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OXIDATIVE SELF-ANNULATION OF 2,5-DIARYL-3,4-DIAMINOTHIOPHENE VIA C–C AND C–S BOND CLEAVAGE OF THE THIOPHENE RING: A NEW SYNTHESIS OF AN AMINO-SUBSTITUTED TRIARYLTHIENO[3,4-*b*]PYRAZINES AND THEIR PHOTOPHYSICAL PROPERTIES

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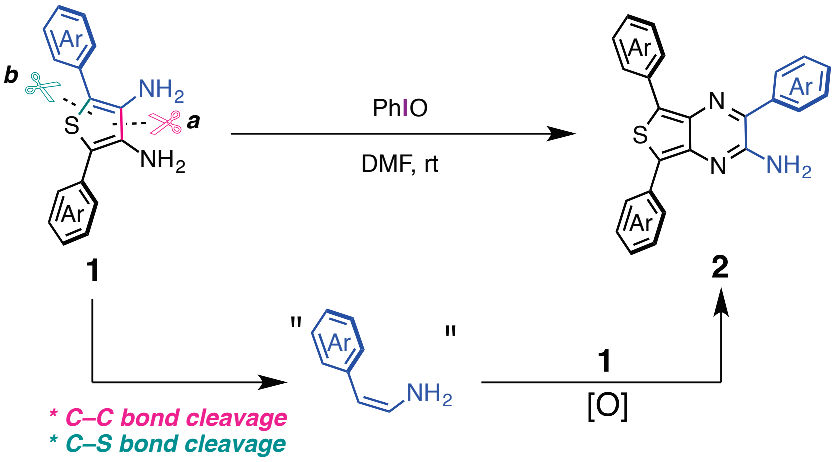
Abstract – A novel oxidative self-annulation of 2,5-diaryl-3,4-diaminothiophenes that accompanies C–C and C–S bonds cleavage of a thiophene ring to produce 3,5,7-triaryl-2-aminothieno[3,4-*b*]pyrazines in moderate to good yields has been discovered. Photophysical properties of this new family of thienopyrazines have also been disclosed.

Due to highly electron-deficient nature, thieno[3,4-*b*]pyrazine (TP) skeleton has been recognized as a privileged acceptor (A) unit for the construction of functional donor–acceptor (D–A) π-conjugated materials such as low-bandgap polymers,[1] red/NIR-absorbing sensitizers,[2] and red-emitters[3] for optoelectronic applications over the last few decades. In addition to the utility in materials sciences, more recently, a series of 2-alkoxy-3-arylethynyl TPs has been shown to exhibit promising activities for the inhibition of a calcium-dependent crosslinking enzyme, human transglutaminase 2 (TGase 2), in cancer cells.[4] The realization of such a diverse use of TPs as functional molecules mainly owes a great deal to recent advancement in synthetic methodologies and procedures for TPs.[5,6] For example, Rasmussen and co-workers reported versatile synthetic methods for symmetric 2,3-difunctionalized (Br, OSO_2CF_3, CH_2Br, CN, OR, RNH, etc.) TPs[6b,c] that are difficult to directly prepare through a traditional condensation method between the corresponding 3,4-diaminothiophenes and 1,2-diketones.[7]

This paper is dedicated to the celebration of the 70th birthday of Professor Dr. Masakatsu Shibasaki.

