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SYNTHESIS OF NOVEL BITHIOPHENE-SUBSTITUTED HETEROCYCLES BEARING CARBONITRILE GROUPS

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Abstract

Symmetrical and unsymmetrical bithiophene-substituted heterocycles bearing carbonitriles including imidazo[1,2-a]pyridine, benzimidazole, and pyridine derivatives have been synthesized via different synthetic protocols. The bithiophene bis-imidazo[1,2-a]pyridine derivatives 3a,b were achieved in three steps starting from 2-acetyl-5-bromothiophene. Suzuki coupling reaction of 2a with 5-formylthiophen-2-ylboronic acid forms the formyl derivative 5, which by condensation with 3,4-diaminobenzonitrile in the presence of sodium bisulfite furnishes the unsymmetrical bithiophene derivative 6. The bis-benzimidazole derivative 8 was obtained via hexabutylditin-mediated homocoupling of 5-bromothiophene-2-carboxaldehyde, while the benzimidazole derivatives 12a,b were prepared via the formyl derivatives 11a,b, a product of Velsmier formylation reaction of 10a,b. Two synthetic protocols for the aryl/hetaryl-2,2′-bithiophene derivative 14 have also been presented. In addition, the guanyl hydrazones of bithiophenes, 16 and 17, were prepared from bis(tri-n-butylstannyl)-2,2′-bithiophene through a Stille coupling reaction followed by a condensation step.

Keywords

Bithiophene; formylation; Heck coupling; Stille coupling; Suzuki coupling

INTRODUCTION

Bi- and oligothiophenes have recently received increased attention because of their wide applications as advanced materials.[1] They have been heavily investigated as organic semiconductors, with particular application to thin-film transistors (TFTs)[1b,c] and light-emitting devices (LEDs).[1d] Bithiophenes and their derivatives are also important synthetic precursors for biologically active materials.[2] Nitrile-containing compounds serve as precursors of diamidine-containing molecules, which exhibit broad-spectrum antimicrobial activity, including effectiveness against different protozoan diseases.[3–6] Moreover, bifuran diamidines **I** (Fig. 1) and analogs showed specific recognition of G-quadruplex DNA.[7] Very recently, the bithiophene diamidines of type **II** (Fig. 1) showed good activity against *Trypanosoma cruzi*.[8] In this context and in continuation of our interest in preparing biologically active diamidines, we recently reported an efficient homocoupling approach to 5,5′-diaryl-2,2′-bichalcophenes of type **I**.[9] This route allows only the synthesis of symmetrical analogs. Different triaryl/hetaryl systems of nitrile-containing bichalcophenes

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also have been reported.[10] Given the promising properties of pyridines,[11] imidazo[1,2-a]pyridines,[12] and benzimidazoles,[13] we decided to synthesize nitrile-containing bithiophenes of the aforementioned heterocycles. Because of their activity against trypanosomes,[14] this report also described the synthesis of two examples of guanyl hydrazones of a bithiophene derivative.

RESULTS AND DISCUSSION

A three-step preparation of the symmetrical imidazo[1,2-a]pyridyl bithiophene derivatives **3a,b** starting from 2-acetyl-5-bromothiophene is described as outlined in Scheme 1; thus, 2-acetyl-5-bromothiophene was brominated by using bromine in a mixed solvent of dioxane/ether (1:2) to give compound **1** in 71% yield. A condensation reaction of 6-aminonicotinonitrile or its methyl analog with **1** yielded the bromothiophen-2-yl-imidazo[1,2-a]pyridine-6-carbonitrile**s 2a,b,** which underwent a Stille-type homocoupling reaction in the presence of hexabutylditin with a catalytic amount of $Pd(PPh_3)_4$ (~2 mol%), using refluxing toluene as solvent to afford the anticipated bithiophene derivatives **3a,b** in 72 and 75% yields, respectively. On the other hand, the unsymmetrical imidazo[1,2-a]pyridyl-benzimidazolyl bithiophene derivative **6** was obtained in two steps utilizing Suzuki coupling reaction of **2a** with 5-formylthiophen-2-ylboronic acid to form the anticipated 2-(5′-formyl-2,2′-bithiophen-5-yl)imidazo[1,2-a]pyridine-6-carbonitrile **(5)**, which subsequently condensed with 3,4-diaminobenzonitrile in the presence of an equimolar ratio of sodium bisulfite to give the desired dinitrile **6**. An alternative synthesis of the formyl bithiophene derivative **5** was tried through a Stille coupling reaction of **2** with 2-tributyltin thiophene, forming the product **4,** followed by a Vilsmeier formylation reaction. However, the last step gives an inseparable mixture that may be attributed to the nucleophilic reactivity at C-3 of the imidazo[1,2-a]pyridine part of compound **4**. This is consistent with the reported literature.[15]

Scheme 2 outlines the preparation of 2-(2,2′-bithiophene-5,5′-diyl)-bis(1*H*-benzo[d]imidazole-6-carbonitrile) **(8)** via hexabutylditin-mediated homocoupling of 5-bromothiophene-2-carboxaldehyde in the presence of catalytic $Pd(PPh_3)_4$ using refluxing toluene as solvent at 90 °C to form 5,5′-diformyl-2,2′-bithiophene (**7**). Subsequent condensation of the diformyl **7** with 2 equivalents of 3,4-diaminobenzonitrile in the presence of sodium bisulfite gave the desired bithiophene-substituted benzimidazole **8**.

