Bichalcophenes: A Concise Synthesis of Formyl Ester- and Cyano Ester-Substituted Bithiophenes, Bifurans, and Furanothiophenes

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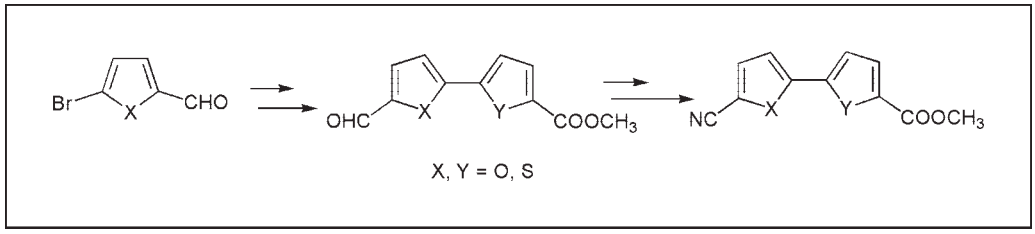

Syntheses of new formyl ester- and cyano ester-substituted bithiophenes, bifurans, and furanothiophenes in good yield are described. The key synthetic step uses Stille coupling of appropriately substituted bromo 5-ring heterocycles with stannyl-substituted 5-ring heterocycles.

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INTRODUCTION

Compounds containing 2,2′-bithiophene, 2,2′-bifuran, and 2,2′-furanothiophene cores play important roles in material sciences [1], pharmaceutical [2], and agrochemical [3] fields. The various optical properties of these bichalcophenes have lead to their extensive use in nonlinear optical devices [4], sensors [5], solar cells [6], and other advanced materials. These bichalcophene units appear in important medicinal chemical applications including antibacterial [7] and anticancer studies [8]. Bichalcophene diamidines of the type I and II from our laboratory have been shown to recognize G-quadruplex DNA [9]. Formyl and ester bichalcophene analogs can undergo a variety of condensation reactions to prepare more complex molecules of importance to material science as well as for the generation of useful bioactive molecules. Cyano derivatives are key intermediates for the preparation of amidine molecules, which are important molecules in such diverse fields as medicinal chemistry [9] and catalyst development [10]. In view of our interest in molecules that recognize G-quadruplex DNA [9] and other ones, which can potentially function as diagnostics [11] for parasites and as an expansion of our previous bichalcophene work [12(a)]. We report here the synthesis of new bichalcophenes with formyl, ester, and cyano substituents that can serve as versatile building blocks for the preparation of more complex molecules (Fig. 1).

RESULTS AND DISCUSSION

Scheme 1 outlines our approach to the synthesis of both the bichalcophene formyl and cyano esters. We chose to use the Stille approach for the coupling to form the bichalcophene units because this methodology is known to be quite robust and can be performed under neutral conditions [1(b),2,12(b)]. For ease of preparation of the Stille reagent, we chose to use the acetal-protected formyl furan **2a** and thiophene **2b**. The commercially available aldehydes **1a**, **b** were converted into the previously unreported acetals **2a**, **b** in high yields (>95%) using NBS as a catalyst, under mild conditions [13].The new tri-*n*-butylstannyl reagents were prepared in good yields (>80%) by a conventional *n*-butyllithium debromination of **2a**, **b** at −78°C followed by reaction with tri-*n*-butyltin chloride. The Stille coupling reaction between **3a**, **b** and commercially available **4a**, **b** in the presence of a 5 mol % of Pd $(PPh_3)_4$ using 1,4-dioxane as solvent at 100°C for 24 h followed by deprotection of the acetal product by stirring with conc. HCl solution for 6 h gave the desired new formyl analogs **5a–d** in good yields (>73%). The formyl esters were converted into the cyano esters (**6a–d**) using a conventional two-step process of conversion of the aldehydes into the corresponding oximes followed by acetic anhydride-facilitated dehydration to provide the new nitriles in good isolated yields (>75%).

