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New Amidino-Benzimidazolyl Thiophenes: Synthesis and Photochemical Synthesis

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ABSTRACT: *New amidino-benzimidazolyl-substituted bis-1,2-(2-thienyl)ethenes (***4, 5***, and* **6***) and benzo[1,2-*b*:4,3-*b′*]dithiophenes (***8, 9***, and* **10***) were prepared by the condensation of amidino-substituted* o*-phenylene diamines with corresponding dialdehydes (***3** *and* **7***). All prepared amidino-benzimidazolyl-substituted compounds are of particular interest, because they can serve as intercalators or groove binders on DNA in anticancer therapy.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:218–222, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10126

INTRODUCTION

Amidino-benzimidazolyl-substituted heterocyclic compounds are widely investigated on their biological activity [1–6]. The amidine groups at the termini of the molecules seemed to contribute significantly to the dications and the DNA complex stability [7,8]. A number of aromatic diamidines have been shown to bind in minor groove on DNA at AT-rich sites and to be affective against many opportunistic organisms [9,10]. Several hypotheses have been proposed to explain the mode of action of these compounds. The factors important in minor groove binding are hydrogen bonding, electrostatic interactions, van der Waals interactions, and the radius of curvature of the observed molecule [11].

Amidinic compounds also showed antiparasitic activity [12]. Some dicationic amidino bisbenzimidazoles were found to have potent fungicidal activity [13]. A series of amidino-substituted carbazoles, furans, and benzimidazoles possess antimicrobial activity against a wide range of eukaryotic pathogens and show inhibitory and fungicidal activities against *Candida albicans* and *Cryptococeus neoformans*. Selected compounds were also found to be active against *Aspergillus fumigantus*, *Fusarium solani*, and *Candida* species other than *C. albicans* [14].

Recently, synthesized bis-cationic bis-amidino benzimidazolyl substituted diphenylfurans were found to inhibit HIV-1 infection [15]. Wang found that a series of an aromatic dication with an amidine-phenyl-furan-benzimidazole-amidine structure could recognize specific sequences of DNA by binding in the minor groove of DNA as a dimer [16]. Nguyen examined the influence of compound structure on affinity, sequence selectivity, and mode of

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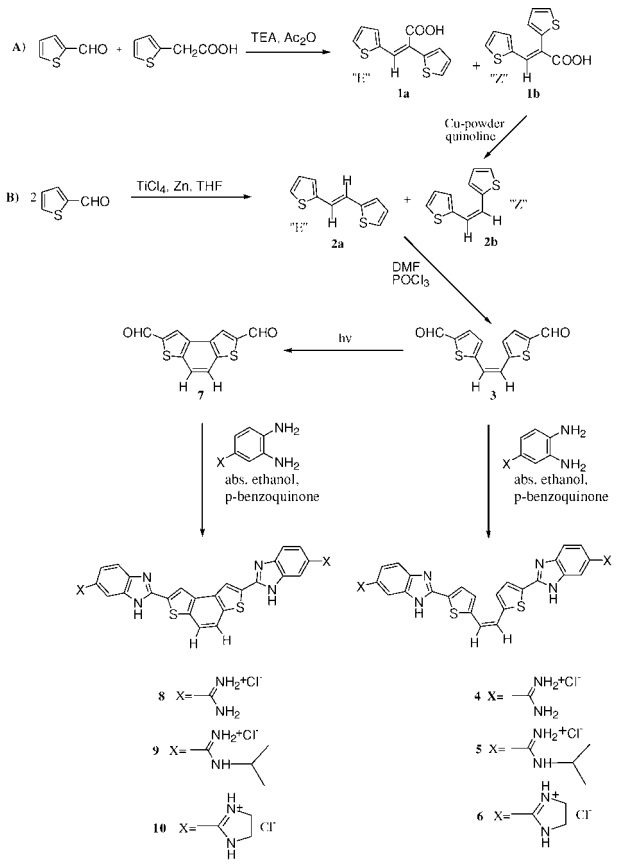
binding to DNA for unfused aromatic dications related to furamidine [17].

RESULTS AND DISCUSSION

The influence of the amidino and substituted amidino groups in heterocyclic compounds, on the biological activity, as well as well-known different biological activities of a number of amidino-substituted benzimidazoles, prompted us to synthesize new amidino-substituted heterocyclic systems from the thiophene series [18,19].

