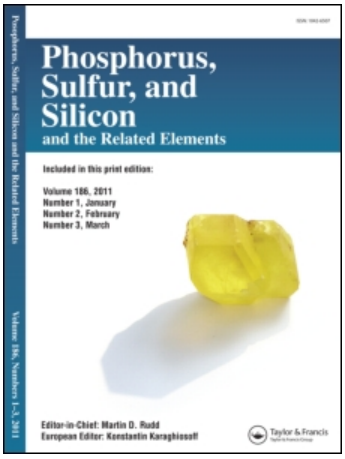

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The Synthesis and Antibacterial Activities of 1,4-Bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]Butanes

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1,4-Bis[(3-aryl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]butanes ***(2a–o)*** *were synthesized in high yields by cyclization of 3-aryl-4-amino-5-mercapto-1,2,4-triazoles* ***(1a–o)*** *with hexanedioic acid in the presence of* $POCl_3$ *and tetrabutylammonium iodide as a catalyst. The newly prepared compounds were characterized by analytical and IR,* ^1H *NMR, and EI-MS spectral analysis. The preliminary antibacterial tests showed that most of them were effective against Staphylococcas aureus, Escherichia coli, and Bacillus subtilis. Compounds* ***2d***, ***2n***, *and* ***2o*** *exhibited promising antibacterial activity.*

Keywords 3-aryl-4-amino-5-mercapto-1,2,4-triazoles; bis[1,2,4-triazolo-[3,4-*b*]-[1,3,4] thiadiazoles; antibacterial activities; synthesis

INTRODUCTION

1,2,4-Triazolo[3,4-*b*]-[1,3,4]thiadiazole derivatives are reported to possess antibacterial, antifungal, antiinflammatory, antiviral, analgesic, antihelmintic, herbicidal, and plant growth regulatory effects.[1–7] Recently, some bis[1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-4-yl]alkanes were reported to possess antibacterial activities,[8] and bis[1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-3-ylmethoxy] phenylenes possess anticancer activity against a panel of 60 cell lines derived from 7 cancer types, namely lung, colon, melanoma, renal,

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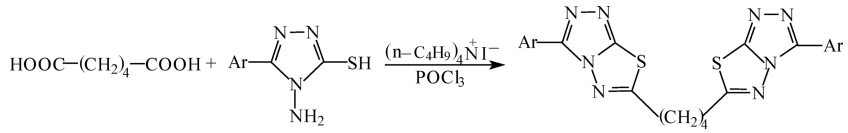
ovarian, CNS, and leukemia.[9] 2,6-Bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]pyridines endowed with good fungicidal activities against *Cerospora beticola sacc* have been reported from our laboratory.[10]Prompted by these observations and in continuation of our search for bioactive molecules, we designed a facile one-pot method to prepare a series of novel 1,4-bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]butanes by cyclization of 3-aryl-4-amino-5-mercapto-1,2,4-triazoles with hexanedioic acid. The synthesis, characterization, and results of antibacterial activities–screening studies of the newly synthesized compounds are presented in this article.

RESULTS AND DISCUSSION

Chemistry

The synthesis of 1,4-bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]butanes (**2a–o**) were accomplished in one step with good yields by condensing 3-aryl-4-amino-5- mercapto-1,2,4-triazoles **1** with hexanedioic acid in the presence of $POCl_3$ and tetrabutylammonium iodide as a catalyst (Scheme 1, Table 1). Because of the poor solubility of **1** and hexanedioic acid in $POCl_3$, the yield of **2** was very low. For example, the yield of **2m** was 32%. However, where tetrabutylammonium iodide as a phase transfer catalyst was utilized, the mixture was first stirred for 3 h at 55–60°C, and then refluxed for 8–12 h at 115–120°C. For example, **2m** was obtained in a 75% yield.