The preparation of bithiophene-substituted benzimidazole derivatives **12a,b** is presented in Scheme 3. Thus, compound **12b** was obtained in three steps starting with the Stille coupling reaction of 5-(tri-*n*-butylstannyl)-2,2′-bithiophene with 6-chloronicotinonitrile to form the anticipated 6-(2,2′-bithiophen-5-yl)nicotinonitrile (**10b**). A Vilsmeier formylation reaction of **10b** furnished the formyl derivative **11b**, which, upon condensation with 3,4-diaminobenzonitrile in the presence of sodium bisulfite, gave the desired dinitrile **12b**. Two synthetic approaches for the synthesis of 6-[5′-(4-cyanophenyl)-2,2′-bithiophen-5-yl]nicotinonitrile (**14**) are also presented in Scheme 3. The first approach uses bromination of **10b** with *N*-bromosuccinimide in dimethylformamide (DMF) to furnish 6-(5′-bromo-2,2′-bithiophen-5-yl)nicotinonitrile (**13**) in 93% yield followed by Suzuki coupling of **13** with 4-cyanophenylboronic acid to afford **14** in 69% yield. The second approach employs a Heck coupling reaction directly from the reaction of compound **10b** with 4-bromobenzonitrile to afford **14** in 28% yield.

Guanylhydrazones are normally included in the DNA minor-groove binding category and have frequently been found to have activity against trypanosomes.[14] Thus, the preparation of the guanylhydrazone derivative **16** involved the condensation reaction between diformyl derivative **15**, a Stille product of bis(tri-*n*-butylstannyl)-2,2′-bithiophene with 4-

bromobenzaldehyde, and aminoguanidine hydrochloride in the presence of Et_3N. In a similar manner, compound **17** was synthesized from the corresponding starting material. It should be noted that 4 equivalents of aminoguanidine or 2-hydrazino-2-imidazoline are necessary to drive the reaction to completion to form guanylhydrazones.

In conclusion, we have described concise synthetic approaches for novel bithiophene-substituted benzimidazole, imidazo[1,2-a]pyridine, and pyridine derivatives. The use of these nitrile-containing heterocycles in the synthesis of diamidines for biological evaluation will be reported in due course.

EXPERIMENTAL

General

Melting points were recorded using a Thomas-Hoover (Uni-Melt) capillary melting-point apparatus and are uncorrected. Thin-layer chromatography (TLC) analysis was carried out on silica-gel 60 F_{254} precoated aluminum sheets and detected under ultraviolet (UV) light. Infrared (IR) spectra were recorded on a Mattson 5000 Fourier transform FT–IR spectrometer. ^1H and ^{13}C NMR spectra were recorded employing a Varian Unity Plus 300 spectrometer at Georgia State University, and chemical shifts (δ) are in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on a VG analytical 70-SE spectrometer. Elemental analyses were obtained from Atlantic Microlab Inc. (Norcross, GA) and are within ±0.4 of the theoretical values. All chemicals and solvents were purchased from Aldrich Co., Fisher Scientific, Frontier and Lancaster. N-Bromosuccinimide (NBS) was recrystallized from nitromethane prior to use. All solvents were reagent grade. 4-(2,2′-Bithiophen-5-yl)benzonitrile[10] (**10a**), 5-(tri-*n*-butylstannyl)-2,2′-bithiophene[16], and bis(tri-*n*-butylstannyl)-2,2′-bithiophene[17] were prepared according to the reported literature.

2-Bromo-1-(5-bromothiophen-2-yl)-ethanone (1)

Bromine (2.08 mL, 40 mmol) was added portionwise to a solution of 2-acetyl-5-bromothiophene (8.20 g, 40 mmol) in 48 mL dioxane/ether (1:2) with cooling at 0–5 °C and stirring over 1 h. The reaction mixture was further stirred with cooling. After TLC indicated complete bromination, the reaction mixture was diluted with ether (200 mL) and water (200 mL). The ethereal layer was separated, washed with 1 M sodium bicarbonate aqueous solution, and dried over Na_2SO_4. The ether extract was distilled off to afford **1** in 71% yield as a colorless sheet, mp 89–90 °C (hexanes/ether) (lit.[18] mp 90–91 °C); IR (KBr) ν 3083, 3000, 2952, 1670 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.28 (s, 2H), 7.14 (d, J =4.2 Hz, 1H), 7.54 (d, J =4.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 183.4, 142.1, 133.7, 131.5, 124.5, 29.6. MS (EI) *m*/*e* (rel. int.): 284, 286 (M^+, 14, 7 bromine isotopes), 204 (2), 191 (100), 189 (92), 175 (7), 123 (4).

