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# Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Biological Activities of Some Novel Triazolothiadiazines and Schiff Bases Derived from 4-Amino-3-(4hydroxyphenyl)-1H-1,2,4-triazole-5(4H)thione

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#### SYNTHESIS AND BIOLOGICAL ACTIVITIES OF SOME NOVEL TRIAZOLOTHIADIAZINES AND SCHIFF BASES DERIVED FROM 4-AMINO-3-(4-HYDROXYPHENYL)-1*H*-1,2,4-TRIAZOLE-5(4*H*)-THIONE

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A series of novel 4-(6-substituted-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)phenols (5a-5n) and (E)-4-substituted-3-(4-hydroxyphenyl)-1H-1,2,4-triazole-5(4H)-thiones (6a-6h) has been synthesized in high yields. The structures of all the title compounds have been determined by elemental analysis, IR, MS, <sup>1</sup>H NMR, and <sup>13</sup>C NMR, and the compound 5a was investigated with X-ray crystallography (CCDC No. 666889). Most of the title compounds possessed high plant growth-regulating activities.

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements to view the free supplemental file.

**Keywords** Biological activities; hydroxyphenyl; Schiff base; synthesis; 1,2,4-triazoles; triazolothiadiazines

#### INTRODUCTION

The broad biological and pharmacological activities of various thiadiazines fused with an *s*-triazole ring have been extensively studied, and *s*-triazolo[3,4-*b*][1,3,4]thiadiazines especially have been shown to possess a wide spectrum of bioactivities<sup>1</sup> such as analgesic,<sup>2</sup> anthelmintic,<sup>3</sup> antitubercular,<sup>4</sup> plant-growth regulating,<sup>5</sup> antiviral,<sup>6</sup> antifungal,<sup>7</sup> and anticancer properties.<sup>8</sup> In a previous article, we have reported the synthesis of some compounds containing the thiadiazine ring, which possessed moderate regulating effects on the growth of mung bean sprouts.<sup>9</sup> Recently, progress has been made into combining the 1,2,4triazole nucleus with *N*-bridged heterocycles.<sup>10–13</sup> As a continuation of our research on the synthesis and biological properties of triazole derivatives, we have synthesized a series of substituted fused triazole systems containing a 4-hydroxyphenyl group and determined the plant growth–regulating effects of some title compounds.

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#### **RESULTS AND DISCUSSION**

All the compounds have been characterized by elemental analysis, <sup>1</sup>H NMR, and <sup>13</sup>C NMR. The signals at  $\delta$  4.29–4.50 ppm in the <sup>1</sup>H NMR and 20.29–25.77 in the <sup>13</sup>C NMR spectra that are attributed to SCH<sub>2</sub> (SCH for **5n**) clearly confirm that the thiadiazine rings are all formed. In the <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra, the peaks of the N=CH proton at 9.36–10.08 ppm and the corresponding carbon at about 150 ppm correspond to the above-mentioned open chain structure. When looking at the <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of the fluoro-substituted compounds **5a**, **5f**, **5m**, **6b**, and **6c**, it should be noted that the second-order pattern representative of a substituted phenyl ring is further complicated due to the presence of the couplings with <sup>19</sup>F.

The title compounds have been investigated for their biological activities in regulating the growth of wheat and radishes using sterilized distilled water as a reference (see Table S1, available online in the Supplemental Materials).

Ethyl 4-hydroxybenzoate **1** reacted with 85% hydrazine hydrate to give the corresponding hydrazide **2**, which was heated with carbon disulfide in the presence of absolute ethanol and potassium hydroxide to afford the intermediate potassium acylhydrazine dithioformate **3** (Scheme 1). This salt underwent ring closure with an excess of 85% hydrazine hydrate, and then 4-amino-3-(4-hydroxyphenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione **4** was obtained. The appropriate substituted  $\omega$ -bromoacetophenones were added into a solution of **4** in absolute ethanol and 4-(6-substituted-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)phenol **5a**–**5m** were formed (Scheme 2). The reaction of the triazole **4** and the appropriate benzaldehyde in refluxing absolute ethanol for about 4 h, while maintaining a pH value at 5–6 during the reaction, afforded Schiff bases **6a–6h** (Scheme 2). After concentration under reduced pressure, the crude products were recrystallized from alcohol to afford the pure Schiff bases.



Scheme 1 The synthesis of 4-amino-3-(4-hydroxyphenyl)-1H-1,2,4-triazole-5(4H)-thione 4.

