FUNGICIDAL ACTIVITIES OF 1,4-BIS[(3-ARYL)-S-TRIAZOLO[3,4-*B*]-[1,3,4]THIADIAZOLE-6-YL]NAPHTHALENES

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Abstract: 1,4-Bis[(3-aryl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]naphthalenes **2** were synthesized in high yields by reaction of 3-aryl 4-amino-5-mercapto-1,2,4-triazole **1** with 1,4-naphthalic acid in the presence of $POCl_3$ and tetrabutylammonium iodide as catalyst. The structures have been established on the basis of elemental analysis and spectral date. The preliminary antibacterial tests showed that **2b**, **2c** and **2d** exhibited good fungicidal activities against *Cerospora beticola sacc.*

Introduction

Bis[1,2,4-Bis[1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-4-yl]alkanes were reported to possess antibacterial property (1) and bis[1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazol-3-yl-meth-oxy]phenylenes possess anticancer activity against a panel of 60 cell lines derived from seven cancer types namely, lung, colon, melanoma, renal, ovarian, and leukemia (2). 2,5-Bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]
thiadiazole-6-yl]pyridines (3) and 2,6-Bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl] pyridines (4) endowed with good fungicidal activities against *Cerospora beticola sacc* have been reported from our laboratory. 1,4-Bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4] thiadiazole-6-yl]butanes (5) and trans-1,2-bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4] thiadiazole-6-yl]ethenes (6) were found to show significant antibacterial activities. Prompted by these observation and in continuation of our search for bio-active molecules, We designed a facile one-pot method to prepare fifteen new 1,4-Bis[(3-aryl)-s-
triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]naphthalenes by cyclization of 3-aryl-4-amino-5-mercapto-1,2,
4-triazoles with 1,4-naphthalic acid. The synthesis, characterization and the results of fungicidal activities screening studies of the newly synthesized compounds are presented in this paper.

