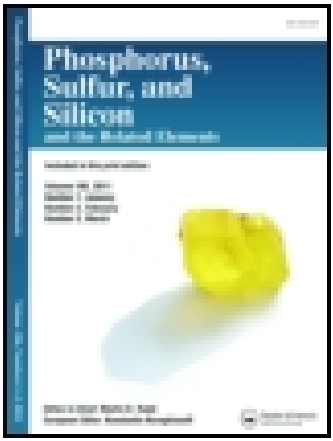

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The Synthesis and Antibacterial Activities of 2,5-Bis[(3-aryl)-1,2,4-triazolo[3,4-b]-[1,3,4] thiadiazole-6-yl]thiophenes

Dejiang Li [a] & Heqing Fu [b]
[a] College of Chemistry and Life Science , China Three Gorges University , Yichang, P. R. China
[b] Research Institute of Chemical Engineering , South China University of Technology , Guangzhou, P. R. China

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The Synthesis and Antibacterial Activities of 2,5-Bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4] thiadiazole-6-yl]thiophenes

Dejiang Li[1] and Heqing Fu[2]
[1]College of Chemistry and Life Science, China Three Gorges University, Yichang, P. R. China
[2]Research Institute of Chemical Engineering, South China University of Technology, Guangzhou, P. R. China

2,5-bis[(3-aryl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]thiophenes ***2*** *were synthesized in high yields by cyclization of 3-aryl 4-amino-5-mercapto-1,2,4-triazole* ***1*** *with thiophene-2,5-dicarboxylic acid in the presence of* $POCl_3$ *and tetrabutylammonium iodide as catalyst. The preliminary antibacterial tests showed that most of them were effective against* S. aureus, E. coli *and* B. subtilis. *Compounds* ***2b, 2c, 2d, 2m, 2n,*** *and* ***2o*** *exhibited promising antibacterial activity. Compounds* ***2*** *were screened for their fungicidal activities against* Gibberella zeae, Cerospora beticola sacc, Physalospora piricola *and* Pellicularia sasakii. *Compounds* ***2b, 2c,*** *and* ***2d*** *showed a high degree of inhibition against* Cerospora beticola sacc.

Keywords 2,5-Bis[(3-aryl)-1,2,4-triazolo-[3,4-*b*]-[1,3,4]thiadiazole-6-yl]thiophenes; antibacterial activities; synthesis

INTRODUCTION

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]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.[2] 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.[3] Prompted by these

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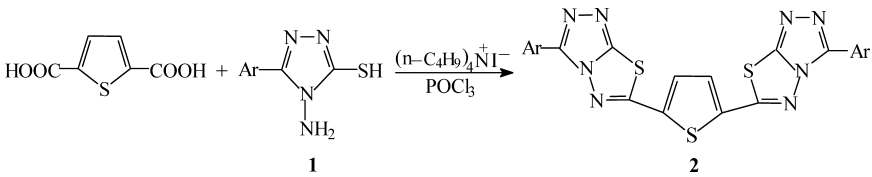
Address correspondence to Dejiang Li, College of Chemistry and Life Science, China Three Gorges University, Yichang 443002, P. R. China. E-mail: lidejiang999@yahoo.com.cn

observations and in continuation of our search for bioactive molecules, we designed a facile one-pot method to prepare a series of novel 2,5-bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]thiophene by cyclization of 3-aryl-4-amino-5-mercapto-1,2,4-triazoles with thiophene-2,5-dicarboxylic acid. The synthesis, characterization and the results of antibacterial activities screening studies of the newly synthesized compounds are presented in this paper.