In conclusion, we have reported a concise synthesis, in good yields, of new cyano and formyl ester-substituted bichalcophenes, which can be used for the

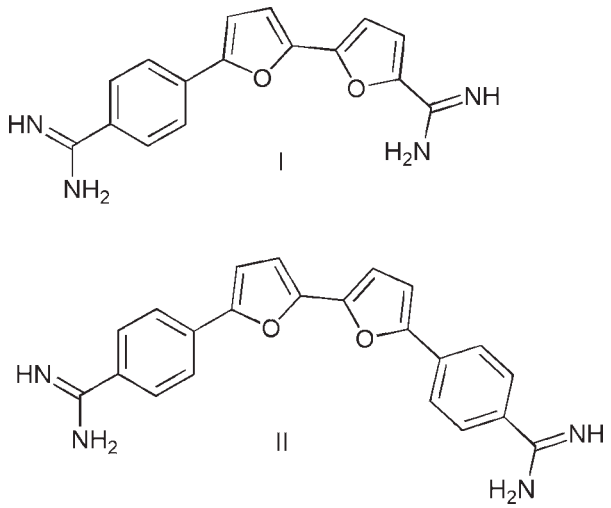


Figure 1. Bichalcophenes which recognize G-quadruplex DNA.

preparation of more complex molecules for multiple applications.

EXPERIMENTAL

All commercial reagents were used without purification. Melting points were determined on a Mel-Temp 3.0 melting point apparatus and are uncorrected. TLC analysis was carried out on silica gel 60 F254 precoated aluminum sheets using UV light for detection. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker 400 MHz spectrometer using the indicated solvents. Mass spectra were obtained from the Georgia State University Mass Spectrometry Laboratory, Atlanta, GA. Elemental analysis were performed by Atlantic Microlab, Norcross, GA.

General procedure for the synthesis of 2a, b. A 1.06 g NBS (6 mmol) was added in portions to a stirred mixture of **1a**, **b** (130 mmol) and 19.55 mL trimethyl orthoformate (190 mmol) in 150 mL anhydrous CH_2Cl_2 and 15 mL anhydrous CH_3OH at 0°–5°. After the addition was completed, the resulting mixture was stirred overnight at room temperature, quenched with water, and the organic layer was separated, washed with water again, dried (sodium sulfate), and evaporated. The resulting oil was purified by distillation.

2-Bromo-5-(dimethoxymethyl) furan (2a). Colorless liquid, yield 95%; bp 45°C (0.35 mmHg); ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 6.91$ (d, $J = 2.8$ Hz, 1 H), 6.85 (d, $J = 2.8$ Hz, 1 H), 5.38 (s, 1 H), 3.36 (s, 6 H); ^{13}C-NMR ($CDCl_3$): $\delta = 52.3$, 99.6, 112.7, 125.7, 130.4, 143.1; ESI-MS: *m/z* calculated for $C_7H_9BrO_3$: 221.05, Found: 222.1 ($M^+ + 1$), 223.1 ($M^+ + 2$); Anal. Calcd. for $C_7H_9BrO_3$: C, 38.03; H, 4.10; Found: C, 37.81; H, 4.25.

2-Bromo-5-(dimethoxymethyl) thiophene (2b). Colorless liquid, yield 97%; bp 69°C (0.25 mm Hg). ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 6.96$ (d, $J = 4$ Hz, 1 H), 6.83 (dd, $J = 1.2$, 4 Hz, 1 H), 5.54 (d, $J = 1.2$, 1 H), 3.33 (s, 6 H); ^{13}C-NMR ($CDCl_3$): $\delta = 52.5$, 99.7, 112.5, 125.9, 131.1, 142.8; ESI-MS: *m/z* calculated for $C_7H_9BrO_2S$: 237.11, Found: 238.3 ($M^+ + 1$), 239.3 ($M^+ + 2$); Anal. Calcd. for $C_7H_9BrO_2S$: C, 35.46; H, 3.83; Found: C, 35.22; H, 4.15.

General procedure for the synthesis of 3a, b. A 101 mL 1.6*M* *n*-butyllithium solution in hexane (150 mmol) was added slowly to a stirred solution of **2a**, **b** (130 mmol) in 150 mL anhydrous THF under nitrogen atmosphere at –78°C. After the addition was completed, the mixture was stirred for 4 h and then 40.6 mL tri-*n*-butyltin chloride (150 mmol) was added slowly at –78°C. After stirring overnight, the solution was quenched with 50 mL water and solvents were removed under reduced pressure. The residue was extracted with 200 mL ether, the organic layer was washed with 30 mL 10% NaF solution and 100 mL water, dried (sodium sulfate), and concentrated. The resulting oil was purified by distillation.