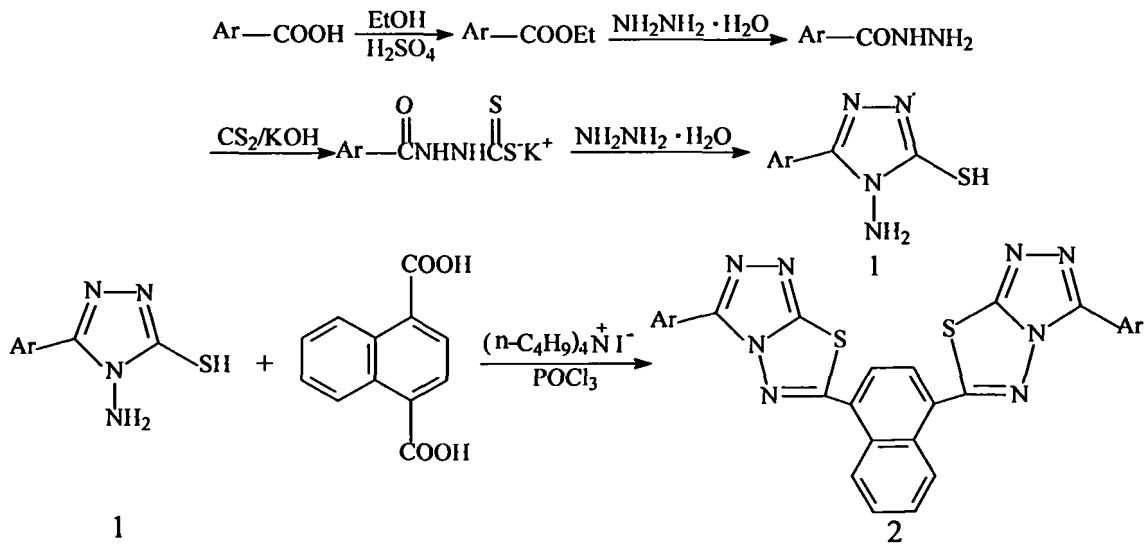
Result and Discussion

The synthesis of 1,4-Bis[(3-aryl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]naphthalenes **2** was accomplished in one step with good yields by condensing 3-aryl-4-amino-5- mercapto-1,2,4-triazoles **1** with 1,4-naphthalic acid in the presence of $POCl_3$ and tetrabutylammonium iodide as catalyst (**Scheme-1, Table-1**). Because of the poor solubility of **1** and 1,4-naphthalic acid in $POCl_3$, the yield of **2** is very low. For example, the yield of **2a** was 28%. However, where the tetrabutylammonium iodide as phase transfer catalyst were utilized and the mixture was first stirred for 4 h at 55-60□, then refluxed for 12 h at 115-120 □, **2a** was obtained in 78% yield.

The structures of all compounds **2** were established on the basis of elemental analysis and spectral data. The IR spectral data of compounds **2** showed bands at 1622-1640 cm^{-1}, 1233-1263 cm^{-1}, and 695-710 cm^{-1} due to C=N, N-N=C and C-S-C, respectively. The ^1H NMR spectra of **2** exhibited multiple signals in the δ 8.40-7.30 range accounting for hydrogen of aryl group. With compound **2a** as an example, it exhibited multiple signals in the δ 8.07-8.00, 7.50-7.38 ranges

accounting for the 16 hydrogens of phenyl groups. The EI-MS for compounds **2** exhibited molecular ion peaks. For example, **2a** showed strong molecular ion peak M^+ with m/z 528 and 5% relative abundance.

The biological activities of compounds **2** were investigated and the results showed that they exhibited fungicidal activities, especially against *Cerospora beticola sacc.* For example, **2b, 2c** and **2d** showed 95% of *Cerospora beticola sacc* inhibition of in 50 mg/L (Table **2**).



Scheme-1

Table-1 Preparation of 1,4-Bis[(3-aryl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]naphthalenes **2** from 3-aryl-4-amino-5-mercapto-1, 2, 4-triazoles **1**.

Entry	Ar	Condition	Yield(%)[a]	m.p.(□)
2a	Ph	115-120□/12h	78	197-196
2b	2-Cl-Ph	115-120□/10h	70	204-202
2c	3-Cl-Ph	115-120□/10h	63	201-200
2d	4-Cl-Ph	115-120□/11h	70	206-205
2e	2-CH_3-Ph	115-120□/12h	65	190-188
2f	3-CH_3-Ph	115-120□/12h	70	187-185
2g	4-CH_3-Ph	115-120□/12h	65	195-193
2h	3-Br-Ph	115-120□/11h	65	210-209
2i	4-Br-Ph	115-120□/11h	72	205-203
2j	2-I-Ph	115-120□/12h	55	198-197
2k	3-I-Ph	115-120□/12h	63	193-192
2l	4-I-Ph	115-120□/11h	70	200-198
2m	4-OCH_3-Ph	115-120□/13h	70	194-192

Table-2 The Fungicidal Activities 2 (50 mg/L, relative inhibition %)

Compd.	*Gibberella zeae*	*Cerospora beticola sacc*	*Physalospora piricola*
2a	40	70	72
2b	72	95	63
C	61	95	73
2d	83	96	72
2e	33	75	42
2f	32	70	51
2g	41	60	45
2h	30	71	32
2i	35	82	50
2j	28	77	61
2k	33	70	50
2l	27	80	45
2m	30	80	32

Experimental

Melting points were determined on an X_4 melting point apparatus and were uncorrected. The IR spectra were recorded on a Nicolet Nexus 470 FT-IR spectrophotometer using KBr discs in the range 4000-400 cm^{-1}. ^1H NMR spectra were recorded on a Varian Mercury-Plus 400 NMR spectrometer in CF_3COOD. The chemical shifts are reported as parts per million relative to internal TMS. MS spectra were recorded on a Finnigan Trace GC-MS spetrometer. Elemental Analyses were taken on a Perkin-Elemer-2400-CHN Elemental Analysis Instrument.