Under the same conditions described for 5a-5m, 4-amino-3-(4-hydroxyphenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione **4** reacted with 2-bromocyclohexanone to yield compound **5**n, which contains four rings (Scheme 3).

The purified product **5a** was dissolved in absolute acetic acid and kept at room temperature for 20 days, and the single crystals were formed, but it is very interesting that the crystals of **5a** separated out in a form of an acetate coordinate (CCDC No. 666889).





Scheme 3 The reaction of 4 and 2-bromocyclohexanone.

Unfortunately the low quality of the crystal led to an unacceptable R factor (>0.100), so it is not appropriate to discuss the structure in detail or present a table of bond lengths/angles, but we do present the result of the X-ray structure in Figure 1 to show the novel nature of the compounds formed in this synthesis.



Figure 1 ORTEP drawing of the compound 5a showing the atom numbering scheme.

#### **EXPERIMENTAL**

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker Advance-300 NMR spectrometer in DMSO- $d_6$  solution using TMS as internal reference. Carbon, hydrogen, and nitrogen analyses were determined on a Flash-1112 series elemental analyzer. IR spectra were recorded on a Nicolet 670FT-IR using the smart OMNI-Sampler in the range 4000–400 cm<sup>-1</sup>. MS spectra were recorded on an Agilent 1100 LC/MS. Melting points were determined on an XT-4 melting point apparatus and were uncorrected. Melting points of these newly synthesized compounds are much higher than those congeneric ones which have no hydrogen bonds. The crystal structure was determined on Bruker APEX areadetector diffractometer. All chemicals and solvents used were of AR grade.

4-Amino-3-(4-hydroxyphenyl)-1*H*-1,2,4-triazole-5(4H)-thione, whose tautomer is 4-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)phenol, was prepared from ethyl 4-hydroxybenzoate **1** (Scheme 1), following the literature of Zhang et al.<sup>14</sup>.

# Synthesis of 4-(6-Substituted-7H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazin-3-yl)phenol (5a–5m)

The appropriate substituted  $\omega$ -bromoacetophenone (0.02 mol) was added into a solution of 4 (0.02 mol) in absolute ethanol (20 mL), and the mixture was refluxed on an oil-bath for about 2 h. After concentration under reduced pressure, the crude products were recrystallized from ethanol to afford the compounds **5a–5m**. In the same conditions, 4 (0.02 mol) reacted with 2-bromocyclohexanone (0.02 mol) to give compound **5n**. An example of

the characterization is provided for compound **5a**; the complete characterization data can be found in the Supplemental Materials (available online).

**5a: 4-(6-(Trifluoromethyl)-7***H***-[<b>1**,**2**,**4**]triazolo[**3**,**4**-*b*][**1**,**3**,**4**]thiadiazin-**3**-*y*]) phenol. Yield: 88.0%; Mp 258–260°C; IR (cm<sup>-1</sup>): 3428 (OH), 3052 (ArH), 1523 (C=N), 1470 (N=C-S), 1102 (C-F), 687 (C-S-C); MS-ESI (*m*/*z*): 299.3 (M-1); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, 25°C, TMS)  $\delta$  (ppm) = 10.11 (s, 1H, OH), 7.74 (d, *J* = 8.6 Hz, 2H, ArH), 6.92 (d, *J* = 8.6 Hz, 2H, ArH), 4.29 (s, 2H, SCH<sub>2</sub>); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>)  $\delta$ (ppm) = 159.92 (1C, *C*-OH), 152.16 (1C, CH<sub>2</sub>*C*=N), 145.46 (1C, N-*C*=N), 141.24 (1C, S-*C*=N), 129.82 (2C, aromatic *C*H), 121.38 (q, *J* = 271.2 Hz, 1C, *C*F<sub>3</sub>), 117.31 (1C, aromatic quaternary *C*), 115.80 (2C, aromatic *C*H), 20.29 (1C, S*C*H<sub>2</sub>); Elemental anal. calc. (%) for C<sub>11</sub>H<sub>7</sub>F<sub>3</sub>N<sub>4</sub>OS (300.26): C 44.00, H 2.35, N 18.66; Found: C 44.15, H 2.22, N 18.54.

