SYNTHESIS AND ANTIBACTERIAL ACTIVITIES OF 1,5-BIS[(3-ARYL)-1,2,4-TRIAZOLO[3,4-B]-[1,3,4]THIADIAZOLE-6-YL]PENTANES

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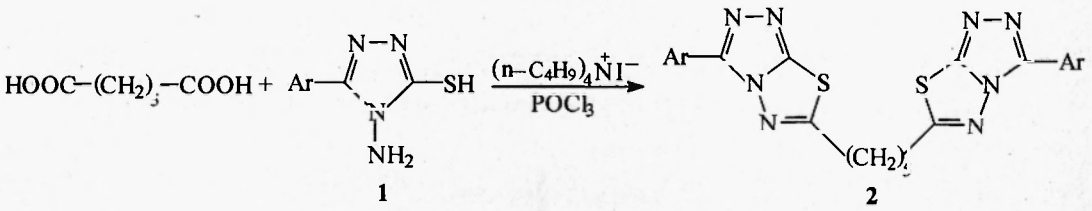
Abstract : A series of 1,5-bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]pentanes were synthesized in high yields by reaction of 3-aryl-4-amino-5-mercapto-1,2,4-triazole with heptanedioic acid in the presence of $POCl_3$ and tetrabutylammonium iodide as catalyst. The newly synthesized compounds were characterized by elemental analysis, IR, ^1H NMR and MS. The preliminary antibacterial tests showed that most of them were effective against *S.aureus*, *E.coli* and *B.subtilis*.

Introduction

Some of bis[1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-4-yl]alkanes were reported to possess antibacterial property (1-3) 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 seven cancer types namely, lung, colon, melanoma, renal, ovarian, CNS and leukemia (4). 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 (5). Prompted by these observation and in continuation of our search for bio-active molecules, We designed a facile one-pot method to prepare a series of new 1,5-bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]pentanes by cyclization of 3-aryl-4-amino-5-mercapto-1,2,4-triazoles with heptanedioic acid. The synthesis, characterization and the results of antibacterial activities screening studies of the newly synthesized compounds are presented in this paper.

Result and Discussion

The synthesis of 1,5-bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]pentanes **2** were accomplished in one step with good yields by condensing 3-aryl-4-amino-5-mercapto-1,2,4-triazoles **1** with heptanedioic acid in the presence of $POCl_3$ and tetrabutylammonium iodide as catalyst (**Scheme-1**). Because of the poor solubility of **1** and heptanedioic acid in $POCl_3$, the yield of **2** is very low. For example, the yield of **2a** was 33%. 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 8-10 h at 115-120 ℃, **2a** was obtained in 73% yield (**Table-1**).



Scheme-1

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 1615-1640 cm^{-1}, 1240-1260 cm^{-1}, and 705-720 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 7.24-8.70 range accounting for hydrogen of aryl group, 3.42-3.55 range accounting for the 4 hydrogens of $-2SCH_2$, 2.20-2.45 range accounting for the 6 hydrogens of $-CH_2CH_2CH_2-$. With compound **2a** as an example, it exhibited multiple signals in the *δ* 7.61-7.74, 8.25-8.36 ranges accounting for 10 hydrogens of phenyl group, *δ* 3.42 accounting for the 4 hydrogens of $-2SCH_2$, *δ* 2.26-2.41 accounting for the 6 hydrogens of $-CH_2CH_2CH_2-$. The EI-MS for compounds **2** exhibited molecular ion peaks. For example, **2a** showed strong molecular ion peak M^+ with m/z 472 and 4% relative abundance.

Table-1 : Preparation of 1,5-bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]pentanes **2** from 3-aryl-4-amino-5-mercapto-[1,2,4]triazoles **1**

Entry	Ar	Condition	Yield (%)[a]	m.p. (℃)
2a	Ph	115-120℃/7 h	73	>250
2b	2-Cl-Ph	115-120℃/8 h	60	>250
2c	3-Cl-Ph	115-120℃/8 h	62	>250
2d	4-Cl-Ph	115-120℃/7 h	67	>250
2e	2-CH_3-Ph	115-120℃/9 h	56	>250
2f	3-CH_3-Ph	115-120℃/9 h	60	>250
2g	4-CH_3-Ph	115-120℃/10 h	70	>250
2h	3-Br-Ph	115-120℃/10 h	58	>250
2i	4-Br-Ph	115-120℃/10 h	54	>250
2j	2-I-Ph	115-120℃/8 h	60	>250
2k	3-I-Ph	115-120℃/8 h	62	>250
2l	4-I-Ph	115-120℃/9 h	71	>250
2m	4-OCH_3-Ph	115-120℃/9 h	72	>250
2n	4-Pyridyl	115-120℃/10 h	60	>250
2o	3-Pyridyl	115-120℃/9 h	63	>250

[a]Isolated yields based on heptanedioic acid.