Compound 3-Aryl-4-amino-5-mercapto-1,2,4-triazole **1** was prepared from aromatic carboxylic acids by four steps according to the literature (7-8).

General preparation of 2-A mixture of compound 3-aryl-4-amino-5-mercapto-1,2,4-triazole (2.2 mmol), 1,4-naphthalic acid (1.0 mmol), tetrabutylammonium iodide (0.5 mmol), and $POCl_3$ (7 mL) was stirred for 4 h at 55-60 □, and then refluxed for 10-13 h at 115-120 □. Excess $POCl_3$ was removed under reduced pressure. The concentrated mass was cooled and poured into crushed ice, and neutralized with potassium carbonate. The separated solid was filtered, washed with water, ethanol, and then dried. The crude material was recrystallized from a mixture of ethanol and pyridine to afford pure title compounds **2a-2m** .

2a :White powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.07-8.00 (m, 7H, Ar-H), 7.50-7.38 (m, 9H, Ar-H); IR (KBr, cm^{-1}): 1630, 1241, 702. MS-EI (*m/z*): 528 (M^+, 5%), 430 (10%), 332 (17%), 103 (100%). Elemental Anal. Calcd. For $C_{28}H_{16}N_8S_2$: C, 63.63; H, 3.03; N, 21.21. Found: C, 63.75; H, 3.14; N, 21.03.

2b : Yellow powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.14-8.07 (m, 5H, Ar-H), 8.02-7.83 (m, 5H, Ar-H), 7.47-7.32 (m, 4H, Ar-H); IR (KBr, cm^{-1}): 1625, 1254, 698. MS-EI (*m/z*): 596 (M^+, 4%), 500 (10%), 402 (17%), 137 (100%). Elemental Anal. Calcd. For $C_{28}H_{14}N_8S_2Cl_2$: C,56.28; H, 2.36; N, 18.75. Found: C, 56.12; H, 2.49; N, 18.89.

2c : Yellow powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.20-8.11 (m, 3H, Ar-H), 8.09-7.73 (m, 6H, Ar-H), 7.41-7.28 (m,

5H, Ar-H); IR (KBr, cm^{-1}): 1633, 1246, 705. MS-EI (*m/z*): 596 (M^+, 3%), 500 (9%), 402 (13%), 137 (100%). Elemental Anal. Calcd. For $C_{28}H_{14}N_8S_2Cl_2$: C,56.28; H, 2.36; N, 18.75. Found: C, 56.10; H, 2.52; N, 18.85.

2d :Light yellow powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.20-8.09 (m, 6H, Ar-H), 7.40-7.15 (m, 8H, Ar-H); IR (KBr, cm^{-1}): 1630, 1237, 700. MS-EI (*m/z*): 596 (M^+, 5%), 500 (12%), 402 (26%), 137 (100%). Elemental Anal. Calcd. For $C_{28}H_{14}N_8S_2Cl_2$: C,56.28; H, 2.36; N, 18.75. Found: C, 56.39; H, 2.23; N, 18.69.

2e : White powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.31-8.19 (m, 6H, Ar-H), 7.47-7.10 (m, 8H, Ar-H), 2.43 (m, 6H, $2CH_3$); IR (KBr, cm^{-1}): 1635, 1240, 700. MS-EI (*m/z*): 556 (M^+, 7%), 458 (32%), 360 (21%), 117 (100%). Elemental Anal. Calcd. For $C_{30}H_{20}N_8S_2$: C,64.73; H, 3.62; N, 20.13. Found: C, 64.87; H, 3.49; N, 20.01.

2f : White powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.32-8.21 (m, 4H, Ar-H), δ 8.29-8.17 (m, 4H, Ar-H), 7.38-7.13 (m, 6H, Ar-H), 2.38 (m, 6H, $2CH_3$); IR (KBr, cm^{-1}): 1629, 1235, 708. MS-EI (*m/z*): 556 (M^+, 4%), 458 (21%), 360 (15%), 117 (100%). Elemental Anal. Calcd. For $C_{30}H_{20}N_8S_2$: C,64.73; H, 3.62; N, 20.13. Found: C, 64.68; H, 3.75; N, 20.29.