2-(5-Bromothiophen-2-yl)-imidazo[1,2-a]pyridine-6-carbonitrile (2a)

A mixture of 6-aminonicotinonitrile (1.19 g, 10 mmol) and 2-bromo-1-(5-bromothiophen-2-yl)-ethanone (**1**) (2.84 g, 10 mmol) in ethanol (50 mL) was heated at reflux for 24 h. The precipitated salt was filtered, suspended in water, and neutralized with aqueous $NaHCO_3$ solution. The free base precipitate was filtered and dried to furnish **2a** in 79% yield as an off-white solid, mp 249–250.5 °C (EtOH). IR (KBr) ν 3089, 3048, 2225 (CN), 1625, 1573, 1529 cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.28 (d, J =4.2 Hz, 1H), 7.49–7.55 (m, 2H), 7.72 (d, J =9.6 Hz, 1H), 8.42 (s, 1H), 9.33 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 143.8, 140.5, 138.2, 133.9, 131.4, 125.2, 125.1, 117.0, 116.7, 111.6, 109.4, 97.3. MS (EI) *m*/*e* (rel. int.): 303, 305 (M^+, 54, 52 bromine isotopes), 224 (100), 180 (30). Anal. calcd. for $C_{12}H_6BrN_3S$: C, 47.38; H, 1.99; N, 13.81. Found. C, 47.61; H, 2.10; N, 13.64.

2-(5-Bromothiophen-2-yl)-8-methylimidazo[1,2-a]pyridine-6-carbonitrile (2b)

The same procedure described for preparation of **2a** was used starting with 6-amino-5-methylnicotinonitrile instead of 6-aminonicotinonitrile. Yield 68% as off-white needles, mp 213–214.5 °C. IR (KBr) *v* 3100, 3083, 2925, 2223 (CN), 1643, 1617 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.46 (s, 3H), 7.21 (d, J =3.6 Hz, 1H), 7.28 (s, 1H), 7.40 (d, J =3.6 Hz, 1H), 8.31 (s, 1H), 9.09 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 144.4, 139.8, 138.3, 131.4, 131.1, 127.1, 124.8, 122.9, 116.7, 111.2, 109.8, 97.1, 15.9. MS (ESI) *m*/*e* (rel. int.): δ 318, 320 (M^+ + 1, 100, 96 bromine isotopes). Anal. calcd. for $C_{13}H_8BrN_3S$: C, 49.07; H, 2.53; N, 13.21. Found. C, 49.40; H, 2.69; N, 13.02.

2,2′-(2,2′-Bithiophene-5,5′-diyl)-bis(imidazo[1,2-a]pyridine-6-carbonitrile) (3a)

Hexa-*n*-butylditin (2.9 g, 5 mmol) was added to a solution of **2a** (1.52 g, 5 mmol) and tetrakis(triphenylphosphine) palladium (100 mg, 0.085 mmol) in toluene (40 mL). The reaction mixture was heated under N_2 at 120 °C for 6 h, then cooled, and the precipitate was filtered and washed with hexanes. Recrystallization from DMF gave compound **3a** in 72% as a dark-green powder, mp > 320 °C. IR (KBr) *v* 3083, 3050, 2225 (CN), 1629, 1567 cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.36–7.69 (m, 8H), 8.37 (s, 2H), 9.23 (s, 2H). MS (ESI) *m*/*e* (rel. int.): 448 (M^+, 13), 449 (M^+ + 1, 87), 409 (24), 320 (100). High-resolution mass calcd. for $C_{24}H_{13}N_6S_2$: 449.0643. Observed: 449.0641. Anal. calcd. for $C_{24}H_{12}N_6S_2$: C, 64.27; H, 2.70. Found. C, 63.94; H, 2.81.

2,2′-(2,2′-Bithiophene-5,5′-diyl)-bis(8-methylimidazo[1,2-a]pyridine-6-carbonitrile) (3b)

The same procedure described for preparation of **3a** was used starting with **2b**. Yield 75% as a dark-green powder, mp 304–306 °C. IR (KBr) *v* 3072, 2954, 2921, 2225 (CN), 1623, 1573 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.54 (s, 6H, 2 × CH_3), 7.27–7.54 (m, 6H), 8.33 (s, 2H), 9.07 (s, 2H). MS (ESI) *m*/*e* (rel. int.): 477 (M^+ + 1, 33), 478 (M^+ + 2, 10), 452 (22), 409 (58), 331 (100). High-resolution mass calcd. for $C_{26}H_{17}N_6S_2$: 477.0956. Observed: 477.0967. Anal. calcd. for $C_{26}H_{16}N_6S_2$: C, 65.53; H, 3.38. Found. C, 65.22; H, 3.19.

2-(2,2′-Bithiophen-5-yl)imidazo[1,2-a]pyridine-6-carbonitrile (4)

A mixture of **2a** (3.03 g, 10 mmol), 2-tri-*n*-butyltin thiophene (3.72 g, 10 mmol), and tetrakis(triphenylphosphine) palladium (200 mg) in dry dioxane (50 mL) was heated under nitrogen at 100–110 °C for 24 h. The solvent was evaporated under reduced pressure, and the resulting residue was dissolved in ethyl acetate. This solution was passed through celite to remove Pd. The solution was evaporated, and the residue was chromatographed on silica gel using hexanes/EtOAc (3:7) as an eluent to furnish compound **4** in 76% yield as a pale yellow solid, mp 219–220.5 °C. ^1H NMR (DMSO-d_6): δ 7.08–7.11 (m, 1H), 7.27–7.34 (m, 2H), 7.43–7.54 (m, 3H), 7.68 (d, J =9.6 Hz, 1H), 8.35 (s, 1H), 9.24 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 143.9, 141.1, 136.6, 136.2, 135.1, 133.8, 128.3, 125.7, 125.5, 125.1, 124.8, 124.1, 116.9, 109.5, 97.1. MS (EI) *m*/*e* (rel. int.): 307 (M^+, 100), 308 (M^++1, 23), 274 (5), 262 (5), 131 (13). High-resolution mass calcd. for $C_{16}H_9N_3S_2$: 307.0237. Observed: 307.0234. Anal. calcd. for $C_{16}H_9N_3S_2$: C, 62.52; H, 2.95. Found. C, 62.60; H, 3.01.

