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

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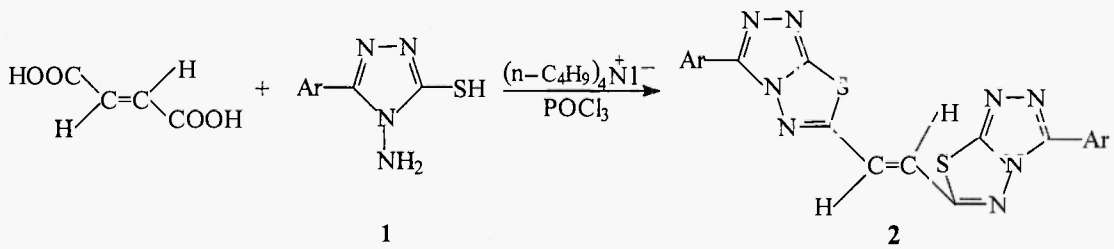
Abstract: A series of trans-1,2-bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]ethenes were synthesized in high yields by reaction of 3-aryl-4-amino-5-mercapto-1,2,4-triazole with trans-butenedioic acid in the presence of $POCl_3$ and tetrabutylammonium iodide as catalyst. The newly synthesized 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

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). 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 trans-1,2-bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]ethenes by cyclization of 3-aryl-4-amino-5-mercapto-1,2,4-triazoles with trans-butenedioic acid. The synthesis, characterization and the results of antibacterial activities screening studies of the newly synthesized compounds are presented in this paper.

Result and Discussions

The synthesis of A series of trans-1,2-bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]ethenes **2** were accomplished in one step with good yields by condensing 3-aryl-4-amino-5-mercapto-1,2,4-triazoles **1** with trans-butenedioic acid in the presence of $POCl_3$ and tetrabutylammonium iodide as catalyst (**Scheme-1**). Because of the poor solubility of **1** and trans-butenedioic acid in $POCl_3$, the yield of **2** is very low. For example, the yield of **2g** was 31%. However, where the tetrabutylammonium iodide as phase transfer catalyst were utilized and the mixture was first stirred for 3 h at 55-60^{0}C, then refluxed for 8-11 h at 115-120^{0}C, **2g** was obtained in 76% yield (Table-1).



1 **2**

Scheme-1

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

Entry	Ar	Condition	Yield (%)[a]	m.p. (^{0}C)
2a	Ph	115-120^{0}C/8 h	80	>300
2b	2-Cl-Ph	115-120^{0}C/9 h	68	>300
2c	3-Cl-Ph	115-120^{0}C/11 h	71	>300
2d	4-Cl-Ph	115-120^{0}C/10 h	75	>300
2e	2-CH_3-Ph	115-120^{0}C/10 h	65	>300
2f	3-CH_3-Ph	115-120^{0}C/9 h	60	>300
2g	4-CH_3-Ph	115-120^{0}C/10h	76	>300
2h	3-Br-Ph	115-120^{0}C/11h	71	>300
2i	4-Br-Ph	115-120^{0}C/10 h	70	>300
2j	2-I-Ph	115-120^{0}C/11 h	66	>300
2k	3-I-Ph	115-120^{0}C/10h	70	>300
2l	4-I-Ph	115-120^{0}C/9 h	72	>300
2m	4-OCH_3-Ph	115-120^{0}C/9 h	77	>300
2n	4-Pyridyl	115-120^{0}C/8 h	62	>300
2o	3-Pyridyl	115-120^{0}C/8 h	65	>300

[a]Isolated yields based on trans-butenedioic acid.

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 1610~1640 cm^{-1}, 1230~1265 cm^{-1}, and 700~710 cm^{-1} due to C=N, N-N=C and C-S-C, respectively. The ^{1}H NMR spectra of **2** exhibited multiple signals in the δ 7.10-8.35 range accounting for hydrogen of aryl group and CH=CH. With compound **2g** as an example, it exhibited multiple signals in the δ 7.57~7.60, 8.09~8.28 ranges accounting for 10 hydrogens of phenyl group and CH=CH, a singlet at δ 2.58 integrating for six protons attributing to the OCH_3 groups. The EI-MS for compounds **2** exhibited molecular ion peaks. For example, **2g** showed strong molecular ion peak M^+ with m/z 456 and 4% relative abundance.

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**.

Table-2 : The Antibacterial Activities of Compounds **2a-2o**

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

Zone diamerter of growth inhibition: <10 mm(-), 10□12 mm(+), 13□15 mm(++),16□20 mm(+++); Diamater 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 or pyridine-d_5 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-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), trans-butenedioic acid (1.0 mmol), the phase transfer catalyst tetrabutylammonium iodide (0.5 mmol), and $POCl_3$ (7 mL) was stirred for 3 h at 55-60 □, and then refluxed for 8-11 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-2o**.