5-(Dimethoxymethyl)furan-2-yl-tri-n-butylstannane (3a). Yellow oil, yield 84%; bp 145°C (0.6 mm Hg); ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 6.53$ (d, $J = 2.8$ Hz, 1 H), 6.44 (d, $J = 2.8$ Hz, 1 H), 5.50 (s, 1 H), 3.39 (s, 6 H). 1.64 (m, 6 H), 1.53 (m, 6 H), 1.25 (m, 6 H), 1.09 (m, 9 H); ^{13}C-NMR ($CDCl_3$): $\delta = 12.5$, 15.5, 26.9, 28.9, 52.4, 100.4, 126.4, 134.8, 135.1, 146.9; ESI-MS: *m/z* calculated for $C_{19}H_{36}O_3Sn$: 431.20, Found: 432.3 ($M^+ + 1$); Anal. Calcd. for $C_{19}H_{36}O_3Sn$: C, 52.92; H, 8.42; Found: C, 52.71; H, 8.55.

5-(Dimethoxymethyl)thiophen-2-yl-tri-n-butylstannane (3b). Yellow oil, yield 81%; bp 185°C (0.7 mm Hg); ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 7.28$ (d, $J = 2.8$ Hz, 1 H), 7.15 (d, $J = 2.8$ Hz, 1 H), 5.69 (s, 1 H), 3.48 (s, 6 H), 1.78 (m, 6 H), 1.60 (m, 6 H), 1.48 (m, 6 H), 1.17 (m, 9 H); ^{13}C-NMR ($CDCl_3$): $\delta = 13.2$, 17.3, 27.4, 28.5, 52.7, 101.1, 126.9, 134.2, 135.7, 146.3; ESI-MS: *m/z* calculated for $C_{19}H_{36}O_2SSn$: 447.26, Found: 448.2 ($M^+ + 1$); Anal. Calcd. for $C_{19}H_{36}O_2SSn$: C, 51.02; H, 8.11; Found: C, 51.17; H, 7.99.

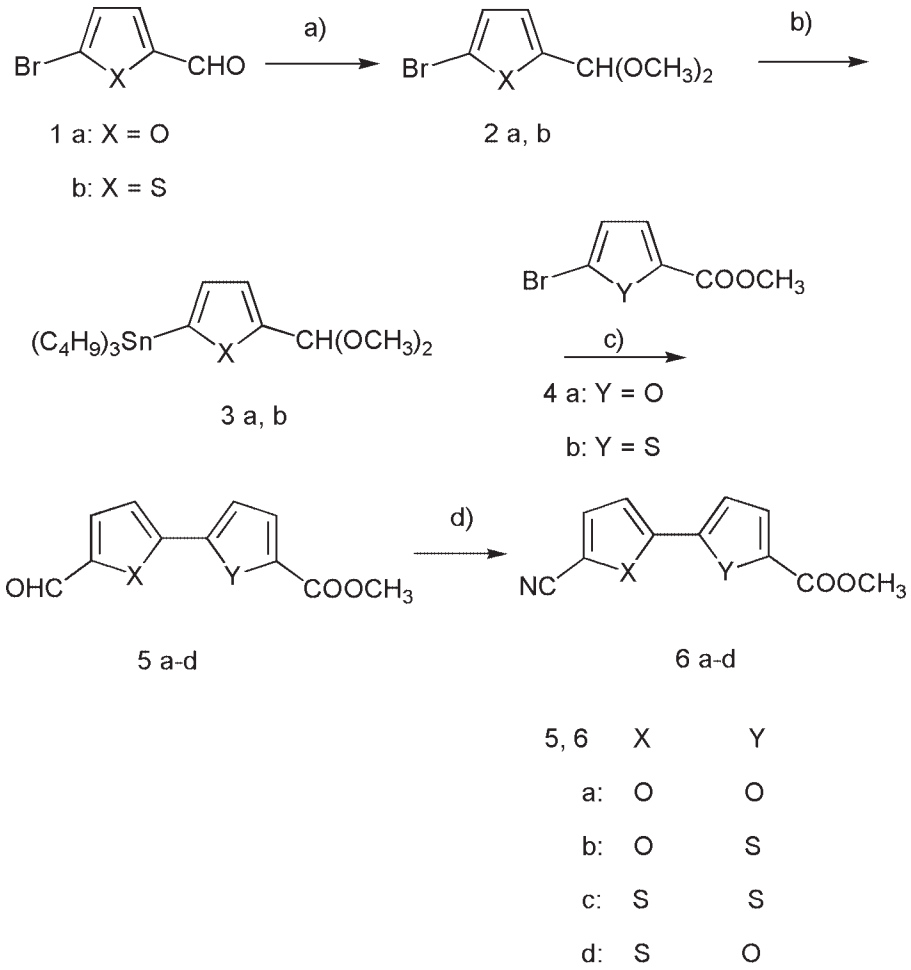
General procedure for the synthesis of 5a–d. A 1.15 g tetrakis-triphenyl-phosphine palladium (1 mmol) was added to a stirred mixture of **3a**, **b** (20 mmol) and **4a**, **b** (20 mmol) in deaerated dry 40 mL dioxane under nitrogen atmosphere. The vigorously stirred mixture was warmed to 90–100°C for 24 h. The solvent was removed under reduced pressure; the residue was dissolved in 150 mL dichloromethane containing 5 mL of concentrated ammonia, then washed with water, and passed through celite. The solution was mixed with conc. 5 mL HCl, stirred for 6 h, separated and washed with water, dried (sodium sulfate), and evaporated. The product was purified by column chromatography on silica gel, using dichloromethane as eluent.