The newly synthesized compounds (**2a–o**) were assigned on the basis of their elemental analysis and spectral data. The IR spectral data of compounds (**2a–o**) showed bands at 1615–1640 cm^{-1}, 1230–1260 cm^{-1}, and 700–710 cm^{-1} due to C=N, N–N=C, and C–S–C, respectively. The ^1H NMR spectra of **2m**, as an example, showed a triplet at δ 2.24 ($J = 7.5$) corresponding to 4 protons in the $-CH_2CH_2-$ and a triplet at δ 3.40 ($J = 7.6$) corresponding to 4 protons in the $-2SCH_2$. A singlet at δ 3.98 was due to 6 protons in the $-2OCH_3$ on the aromatic ring. The multiple signals in the δ 8.30–8.27 and 7.22–7.19 ranges were due to 8 protons on the aromatic ring. Moreover, the EI-MS spectrum **2m**



1 2

SCHEME 1

TABLE I Preparation of 1,4-Bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl] butanes (2*a* – *o*) from 3-Aryl-4-amino-5-mercapto-1,2,4-triazoles (1a–o)

Entry	Ar	Condition	Yield (%)[a]	M.P. (°C)
2a	Ph	115—120°C/8.0 h	82	>300
2b	2-Cl-Ph	115—120°C/9.0 h	70	>300
2c	3-Cl-Ph	115—120°C/8.0 h	72	>300
2d	4-Cl-Ph	115—120°C/10 h	76	>300
2e	2-CH_3-Ph	115—120°C/10 h	62	>300
2f	3-CH_3-Ph	115—120°C/11 h	65	>300
2g	4-CH_3-Ph	115—120°C/11 h	75	>300
2h	3-Br-Ph	115—120°C/10 h	70	>300
2i	4-Br-Ph	115—120°C/10 h	73	>300
2j	2-I-Ph	115—120°C/9.0 h	66	>300
2k	3-I-Ph	115—120°C/10 h	70	>300
2l	4-I-Ph	115—120°C/11 h	78	>300
2m	4-OCH_3-Ph	115—120°C/12 h	75	>300
2n	4-Pyridyl	115—120°C/10 h	65	>300
2o	3-Pyridyl	115—120°C/11 h	61	>300

[a]Purified yields of **2a–2o** were based on hexanedioic acid.

revealed a peak at m/z 518 (M^+, 15%) corresponding to the molecular formula $C_{24}H_{22}N_8O_2S_2$. Characterization data of the compounds are in Table. Spectral data of other compounds are given in the Experimental section.

Antibacterial Activity

Compounds (**2a–o**) were screened for their antibacterial activities against *E. coli*,*S. aureus*, and *B. subtilis* employing the cup-plate method. Antibacterial activity was carried out against 24-hour-old cultures of three bacteria. The culture medium was the nutrient agar for bacteria. Solutions of the tested compounds at 100 μg/mL in DMF were placed separately in the cup (8 mm diameter). The plates were incubated at 37°C, and the resulting inhibition zones were measured. DMF as a blank exhibited no antibacterial activity against any of the tested bacteria used. The preliminary results indicated that most of compounds were effective against *S. aureus, E. coli*, and *B. subtilis* (see Table II).

CONCLUSION

The work described in this article showed an easy way for the synthesis of bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]butanes.

TABLE II The Antibacterial Activities of Compounds 2 (100 mg/L, relative inhibition %)

Compound	*S. aureus*	*E. coli*	*B. subtilis*
2a	35	31	78
2b	92	60	95
2c	75	80	94
2d	96	93	95
2e	28	30	34
3f	72	32	71
2g	17	18	16
2h	40	38	69
2i	72	35	71
2j	11	14	12
2l	13	18	20
2m	23	15	19
2n	94	96	92
2o	95	94	96

Among all the compounds tested, **2d**, **2n**, and **2o** were effective against *S. aureus, E. coli*, and *B. subtilis*. Hence **2d**, **2n**, and **2o** stand to be promising antibacterial agents.

EXPERIMENTAL

Melting points were determined on an X_4 melting point apparatus and are uncorrected. 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 solution using TMS as an internal reference. MS spectra were recorded on a Finnigan Trace GC-MS spectrometer. Elemental analyses were taken on a Perkin-Elemer-2400-CHN elemental analysis instrument.