RESULTS AND DISCUSSION

The synthesis of 2,5-bis[(3-aryl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]thiophenes **2** were accomplished in one-step with good yields by condensing 3-aryl-4-amino-5-mercapto-1,2,4-triazoles **1** with thiophene-2,5-dicarboxylic acid in the presence of $POCl_3$ and tetrabutylammonium iodide as catalyst (Scheme 1) (Table 1). Because of the poor solubility of **1** and thiophene 2,5-dicarboxylic acid in $POCl_3$, the yield of **2** is very low. For example, the yield of **2a** was 41%. However, where the tetrabutylammonium iodide as phase transfer catalyst were utilized and the mixture was first stirred for 6 h at 55–60°C, then refluxed for 10–14 h at 115–120°C. For example, **2a** was obtained in 87% yield.



1 2

SCHEME 1

The IR spectral data of compounds **2** showed bands at 1615–1645 cm^{-1}, 1235–1260 cm^{-1}, and 700–720 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 8.40–7.60 range accounting for hydrogen of aryl group. The ^{13}C NMR spectra displayed the characteristic signals of all carbons. With compound **2a** as an example, it exhibited multiple signals in the δ 8.39–8.37, 8.09–7.78 ranges accounting for the 12 hydrogens of phenyl and thiophene group. The EI-MS for compounds **2** exhibited molecular ion peaks. With compound **2a** as an example, it showed a strong molecular ion peak M^+ with m/z 484 and 33% 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 were effective against *S. aureus, E. coli and B. subtilis* (see Table II).

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

Entry	Ar	Condition	Yield (%)[a]	M.p. (°C)
2a	Ph	115–120°C/13 h	87	>300
2b	2-Cl—Ph	115–120°C/11 h	72	>300
2c	3-Cl—Ph	115–120°C/12 h	85	>300
2d	4-Cl—Ph	115–120°C/12 h	76	>300
2e	2-CH_3—Ph	115–120°C/14 h	64	>300
2f	3-CH_3—Ph	115–120°C/14 h	67	>300
2g	4-CH_3—Ph	115–120°C/13 h	70	>300
2h	3-Br—Ph	115–120°C/12 h	68	>300
2i	4-Br—Ph	115–120°C/13 h	70	>300
2j	2-I—Ph	115–120°C/12 h	65	>300
2k	3-I—Ph	115–120°C/11h	71	>300
2l	4-I—Ph	115–120°C/12 h	77	>300
2m	4-OCH_3—Ph	115–120°C/13 h	80	>300
2n	4-Pyridyl	115–120°C/10 h	71	>300
2o	3-Pyridyl	115–120°C/10 h	65	>300

[a]Purified yields of **2a**–**2o** based on thiophene-2,5-dicarboxylic acid.

Compounds **2** were screened for their fungicidal activities against Gibberella zeae, *Cerospora beticola sacc, Physalospora piricola* and *Pellicularia sasakii.* Among all the compounds tested, **2b, 2c** and **2d** showed a high degree of inhibition against *Cerospora beticola sacc* (see Table III).

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

Compd.	*S .aureus*	*E. coli*	*B. subtilis*
2a	52	47	78
2b	94	75	95
2c	92	87	96
2d	94	91	97
2e	34	42	46
3f	68	40	75
2g	56	25	31
2h	54	43	70
2i	75	52	81
2j	36	32	52
2k	35	46	57
2l	41	32	36
2m	90	68	85
2n	95	97	94
2o	93	95	96

TABLE III The Fungicidal Activities of 2 (50 mg/L, Relative Inhibition %)

Entry	*Gibberella zeae*	*Cerospora beticola sacc*	*Physalospora piricola*	*Pellicularia sasakii*
2a	30	75	62	40
2b	56	95	82	81
2c	63	96	79	90
2d	74	97	81	82
2e	30	79	68	32
2f	35	76	62	42
2g	39	71	56	25
2h	41	76	55	43
2i	35	85	43	39
2j	31	87	50	43
2k	31	84	51	30
2l	28	81	52	32
2m	38	76	32	40
2n	52	92	76	51
2o	61	90	73	55

CONCLUSION

In conclusion, tetrabutylammonium iodide is an efficient catalyst for the synthesis of 2,5-bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]thiophene by reaction of 3-aryl-4-amino-5-mercapto-1, 2, 4-triazoles with thiophene-2,5-dicarboxylic acid. Among all the compounds tested, **2b, 2c, 2d, 2n** and **2o** showed were effective against *S. aureus, E. coli, and B. subtilis*. Hence, **2b, 2c, 2d, 2m, 2n,** and **2o** stand to be a promising antibacterial agent. Among all the compounds tested, **2b, 2c,** and **2d** showed a high degree of inhibition against *Cerospora beticola sacc*.

