SYNTHESIS AND FUNGICIDAL ACTIVITIES OF 2,5-BIS[(3-ARYL)-1,2,4-TRIAZOLO[3,4-*b*]-[1,3,4]THIADIAZOLE-6-YL]PYRIDINES

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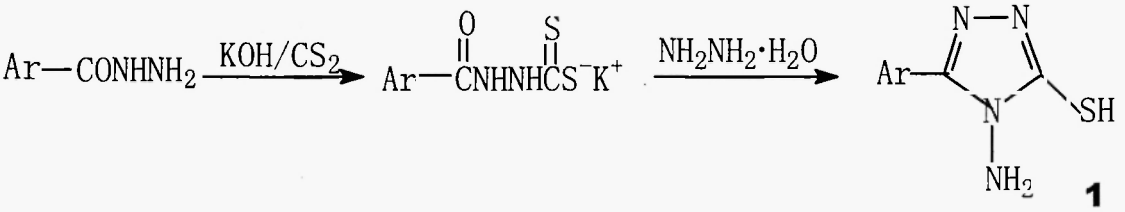
Abstract : In search of better bio-active compounds, a series of novel 2,5-bis[(3-aryl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]pyridines **2** were synthesized in high yields by cyclization of 3-aryl-4-amino-5-mercapto-1,2,4-triazoles **1** with 2,5-pyridine dicarboxylic acid. **2** exhibited good fungicidal activities against *Cerospora beticola sacc.*

Introduction

1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole derivatives are found to possess significant biological activitites such as antiflammatory, antiviral, antifungal, antineoplastic, antidepressant effects(1-4) and electrochemical properties(5). They are highly important heterocycles, and have been used in research and development of agrochemicals and pharmaceutical chemistry. Most of those reported contain only one 1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole unit in one moleclule(6-11). Some of bis[1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-4-yl]alkanes were reported to posses antibacterial property(12) and bis[1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazol-3-ylmethoxy] phenylenes posses anticancer activity against a panel of 60 cell lines derived from seven cancer types namely, lung, colon, melanoma, renal, ovarian, CNS and leukemia (13). Because many native compounds, synthetical drugs, plant growth hormones contain pyridine ring, for example, 3-Aryl-6-(3-pyridyl)-1,2,4-triazolo[3,4-*b*]-[1,3,4] thiadiazole(14), 3-aryl-6-(2-pyrid-yl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole and 3-aryl-6-(4-pyridyl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole were synthesized(15). However, 2,5-bis [(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]pyridines can not be synthesized from the reaction of the corresponding 3-aryl-4-amino-5-mercapto-1,2,4-triazole with 2,5-pyridine dicarboxylic acid in $POCl_3$ *via* the general method(14-15) because of the poor solubility of 2,5-pyridine dicarboxylic acid in $POCl_3$. As part of our current studies on the synthesis of the biologically active1,2,4-triazolo[3,4-*b*]-[1,3,4] thiadiazole derivatives, we now report an efficient synthesis of some novel fused heterocyclic compounds combining two 1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole units in one framework from 3-aryl-4-amino-5-mercapto-1,2,4-triazoles, with the hope to obtain compounds of better biological activities. The synthesis, characterization and the results of fungicidal activity screening studies of the newly synthesized compounds are presented in this paper.

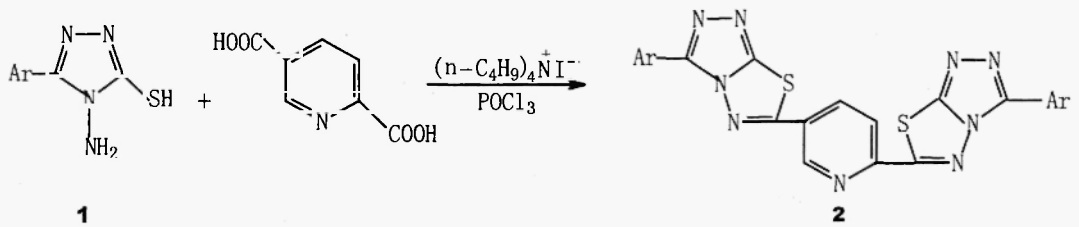
Result and Discussions

The reaction of corresponding aroylhydrazides with CS_2/KOH in absolute ethanol gave potassium aroyldithiocarbazates and then hydrazinolysis of potassium aroyldithiocarbazates with hydrazine hydrate afforded 3-aryl-4-amino-5-mercapto-1,2,4-triazoles **1**(16) (**Scheme-1**).