The General Procedure for the Preparation of 3-Aryl-4-amino-5-mercapto-1,2,4-Triazoles (1a–o) from Aromatic Carboxylic Acids by Four Steps According to the Literature[10–12]

The General Procedure for the Preparation of 1,4-Bis[(3-aryl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]butanes (2a–o)

A mixture of compound 3-aryl-4-amino-5-mercapto-1,2,4-triazole (2.2 mmol), hexanedioic acid (0.146 g, 1.0 mmol), the phase transfer catalyst tetrabutylammonium iodide (0.185 g, 0.5 mmol), and $POCl_3$

(7 mL) was stirred for 3 h at 55–60°C and then refluxed for 8.0–12 h at 115–120°C. 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 and ethanol, and then dried. The crude material was recrystallized (ethanol-pyridine), giving the pure products 2a–o.

1,4-Bis[(3-phenyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]butane (2a)

White powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.28–8.25 (m, 4H, Ar-H), 7.77–7.63 (m, 6H, Ar-H), 3.38 (t, 4H, $J = 7.5$, $2SCH_2$), 2.21 (t, $J =$ 7.3, 4H, CH_2CH_2); IR (KBr, cm^{-1}): 1615, 1237, 710. MS-EI (*m/z*): 458 (M^+, 100%), 382 (11%), 283 (21%), 103 (65%). Elemental anal. calcd. for $C_{22}H_{18}N_8S_2$: C, 57.62; H, 3.96; N, 24.43. Found: C, 57.81; H, 3.87; N, 21.64.

1,4-Bis[(3-o-chlorophenyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]butane (2b)

White powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.37–8.32 (m, 3H, Ar-H), 8.25–8.21 (m, 3H, Ar-H), 7.61–7.58 (m, 2H, Ar-H), 3.39 (t, 4H, $J = 7.5$, $2SCH_2$), 2.17 (t, 4H, $J = 7.4$, CH_2CH_2); IR (KBr, cm^{-1}): 1625, 1240, 703. MS—EI (*m/z*): 528 (M+2, 6%), 526 (M^+, 4%), 491 (7%), 317 (5%), 209 (32%), 137 (100%). Elemental anal. calcd. for $C_{22}H_{16}N_8S_2Cl_2$: C, 50.10; H, 3.06; N, 21.24. Found: C, 50.28; H, 2.96; N, 21.11.

1,4-Bis[(3-m-chlorophenyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]butane (2c)

White powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.32–8.27 (m, 2H, Ar-H), 8.18–8.14 (m, 4H, Ar—H), 7.58–7.54 (m, 2H, Ar—H), 3.41 (t, 4H, $J = 7.5$, $2SCH_2$), 2.21 (t, 4H, $J = 7.4$, CH_2CH_2); IR (KBr, cm^{-1}): 1640, 1252, 709. MS—EI (*m/z*): 528 (M+2, 10%), 526 (M^+, 13%), 491 (12%), 317 (8%), 209 (100%), 137 (68%). Elemental anal. calcd. for $C_{22}H_{16}N_8S_2Cl_2$: C, 50.10; H, 3.06; N, 21.24. Found: C, 50.23; H, 3.12; N, 21.07.

1,4-Bis[(3-p-chlorophenyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]butane (2d)

White plates, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.28–8.25 (m, 4H, Ar-H), 7.67–7.64 (m, 4H, Ar-H), 3.41 (t, 4H, $J = 7.4$, $2SCH_2$), 2.19 (t, 4H, $J = 7.5$, CH_2CH_2); IR (KBr, cm^{-1}): 1627, 1248, 703. MS-EI (*m/z*): 528 (M+2, 8%), 526 (M^+, 10%), 491 (5%), 317 (12%), 209 (38%), 137

(100%). Elemental anal. calcd. for $C_{22}H_{16}N_8S_2Cl_2$: C, 50.10; H, 3.06; N, 21.24. Found: C, 50.31; H, 3.02; N, 21.36.