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 4000–4400 cm^{-1}. ^1H NMR spectra were recorded on a Varian Mercury-Plus (400 MHz) spectrometer in CF_3COOD or pyridine-d_5 solution using TMS as an internal reference, and ^{13}C NMR spectra were recorded on a Varian Mercury-Plus (100 MHz) 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-CHN Elemental Analysis Instrument.

The General Procedure for the Preparation of 3-Aryl-4-amino-5-mercapto-1,2,4-triazoles from Aromatic Carboxylic Acids by Four Steps According to the Literature[3-5]

The General Procedure for the Preparation of 2,5-Bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]thiophene 2

A mixture of compound 3-aryl-4-amino-5-mercapto-1,2,4-triazole (2.2 mmol), thiophene-2,5-dicarboxylic acid (0.182 g, 1.0 mmol), the phase transfer catalyst tetrabutylammonium iodide (0.185 g, 0.5 mmol), and $POCl_3$ (7 mL) was stirred for 6 h at 55–60°C, and then refluxed for 10–14 h at 115–120°C. Excess $POCl_3$ was removed under reduced pressure. The concentrated mass was cooled, 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 (ethanol-pyridine), giving the pure products **2a-o**.

2,5-Bis[(3-phenyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]thiophene (2a)

Yellow powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.39–8.37 (m, 4H, Ar—H), 8.09–7.78 (m, 8H, Ar—H); ^{13}C NMR (100 MHz, ppm): 164.1, 159.3, 152.5, 147.4, 145.6, 138.1, 128.6, 127.4, 122.3; IR (KBr, cm^{-1}): 1630, 1244, 712; MS-EI (*m/z*): 484 (M^+, 33%), 327 (30%), 309 (15%), 152 (100%), 103 (29%). Elemental anal. calcd. for $C_{22}H_{12}N_8S_3$: C, 54.53; H, 2.50; N, 23.12. Found: C, 54.71; H, 2.52; N, 23.01.

2,5-Bis[(3-o-chlorophenyl)-1,2,4-triazolo[3,4-b]-[1,3,4] thiadiazole-6-yl]thiophene (2b)

Pale yellow powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.38–8.34 (m, 4H, Ar—H), 8.07–7.66 (m, 6H, Ar—H); ^{13}C NMR (100 MHz, ppm): 160.6, 157.8, 147.9, 146.3, 142.7, 138.2, 132.9, 128.7, 128.5, 126.7, 125.1; IR (KBr, cm^{-1}): 1621, 1234, 708. MS-EI (*m/z*): 556 (M+4, 3%), 554 (M+2, 14%), 552 (M^+, 22%), 361 (15%), 343 (14%), 152 (100%), 102 (16%). Elemental anal. calcd. for $C_{22}H_{10}N_8S_3Cl_2$: C, 47.74; H, 1.82; N, 20.24. Found: C, 47.89; H, 1.76; N, 20.08.

2,5-Bis[(3-m-chlorophenyl)-1,2,4-triazolo[3,4-b]-[1,3,4] thiadiazole-6-yl]thiophene (2c)

Pale yellow powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.33–8.27 (m, 4H, Ar—H), 8.18–8.12 (m, 3H, Ar—H), 7.85–7.78 (m, 3H, Ar—H);^{13}C NMR (100 MHz, ppm): 162.1, 158.3, 156.4, 153.3, 148.7, 139.1, 126.7, 135.1, 129.3, 128.9, 124.5; IR (KBr, cm^{-1}): 1620, 1231, 711. MS-EI (*m/z*): 556 (M+4, 4%), 554 (M+2, 10%), 552 (M^+, 19%), 361 (12%), 343 (21%), 152 (100%), 102 (4%). Elemental anal. calcd. for $C_{22}H_{10}N_8S_3Cl_2$: C, 47.74; H, 1.82; N, 20.24. Found: C, 47.91; H, 1.85; N, 20.11.