In this work, we prepared in a multistep synthesis new amidino-benzimidazolyl-substituted bis-1,2-(2-thienyl)ethenes **4, 5**, and **6** and amidino-benzimidazolyl-substituted benzo[1,2-*b*:4,3-*b*′]-dithiophenes **8, 9**, and **10**. In the first steps were prepared amidino-substituted *o*-phenylene diamines starting from acetamidobenzonitrile, which was nitrated and hydrolyzed into 4-amino-3-nitrobenzonitrile. Cyano group of the starting compound reacted in the Pinner reaction in absolute EtOH with dry HCl gas to give intermediate imidoesters. Reaction of imidoester hydrochlorides with gaseous ammonia, isopropylamine, or ethylenediamine in dry EtOH and subsequent catalytic reduction gave corresponding 4-amidino-substituted 1,2-phenylene diamines [20].

These compounds are used later in the condensation with earlier prepared dialdehydes **3** and **7** [11]. Dialdehyde **3** was prepared in two ways. Starting from 2-thiophenecarbaldehyde and 2-thienylacetic acid by the condensation reaction in Ac_2O and in the presence of TEA, were prepared *E*- and *Z*-2,3-di-(2-thienyl)acrylic acids **1a** and **1b**. The Z isomer of 2,3-di-(2-thienyl)acrylic acid **1b** was isolated from the reaction mixture described earlier [21]. Compound **1b** was decarboxylated in quinoline and in the presence of Cu powder into the *Z*-2-di-(2-thienyl)-ethene **2b** [22]. Compound **2b** was also prepared by the McMurry reaction in the mixture with *E* isomer **2a** by treatment of thiophene-2-carbaldehyde with a low-valent titanium reagent, prepared from titanium(IV)chloride and zinc powder in boiling THF [23]. Compound **2b** was formylated into 1,2-di[(5-formyl)2-thienyl]ethene (**3**) by Vilsmeier formylation [24]. Dialdehyde **3** was photochemically dehydrocyclized into 2,7-bis-formyl-benzo[1,2-*b*:4,3-*b*′] (**7**) by the reaction of photochemical dehydrogenation described earlier [21]. Both dialdehydes **3** and **7** reacted later with earlier prepared amidino-substituted phenylenediamines in the presence of *p*-benzoquinone [6]. In this way were prepared the dihydrochlorides **4–6** and **8–10** according to Scheme 1.



SCHEME 1

EXPERIMENTAL

Instruments

Melting points were determined on a Kofler block apparatus and are uncorrected. IR spectra were determined with a Nicolet Magna 760 infrared spectrophotometer in KBr pellets. ^{1}H NMR and ^{13}C NMR spectral data were determined using Bruker Avance DPX 300 MHz NMR or Varian-Gemini 300 MHz spectrometers with tetramethylsilane as an internal standard. Elemental analyses were carried out in the Microanalytical Laboratory at the Rugjer Boskovic Institute.

*E- and Z-2,3-Di-(2-thienyl)acrylic Acids (***1a** *and* **1b***)*

Compounds **1a** and **1b** were prepared by a 45-min heating of 2-thiophenecarbaldehyde (8.0 g, 70 mmol) and 2-thiopheneacetic acid (10 g, 70 mmol) in triethylamine (10 ml), and acetic anhydride (10 ml). After the reaction was completed, the mixture was cooled, acidified with diluted hydrochloric acid (1:1), and extracted with diethylether (350 ml). The organic layer was washed with water and the mixture

of acids **1a** and **1b** was extracted into 10% sodium carbonate solution (1000 ml). The alkaline solution of sodium salts of compounds **1a** and **1b** was boiled with charcoal, filtered off, cooled, and acidified to pH 5 with acetic acid. The precipitated Z isomer **1b** was filtered off and recrystallized from methanol. It was obtained in a yield of 6.80 g (42%) as light yellow crystals of mp 239–241°C (lit [24] mp 240–241°C). Concentrated hydrochloric acid was added to the filtrate and additional crystalline crops consisting of the *E* isomer were filtered off. The yield of the *E* isomer **1a** was 1.67 g (7%), mp 174–175°C (lit [24] mp 174.5–175.5°C).