1,4-Bis[(3-o-methylphenyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]butane (2e)

White powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.25–8.22 (m, 3H, Ar-H), 8.16–8.13 (m, 3H, Ar-H), 7.65–7.61 (m, 2H, Ar-H), 3.38 (t, 4H, $J = 7.4$, $2SCH_2$), 2.50 (s, 6H, $2CH_3$), 2.31 (t, 4H, $J = 7.5$, CH_2CH_2); IR (KBr, cm^{-1}): 1633, 1245, 705. MS-EI (*m/z*): 486 (M^+, 14%), 432 (3%), 297 (32%), 117 (100%), 115 (78%). Elemental anal. calcd. for $C_{24}H_{22}N_8S_2$: C, 59.24; H, 4.56; N, 23.03. Found: C, 59.38; H, 4.51; N, 23.20.

1,4-Bis[(3-m-methylphenyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]butane (2f)

White powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.23∼8.17 (m, 2H**,** Ar-H), 810∼8.06 (m, 3H, Ar-H), 7.87∼7.82 (m, 3H, Ar-H), 3.42 (t, 4H, $J = 7.3$, $2SCH_2$), 2.54 (s, 6H, $2CH_3$), 2.33 (t, 4H, $J = 7.4$, CH_2CH_2); IR (KBr, cm^{-1}): 1624, 1257, 711. MS-EI (*m/z*): 486 (M^+, 16%), 432 (3%), 297 (37%), 117 (38%), 115 (100%). Elemental anal. calcd. for $C_{24}H_{22}N_8S_2$: C, 59.24; H, 4.56; N, 23.03. Found: C, 59.12; H, 4.63; N, 23.27.

1,4-Bis[(3-p-methylphenyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]butane (2g)

White powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.20–8.17 (m, 4H, Ar-H), 7.50–7.71 (m, 4H, Ar-H), 3.41 (t, 4H, $J = 7.3$, $2SCH_2$), 2.52 (s, 6H, $2CH_3$), 2.34 (t, 4H, $J = 7.5$, CH_2CH_2); IR (KBr, cm^{-1}): 1621, 1234, 703. MS-EI (*m/z*): 486 (M^+, 21%), 432 (6%), 297 (29%), 117 (43%), 115 (100%). Elemental anal. calcd. for $C_{24}H_{22}N_8S_2$: C, 59.24; H, 4.56; N, 23.03. Found: C, 59.09; H, 4.47; N, 23.18.

1,4-Bis[(3-m-bromophenyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]butane (2h)

Yellow powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.20–8.17 (m, 3H, Ar-H), 8.04–7.96 (m, 2H, Ar-H), 7.78–7.74 (m, 3H, Ar-H), 3.40 (t, 4H, $J = 7.6$, $2SCH_2$), 2.21 (t, $J = 7.5$, 4H, CH_2CH_2); IR (KBr, cm^{-1}): 1637, 1242, 701. MS-EI (*m/z*): 618 (M+4, 3%), 616 (M+2, 4%), 614 (M^+, 4%), 535 (10%), 456 (3%), 256 (100%), 182 (35%), 102 (61%). Elemental anal. calcd. for $C_{22}H_{16}N_8S_2Br_2$: C, 42.87; H, 2.62; N, 18.18. Found: C, 42.69; H, 2.54; N, 18.29.

1,4-Bis[(3-p-bromophenyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]butane (2i)

Yellow powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.16–8.13 (m, 4H, Ar-H), 7.83–7.80 (m, 4H, Ar-H), 3.38 (t, 4H, $J = 7.5$, $2SCH_2$), 2.20 (t, $J = 7.5$, 4H, CH_2CH_2); IR (KBr, cm^{-1}): 1639, 1233, 707. MS-EI (*m/z*): 618 (M+4, 4%), 616 (M+2, 9%), 614 (M^+, 5%), 535 (8%), 456 (4%), 256 (100%), 182 (43), 102 (67%). Elemental anal. calcd. for $C_{22}H_{16}N_8S_2Br_2$: C, 42.87; H, 2.62; N, 18.18. Found: C, 42.98; H, 2.67; N, 18.06.

1,4-Bis[(3-o-iodophenyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]butane (2j)

White powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.57–8.53 (m, 3H, Ar-H), 8.32–8.30 (m, 2H, Ar-H), 7.35–7.31 (m, 3H, ArH), 3.29 (t, 4H, $J = 7.6$, $2SCH_2$), 2.24 (t, 4H, $J = 7.5$, CH_2CH_2); IR (KBr, cm^{-1}): 1624, 1247, 703. MS-EI (*m/z*): 710 (M^+, 3%), 583 (100%), 409 (26%), 229 (38%), 102 (31%). Elemental anal. calcd. for $C_{22}H_{16}N_8S_2I_2$: C, 37.20; H, 2.27; N, 15.77. Found: C, 37.35; H, 2.21; N, 15.89.