2,5-Bis[(3-p-chlorophenyl)-1,2,4-triazolo[3,4-b]-[1,3,4] thiadiazole-6-yl]thiophene (2d)

Yellow powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.38–8.35 (m, 4H, Ar—H), 8.10 (s, 2H, Ar—H), 7.80–7.77 (m, 4H, Ar—H);^{13}C NMR (100 MHz, ppm): 159.2, 157.3, 155.1, 148.7, 145.6, 136.1, 134.5, 129.7, 127.5; IR (KBr, cm^{-1}): 1631, 1246, 715. MS-EI (*m/z*): 556 (M+4, 4%), 554 (M+2, 21%), 552 (M^+, 25%), 361 (18%), 343 (25%), 152 (100%), 102 (5%). Elemental anal. calcd. for $C_{22}H_{10}N_8S_3Cl_2$: C, 47.74; H, 1.82; N, 20.24. Found: C, 47.60; H, 1.79; N, 20.38.

2,5-Bis[(3-o-methylphenyl)-1,2,4-triazolo[3,4-b]-[1,3,4] thiadiazole-6-yl]thiophene (2e)

Yellow powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.37–8.34 (m, 2H, ArH), 8.19–8.15 (m, 3H, Ar—H), 7.62–7.57 (m, 5H, Ar—H), 2.58 (s, 6H, $2CH_3$); ^{13}C NMR (100 MHz, ppm): 156.1, 153.3, 149.1, 142.7, 140.5, 138.7, 135.4, 129.1, 128.2, 126.4, 123.2, 20.79 (CH_3); IR (KBr, cm^{-1}): 1642, 1251, 718. MS-EI (*m/z*): 512 (M^+, 25%), 341 (12%), 323 (51%), 152 (100%). Elemental anal. calcd. for $C_{24}H_{16}N_8S_3$: C, 56.23; H, 3.14; N, 21.86. Found: C, 56.05; H, 3.18; N, 21.98.

2,5-Bis[(3-m-methylphenyl)-1,2,4-triazolo[3,4-b]-[1,3,4] thiadiazole-6-yl]thiophene (2f)

Pale yellow powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.41–8.38 (m, 3H, ArH), 8.21–8.16 (m, 2H, Ar—H), 7.79–7.74 (m, 5H, Ar—H), 2.57 (s, 6H, $2CH_3$); ^{13}C NMR (100 MHz, ppm): 153.7, 150.5, 148.7, 145.3, 140.2, 137.6, 128.1, 126.3, 123.2, 21.5(CH_3); IR (KBr, cm^{-1}): 1628, 1236, 714. MS-EI (*m/z*): 512 (M^+, 39%), 341 (28%), 323 (40%), 152 (100%). Elemental anal. calcd. for $C_{24}H_{16}N_8S_3$: C, 56.23; H, 3.14; N, 21.86. Found: C, 56.41; H, 3.20; N, 21.71.

2,5-Bis[(3-p-methylphenyl)-1,2,4-triazolo[3,4-b]-[1,3,4] thiadiazole-6-yl]thiophene (2g)

Yellow powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.30–8.27 (m, 4H, ArH), 8.09 (s, 2H, Ar—H), 7.65–7.62 (m, 4H, Ar—H), 2.60 (s, 6H, $2CH_3$);^{13}C NMR (100 MHz, ppm): 148.7, 145.4, 142.2, 140.7, 138.2,136.9, 133.1, 129.4, 126.5, 19.8(CH_3); IR (KBr, cm^{-1}): 1640, 1243, 717. MS-EI (*m/z*): 512 (M^+, 48%), 341 (41%), 323 (50%), 152 (100%). Elemental anal. calcd. for $C_{24}H_{16}N_8S_3$: C, 56.23; H, 3.14; N, 21.86. Found: C, 56.36; H, 3.01; N, 21.69.