2-(5′-Formyl-2,2′-bithiophen-5-yl)imidazo[1,2-a]pyridine-6-carbonitrile (5)

To a stirred solution of **2a** (1.51 g, 5 mmol), and tetrakis(triphenylphosphine) palladium (200 mg) in toluene (10 mL) under a nitrogen atmosphere, 10 mL of a 1 M aqueous solution of $NaHCO_3$ were added, followed by 5-formylthiophen-2-ylboronic acid (936 mg, 6 mmol) in 5 mL of methanol. The vigorously stirred mixture was warmed to 80 °C for 16 h. The solvent was evaporated, and the precipitate was partitioned between methylene chloride (300 mL) and aqueous solution containing 5 mL of concentrated ammonia. The organic layer was dried (Na_2SO_4) and then concentrated to dryness under reduced pressure to afford

5 in 61% yield as a brown-yellow solid, mp 268–270 °C (DMF). IR (KBr) *v* 3137, 3081, 2227 (CN), 1650 (CO), 1573 cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.46–7.69 (m, 6H), 8.43 (s, 1H), 9.26 (s, 1H), 9.87 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 183.2, 145.1, 143.8, 141.2, 140.5, 138.5, 138.0, 134.9, 133.7, 127.5, 125.8, 125.1, 124.9, 116.9, 116.5, 110.0, 97.2. MS (EI) *m*/*e* (rel. int.): 335 (M^+, 100), 307 (12), 262 (28). Anal. calcd. for $C_{17}H_9N_3OS_2$: C, 60.88; H, 2.70; N, 12.53. Found. C, 60.75; H, 2.73; N, 12.67.

2-{5′-(6-Cyanoimidazo[1,2-a]pyridin-2-yl)-2,2′-bithiophen-5-yl}-1H-benzimidazole-6-carbonitrile (6)

A solution of **5** (670 mg, 2 mmol), 3,4-diaminobenzonitrile (267 mg, 2 mmol), and sodium bisulfite (261 mg, 2.5 mmol) in 10 mL DMF was allowed to reflux overnight. After cooling, the reaction mixture was poured onto water. The solid was collected by filtration and washed with aqueous sodium bicarbonate (2.5%) and water to furnish **3a** in 77% yield as a brown solid, mp > 320 °C (DMF). IR (KBr) *v* 3353 (NH), 3083, 2962, 2221 (CN), 1619, 1567 cm^{-1}. ^1H NMR (DMSO-d_6): *δ* 7.45–7.85 (m, 8H), 8.04 (s, 1H), 8.41 (s, 1H), 9.26 (s, 1H), 13.30 (s, 1H, NH). MS (ESI) *m*/*e* (rel. int.); 449 (M^+ + 1, 60), 413 (30), 365 (32), 331 (100). High-resolution mass calcd. for $C_{24}H_{13}N_6S_2$: 449.0643. Observed: 449.0641. Anal. calcd. for $C_{24}H_{12}N_6S_2$: C, 64.27; H, 2.70. Found. C, 64.05; H, 2.79.

2,2′-Bithiophene-5,5′-dicarboxaldehyde (7)

The same procedure described for preparation of **3a** was used starting with 5-bromothiophene-2-carboxaldehyde (the temperature of the reaction maintained at 90 °C). Yield 70% as a golden solid, mp 212.5–214 °C (lit.[19] mp 215–217 °C; lit.[20] mp 185–195 °C). IR (KBr) *v* 3100, 1654 (CO), 1538, 1436 cm^{-1}. ^1H NMR (DMSO-d_6): *δ* 7.73 (d, *J* =3.9 Hz, 2H), 8.02 (d, *J* =3.9 Hz, 2H), 9.93 (s, 2H). ^{13}C NMR (DMSO-d_6): *δ* 184.3, 143.5, 143.4, 138.9, 127.9. MS (EI) *m*/*e* (rel. int.): 222 (M^+, 100), 193 (18), 149 (32).

2,2′-(2,2′-Bithiophen-5,5′-diyl)-bis(1H-benzimidazole-6-carbonitrile) (8)

The same procedure described for the preparation of **6** was used, employing dialdehyde derivative **7** (1 equiv) and 3,4-diaminobenzonitrile (2 equiv). Yield 75% as a brown powder, mp > 320 °C (DMF). IR (KBr) *v* 3455 (NH), 3089, 2215 (CN), 1614, 1563 cm^{-1}. ^1H NMR (DMSO-d_6): *δ* 7.31–7.71 (m, 6H), 7.88 (d, *J* =3.9 Hz, 2H), 8.08 (s, 2H), 13.70 (br s, 2H, 2NH). MS (EI) *m*/*e* (rel. int.): 448 (M^+, 100), 321 (38). Anal. calcd. for $C_{24}H_{12}N_6S_2$: C, 64.27; H, 2.70; N, 18.74. Found. C, 63.90; H, 2.85; N, 18.46.