#### Synthesis of (E)-3-(4-hydroxyphenyl)-4-arylideneamino-1H-1,2,4triazole-5(4H)-thiones (6a–6i)

To a solution of compound 4 (0.02 mol) dissolved in absolute alcohol (20 mL), the appropriate benzaldehyde (0.02 mol) was added. The mixture was refluxed for 4 h with stirring. The solid that was obtained upon cooling was filtered, washed with cold water, dried, and recrystallized from alcohol to give the Schiff bases **6a–6h**. An example of the characterization is provided here for **6a**; the complete characterization data can be found in the Supplemental Materials (available online).

**6a:** (*E*)-4-(Benzylideneamino)-3-(4-hydroxyphenyl)-1*H*-1,2,4-triazole-5 (4*H*)-thione. Yield: 83.2%; Mp 247–249°C; IR (cm<sup>-1</sup>): 3425 (OH), 3324 (NH), 3015 (ArH), 1536 (C=N), 1478 (N–C=S), 1276 (C=S); MS-ESI (*m/z*): 295.3 (M–1); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, 25°C, TMS) δ (ppm) = 14.09 (s, 1H, NH),10.09 (s, 1H, OH), 10.07 (s, 1H, CH), 8.02–7.97 (m, 2H, ArH), 7.71–7.66 (m, 2H, ArH), 7.43–7.35 (m, 3H, ArH), 6.89–6.86 (m, 2H, ArH); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ (ppm) = 163.56 (1C, CH=N), 161.94 (1C, C=S), 159.75 (1C, C-OH), 149.19 (1C, N–C=N), 135.14 (1C, aromatic quaternary *C*), 130.25 (1C, aromatic *C*H), 127.64 (2C, aromatic *C*H), 125.51 (2C, aromatic *C*H), 125.48 (2C, aromatic *C*H), 120.05 (2C, aromatic *C*H), 115.58 (2C, aromatic *C*H); Elemental anal. calc. (%) for C<sub>15</sub>H<sub>12</sub>N<sub>4</sub>OS (296.35): C 60.79, H 4.08, N 18.91; Found: C 60.54, H 4.13, N 18.76.

#### REFERENCES

- A. R. Prasad, T. Ramalingam, A. B. Rao, P.V. Daiwan, and P. B. Sattur, *Eur. J. Med. Chem.*, 24, 199 (1989).
- 2. G. Turan-Zitouni, Z. A. Kaplancikli, K. Erol, and F. S. Kiliç, Farmaco, 54, 218 (1999).
- 3. B. A. Nadkarni, V. R. Kamat, and B. G. Khadse, Arzneim. Forsch., 51, 569 (2001).
- 4. R. H. Udupi, P. Purushottamachar, and A. R. Bhat, Indian J. Heterocycl., 9, 287 (2000).
- 5. V. K. Chadha, N. S. Ranwa, and P. K. Dadheech, J. Phytol. Res., 11, 201 (1998).
- S. S. Papakonstantinou-Garoufalias, E. Tani, O. Todoulou, A Papadaki-Valiraki, E. Filippatos, E. D. Clercq, and P. N. Kourounakis, *J.Pharm. Pharmacol.*, 50, 117 (1998).
- Y. A. Ammar, M. M. Ghorab, A. M. S. El-Sharief, and S. I. Mohamed, *Heteroatom Chem.*, 13, 199 (2002).
- 8. B. S. Holla, B. Veerendra, M. K. Shivananda, and B. Poojary, Eur. J. Med. Chem., 38, 759 (2003).

#### Q. DING ET AL.

- X. Q. Ye, L. X. Zhang, A. J. Zhang, X. X. Chen, and Z. Y. Zhang, *Chem. Res. Chin. Univ.*, 18, 411 (2002).
- M. Li, F. K. Yang, L. R. Wen, G. Q. Li, and S. S. Zhang, *Chin. J. Org. Chem. (in Chinese)*, 21, 672 (2001).
- 11. A. J. Zhang, L. X. Zhang, Y. Xiong, D. J. Xu, and X. J. Li, *Chin. J. Org. Chem. (in Chinese)*, 23, 456 (2003).
- 12. M. S. Chande, B. M. Karnik, and N. Ganguly, J. Indian Chem. Soc., 67, 695 (1990).
- J. U. V. Laddi, M. B. Talawar, S. R. Desai, R. S. Bennur, and S. C. Bennur, *Indian J. Chem.*, 40B, 828 (2001).
- L. X. Zhang, A. J. Zhang, M. L. Hu, X. X. Lei, Z. X. Xu, and Z. Y. Zhang, *Acta Chim. Sinica*, 61, 917 (2003).

572