  $\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS}$ : C, 63.58; H, 4.62; N, 14.83; S, 11.32; Found: C, 63.76; H, 4.53; N, 14.70.

#### 5-(4-Hydroxyphenyl)-2-benzylamino-1,3,4-thiadiazole (4g)

Mp 238–240°C.  $^1\text{H}$  NMR:  $\delta$  3.27 (s, 2H), 6.84 (d, 2H,  $J = 8.4$  Hz), 6.93 (m, 1H), 7.55 (m, 2H), 7.62 (d, 2H,  $J = 8.4$  Hz), 7.86 (m, 2H), 9.59 (s, 1H), 10.31 (s, 1H).  $^{13}\text{C}$  NMR:  $\delta$  20.32, 117.71, 120.49, 125.76, 129.45, 130.86, 131.14, 132.75, 138.23, 162.34, 164.00, 169.71. MS (m/e%): 283 ( $\text{M}^+$ , 100), 192 (60), 121 (40). IR: 3186, 3058, 2953, 1606, 1588,

1382, 1278  $\text{cm}^{-1}$ . Calcd. for  $\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS}$ : C, 63.58; H, 4.62; N, 14.83; S, 11.32; Found: C, 63.42; H, 4.73; N, 14.88.

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