Compounds **2** were screened for their antibacterial activities against *E. coli*, *S. aureus*, and *B. subtilis* employing the cup-plate method at the concentration of 100 μg/mL in the nutrient agar. The preliminary results indicated that most of compounds express significant antibacterial activity. The results of such studies are given in **Table-2**.

348 **le-2** : The Antibacterial Activities of Compounds **2a-2o**

mpd.	*S.aureus*	*E.coli*	*B.subtilis*
2a	++	++	++
2b	+++	++	++
2c	+++	+++	+++
2d	+++	+++	+++
2e	+	-	+
2f	-	+	+
2g	-	-	-
2h	+	-	+
2i	+	+	+
2j	-	-	+
2k	-	-	+
2l	-	-	-
2m	+	-	+
2n	++	++	+++
2o	++	++	+++

Zone diameter of growth inhibition: <10 mm (-), 10 ~ 12 mm (+), 13 ~ 15 mm (+ +),

16 ~ 20 mm (+ + +); Diameter of the cup=8 mm.

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 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-C H N 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 (5-7).

General preparation of 2-A mixture of compound 3-aryl-4-amino-5-mercapto-1,2,4-triazole (2.2 mmol), heptanedioic 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 7-10 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 ltered, washed with water, ethanol, and then dried. The crude material was recrystallized from a mixture of ethanol and pyridine to afford the pure products **2a** 349

2a: Gray powder, IR (KBr, cm^{-1}): 1626, 1243, 712; ^1H NMR (CF_3COOD, 400 MHz): 2.26-2.41 (m, 6H, $-CH_2CH_2CH_2-$), 3.42 (t, 4H, *J*=7.5, $2SCH_2$), 7.61-7.74 (m, 6H, Ar-H), 8.25-8.36 (m, 4H, Ar-H); MS (m/z): 472 (M^+, 4%), 297 (25%), 176 (100%), 102 (87%), 77 (66%). Anal. Calcd For $C_{23}H_{20}N_8S_2$: C, 58.45; H, 4.27; N, 23.71. Found: C, 58.27; H, 4.33; N, 23.90.

2b: Pale yellow powder, IR(KBr, cm^{-1}): 1619, 1262, 720; ^1H NMR (CF_3COOD, 400 MHz): 2.21-2.36 (m, 6H, $-CH_2CH_2CH_2-$), 3.49 (t, 4H, *J*=7.4, $2SCH_2$), 7.52-7.82 (m, 3H, Ar-H), 7.89-8.04 (m, 3H, Ar-H), 8.18-8.29 (m, 2H, Ar-H); MS (m/z): 542 (2%), 540 (M^+, 3%), 331 (12%), 210 (46%), 137 (100%), 111 (31%). Anal. Calcd For $C_{23}H_{18}N_8S_2Cl_2$: C, 51.01; H, 3.35; N, 20.69. Found: C, 51.22; H, 3.24; N, 20.51.

2c: Pale yellow powder, IR(KBr, cm^{-1}): 1631, 1234, 718; ^1H NMR (CF_3COOD, 400 MHz): 2.24-2.35 (m, 6H, $-CH_2CH_2CH_2-$), 3.50 (t, 4H, *J*=7.4, $2SCH_2$), 7.49-7.76 (m, 5H, Ar-H), 8.21-8.27 (m, 3H, Ar-H); MS (m/z): 542 (2%), 540 (M^+, 4%), 331 (18%), 210 (32%), 137 (100%), 111 (29%). Anal. Calcd For $C_{23}H_{18}N_8S_2Cl_2$: C, 51.01; H, 3.35; N, 20.69. Found: C, 51.18; H, 3.39; N, 20.48.

2d: Yellow powder, IR(KBr, cm^{-1}): 1627, 1230, 719; ^1H NMR (CF_3COOD, 400 MHz): 2.22-2.34 (m, 6H, $-CH_2CH_2CH_2-$), 3.46 (t, 4H, *J*=7.4, $2SCH_2$), 7.58-7.72 (m, 4H, Ar-H), 8.17-8.23 (m, 4H, Ar-H); MS (m/z): 542 (1%), 540 (M^+, 2%), 331 (32%), 210 (28%), 137 (100%), 111 (54%). Anal. Calcd For $C_{23}H_{18}N_8S_2Cl_2$: C, 51.01; H, 3.35; N, 20.69. Found: C, 51.20; H, 3.47; N, 20.52.