Scheme-1

The synthesis of **2** were accomplished in one step with good yields by condensing 3-aryl-4-amino-5-mercapto-1,2,4-triazoles **1** with 2,5-pyridine dicarboxylic acid in the presence of $POCl_3$ and tetrabutylammonium iodide as phase transfer catalyst (Scheme-2, Table-1). Because of the poor solubility of 2,5-pyridine dicarboxylic acid in $POCl_3$, the yield of **2** was very low. For example, the yield of **2g** was 2%. However, where the tetrabutylammonium iodide as phase transfer catalyst was utilized, and the mixture was first stirred for 6 h at 55-60 °C, then refluxed for 14 h at 115-120 °C, **2g** were obtained in 71% yield.



Scheme-2

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

Entry	Ar	Yield(%)[a]
2a	Ph	71
2b	2-Cl-Ph	60
2c	3-Cl-Ph	62
2d	4-Cl-Ph	67
2e	2-CH_3-Ph	56
2f	3-CH_3-Ph	62
2g	4-CH_3-Ph	71
2h	3-Br-Ph	64
2i	4-Br-Ph	66
2j	2-I-Ph	61
2k	3-I-Ph	67
2l	4-I-Ph	69
2m	4-OCH_3-Ph	64
2n	4-Pyridyl	60
2o	3-Pyridyl	56
2p	2-Furyl	50

[a]Isolated yields based on 2,5-pyridine dicarboxylic acid.

[b]Melting points of all compounds exceeded 300°C.

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 1605-1630 cm^{-1}, 1235-1265cm^{-1}, and 700cm^{-1} due 384 N, N-N=C and C-S-C, respectively. The ^1H NMR spectra of **2** exhibited multiple signals in the 7.00-8.00 range accounting for hydrogens of aryl group. With compound **2k** as an example, it exhibited multiple signals in the δ7.47-7.58, δ8.14-8.16, δ8.35-8.42, δ8.71-8.75 range accounting for the 11 hydrogens of aryl group. The EI-MS for compounds **2** exhibited molecular ion peaks. With compound **2k** as an example, it showed a strong molecular ion peak M^+ with m/z 731 and 34% relative abundance.

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

Table-2 : The Fungicidal Activities of 2,5-Bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4] thiadiazole-6-yl] pyridines **2** (50 mg/L, relative inhibition %)

Entry	*Gibberella zeae*	*Cerospora beticola sacc*	*Physalospora piricola*	*Pelliculari sasakii*
2a	30	75	60	20
2b	45	86	75	84
2c	60	89	85	80
2d	80	95	75	80
2e	30	75	65	30
2f	35	70	60	32
2g	40	70	56	23
2h	31	75	41	40
2i	33	80	42	45
2j	30	84	38	32
2k	20	86	40	28
2l	29	80	45	25
2m	32	70	27	30
2n	48	95	70	35
2o	52	95	65	42

2p	40	77	80	55

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 4000-400cm-1. ^{1}H NMR spectra were recorded on a Varian Mercury-Plus 400 NMR spectrometer in CF_3COOD or Pyridine-d_5 solution. 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.

General preparation of **2**-A mixture of 3-aryl-4-amino-5-mercapto-1, 2, 4-triazoles (2.2 mmol), 2,5-pyridine dicarboxylic acid (1.0 mmol), tetrabutylammonium iodide (0.5 mmol) and $POCl_3$ (7 mL) was stirred for 6 h at 55-60 ^{0}C, then refluxed for 11-15 h at 115-120 ^{0}C. Excess $POCl_3$ was removed under reduced pressure. The concentrated mass was cooled and poured into crushed ice, neutralized with potassium carbonate. The separated solid was filtered, washed with water, ethanol, then dried. The crude material was recrystallized from ethanol-pyridine, giving the pure products **2a-p**.

2a: pale yellow powder, IR(KBr, cm^{-1}): 1625, 1264, 701; ^{1}H NMR (CF_3COOD, 400MHz): 7.31-7.43(m, 5H, Ar-H),7.65-8.17(m, 3H, Ar-H), 8.23-8.41 (m, 5H, Ar-H); MS (m/z): 480(M^+, 1%), 304(5%), 250(100%), 146(7%), 103(3%). Anal. Calcd For $C_{23}H_{13}N_9S_2$: C, 57.61; H, 2.73; N, 26.29. Found: C, 57.53; H, 2.89; N, 26.13.

2b: yellow powder, IR(KBr, cm^{-1}): 1627, 1260, 698; ^{1}H NMR (Pyridine-d_5, 400MHz): 7.43-7.56(m, 5H, Ar-H), 8.31-8.37(m, 3H, Ar-H), 8.45-8.61(m, 3H, Ar-H); MS (m/z): 548(M^+, 2%), 338(21%), 146(67%), 137(85%), 102(100%). Anal. Calcd For $C_{23}H_{11}N_9S_2Cl_2$: C, 52.56; H, 2.02; N, 22.99. Found: C, 52.67; H, 2.01; N, 22.84.