Methyl 5′-formyl-2,2′-bifuran-5-carboxylate (5a). Yellow solid, yield (two steps) 79%; mp 129–130°C; ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 9.65$ (s, 1 H), 7.69 (d, $J = 3.6$ Hz, 1 H), 7.49 (d, $J = 3.6$ Hz, 1 H), 7.24 (brs, 1 H), 7.25 (brs, 1 H), 3.86 (s, 3 H); ^{13}C-NMR ($CDCl_3$): $\delta = 53.1$, 111.2, 125.6, 127.6, 133.8, 135.2, 137.4, 152.3, 152.7, 161.9, 178.5; ESI-MS: *m/z* calculated for $C_{11}H_8O_5$: 220.18, Found: 221 ($M^+ + 1$); Anal. Calcd. for $C_{11}H_8O_5$: C, 60.00; H, 3.66; Found: C, 60.28; H, 3.79.

Methyl 5-(5-formylfuran-2-yl) thiophene-2-carboxylate (5b). Yellowish white solid, yield (two steps) 85%; mp 143–143.5°C. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 9.62$ (s, 1 H), 7.85 (d, $J = 4$ Hz, 1 H), 7.79 (d, $J = 4$ Hz, 1 H), 7.68 (d, $J = 4$ Hz, 1 H), 7.34 (d, $J = 4$, 1 H), 3.91 (s, 3 H); ^{13}C-NMR ($CDCl_3$): $\delta = 53.1$, 111.3, 125.7, 127.8, 133.8, 135.1, 137.9, 152.3, 152.9, 162.1, 177.3; ESI-MS: *m/z* calculated for $C_{11}H_8O_4S$: 236.24, Found: 237 ($M^+ + 1$); Anal. Calcd. for $C_{11}H_8O_4S$: C, 55.92; H, 3.41; Found: C, 56.21; H, 3.48.

Methyl-5′-formyl-2,2′-bithiophene-5-carboxylate (5c). White solid, yield (two steps) 73%; mp 161°C. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 9.93$ (s, 1 H), 8.05 (d, $J = 4$ Hz, 1 H), 7.82 (d, J

Scheme 1



Reagents and conditions: a) Trimethyl orthoformate, NBS, CH_2Cl_2, CH_3OH; b) *n*-Bu Li(1.6mol), $(Bu)_3SnCl$, THF; c) (i) $Pd(PPh_3)_4$, 1,4-dioxane; (ii) Aq HCl; d) (i) $NH_2OH.HCl$, Na_2CO_3, H_2O, CH_3OH; (ii) Ac_2O.

= 4 Hz, 1 H), 7.79 (d, *J* = 4, 1 H), 7.50 (d, *J* = 4, 1 H), 3.89 (s, 3 H); ^{13}C-NMR ($CDCl_3$): δ = 51.5, 111.6, 121.9, 126.4, 139.3, 139.4, 142.2, 144.8, 150.7, 162.4, 181.1; ESI-MS: *m/z* calculated for $C_{11}H_8O_3S_2$: 252.31, Found: 253 (M^+ + 1); Anal. Calcd. for $C_{11}H_8O_3S_2$: C, 52.36; H, 3.2; Found: C, 52.46; H, 3.13.

Methyl-5-(5-formylthiophen-2-yl) furan-2-carboxylate (5d). Yellowish brown solid, yield (two steps) 78%; mp 178–180°C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.96 (s, 1 H), 8.07 (d, *J* = 4 Hz, 1 H), 7.78 (d, *J* = 4 Hz, 1 H), 7.48 (d, *J* = 4, 1 H), 7.30 (d, *J* = 4, 1 H), 3.86 (s, 3 H); ^{13}C-NMR ($CDCl_3$): δ = 52.5, 111.6, 121.2, 127.1, 139.1, 139.5, 143.4, 144.2, 151.3, 158.4.1, 184.7. ESI-MS: *m/z* calculated for $C_{11}H_8O_4S$: 236.24, Found: 237 (M^+ + 1); Anal. Calcd. for $C_{11}H_8O_4S$: C, 55.92; H, 3.41; Found: C, 56.01; H, 3.44.