2,5-Bis[(3-m-bromophenyl)-1,2,4-triazolo[3,4-b]-[1,3,4] thiadiazole-6-yl]thiophene (2h)

Brown powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.32–8.28 (m, 3H, Ar—H), 8.09–8.05 (m, 3H, Ar—H), 7.71–7.68 (m, 4H, Ar—H); ^{13}C NMR

(100 MHz, ppm): 160.2, 157.3, 153.1, 147.6, 145.1, 140.2, 131.2, 130.8, 128.7, 125.5. 123.3; IR (KBr, cm^{-1}): 1619, 1252, 704. MS-EI (*m/z*): 644 (M+4, 5%), 642 (M+2, 5%), 640 (M^+, 6%), 405 (19%), 387 (42%), 181 (63), 152 (100%). Elemental anal. calcd. for $C_{22}H_{10}N_8S_3Br_2$: C, 41.13; H, 1.57; N, 17.44. Found: C, 41.02; H, 1.63; N, 17.59.

2,5-Bis[(3-p-bromophenyl)-1,2,4-triazolo[3,4-b]-[1,3,4] thiadiazole-6-yl]thiophene (2i)

Brown powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.30–8.27 (m, 4H, Ar—H), 8.09 (s, 2H, Ar—H), 7.65–7.62 (m, 4H, Ar—H);^{13}C NMR (100 MHz, ppm): 159.4, 156.5, 153.1, 147.2, 142.5, 137.1, 132.2, 128.9, 122.1; IR (KBr, cm^{-1}): 1621, 1230, 708. MS-EI (*m/z*): 644 (M+4, 7%), 642 (M+2, 6%), 640 (M^+, 7%), 405 (16%), 387 (53%), 181 (72), 152 (100%). Elemental anal. calcd. for $C_{22}H_{10}N_8S_3Br_2$: C, 41.13; H, 1.57; N, 17.44. Found: C, 41.29; H, 1.49; N, 17.30.

2,5-Bis[(3-o-iodophenyl)-1,2,4-triazolo[3,4-b]-[1,3,4] thiadiazole-6-yl]thiophene (2j)

Yellow powder, ^1H NMR (Pyridine-d_5, 400 MHz): δ 8.31–8.28 (m, 3H, Ar—H), 8.24–8.21 (m, 2H, Ar—H), 7.53–7.49 (m, 5H, Ar—H); ^{13}C NMR (100 MHz, ppm):161.3, 157.2, 154.1, 150.2, 147.8, 142.6, 139.9, 130.9, 127.7, 98.6; IR (KBr, cm^{-1}): 1638, 1241, 716. MS-EI (*m/z*): 736 (M^+, 29%), 453 (3%), 435 (11%), 152 (60%), 102 (100%). Elemental anal. calcd. for $C_{22}H_{10}N_8S_3I_2$: C, 35.88; H, 1.37; N, 15.22. Found: C, 36.05; H, 1.30; N, 15.03.

2,5-Bis[(3-m-iodophenyl)-1,2,4-triazolo[3,4-b]-[1,3,4] thiadiazole-6-yl]thiophene (2k)

Yellow powder, ^1H NMR (Pyridine-d_5, 400 MHz): δ 8.29–8.26 (m, 2H, Ar—H), 8.16–8.12 (m, 5H, Ar—H), 7.67–7.62 (m, 3H, Ar—H);^{13}C NMR (100 MHz, ppm):159.4, 155.1, 150.2, 147.6, 145.3, 143.2, 140.9, 138.7, 136.7, 127.4, 96.8; IR (KBr, cm^{-1}): 1627, 1239, 713. MS-EI (*m/z*): 736 (M^+, 31%), 453 (7%), 435 (10%), 152 (48%), 102 (100%). Elemental anal. calcd. for $C_{22}H_{10}N_8S_3I_2$: C, 35.88; H, 1.37; N, 15.22. Found: C, 36.03; H, 1.42; N, 15.10.