2c: pale yellow powder, IR(KBr, cm^{-1}): 1611, 1254, 700; ^{1}H NMR (Pyridine-d_5, 400MHz): 7.37-7.42(m, 3H, Ar-H), 8.21-8.35(m, 5H, Ar-H), 8.38-8.47(m, 3H, Ar-H); MS (m/z): 548(M^+, 3%), 338(32%), 146(70%), 136(90%), 102(100%). Anal. Calcd For $C_{23}H_{11}N_9S_2Cl_2$: C, 52.56; H, 2.02; N, 22.99. Found: C, 52.39; H, 2.21; N, 22.78.

2d: yellow powder, IR(KBr, cm^{-1}): 1621, 1236, 701; ^{1}H NMR (Pyridine-d_5, 400MHz): 7.41-7.56(m, 4H, Ar-H), 8.23-8.31(m, 3H, Ar-H), 8.39-8.45(m, 2H, Ar-H), 8.53-8.621(m, 2H, Ar-H); MS (m/z): 548(M^+, 2%), 356(2%), 338(28%), 146(79%), 136(100%), 102(7%). Anal. Calcd For $C_{23}H_{11}N_9S_2Cl_2$: C, 52.56; H, 2.02; N, 22.99. Found: C, 52.41; H, 2.16; N, 22.82.

2e: pale yellow powder, IR(KBr, cm^{-1}): 1618, 1349, 701; ^{1}H NMR (Pyridine-d_5, 400MHz): 2.55(s, 6H, $2CH_3$), 7.40-7.54(m, 5H, Ar-H), 8.10-8.17(m, 4H, Ar-H), 8.32-8.41(m, 2H, Ar-H); MS (m/z): 507(M^+, 5%), 318(21%), 147(33%), 117(91%), 102(100%). Anal. Calcd For $C_{25}H_{17}N_9S_2$: C, 59.16; H, 3.38; N, 24.83. Found: C, 59.23; H, 3.25; N, 24.82.

2f: yellow powder, IR(KBr, cm^{-1}): 1624, 1339, 700; ^{1}H NMR (Pyridine-d_5, 400MHz): 2.54(s, 6H, $2CH_3$), 7.46-7.51(m, 4H, Ar-H), 8.02-8.11(m, 5H, Ar-H), 8.26-8.39(m, 2H, Ar-H); MS (m/z): 507(M^+, 2%), 318(33%), 147(25%), 117(100%), 102(6%). Anal. Calcd For $C_{25}H_{17}N_9S_2$: C, 59.16; H, 3.38; N, 24.83. Found: C, 59.11; H, 3.47; N, 24.89.

2g: yellow powder, IR(KBr, cm^{-1}): 1630, 1356, 702; ^{1}H NMR (Pyridine-d_5, 400MHz): 2.57(s, 6H, $2CH_3$), 7.59-7.56(m, 3H, Ar-H), 8.07-8.05(m, 3H, Ar-H), 8.30-8.24(m, 3H, Ar-H), 8.59-8.44(m, 2H, Ar-H); MS

(m/z): 507(M^+, 3%), 318(29%), 147(18%), 117(100%), 102(4%). Anal. Calcd For $C_{25}H_{17}N_9S_2$: C, 59.16; H, 3.38; N, 24.83. Found: C, 59.28; H, 3.39; N, 24.72.

2h: pale yellow powder, IR (KBr, cm^{-1}): 1619, 1353, 696; ^1H NMR (Pyridine-d_5, 400MHz): 7.34-7.51(m, 386 ar-H), 8.04-8.21(m, 5H, Ar-H), 8.40-8.45(m, 3H, Ar-H); MS (m/z): 637(M^+, 13%), 401(7%), 382(30%), 182(59%), 146(26%), 102(100%). Anal. Calcd For $C_{23}H_{11}N_9S_2Br_2$: C, 43.34; H, 1.74; N, 19.78. Found: C, 43.29; H, 1.68; N, 19.86.

2i: yellow powder, IR (KBr, cm^{-1}): 1626, 1343, 700; ^1H NMR (Pyridine-d_5, 400MHz): 7.54-7.50(m, 4H, Ar-H), 8.09-8.04(m, 3H, Ar-H), 8.31-8.25(m, 2H, Ar-H), 8.48-8.41(m, 2H, Ar-H); MS (m/z): 637(M^+, 17%), 382(36%), 182(20%),146(100%), 102(64%). Anal. Calcd For $C_{23}H_{11}N_9S_2Br_2$: C, 43.34; H, 1.74; N, 19.78. Found: C, 43.45; H, 1.76; N, 19.66.