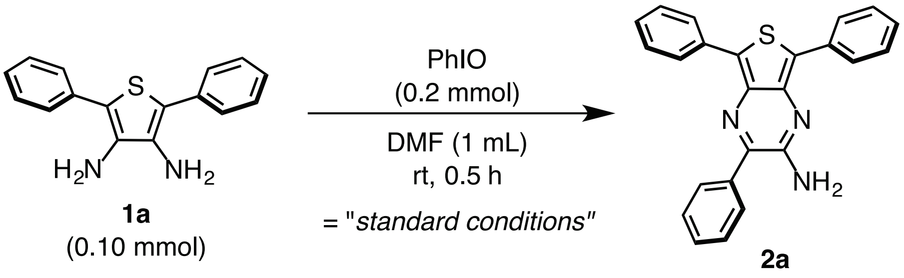
Herein we present a new synthetic strategy for a new class of TPs, that is, 3,5,7-triaryl-2-amino TPs, through a novel oxidative self-annulation of 2,5-diaryl-3,4-diaminothiophenes **1** (Scheme 1). Most importantly, this oxidative self-annulation formally involved the C–C (***a***, shown in pink) and C–S (***b***, shown in green) bonds cleavage of a thiophene unit, and the formal oxidative fusion of the resulting C_2 unit (colored in blue) with another diaminothiophene molecule **1** would lead to amino-substituted TPs **2**. To the best of our knowledge, this is the first example to synthesize the TPs bearing an amino functionality on the pyrazine ring, although the synthetic methods for symmetric 2,3-diamino-substituted TPs thorough a Cu-catalyzed diamination of the corresponding dihalothienopyrazines[6b,c] and through a condensation of 2,3-diaminothiophene with bis(2,2,2-trifluoroethyl) oximidate[8] have been known.



Scheme 1. Oxidative self-annulation of 2,5-diaryl-3,4-diaminothiophenes

During our studies on developing oxidative transformations of aromatic (di)amines toward the construction of nitrogen-containing π-conjugated systems,[9] we serendipitously found out that a hitherto unknown TP **2a** was produced in a moderate yield (75%) when 2,5-diphenyl-3,4-diaminothiophene (**1a**, 0.10 mmol)[10] was treated with PhIO (0.20 mmol) as an oxidant at room temperature in DMF for 30 min (entry 1, Table 1; these conditions are referred to "*standard conditions*").[11] The structure of **2a** was fully characterized with a set of conventional spectroscopy (NMR, IR, and MS, etc).[12] Furthermore, the X-ray single crystallographic analysis of the product (**2e**, Figure 1) obtained from 2,5-bis(*p*-bromophenyl)-3,4-diaminothiophene (**1e**) as a substrate unambiguously confirmed the 3,5,7-triaryl-2-amino TP structure.[13] Under a more diluted condition, the yield of **2a** slightly decreased (entry 2). Among the tested hypervalent iodine(III) oxidants, $PhI(OAc)_2$ gave a comparable yield with that gained using PhIO (entry 2 vs entries 3–5), suggesting an alternative option of using $PhI(OAc)_2$ as an oxidant in some cases. As the reaction temperature lowered, the product yields decreased (entry 1 vs entries 6 and 7).

Table 1. The effects of the reaction conditions



entry	alternations from the "*standard conditions*"	yield (%)[a]	recovery of **1a** (%)
1	none	75	0
2	3 mL of DMF	67	0
3^b	$PhI(OAc)_2$ instead of PhIO	66	0
4^b	$PhI(OCOCF_3)_2$ instead of PhIO	4	0
5^b	PhI(OH)OTs instead of PhIO	0	70
6	*T* = 0 ˚C	64	0
7	*T* = –20 ˚C	46	0

[a] Yields were calculated based on the assumption that 2 molecules of **1a** gives one molecule of **2a** (i.e., if 0.10 mmol of **1a** is transformed into **2a** quantitatively, 0.05 mmol of **2a** is supposed to be produced). [b] 3 mL of DMF was used.