6-(2,2′-Bithiophen-5-yl)nicotinonitrile (10b)

Adopting the same procedure used for the preparation of **4**, a Stille coupling reaction was performed using 6-chloronicotinonitrile and 5-(tri-*n*-butylstannyl)-2,2′-bithiophene to yield the cyano derivative **10b** in 85% yield as a yellow solid; mp 176–177 °C (EtOH). IR (KBr) *v* 2217 (CN), 1639, 1583, 1513 cm^{-1}. ^1H NMR (DMSO-d_6): *δ* 7.10–7.14 (m, 1H), 7.40 (d, *J* =3.9 Hz, 1H), 7.45 (d, *J* =3.9 Hz, 1H), 7.59 (dd, *J* =5.1, 1.2 Hz, 1H), 7.95 (d, *J* =3.9 Hz, 1H), 8.11 (d, *J* =8.4 Hz, 1H), 8.28 (dd, *J* =8.4, 2.1 Hz, 1H), 8.92 (d, *J* =2.1 Hz, 1H). ^{13}C NMR (DMSO-d_6): *δ* 154.3, 152.6, 141.13, 141.08, 140.5, 136.0, 129.4, 128.6, 126.7, 125.4, 125.3, 118.4, 117.3, 106.4. Anal. calcd. for $C_{14}H_8N_2S_2$: C, 62.66; H, 3.00; N, 10.44. Found. C, 62.57; H, 2.97; N, 10.45.

4-(5′-Formyl-2,2′-bithiophen-5-yl)benzonitrile (11a)

Freshly distilled DMF (4.2 mL) was stirred in an ice bath with dropwise addition of $POCl_3$ (14 mL), followed by a suspension of compound **10a** (1.86 g, 7 mmol) in methylene chloride (12 mL). The reaction mixture was stirred under heating at 85–95 °C for 6 h. The solvent was distilled off under reduced pressure, then poured onto ice water, and the solid

was collected by filtration and washed with aqueous sodium bicarbonate (2.5%) and water to furnish **11a** in 81% yield as a golden solid, mp 197–198 °C (EtOH). IR (KBr) *v* 3095, 2921, 2223 (CN), 1654 (CO), 1600 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.59 (d, *J* =3.3 Hz, 1H), 7.66 (d, *J* =3.9 Hz, 1H), 7.79 (d, *J* =3.9 Hz, 1H), 7.87 (s, 4H), 8.00 (d, *J* =3.3 Hz, 1H), 9.88 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 184.0, 144.7, 142.5, 141.8, 139.2, 137.1, 136.5, 133.2, 128.5, 127.8, 126.0, 125.8, 110.2, 99.5. MS (EI) *m*/*e* (rel. int.): 295 (M^+, 100), 267 (8), 222 (29). High-resolution mass calcd. for $C_{16}H_9NOS_2$: 295.0125. Observed: 295.0126. Anal. Calcd for $C_{16}H_9NOS_2$: C, 65.06; H, 3.07. Found. C, 65.15; H, 3.13.

6-(5′-Formyl-2,2′-bithiophen-5-yl)nicotinonitrile (11b)

The same procedure described for preparation of **11a** was used starting with **10b**. Yield 77% as a golden solid, mp 258–259.5 °C. IR (KBr) *v* 3085, 3050, 2794, 2223 (CN), 1656 (CO), 1587, 1515 cm^{-1}. ^{1}H NMR (DMSO-d_6): *δ* 7.65 (d, *J* =3.9 Hz, Hz, 1H), 7.68 (d, *J* =3.9 Hz, 1H), 8.00 (d, *J* =3.9 Hz, 1H), 8.03 (d, *J* =3.9 Hz, 1H), 8.16 (d, *J* =8.4 Hz, 1H), 8.31 (dd, *J* =8.4, 2.1 Hz, 1H), 8.95 (d, *J* =2.1 Hz, 1H), 9.90 (s, 1H). Anal. calcd. for $C_{15}H_8N_2OS_2$: C, 60.79; H, 2.72; N, 9.45. Found. C, 60.60; H, 2.82; N, 9.23.

2-[5′-(4-Cyanophenyl)-2,2′-bithiophen-5-yl]-1H-benzimidazole-6-carbonitrile (12a)

The same procedure described for preparation of **6** was used starting with **11a**. Yield 74% as a brown powder, mp 320–322 °C (DMF). IR (KBr) *v* 3415 (NH), 3075, 2221 (CN), 1596, 1577, 1536 cm^{-1}. ^{1}H NMR (DMSO-d_6): *δ* 7.52–7.61 (m, 3H), 7.70–7.88 (m, 6H), 7.97–8.08 (m, 2H), 13.40 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): *δ* 149.0, 141.1, 139.5, 138.8, 137.2, 136.9, 133.1, 130.7, 130.2, 130.0, 127.6, 126.9, 126.2, 125.8, 125.2, 120.0, 119.8, 118.7, 115.4, 109.9, 104.4. MS (EI) *m*/*e* (rel. int.): 408 (M^+, 100). High-resolution mass calcd. for $C_{23}H_{12}N_4S_2$: 408.0503. Observed: 408.0519. Anal. calcd. for $C_{23}H_{12}N_4S_2$: C, 67.62; H, 2.96. Found. C, 67.30; H, 3.07.