2a: Pale yellow powder, IR (KBr, cm^{-1}): 1615, 1234, 701; ^1H NMR (CF_3COOD, 400 MHz): 7.75-7.85 (m, 7H, Ar-H, CH=CH), 8.06-8.17 (m, 2H, Ar-H), 8.20-8.35 (m, 3H, Ar-H); MS (m/z): 428 (M^+, 2%), 253 (5%), 103 (54%), 76 (42%), 74 (100%). Anal. Calcd For $C_{20}H_{12}N_8S_2$: C, 50.06; H, 2.82; N, 22.53. Found: C, 50.19; H, 2.75; N, 22.40.

2b: Pale yellow powder, IR(KBr, cm^{-1}): 1618, 1231, 703; ^1H NMR (CF_3COOD, 400MHz): 7.62-7.70 (m, 3H, Ar-H, CH=CH), 7.87-7.91 (m, 5H, Ar-H), 8.24-8.28 (m, 2H, Ar-H); MS (m/z): 498 (3%), 496 (M^+, 7%), 461 (41%), 287 (78%), 137 (100%), 102 (9%). Anal. Calcd For $C_{20}H_{10}N_8S_2Cl_2$: C, 48.30; H, 2.03; N, 22.53. Found: C, 48.47; H, 2.11; N, 22.42.

2c: Yellow powder, IR(KBr, cm^{-1}): 1635, 1243, 700; ^1H NMR (CF_3COOD, 400MHz): 7.54-7.60 (m, 3H, Ar-H, CH=CH), 7.87-7.91 (m, 2H, Ar-H), 8.12-8.19 (m, 3H, Ar-H), 8.50-8.54 (m, 2H, Ar-H); MS (m/z): 498 (5%), 496 (M^+, 12%), 461 (38%), 287 (100%), 137 (29%), 102 (7%). Anal. Calcd For $C_{20}H_{10}N_8S_2Cl_2$: C, 48.30; H, 2.03; N, 22.53. Found: C, 48.21; H, 1.97; N, 22.67.

2d: Yellow powder, IR(KBr, cm^{-1}): 1624, 1238, 707; ^1H NMR (CF_3COOD, 400MHz): 7.82-7.89 (m, 6H, Ar-H, CH=CH), 8.21-8.29 (m, 4H, Ar-H); MS (m/z): 498 (5%), 496 (M^+, 12%), 461 (38%), 287 (100%), 137 (29%), 102 (7%). Anal. Calcd For $C_{20}H_{10}N_8S_2Cl_2$: C, 48.30; H, 2.03; N, 22.53. Found: C, 48.42; H, 2.09; N, 22.61.

2e: Pale yellow powder, IR (KBr, cm^{-1}): 1614, 1247, 708; ^1H NMR (CF_3COOD, 400 MHz): 2.54 (s, 6H, $2CH_3Ph$), 7.32-7.41 (m, 3H, Ar-H, CH=CH), 7.51-7.57 (m, 3H, Ar-H), 8.14-8.32 (m, 4H, Ar-H); MS (m/z): 456 (M^+, 2%), 267 (1%), 117 (100%), 116 (48%). Anal. Calcd For $C_{22}H_{16}N_8S_2$: C, 57.88; H, 3.53; N, 24.54. Found: C, 57.80; H, 3.59; N, 24.62.

2f: Pale yellow powder, IR (KBr, cm^{-1}): 1637, 1242, 708; ^1H NMR (CF_3COOD, 400 MHz): 2.52 (s, 6H, $2CH_3Ph$), 7.28-7.34 (m, 4H, Ar-H, CH=CH), 7.56-7.59 (m, 3H, Ar-H), 8.07-8.21 (m, 3H, Ar-H); MS (m/z): 456 (M^+, 6%), 267 (8%), 117 (42%), 116 (100%).Anal. Calcd For $C_{22}H_{16}N_8S_2$: C, 57.88; H, 3.53; N, 24.54. Found: C, 57.72; H, 3.42; N, 24.67.

2g: Yellow powder, IR (KBr, cm^{-1}): 1620, 1252, 703; ^1H NMR (CF_3COOD, 400 MHz): 2.57 (s, 6H, $2CH_3Ph$), 7.57-7.60 (m, 4H, Ar-H, CH=CH), 8.09-8.28 (m, 6H, Ar-H); MS (m/z): 456 (M^+, 4%), 267 (3%), 117 (33%), 116 (53%), 114 (100%). Anal. Calcd For $C_{22}H_{16}N_8S_2$: C, 57.88; H, 3.53; N, 24.54. Found: C, 57.97; H, 3.48; N, 24.41.

2h: Yellow powder, IR(KBr, cm^{-1}): 1633, 1230, 701; ^1H NMR (CF_3COOD, 400MHz): 7.42-7.48 (m, 5H, Ar-H, CH=CH), 7.52-7.57 (m, 3H, Ar-H), 8.17-8.21 (m, 2H, Ar-H); MS (m/z): 586 (9%), 584 (M^+, 10%), 505 (16%), 331 (100%), 181 (37%), 102 (14%). Anal. Calcd For $C_{20}H_{10}N_8S_2Br_2$: C, 40.97; H, 1.72; N, 19.11. Found: C, 40.81; H, 1.67; N, 19.23.