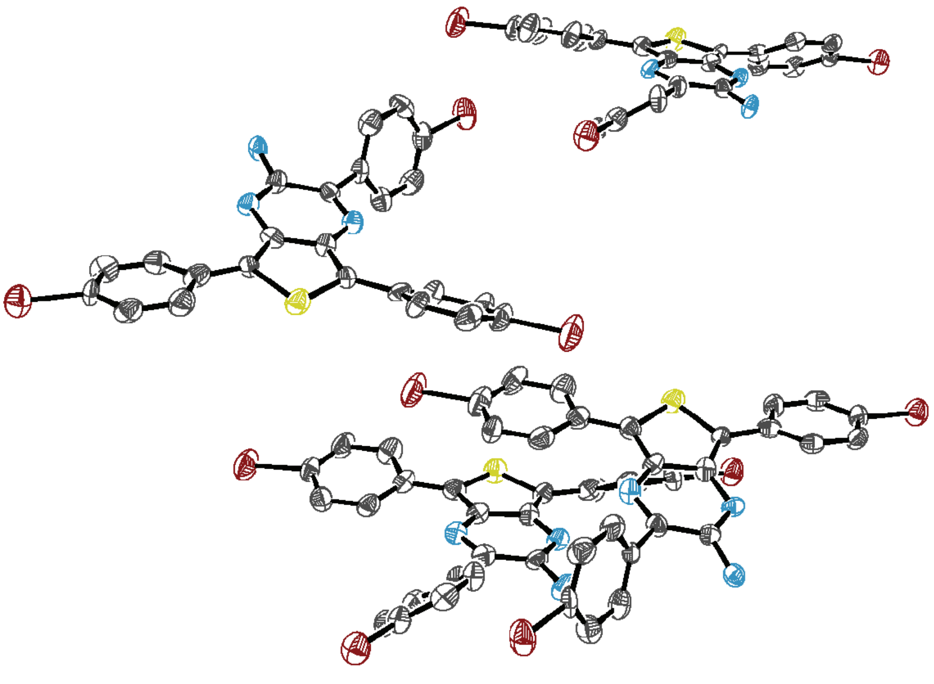
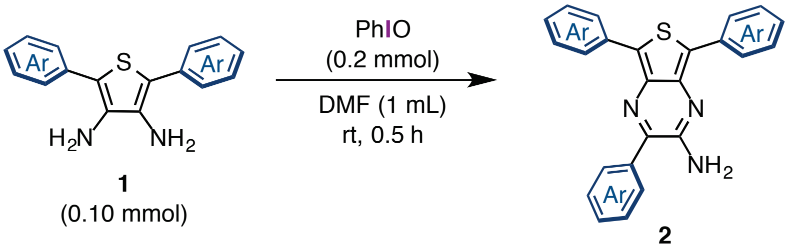


Figure 1. ORTEP drawing of **2e** (H atoms are omitted for clarity; thermal ellipsoids are set at the 50% probability level)

Table 2 shows the results of a brief survey of the substrates scope. Diaminothiophenes **1b**–**1e** bearing a variety of *p*-substituents gave the corresponding annulated products **2** in moderate yields under the standard conditions (entries 1–4).[14] It is noted that triaryl-halogenated TPs **2d** and **2e** might serve as a unique monomer for 2D-polymers or dendrimers. On the other hand, the reaction using sterically demanding *o*-tolyl group-substituted diamine **1f** gave a complex mixture and the product yield was significantly lowered (entry 5). Electronically-rich terthiophene-type diamine **1g** did not gave annulated product at all (entry 6). To obtain some mechanistic aspects of the unexpected reaction, we conducted a cross-over experiment using an equimolar mixture of **1a** (0.05 mmol) and **1e** (0.05 mmol) under the optimal reaction conditions. The analysis of ^{1}H NMR of the crude product of the reaction implied that the all four possible cross-over aminothienopyrazines compounds were formed in an almost equal proportion (i.e., 1:1:1:1). This result could suggest that the oxidative self-annulation proceeds step-by-step like illustrated in Scheme 1: oxidative cleavage of a thiophene ring followed by the formation of an "enamine" equivalent intermediate that reacts with another molecule of **1** under oxidative conditions might lead to **2**.

Table 2. Scope of the oxidative self-annulation



entry	Ar (**1**)	**2**	yield (%)
1	*p*-$MeOC_6H_4$ (**1b**)	**2b**	56
2	*p*-MeC_6H_4 (**1c**)	**2c**	48
3	*p*-ClC_6H_4 (**1d**)	**2d**	60
4	*p*-BrC_6H_4 (**1e**)	**2e**	62
5	*o*-MeC_6H_4 (**1f**)	**2f**	complex mixture[a]
6	2-thienyl (**1g**)	**2g**	0

[a] Inseparable from some impurities; Estimated ^{1}H NMR yield was 11%.