2-[5′-(5-Cyanopyridin-2-yl)-2,2′-bithiophen-5-yl]-1H-benzimidazole-6-carbonitrile (12b)

The same procedure described for preparation of **6** was used starting with **11b**. Yield 70% as a brown powder, mp > 320 °C (DMF). IR (KBr) *v* 3097, 2223 (CN), 1658, 1621, 1587 cm^{-1}. ^{1}H NMR (DMSO-d_6): *δ* 7.50–7.57 (m, 3H), 7.71 (d, *J* =8.1 Hz, 1H), 7.89 (d, *J* =3.9 Hz, 1H), 7.97 (d, *J* =3.9 Hz, 1H), 8.04 (s, 1H), 8.10 (d, *J* =8.4 Hz, 1H), 8.27 (dd, *J* =8.4, 2.1 Hz, 1H), 8.93 (d, *J* =2.1 Hz, 1H) 13.65 (s, 1H, NH). MS (EI) *m*/*e* (rel. int.): 409 (M^+, 100), 376 (4), 320 (10). High-resolution mass calcd. for $C_{22}H_{11}N_5S_2$: 409.0456. Observed: 409.0464. Anal. calcd. for $C_{22}H_{11}N_5S_2$: C, 64.53; H, 2.71. Found: C, 64.21; H, 2.86.

6-(5′-Bromo-2,2′-bithiophen-5-yl)nicotinonitrile (13)

NBS (1.78 g, 10 mmol) was added portionwise to a solution of **10b** (2.67 g, 10 mmol) in DMF (30 mL) with stirring. The reaction mixture was stirred overnight, then poured onto cold water. The precipitate that formed was collected, washed with water, and dried to give **13** in 93% yield as a yellow solid, mp 209–210 °C. IR (KBr) *v* 3077, 3045, 2229 (CN), 1641, 1585, 1550 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.26–7.33 (m, 2H), 7.43 (d, *J* =4.2 Hz, 1H), 7.98 (d, *J* =4.2 Hz, 1H), 8.15 (d, *J* =8.4 Hz, 1H), 8.31 (dd, *J* =8.4, 2.1 Hz, 1H), 8.93 (d, *J* =2.1 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 150.1, 148.6, 137.8, 136.6, 135.6, 133.7, 127.9, 125.3, 122.0, 121.8, 114.5, 113.2, 107.5, 102.6. MS (EI) *m*/*e* (rel. int.): 346, 348 (M^+, 100, 95 bromine isotopes), 267 (13), 223 (40). High-resolution mass calcd. for $C_{14}H_7BrN_2S_2$: 345.9234. Observed: 345.9234. Anal. calcd. for $C_{14}H_7BrN_2S_2$: C, 48.42; H, 2.03. Found. C, 48.29; H, 2.01.

6-[5′-(4-Cyanophenyl)-2,2′-bithiophen-5-yl]nicotinonitrile (14)

Method A—Adopting the same procedure used for the preparation of **5**, a Suzuki coupling reaction was performed using **13** and 4-cyanophenylboronic acid to yield **14** in 69% yield as a brick-red solid, mp 307–309.5 °C (DMF). IR (KBr) *v* 3062, 2225 (CN), 1635, 1587 cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.45–7.57 (m, 3H), 7.70–7.93 (m, 5H), 8.08–8.25 (m, 2H), 8.91 (s, 1H). MS (EI) *m*/*e* (rel. int.): 369 (M^+, 100). High-resolution mass calcd. for $C_{21}H_{11}N_3S_2$: 369.0394. Observed: 369.0382. Anal. calcd. for $C_{21}H_{11}N_3S_2$: C, 68.27; H, 3.00. Found. C, 67.88; H, 3.12.

Method B—A mixture of compound **10b** (1.34 g, 5 mmol), 4-bromobenzonitrile (925 mg, 5 mmol), tetrakis(triphenylphosphine) palladium (200 mg), and potassium acetate (2.5 g, 25 mmol) in dry DMF (20 mL) was heated under nitrogen at 130–135 °C overnight. The reaction mixture then poured onto cold water. The precipitate that formed was collected and recrystallized from DMF to afford compound **14** in 28% yield.

4,4′-(2,2′-Bithiophen-5,5′-diyl)dibenzaldehyde (15)

Adopting the same procedure used for the preparation of **4**, a Stille coupling reaction was performed using 4-bromobenzaldehyde (2 equiv) and bis(tri-*n*-butylstannyl)-2,2′-bithiophene (1 equiv) to yield **15** in 82% yield as a green-yellow solid; mp 244–246 °C (DMF). IR (KBr) *v* 3100, 3062, 2861, 1694 (CHO), 1598, 1563 cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.47 (d, *J* =3.6 Hz, 2H), 7.71 (d, *J* =3.6 Hz, 2H), 7.89 (d, *J* =7.5 Hz, 4H), 7.95 (d, *J* =7.5 Hz, 4H), 10.01 (s, 2H). MS (EI) *m*/*e* (rel. int.): 374 (M^+, 100), 346 (87). High-resolution mass calcd. for $C_{22}H_{14}O_2S_2$: 374.0435. Observed: 374.0412. Anal. calcd. for $C_{22}H_{14}O_2S_2$: C, 70.56; H, 3.77. Found. C, 70.75; H, 3.63.