2e: White powder, IR (KBr, cm^{-1}): 1632, 1253, 714; ^1H NMR (CF_3COOD, 400 MHz): 2.27-2.32 (m, 6H, $-CH_2CH_2CH_2-$), 2.52 (s, 6H, $2CH_3Ph$), 3.40 (t, 4H, *J*=7.3, $2SCH_2$), 7.40-7.52 (m, 3H, Ar-H), 7.51-7.62 (m, 2H, Ar-H), 8.11-8.22 (m, 3H, Ar-H); MS (m/z): 500 (M^+, 1%), 341 (23%), 190 (31%), 117 (100%). Anal. Calcd For $C_{25}H_{24}N_8S_2$: C, 59.97; H, 4.83; N, 22.38. Found: C, 59.78; H, 4.98; N, 22.49.

2f: Gray powder, IR (KBr, cm^{-1}): 1624, 1241, 711; ^1H NMR (CF_3COOD, 400 MHz): 2.21-2.28 (m, 6H, $-CH_2CH_2CH_2-$), 2.48 (s, 6H, $2CH_3Ph$), 3.47 (t, 4H, J=7.3, $2SCH_2$), 7.40-7.64 (m, 5H, Ar-H), 8.21-8.27 (m, 3H, Ar-H); MS (m/z): 500 (M^+, 2%), 341 (30%), 190 (27%), 117 (100%). Anal. Calcd For $C_{25}H_{24}N_8S_2$: C, 59.97; H, 4.83; N, 22.38. Found: C, 59.80; H, 4.69; N, 22.51.

2g: White powder, IR (KBr, cm^{-1}): 1617, 1257, 710; ^1H NMR (CF_3COOD, 400 MHz): 2.26-2.31 (m, 6H, $-CH_2CH_2CH_2-$), 2.49 (s, 6H, $2CH_3Ph$), 3.50 (t, 4H, J=7.3, $2SCH_2$), 7.51-7.60 (m, 4H, Ar-H), 8.18-8.24 (m, 4H, Ar-H); MS (m/z): 500 (M^+, 4%), 341 (43%), 190 (39%), 117 (100%). Anal. Calcd For $C_{25}H_{24}N_8S_2$: C, 59.97; H, 4.83; N, 22.38. Found: 350).14; H, 4.72; N, 22.21.

2h: Pale yellow powder, IR(KBr, cm^{-1}): 1631, 1243, 713; ^1H NMR (CF_3COOD, 400 MHz): 2.21-2.29 (m, 6H, $-CH_2CH_2CH_2-$), 3.47 (t, 4H, J=7.3, $2SCH_2$), 7.58-7.67 (m, 5H, Ar-H), 8.43-8.48 (m, 3H, Ar-H); MS (m/z): 630 (2%), 628 (M^+, 3%), 375 (16%), 254 (100%), 181 (37%), 102 (14%). Anal. Calcd For $C_{23}H_{18}N_8S_2Br_2$: C, 43.82; H, 2.88; N, 17.78. Found: C, 43.65; H, 2.71; N, 17.96.

2i: Yellow powder, IR(KBr, cm^{-1}): 1652, 1249, 719; ^1H NMR (CF_3COOD, 400 MHz): 2.26-2.31 (m, 6H, $-CH_2CH_2CH_2-$), 3.51 (t, 4H, J=7.3, $2SCH_2$), 7.46-7.57 (m, 4H, Ar-H), 8.35-8.41 (m, 4H, Ar-H); MS (m/z): 630 (3%), 628 (M^+, 5%), 375 (21%), 254 (48%), 181 (100%), 102 (14%). Anal. Calcd For $C_{23}H_{18}N_8S_2Br_2$: C, 43.82; H, 2.88; N, 17.78. Found: C, 43.97; H, 2.92; N, 17.61.

2j: Pale yellow powder, IR (KBr, cm^{-1}): 1627, 1241, 711; ^1H NMR (CF_3COOD, 400 MHz): 2.21-2.28 (m, 6H, $-CH_2CH_2CH_2-$), 3.46 (t, 4H, J=7.3, $2SCH_2$), 7.41-7.47 (m, 3H, Ar-H), 7.59-7.63 (m, 3H, Ar-H), 8.44-8.48 (m, 2H, Ar-H); MS (m/z): 724 (M^+, 2%), 423 (100%), 302 (17%), 229 (50%). Anal. Calcd For $C_{23}H_{18}N_8S_2I_2$: C, 38.13; H, 2.50; N, 15.47. Found: C, 38.29; H, 2.41; N, 15.31.