General procedure for the synthesis of 6a–d. A 10 mL aqueous solution of 0.7 g hydroxylamine hydrochloride (10 mmol) and 1.06 g sodium carbonate (10 mmol) was added to a stirred solution of **5a–d** (10 mmol) in 25 mL methanol and heated at reflux for 24 h. Evaporation of the solvent under reduced pressure to yield a precipitate that was partitioned between water and 100 mL ethyl acetate, and the organic layer was dried (sodium sulfate) and then concentrated to dryness under reduced pressure. The crude oxime was allowed to reflux in 20 mL acetic anhydride for 24 h, and the solvent was evaporated under reduced pressure. The product was purified by column chromatography on silica gel, using hexanes/ethyl acetate (80/20, v/v) as eluent.

Methyl 5′-cyano-2,2′-bifuran-5-carboxylate (6a). Yellowish brown solid, yield (two steps) 81%; mp 99–100°C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.77 (d, *J* = 3.6 Hz, 1 H), 7.46 (d, *J* = 3.6 Hz, 1 H), 7.20 (brs, 2 H), 3.85 (s, 3 H); ^{13}C-NMR (DMSO-d_6): δ = 52.5, 108.5, 111.3, 114.5, 121, 126.3, 138.5, 140.6, 144.2, 150.6, 158.4; ESI-MS: *m/z* calculated for $C_{11}H_7NO_4$: 217.18, Found: 218 (M^+ + 1); Anal. Calcd. for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45; Found: C, 60.88; H, 3.38; N, 6.08.

Methyl 5-(5-cyanofuran-2-yl)thiophene-2-carboxylate (6b). Yellowish brown solid, yield (two steps) 78%; mp 115-116°C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.85 (d, J = 4 Hz, 1 H), 7.80 (d, J = 4 Hz, 1 H), 7.70 (d, J = 3.6, 1 H), 7.31 (d, J = 3.6, 1 H), 3.86 (s, 3 H); ^{13}C-NMR (DMSO-d_6): δ = 49.9, 107.1, 111.9, 113.2, 121, 126.1, 138.9, 139.2, 145.8, 151.9, 165.9; ESI-MS: *m/z* calculated for $C_{11}H_7NO_3S$: 233.24, Found: 234 (M^+ + 1); Anal. Calcd. for $C_{11}H_7NO_3S$: C, 56.64; H, 3.02; N, 6.01; Found: C, 56.95; H, 3.16; N, 5.77.

Methyl 5′-cyano-2,2′-bithiophene-5-carboxylate (6c). Yellow solid, yield (two steps) 75%; mp 142-144°C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.01 (d, J = 4 Hz, 1 H), 7.71 (d, J = 4 Hz, 1 H), 7.45 (d, J = 3.6, 1 H), 7.28 (d, J = 3.6, 1 H), 3.85 (s, 3 H); ^{13}C-NMR (DMSO-d_6): δ = 55.1, 105.2, 110.2, 113.8, 121.2, 126.7, 134.5, 137.2, 147.1, 152.4, 162.4; ESI-MS: *m/z* calculated for $C_{11}H_7NO_2S_2$: 249.31, Found: 250.2 (M^+ + 1); Anal. Calcd. for $C_{11}H_7NO_2S_2$: C, 52.99; H, 2.83; N, 5.62; Found: C, 53.12; H, 3.06; N, 5.39.

Methyl 5-(5-cyanothiophen-2-yl) furan-2-carboxylate (6d). Brown solid, yield (two steps) 78%; mp 126-126.5°C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.61 (d, J = 4 Hz, 1 H), 7.54 (d, J = 4 Hz, 1 H), 7.25 (d, J = 4, 1 H), 6.80 (d, J = 4, 1 H), 3.94 (s, 3 H); ^{13}C-NMR (DMSO-d_6): δ = 51.3, 109.2, 111.9, 115.4, 120.7, 124.9, 137.7, 140.1, 144.7, 151.1, 161.8; ESI-MS: *m/z* calculated for $C_{11}H_7NO_3S$: 233.24, Found: 234 (M^+ + 1); Anal. Calcd. for $C_{11}H_7NO_3S$: C, 56.64; H, 3.02; N, 6.01; Found: C, 56.67; H, 3.09; N, 5.98.

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