N-[4,4′-(2,2′-Bithiophen-5,5′-diyl)dibenzylidene]-N′-amidino Hydrazine (16)

A mixture of **15** (374 mg, 1 mmol), aminoguanidine hydrochloride (440 mg, 4 mmol), and triethylamine (4 mmol) in absolute ethanol (40 mL) was heated at reflux overnight. The formed precipitate was filtered, washed with water, and dried to give **16** in 65% yield as a brown-yellow solid, mp > 320 °C (DMF/EtOH). IR (KBr) *v* 3432, 3365, 3342 (NH, NH_2), 3070, 1687, 1598 cm^{-1}. ^1H NMR (DMSO-d_6): δ 5.53 (br s, 4H), 5.95 (br s, 4H), 7.37 (d, *J* =4.2 Hz, 2H), 7.53 (d, *J* = 4.2 Hz, 2H), 7.62 (d, *J* =8.4 Hz, 4H), 7.71 (d, *J* =8.4 Hz, 4H), 7.98 (s, 2H). Anal. calcd. for $C_{24}H_{22}N_8S_2$: C, 59.24; H, 4.56; N, 23.03. Found: C, 59.50; H, 4.60; N, 22.73.

N-[4,4′-(2,2′-Bithiophen-5,5′-diyl)dibenzylidene]-N′-(4,5-dihydro-1H-imidazol-2-yl) Hydrazine (17)

The same procedure described for **16** was used, employing 2-hydrazino-2-imidazoline hydrobromide instead of aminoguanidine hydrochloride. Yield 69% as an orange solid, mp > 320 °C. IR (KBr) *v* 3430 (NH), 3143, 3066, 2923, 2883, 2829, 1635, 1573, 1544 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.44 (s, 8H), 6.23 (br s, 2H), 6.61 (br s, 2H), 7.34 (d, *J* =3.9 Hz, 2H), 7.49 (d, *J* =3.9 Hz, 2H), 7.63 (d, *J* =8.4 Hz, 4H), 7.71 (d, *J* =8.4 Hz, 4H), 8.00 (s, 2H). Anal. calcd. for $C_{28}H_{26}N_8S_2$: C, 62.43; H, 4.86; N, 20.80. Found: C, 62.09; H, 4.87; N, 20.94.

Acknowledgments

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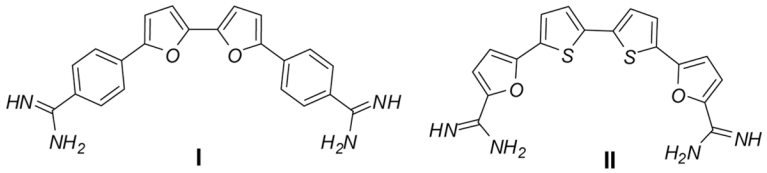
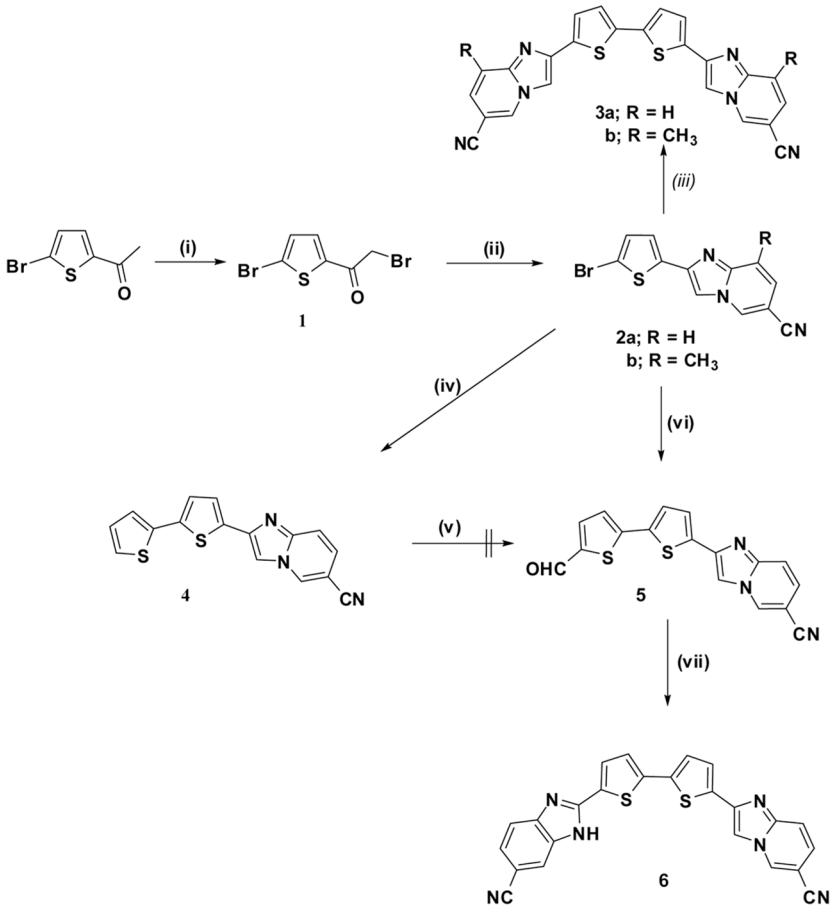
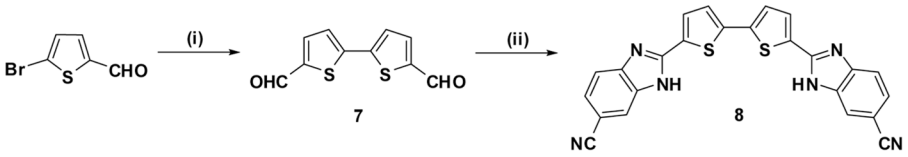