*1,2-Di-(2-thienyl)ethene (**2**)*

Method A. Decarboxylation of the corresponding acid **1b** (2.45 g, 10 mmol) was accomplished by the method described earlier [22], by heating with Cu powder (2.5 g) in quinoline (12.5 ml) (dried over molecular sieves) for 1 h at boiling point. The reaction mixture was transfered into ether (100 ml) and washed with 10% hydrochloric acid (150 ml). All ethereal extracts were collected, washed with water, 10% hydrochloric acid, and then again with water, and were dried over magnesium sulfate. The ether was evaporated and the residue was recrystallized from methanol. Yellow crystals were obtained in a yield of 0.98 g (51.0%), mp 130–132°C (lit [25] mp 133–134°C). ^{1}H NMR ($CDCl_3$) (δ ppm): 6.98 (1H, $AB_{syst.}$, J = 5.05 and 3.65 Hz, $H_{thioph.}$), 7.03 (d, J = 3.65 Hz, 1H, $H_{thioph.}$), 7.05 (s, 1H, $H_{ethylenic}$), 7.17 (d, J = 5.05 Hz, 1H, $H_{thioph.}$).

Method B. To a slurred solution of 2-thiophenecarbaldehyde (5.6 g, 50 mmol) in THF (100 ml) was added, dropwise and by stirring, titanium(IV) chloride (6.5 ml) over a period of 30 min at −18°C. After stirring at this temperature for 30 min, zinc powder (7.8 g) was added in small portions over a period of 30 min. The mixture was stirred at −18°C for 30 min, warmed to room temperature, and refluxed for 3.5 h. The reaction was quenched by addition of ice water (100 ml) and the resulting solid was collected by filtration and dried. The solid was dissolved in methylene chloride (80 ml) and the insoluble inorganic material was removed by filtration. The filtrate was evaporated and the residue was recrystallized from cyclohexane to give 4.70 g (98%) of pure *E* isomer **2a**, mp 133–134°C (lit [23] mp 133–134°C).

*1,2-Di-[5-formyl-2-(2-thienyl)]ethene (**3**)*

Compound **3** was prepared by the Vilsmeier reaction described earlier [24] from **2b** (3.00 g, 24 mmol) in DMF (10 ml) by dropwise addition of (with stirring and cooling) $POCl_3$ (10 ml) in such a way that the temperature of the reaction mixture did not exceed 10°C. After complete addition, the mixture was stirred for 30 min at room temperature, and then heated at 90–95°C for 45 min, cooled, and poured into crushed ice (300 g), made weakly alkaline with 10% sodium hydroxide solution and left overnight on ice. The gummy product was decanted, washed with water, and recrystallized from methanol. The yield was 2.77 g (72%), mp 205–208°C. IR (cm^{-1}) (KBr): 1640 (CHO), 1660 (CHO). ^{1}H NMR ($CDCl_3$) (δ ppm): 7.22 (d, J = 3.93 Hz, 1H, $H_{thioph.}$), 7.26 (s, 1H, $H_{ethylenic}$), 7.69 (d, J = 3.93 Hz, 1H, $H_{thioph.}$), 9.94 (s, 1H, CHO). ^{13}C NMR (δ ppm) ($CDCl_3$): 124.6, 129.0, 138.5, 142.5, 149.8, 183.9. Anal. Calcd for $C_{12}H_8O_2S_2$: C, 58.04; H, 3.25; S, 25.83. Found: C, 58.52; H, 3.48; S, 26.12.

*1,2-Bis-{[5-(5-amidino-2-benzimidazolyl)]-2-thienyl}ethene Dihydrochloride (**4**)*

Compound **4** was prepared using the method described earlier [6]. A mixture of compound **3** (0.50 g, 2 mmol), 3,4-diaminobenzamidine (0.6 g, 4 mmol), and *p*-benzoquinone (0.43 g, 4 mmol) in absolute EtOH (80 ml) was stirred at reflux for 4 h (under nitrogen). The reaction mixture was cooled to room temperature and precipitated dark crystals were filtered off. The crude product was suspended in conc. HCl, heated to boiling, and stirred overnight at room temperature. Acetone was added to the solution. Dark green crystals were filtered off and washed with dry ether. The crystals of **4** were dissolved in water and precipitated with acetone again, filtered off, and dried. It was repeated a few times until the crystals were analytically pure. It was obtained in a yield of 0.75 g (64%) dark crystals, mp >300°C. IR (cm^{-1}) (KBr): 3372, 3067, 2927, 1672, 1625, 1578. ^{1}H NMR (δ ppm) (DMSO-d_6): 9.3 (s, 4H, NH), 9.0 (s, 4H, NH), 8.13 (d, J = 3.65 Hz, 2H, $H_{thioph.}$), 8.05 (s, 2H, $H_{arom.}$), 7.78 (d, J = 8.54 Hz, 2H, $H_{arom.}$), 7.69 (d, J = 8.48 Hz, 1H, $H_{arom.}$), 7.47 (d, J = 4.03 Hz, 1H, $H_{thioph.}$), 7.42 (s, 2H, $H_{ethylenic}$). ^{13}C NMR (δ ppm) (DMSO-d_6): 165.9, 149.6, 144.9, 131.435, 129.5, 128.7, 122.7, 122.4, 121.6. Anal. Calcd for $C_{26}H_{22}Cl_2N_8S_2$: C, 53.69; H, 3.81; N, 19.27. Found: C, 53.92; H, 3.59; N, 19.31.