1,4-Bis[(3-m-iodophenyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]butane (2k)

White powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.64–8.61 (m, 2H, Ar-H), 8.27–8.24 (m, 2H, Ar-H), 8.06–8.02 (m, 2H, Ar-H), 7.40–7.36 (m, 2H, Ar-H), 3.31 (t, 4H, $J = 7.6$, $2SCH_2$), 2.24 (t, 4H, $J = 7.5$, CH_2CH_2); IR (KBr, cm^{-1}): 1618, 1236, 705. MS-EI (*m/z*): 710 (M^+, 5%), 583 (100%), 409 (47%), 229 (56%), 102 (37%). Elemental anal. calcd. for $C_{22}H_{16}N_8S_2I_2$: C, 37.20; H, 2.27; N, 15.77. Found: C, 37.08; H, 2.33; N, 15.71.

1,4-Bis[(3-p-iodophenyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]butane (2l)

White powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.03–7.96 (m, 8H, Ar-H), 3.35 (t, 4H, $J = 7.6$, $2SCH_2$), 2.12 (t, 4H, $J = 7.3$, CH_2CH_2); IR (KBr, cm^{-1}): 1615, 1247, 706. MS-EI (*m/z*): 710 (M^+, 10%), 583 (45%), 409 (98%), 229 (100%), 102 (82%). Elemental anal. calcd. for $C_{22}H_{16}N_8S_2I_2$: C, 37.20; H, 2.27; N, 15.77. Found: C, 37.39; H, 2.09; N, 15.61.

1,4-Bis[(3-p-methoxyhenyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]butane (2m)

White powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.30–8.27 (m, 4H, Ar-H), 7.22–7.19 (m, 4H, Ar-H), 3.98 (s, 6H, $2OCH_3$), 3.40 (t, 4H, $J = 7.6$, $2SCH_2$,), 2.24 (t, 4H, $J = 7.5$, CH_2CH_2); IR (KBr, cm^{-1}): 1635, 1237,

703. MS-EI (*m/z*): 518 (M^+, 15%), 313 (100%), 207 (44%), 133 (57%). Elemental anal. calcd. for $C_{24}H_{22}N_8O_2S_2$: C, 55.58; H, 4.27; N, 21.61. Found: C, 55.71; H, 4.19; N, 21.57.

1,4-Bis[3-(3-4′-pyridyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]butane (2n)

White powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.51–8.38 (m, 4H, Ar-H), 7.77–7.72 (m, 4H, Ar-H), 3.31 (t, 4H, $J = 7.2$, $2SCH_2$), 2.21 (t, 4H, $J = 7.4$, CH_2CH_2); IR (KBr, cm^{-1}): 1627, 1251, 706. MS-EI (*m/z*): 460 (M^+, 15%), 284 (53%), 176 (100%), 104 (55%). Elemental anal. calcd. for $C_{20}H_{16}N_{10}S_2$: C, 52.17; H, 3.50; N, 30.42. Found: C, 52.01; H, 3.61; N, 30.57.

1,4-Bis[3-(3-3′-pyridyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]butane (2o)

White powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.49–8.42 (m, 3H, Ar-H), 8.27–8.23 (m, 3H, Ar-H), 7.25–7.20 (m, 2H, Ar-H), 3.35 (t, 4H, $J = 7.3$, $2SCH_2$), 2.19 (t, 4H, $J = 7.5$, CH_2CH_2); IR (KBr, cm^{-1}): 1621, 1249, 701. MS-EI (*m/z*): 460 (M^+, 11%), 284 (46%), 176 (100%), 104 (37%). Elemental anal. calcd. for $C_{20}H_{16}N_{10}S_2$: C, 52.17; H, 3.50; N, 30.42. Found: C, 52.31; H, 3.39; N, 30.41.

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