2g : White powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.37-8.25 (m, 6H, Ar-H), 7.30-7.15 (m, 8H, Ar-H), 2.34 (m, 6H, $2CH_3$); IR (KBr, cm^{-1}): 1625, 1240, 701. MS-EI (*m/z*): 556 (M^+, 8%), 458 (32%), 360 (11%), 117 (100%). Elemental Anal. Calcd. For $C_{30}H_{20}N_8S_2$: C,64.73; H, 3.62; N, 20.13. Found: C, 64.85; H, 3.53; N, 20.09.

2h: Yellow powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.10-8.06 (m, 5H, Ar-H), 8.03-7.81 (m, 5H, Ar-H), 7.51-7.39 (m, 4H, Ar-H); IR (KBr, cm^{-1}): 1632, 1244, 701. MS-EI (*m/z*): 686 (M^+, 5%), 588(17%), 490 (12%), 182 (100%). Elemental Anal. Calcd. For $C_{28}H_{14}N_8S_2Br_2$: C,48.99; H, 2.05; N, 16.32. Found: C, 48.81; H, 2.19; N, 16.47

2i: Light yellow powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.17-8.09 (m, 8H, Ar-H), 8.05-7.74 (m, 6H, Ar-H); IR (KBr, cm^{-1}): 1626, 1260, 698. MS-EI (*m/z*): 686 (M^+, 7%), 588(25%), 490 (31%), 182 (100%). Elemental Anal. Calcd. For $C_{28}H_{14}N_8S_2Br_2$: C,48.99; H, 2.05; N, 16.32. Found: C, 48.85; H, 2.13; N, 16.43

2j: Light yellow powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.15-8.07 (m, 5H, Ar-H), 8.06-7.89 (m, 5H, Ar-H), 7.42-7.37 (m, 4H, Ar-H); IR (KBr, cm^{-1}): 1638, 1239, 705. MS-EI (*m/z*): 780 (M^+, 3%), 682 (16%), 584 (10%), 229(100%). Elemental Anal. Calcd. For $C_{28}H_{14}N_8S_2I_2$: C, 43.09; H, 1.81; N, 14.36. Found: C, 43.20; H, 2.10; N, 14.21

2k: Light yellow powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.25-8.16 (m, 6H, Ar-H), 8.11-7.95 (m, 4H, Ar-H), 7.38-7.21 (m, 4H, Ar-H); IR (KBr, cm^{-1}): 1632, 1254, 703. MS-EI (*m/z*): 780 (M^+, 4%), 682 (20%), 584 (9%), 229(100%). Elemental Anal. Calcd. For $C_{28}H_{14}N_8S_2I_2$: C, 43.09; H, 1.81; N, 14.36. Found: C, 43.17; H, 1.70; N, 14.25

2l: Yellow powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.35-8.19 (m, 8H, Ar-H), 7.94-7.76 (m, 6H, Ar-H); IR (KBr, cm^{-1}): 1629, 1247, 699. MS-EI (*m/z*): 780 (M^+, 5%), 682 (32%), 584 (21%), 229(100%). Elemental Anal. Calcd. For $C_{28}H_{14}N_8S_2I_2$: C, 43.09; H, 1.81; N, 14.36. Found: C, 43.00; H, 1.95; N, 14.48

2m: Light yellow powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.65-8.45 (m, 6H, Ar-H), 7.45-7.26 (m, 8H, Ar-H), 3.85(s, 6H, $2OCH_3$); IR (KBr, cm^{-1}): 1630, 1242, 706. MS-EI (*m/z*): 588 (M^+, 9%), 490 (35%), 392 (14%), 132 (100%). Elemental Anal. Calcd. For $C_{30}H_{20}N_8S_2O_2$: C,61.21; H, 3.42; N, 19.03. Found: C, 61.12; H, 3.49; N, 19.15.

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