2i: Yellow powder, IR(KBr, cm^{-1}): 1640, 1241, 706; ^1H NMR (CF_3COOD, 400MHz): 7.47-7.52 (m, 6H, Ar-H, CH=CH), 8.12-8.18 (m, 5H, Ar-H); MS (m/z): 586 (14%), 584 (M^+, 16%), 505 (30%), 331 (78%), 181 (100%), 102 (26%). Anal. Calcd For $C_{20}H_{10}N_8S_2Br_2$: C, 40.97; H, 1.72; N, 19.11. Found: C, 40.86; H, 1.75; N, 19.28.

2j: Pale yellow powder,r, IR (KBr, cm^{-1}): 1622, 1247, 701; ^1H NMR (CF_3COOD, 400 MHz): 7.46-7.54 (m, 4H, Ar-H), 7.73-7.79 (m, 2H, Ar-H, CH=CH), 8.01-8.09 (m, 4H, Ar-H); MS (m/z): 680 (M^+, 42%), 553 (12%), 379 (100%), 301 (12%), 229 (56%). Anal. Calcd For $C_{20}H_{10}N_8S_2I_2$: C, 35.31; H, 1.48; N, 16.47. Found: C, 35.20; H, 1.34; N, 16.62.

2k: Yellow powder, IR (KBr, cm^{-1}): 1631, 1252, 704; ^1H NMR (CF_3COOD, 400 MHz): 7.31-7.37 (m, 3H, Ar-H, CH=CH), 7.42-7.51 (m, 4H, Ar-H), 7.76-7.84 (m, 3H, Ar-H); MS (m/z): 680 (M^+, 52%), 553 (10%), 379 (100%), 229 (32%). Anal. Calcd For $C_{20}H_{10}N_8S_2I_2$: C, 35.31; H, 1.48; N, 16.47. Found: C, 35.46; H, 1.43; N, 16.32.

2l: Yellow powder, IR (KBr, cm^{-1}): 1614, 1239, 700; ^1H NMR (CF_3COOD, 400 MHz): 7.53-7.62 (m, 4H, Ar-H, CH=CH), 7.80-7.96 (m, 6H, Ar-H); MS (m/z): 680 (M^+, 76%), 553 (12%), 379 (100%), 301 (57%), 229 (48%). Anal. Calcd For $C_{20}H_{10}N_8S_2I_2$: C, 35.31; H, 1.48; N, 16.47. Found: C, 35.43; H, 1.42; N, 16.59.

2m: Yellow powder, IR (KBr, cm^{-1}): 1633, 1241, 708; ^1H NMR (CF_3COOD, 400 MHz): 3.98 (s, 6H, $2OCH_3Ph$), 7.14-7.29 (m, 4H, Ar-H, CH=CH), 7.94-7.99 (m, 3H, Ar-H), 8.25-8.28 (m, 3H, Ar-H); MS (m/z): 488 (M^+, 17%),283 (12%), 133 (100%), 103 (11%). Anal. Calcd For $C_{22}H_{16}N_8O_2S_2$: C, 54.09; H, 3.30; N, 22.94. Found: C, 54.21; H, 3.21; N, 22.81.

2n: Pale yellow powder, IR (KBr, cm^{-1}): 1617, 1235, 701; ^1H NMR (CF_3COOD, 400 MHz): 7.21-7.28 (m, 4H, Ar-H, CH=CH), 7.36-7.40 (m, 3H, Ar-H), 8.18-8.23 (m, 3H, Ar-H); MS (m/z): 430 (M^+, 17%), 254 (100%), 104 (70%), 76 (42%). Anal. Calcd For $C_{18}H_{10}N_{10}S_2$: C, 50.22; H, 2.34; N, 32.54. Found: C, 50.08; H, 2.27; N, 32.68.

2o: Yellow powder, IR (KBr, cm^{-1}): 1621, 1242, 704; ^1H NMR (CF_3COOD, 400 MHz): 7.13-7.18 (m, 3H, Ar-H, CH=CH), 7.24-7.29 (m, 4H, Ar-H), 8.21-8.25 (m, 3H, Ar-H); MS (m/z): 430 (M^+, 17%), 254 (100%), 104 (70%), 76 (42%). Anal. Calcd For $C_{18}H_{10}N_{10}S_2$: C, 50.22; H, 2.34; N, 32.54. Found: C, 50.35; H, 2.42; N, 32.41.

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References

1. B.S. Holla, R. Gonsalves and S. IL Shenoy, *Farmco* **53**, 574 (1998).
2. B.S. Holla and R. Gonsalves, *Chim. Farmaceutico* **137**, 467 (1998).
3. B.S. Holla, R.Gonsalves and S. Shenoy, *Eur. J. Med. Chem.* **35**, 574 (2000).
4. B.S. Holla, K.N. Poojary and B.S. Rao, et al. *Eur. J. Med. Chem.* **37**, 511 (2002).
5. J.A. Reid, *J. Heterocycl Chem.* **13**, 925 (1976).
6. D.J. Li, D.Q. Long and H.Q. Fu, *Synth Commun* **35**, 2495 (2005).
7. D.J. Li, D.Q. Long and H.Q. Fu, *Phosphorus, Sulfur, and Silicon*, **181**, 519 (2006).

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