Figure 1.
Bithiophene diamidines of type **II**.



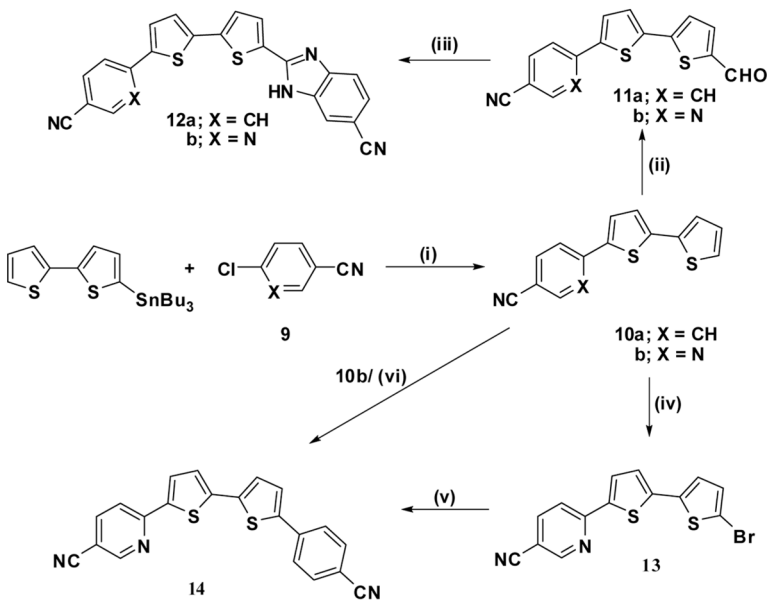
Scheme 1.

Reagents and conditions: (i) Br_2; (ii) EtOH, reflux; (iii) $(Bu_3Sn)_2$, $Pd(PPh_3)_4$; (iv) 2-tributyltin thiophene, $Pd(PPh_3)_4$; (v) DMF-$POCl_3$; (vi) 5-formylthiophen-2-ylboronic acid; (vii) 3,4-diaminobenzonitrile, sodium bisulfite, DMF, reflux.



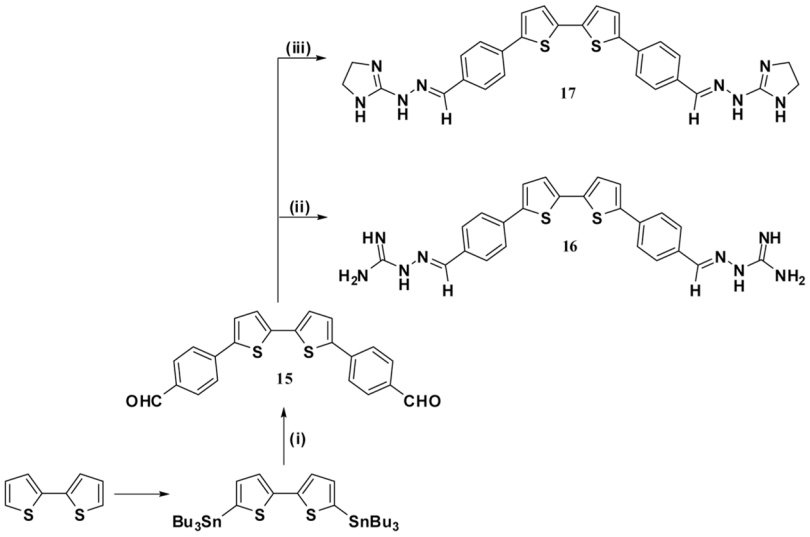
Scheme 2.

Reagents and conditions: (i) toluene, $(Bu_3Sn)_2$, $Pd(PPh_3)_4$; (ii) 3,4-diaminobenzonitrile, sodium bisulfite, DMF, reflux.



Scheme 3.

Reagents and conditions: (i) toluene, $Pd(PPh_3)_4$; (ii) DMF-$POCl_3$; (iii) 3,4-diaminobenzonitrile, sodium bisulfite, DMF, reflux; (iv) NBS, DMF; (v) 4-cyanophenylboronic acid, $Pd(PPh_3)_4$; (vi) 4-bromobenzonitrile, KOAc, $Pd(PPh_3)_4$, 125–135 °C.



Scheme 4.

Reagents and conditions: (i) 4-bromobenzaldehyde, toluene, $Pd(PPh_3)_4$; (ii) aminoguanidine hydrochloride/Et_3N, EtOH; (iii) 2-hydrazino-2-imidazoline hydrobromide/Et_3N, EtOH.