2k: Yellow powder, IR (KBr, cm^{-1}): 1619, 1257, 720; ^1H NMR (CF_3COOD, 400 MHz): 2.20-2.26 (m, 6H, $-CH_2CH_2CH_2-$), 3.52 (t, 4H, J=7.3, $2SCH_2$), 7.48-7.53 (m, 5H, Ar-H), 8.52-8.64 (m, 3H, Ar-H); MS (m/z): 724 (M^+, 1%), 423 (19%), 302 (100%), 229 (42%). Anal. Calcd For $C_{23}H_{18}N_8S_2I_2$: C, 38.13; H, 2.50; N, 15.47. Found: C, 38.26; H, 2.58; N, 15.34.

2l: Pale yellow powder, IR (KBr, cm^{-1}): 1631, 1245, 719; ^1H NMR (CF_3COOD, 400 MHz): 2.25-2.31 (m, 6H, $-CH_2CH_2CH_2-$), 3.46 (t, 4H, J=7.3, $2SCH_2$), 7.51-7.57 (m, 4H, Ar-H), 8.62-8.68 (m, 4H, Ar-H); MS (m/z): 724 (M^+, 3%), 423 (100%), 302 (74%), 229 (35%).

Anal. Calcd For $C_{23}H_{18}N_8S_2I_2$: C, 38.13; H, 2.50; N, 15.47. Found: C, 38.02; H, 2.56; N, 15.61.

2m: Pale yellow powder, IR (KBr, cm^{-1}): 1620, 1241, 711; ^1H NMR (CF_3COOD, 400 MHz): 2.21-2.28 (m, 6H, $-CH_2CH_2CH_2-$), 3.44 (t, 4H, J=7.3, $2SCH_2$), 3.97 (s, 6H, $2OCH_3Ph$), 7.41-7.49 (m, 4H, Ar-H), 8.52-8.59 (m, 4H, Ar-H); MS (m/z): 532 (M^+, 3%), 327 (16%), 206 (45%), 133 (100%). Anal. Calcd For $C_{25}H_{24}N_8O_2S_2$: C, 56.37; H, 4.54; N, 21.04. Found: C, 56.28; H, 4.47; N, 21.21.

2n: Pale yellow powder, IR (KBr, cm^{-1}): 1623, 1242, 708; ^1H NMR (CF_3COOD, 400 MHz): 2.23-2.31 (m, 6H, $-CH_2CH_2CH_2-$), 3.51 (t, 4H, J=7.3, $2SCH_2$), 7.21-7.27 (m, 4H, Ar-H), 8.19-8.24 (m, 4H, Ar-H); MS (m/z): 474 (M^+, 3%), 298 (100%), 176 (29%), 103 (51%). Anal. Calcd For $C_{21}H_{18}N_{10}S_2$: C, 53.15; H, 3.82; N, 29.51. Found: C, 53.02; H, 3.76; N, 29.70.

2o: Yellow powder, IR (KBr, cm^{-1}): 1618, 1253, 705; ^1H NMR (CF_3COOD, 400 MHz): 2.26-2.35 (m, 6H, $-CH_2CH_2CH_2-$), 3.48 (t, 4H, J=7.3, $2SCH_2$), 7.21-7.28 (m, 5H, Ar-H), 8.20-8.25 (m, 3H, Ar-H); MS (m/z): 474 (M^+, 2%), 298 (100%), 176 (31%), 103 (43%). Anal. Calcd For $C_{21}H_{18}N_{10}S_2$: C, 53.15; H, 3.82; N, 29.51. Found: C, 53.29; H, 3.87; N, 29.38.

Acknowledgements

We gratefully acknowledge financial support of this work by the Science Foundation of Hubei Province Education Department, China (Project No. D200660001).

References

1. B. S. Holla, R. Gonsalves; S. Shenoy, *IL Farmco*, **53**, 574 (1998).
2. B. S. Holla, R. Gonsalves, *Chim. Farmaceutico*, **137**, 467 (1998).
3. B. S. Holla, R. Gonsalves, S. Shenoy, *Eur. J. Med. Chem.*, **35**, 574 (2000).
4. B. S. Holla, K. N. Poojary, B. S. Rao, et al. *Eur J. Med. Chem.*, **37**, 511 (2002).
5. D. J. Li, D. Q. Long, H. Q. Fu, *Phosphorus, Sulfur, and Silicon*, **181**, 2079 (2006).
6. D. J. Li, D. Q. Long, H. Q. Fu, *Synth Commun*, **35**, 2495 (2005).
7. D. J. Li, D. Q. Long, H. Q. Fu, *Phosphorus, Sulfur, and Silicon*, **181**, 519 (2006).

Received on March 7, 2007