Basic photophysical properties of the new family of TPs were investigated using their diluted CH_2Cl_2 solutions (10^{-5} M). Representative UV-Vis/PL spectra are shown in Figure 2 and the summary of their photophysical data are listed in Table 3. The absorption spectrum of triphenyl-substituted TP **2a** showed peaks at 460, 360, and 322 nm (Figure 2a), which were assignable to the HOMO→LUMO (red doted arrow), HOMO–1→LUMO (blue doted arrow), and HOMO→LUMO+1 (green doted arrow) transitions by TD-DFT calculations at the B3LYP/6-31+G(d) level using PCM (CH_2Cl_2) model (Figure 2b).[15] The moderately efficient orange-red emission (λ_{em} = 629 nm, Φ_{PL} = 0.46) was observed upon photo-excitation (inserted photograph in Figure 2a). The amino-substituted TP **2a** also showed slightly red-shifted emission even in the solid state (λ_{em} = 635 nm, Φ_{PL} = 0.12), suggesting the possible use of the newly developed TPs as organic emitting materials in the future. The introduction of an electron-donating-group (MeO) on the phenyl rings (**2b**) caused a slight red shift of absorption as well as a significant red shift of the emission (λ_{em} 653 nm) and deteriorated Φ_{PL} (0.12), reflecting the increased charge-transfer nature in the excited states. The emission wavelengths ranged from 627 to 653 nm, depending on the substituents introduced (Table 3).

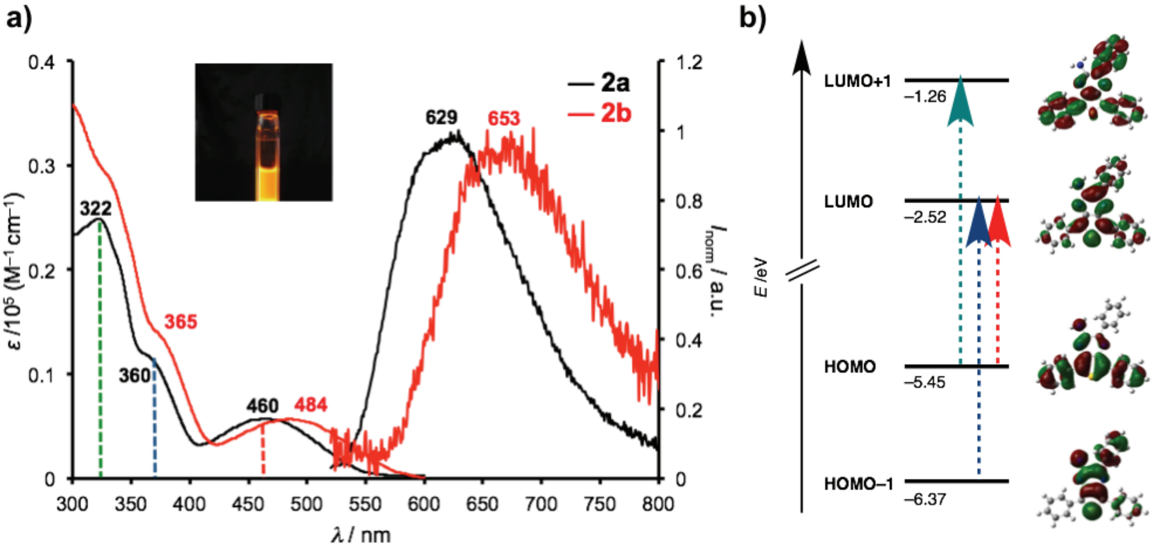


Figure 2. a) UV-Vis/PL spectra of **2a** and **2b** (CH_2Cl_2 solutions, 10^{-5} M); the inset photograph shows the CH_2Cl_2 solution of **2a** under the irradiation of UV light (365 nm); b) Summary of DFT calculations of **2a**

Table 3. A summary of photophysical data of **2**[a]

2	λ_{abs} [nm (ε, $M^{-1}cm^{-1}$)]	λ_{em} (nm)[b]	Φ_{PL}[b]
2a	322 (24800), 360 (12000), 460 (5700)	629 (635)[c]	0.46 (0.12)[c]
2b	365 (15000), 484 (5700)	653	0.12
2c	364 (12500), 470 (5500)	635	0.34
2d	329 (27200), 360 (14100), 466 (6400)	627	0.48
2e	332 (33400), 362 (16900), 471 (7700)	631	0.50

[a] Measured with dilute CH_2Cl_2 solutions (10^{-5} M). [b] Excited at 470 nm. [c] Solid state.