2j: pale yellow powder, IR(KBr, cm^{-1}): 1616, 1242, 700; ^1H NMR (CF_3COOD, 400MHz): 7.41-7.53(m, 4H, Ar-H), 8.20-8.27(m, 3H, Ar-H), 8.43-8.51(m, 2H, Ar-H), 8.63-8.71(m, 2H, Ar-H); MS (m/z): 731(M^+, 12%), 447(6%), 430 (64%), 146(71%), 129(32%), 102(100%). Anal. Calcd For $C_{23}H_{11}N_9S_2I_2$: C, 37.77; H, 1.52; N, 17.24. Found: C, 37.69; H, 1.41; N, 17.31.

2k: yellow powder, IR(KBr, cm^{-1}): 1625, 1251, 702; ^1H NMR (CF_3COOD, 400MHz): 7.47-7.58(m, 2H, Ar-H), 8.14-8.16(m, 3H, Ar-H), 8.35-8.42(m, 2H, Ar-H), 8.71-8.75(m, 4H, Ar-H); MS (m/z): 731(M^+, 34%), 447(18%), 430 (75%), 146(78%), 129(20%), 102(100%). Anal. Calcd For $C_{23}H_{11}N_9S_2I_2$: C, 37.77; H, 1.52; N, 17.24. Found: C, 37.89; H, 1.59; N, 17.10.

2l: yellow powder, IR(KBr, cm^{-1}): 1621, 1262, 700; ^1H NMR (CF_3COOD, 400MHz): 7.32-7.46(m, 3H, Ar-H), 8.10-8.16(m, 4H, Ar-H), 8.28-8.37(m, 2H, Ar-H), 8.68-8.74(m, 2H, Ar-H); MS (m/z): 731(M^+, 1%), 430 (100%), 146(42%), 129(19%), 102(52%). Anal. Calcd For $C_{23}H_{11}N_9S_2I_2$: C, 37.77; H, 1.52; N, 17.24. Found: C, 37.63; H, 1.47; N, 17.35.

2m: yellow powder, IR(KBr, cm^{-1}): 1614, 1254, 700; ^1H NMR (Pyridine-d_5, 400MHz): 3.89(s, 6H, $2OCH_3$), 7.40-7.43(m, 2H, Ar-H), 8.03-8.12(m, 3H, Ar-H), 8.25-8.32(m, 3H, Ar-H), 8.29-8.41(m, 2H, Ar-H); MS (m/z): 540(M^+, 13%), 334 (51%), 146(21%), 132(100%), 103(16%). Anal. Calcd For $C_{25}H_{17}N_9S_2O_2$: C, 55.65; H, 3.18; N, 23.36. Found: C, 55.61; H, 3.09; N, 23.39.

2n: yellow powder, IR(KBr, cm^{-1}): 1631, 1256, 700; ^1H NMR (Pyridine-d_5, 400MHz): 7.39-7.41(m, 3H, Ar-H), 8.18-8.24(m, 3H, Ar-H), 8.28-8.36(m, 3H, Ar-H), 8.40-8.44(m, 2H, Ar-H); MS (m/z): 481(M^+, 100%), 323(15), 305(45), 146(23%), 104(11%). Anal. Calcd For $C_{21}H_{11}N_{11}S_2$: C, 52.38; H, 2.30; N, 32.01. Found: C, 52.41; H, 2.11; N, 32.21.

2o: pale yellow powder, IR(KBr, cm^{-1}): 1625, 1248, 701; ^1H NMR (Pyridine-d_5, 400MHz): 7.40-7.43(m, 3H, Ar-H), 8.14-8.21(m, 4H, Ar-H), 8.26-8.34(m, 2H, Ar-H), 8.29-8.41(m, 2H, Ar-H); MS (m/z): 481(M^+, 100%), 323(15), 305(45), 146(23%), 104(11%). Anal. Calcd For $C_{21}H_{11}N_{11}S_2$: C, 52.38; H, 2.30; N, 32.01. Found: C, 52.41; H, 2.11; N, 32.21.

2p: pale yellow powder, IR(KBr, cm^{-1}): 1615, 1256, 700; ^1H NMR (Pyridine-d_5, 400MHz): 6.37-7.23(m, 6H, furyl-H), 8.27-8.42(m, 3H, Ar-H); MS (m/z): 459(M^+, 50%), 312(9%), 294(64), 147(32%), 146(100%), 93(27%). Anal. Calcd For $C_{19}H_9N_9O_2S_2$: C, 49.67; H, 1.97; N, 27.44. Found: C, 49.78; H, 2.13; N, 27.31.

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Received on March 2, 2006