2,5-Bis[(3-p-iodophenyl)-1,2,4-triazolo[3,4-b]-[1,3,4] thiadiazole-6-yl]thiophene (2l)

Yellow powder, ^1H NMR (Pyridine-d_5, 400 MHz): δ 8.35–8.31 (m, 4H, Ar—H), 8.07 (s, 2H, Ar—H), 7.61–7.58 (m, 4H, Ar—H);^{13}C NMR (100 MHz, ppm):157.6, 155.3, 153.1, 149.2, 147.5, 139.1, 129.4, 97.2; IR (KBr, cm^{-1}): 1641, 1254, 717. MS-EI (*m/z*): 736 (M^+, 36%), 453 (4%), 435 (12%), 152 (59%), 102 (100%). Elemental anal. calcd. for $C_{22}H_{10}N_8S_3I_2$: C, 35.88; H, 1.37; N, 15.22. Found: C, 35.71; H, 1.33; N, 15.38.

2,5-Bis[(3-p-methoxyhenyl)-1,2,4-triazolo[3,4-b]-[1,3,4] thiadiazole-6-yl]thiophene (2m)

Pale yellow powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.32–8.29 (m, 4H, Ar—H), 8.07 (s, 2H, Ar—H), 7.51–7.49 (m, 4H, Ar—H), 3.97 (s, 6H, $2OCH_3$);^{13}C NMR (100 MHz, ppm):162.1, 160.7, 157.7, 148.9, 145.1, 129.1, 126.5, 113.2, 58.7(OCH_3); IR (KBr, cm^{-1}): 1630, 1241, 706. MS-EI (*m/z*): 544 (M^+, 42%), 357 (6%), 339 (8%), 152 (100%). Elemental anal. calcd. for $C_{24}H_{16}N_8O_3S_2$: C, 52.93; H, 2.96; N, 20.57. Found: C, 51.80; H, 2.89; N, 20.71.

2,5-Bis[(3-(3–4/-pyridyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]thiophene (2n)

Yellow powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.27–8.24 (m, 4H, Ar—H), 7.78–7.72 (m, 6H, Ar—H); ^{13}C NMR (100 MHz, ppm): 164.3, 160.2, 159.1, 148.0, 143.2, 135.7, 123.9; IR (KBr, cm^{-1}): 1621, 1236, 703. MS-EI (*m/z*): 486 (M^+, 21%), 328 (8%), 310 (25%), 152 (100%). Elemental anal. calcd. for $C_{20}H_{10}N_{10}S_3$: C, 49.37; H, 2.07; N, 28.79. Found: C, 49.50; H, 2.01; N, 28.62.

2,5-Bis[(3-(3–3/-pyridyl)-1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazole-6-yl]thiophene (2n)

Yellow powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.22–8.19 (m, 3H, Ar—H), 8.15–8.12 (m, 3H, Ar—H), 7.68–7.64 (m, 4H, Ar—H); ^{13}C NMR (100 MHz, ppm): 161.2, 158.1, 156.9, 153.2, 150.1, 149.3, 146.7, 143.2, 124.8; IR (KBr, cm^{-1}): 1630, 1229, 707. MS-EI (*m/z*): 486 (M^+, 16%), 328 (5%), 310 (30%), 152 (100%). Elemental anal. calcd. for $C_{20}H_{10}N_{10}S_3$: C, 49.37; H, 2.07; N, 28.79. Found: C, 49.21; H, 2.12; N, 28.92.

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