In conclusion, we have developed a new synthetic method for triaryl-substituted mono-aminothienopyrazines based on a discovery of a novel oxidative self-annulation of

2,5-diaryl-3,4-diaminothiophenes. The new family of thienopyrazine compounds is found emissive in orange to red region. The analysis of reaction mechanisms of the reaction, detailed physicochemical properties of **2**, and the creation of functional materials by taking advantage of the amino functionality of **2** will be studied in due course.

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10. 2,5-Diaryl-3,4-diaminothiophenes **1** are prepared according to the literature method: J. Li, Q. Li, and D. Liu, *ACS Appl. Mater. Interfaces*, 2011, **3**, 2099.
11. A representative procedure for the oxidative self-annulation: To a 10 mL reaction tube equipped with a magnetic stirrer, diamine **1a** (26.6 mg, 0.10 mmol) was added. The tube was capped with a septum and subjected to an evacuation-refill (N_2 gas) cycle for three times. DMF (1 mL) was added to the tube through the septum to solve diamine **1a** under the flow of N_2 gas. To the solution, PhIO (44 mg, 0.20 mmol) was added at room temperature, and the resulting mixture was stirred for 30 min. The reaction mixture was washed with water (10 mL), and organic layer was extracted with CH_2Cl_2 (5 mL × 3 times). The organic layer was dried over anhydrous Na_2SO_4 and filtrated. Volatiles were evaporated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel (*n*-hexane/EtOAc 9:1) to give **2a** in 75% yield. For the photophysical measurements, samples were repeatedly recrystallized from CH_2Cl_2/*n*-hexane (*v*/*v* 1:4).
12. Compound data of **2a**: bright orange solid; Mp 218.2–218.7 °C; R_f 0.33 (hexane/AcOEt 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.07 (bs, 2H), 7.28–7.32 (m, 2H), 7.41–7.45 (m, 4H), 7.47–7.56 (m, 3H), 7.84 (d, J = 7.8 Hz, 2H), 8.15 (d, J = 7.2 Hz, 2H), 8.18 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 120.6, 126.4, 126.5, 127.4, 127.7, 128.5, 128.7, 128.8, 128.9, 129.6, 130.7, 132.9, 133.8, 136.6, 137.0, 138.9, 147.9, 150.0; IR (ATR, cm^{-1}): ν 3447, 3290, 3150, 3061, 1632, 1540, 1486, 1423, 1333, 1326, 1264, 1022, 906, 800, 754, 738, 725; MS (EI): *m*/*z* (relative intensity, %) 380 ([M+1]$^+$, 30), 379 ([M]$^+$, 100); HRMS (EI): calcd for $C_{24}H_{17}N_3S$ [M]$^+$ 379.1143, found 379.1142.
13. Crystal data of compound **2e**: Crystal dimensions 0.30 × 0.30 × 0.05 mm^3; $C_{24}H_{14}Br_3N_3S$, M = 616.17; triclinic space group $P1$, a = 14.7254(3) Å, b = 18.6532(4) Å, c = 19.1840(4) Å, α = 62.9625(7)°, β = 88.7708(7)°, γ = 69.6167(7)°, V = 4340.1(2) Å^3, Z = 8, D_{calc} = 1.886 g/cm^3, T = 123 K, 15605 unique and 7846 observed [$I > 2\sigma(I)$] reflections, 1185 parameters, final [$I > 2\sigma(I)$] R_1 = 0.0565, wR_2 = 0.0858, S = 1.480. The X-ray diffraction data of the single crystal of **2e**, which has grown from a CH_2Cl_2/*n*-hexane mixed solution, were collected on a Rigaku R-AXIS RAPID diffractometer with graphite monochromated CuKα radiation (λ = 1.54187 Å) to a $2\theta_{max}$ value of 136.5° at 123 K. The crystal structure was solved by direct methods (SIR92) and refined by full-matrix least-squares method on F^2 (SIR92). The non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using the riding model. Full details of the crystallographic results have been deposited with the Cambridge Crystallographic Data Center [CCDC-1044241].
14. Compound data of **2**:

    2b: bright red solid; Mp 200.3–200.7 °C; R_f 0.10 (hexane/AcOEt 8:2); ^{1}H NMR (400 MHz, $CDCl_3$):

δ 3.85 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 5.01 (bs, 2H), 6.96–7.00 (m, 4H), 7.06 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 8.8 Hz, 2H), 8.05 (d, J = 8.8 Hz, 2H), 8.11 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3 (2C), 55.4, 114.1, 114.2, 114.3, 122.3, 126.6, 126.8, 128.5, 128.9, 129.7, 130.1, 131.2, 133.4, 136.9, 145.9, 148.9, 158.4, 159.0, 160.7; IR (ATR, cm^{-1}): ν 3490, 3377, 2833, 1600, 1499, 1417, 1294, 1246, 1172, 1029, 800, 773; MS (EI): m/z (relative intensity, %) 470 ([M+1]$^+$, 33), 469 ([M]$^+$, 100), 454 ([M–CH_3]$^+$, 38); HRMS (EI): calcd for $C_{27}H_{23}N_3O_3S$ [M]$^+$ 469.1460, found 469.1462.

2c: bright red solid; Mp 209.7–210.0 °C; R_f 0.40 (hexane/AcOEt 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.39 (s, 3H), 2.45 (s, 3H), 5.02 (s, 2H), 7.21–7.23 (m, 4H), 7.33 (d, J = 7.6 Hz, 2H), 7.72 (d, J = 7.6 Hz, 2H) 8.01 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.8 (2C), 21.0, 120.2, 126.3, 127.2, 128.4, 129.2, 129.3, 129.4, 130.0, 130.3, 131.2, 134.3, 135.7, 136.4, 137.1, 138.4, 139.2, 147.6, 149.9; IR (ATR, cm^{-1}): ν 3461, 3297, 3165, 1629, 1503, 1423, 1327, 1264, 1183, 1034, 829, 811, 737; MS (EI): m/z (relative intensity, %) 421 ([M]$^+$, 100); HRMS (EI): calcd for $C_{27}H_{23}N_3S$ [M]$^+$ 421.1613, found 421.1609.

2d: bright red solid; Mp 227.5–227.8 °C; R_f 0.45 (hexane/AcOEt 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.04 (bs, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 8.4 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 119.5, 127.8, 128.6, 128.8, 128.94, 128.99, 129.7, 130.5, 130.8, 131.6, 132.3, 132.6, 134.5, 135.6, 136.6, 139.3, 147.3, 150.2; IR (ATR, cm^{-1}): ν 3463, 3306, 3161, 1635, 1591, 1484, 1419, 1394, 1320, 1257, 1088, 1011, 842, 825, 812, 757, 738; MS (EI): m/z (relative intensity, %) 485 ([M+4]$^+$, 37), 483 ([M+2]$^+$, 100), 481 ([M]$^+$, 96), 448 ([M–Cl+2]$^+$, 3), 446 ([M–Cl]$^+$, 6); HRMS (EI): calcd for $C_{24}H_{14}Cl_3N_3S$ [M]$^+$ 480.9974, found 480.9979.

2e: bright red solid; Mp 221.3–221.8 °C; R_f 0.48 (hexane/AcOEt 8:2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.90 (s, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 8.4 Hz, 2H), 8.18 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 119.8, 120.0, 121.4, 123.7, 128.5, 129.6, 130.2, 131.2, 131.9, 132.2, 132.3, 132.4, 133.4, 136.4, 137.2, 139.8, 147.7, 150.6; IR (ATR, cm^{-1}): ν 3493, 3371, 3363, 1617, 1586, 1483, 1410, 1396, 1388, 1314, 1263, 1174, 1072, 1006, 823, 814, 747; MS (EI): m/z (relative intensity, %) 617 ([M]$^+$, 100); HRMS (EI): calcd for $C_{24}H_{14}Br_3N_3S$ [M]$^+$ 612.8459, found 612.8455.

15. DFT calculations were conducted with Gaussian 09, revision A. 02: M. J. Frisch, et al. Gaussian, Inc., Wallingford CT, 2009.