*1,2-Bis-{[5-(5-N-isopropylamidino-2-benzimidazolyl)]-2-thienyl}ethene Dihydrochloride (**5**)*

Compound **5** was prepared using the method described for the preparation of **4**, from **3** (0.3 g, 1.2 mmol), 3,4-diamino-*N*-isopropylbenzamidine

(0.46 g, 2.43 mmol), and *p*-benzoquinone (0.26 g, 2.42 mmol) in absolute EtOH (80 ml). It was obtained in a yield of 0.31 g (38%) dark green crystals, mp >300°C. IR (cm^{-1}) (KBr): 3415, 3255, 3089, 1673, 1627, 1575. ^1H NMR (δ ppm) (DMSO-d_6): 9.53 (s, 2H, NH), 9.39 (s, 2H, NH), 8.97 (s, 2H, NH), 8.01 (s, 2H, $H_{arom.}$), 7.98 (d, $J = 3.47$ Hz, 2H, $H_{thioph.}$), 7.76 (d, $J = 8.42$ Hz, 2H, $H_{arom.}$), 7.56 (d, $J = 8.36$ Hz, 2H, $H_{arom.}$), 7.45 (d, $J = 3.47$ Hz, 2H, $H_{thioph.}$), 7.40 (s, 2H, $H_{ethylenic}$), 4.10–4.06 (m, 2H, CH), 1.31 (d, $J = 6.23$ Hz, 12H, CH_3). ^{13}C NMR (δ ppm) (DMSO-d_6): 163.7, 149.6, 148.9, 140.7, 137.9, 133.2, 130.9, 129.01, 125.6, 125.2, 124.3, 116.4, 116.4, 47.7, 22.9. Anal calcd for $C_{32}H_{34}N_8S_2Cl_2$: C, 57.73; H, 5.12; N, 16.82. Found: C, 57.56; H, 5.38; N, 16.43.

*1,2-Bis-{[5-(5-imidazolinyl)-2-benzimidazolyl)]-2-thienyl}ethene Dihydrochloride (**6**)*

Compound **6** was prepared in the way described for the preparation of **4**, from **3** (0.22 g, 0.9 mmol), 4-[*N*-(2-imidazolinyl)]-1,2-phenylene-diamine (0.5 g, 1.8 mmol), and *p*-benzoquinone (0.18 g, 1.8 mmol) in absolute EtOH (80 ml). It was obtained in a yield of 0.15 g (39%) dark green crystals mp >300°C. IR (cm^{-1}) (KBr): 3390, 3120, 2976, 1606. ^1H NMR (δ ppm) (DMSO-d_6): 10.59 (s, 4H, NH), 8.31 (s, 2H, $H_{arom.}$), 8.0 (d, $J = 3.55$ Hz, 2H, $H_{thioph.}$), 7.84 (d, $J = 8.45$ Hz, 2H, $H_{arom.}$), 7.79 (d, $J = 8.37$ Hz, 2H, $H_{arom.}$), 7.45 (d, $J = 3.8$ Hz, 2H, $H_{thioph.}$), 7.39 (s, 2H, $H_{ethylenic}$), 4.03 (s, 8H, CH_2). Anal. Calcd for $C_{30}H_{26}Cl_2N_8S_2$: C, 56.87; H, 4.10; N, 17.68. Found: C, 56.61; H, 3.95; N, 17.35.

*2,7-Bis-formyl-benzo[1,2-b:4,3-b′]dithiophene (**7**)*

Compound **7** was prepared from **3** (0.3 g, 1.2 mmol), which was dissolved in toluene (300 ml) and irradiated with 400 W high-pressure mercury arch lamp during 5 h. J_2 (0.1 g) was added into the solution and the air was bubbled through. The solvent was evaporated and the residue recrystallized from methanol. It was obtained in a yield of 0.19 g (63.8%) dark yellow crystals, mp 243–247°C. IR (cm^{-1}) (KBr): 1668, 1508, 1224. ^1H NMR (δ ppm) (DMSO-d_6): 10.22 (s, 2H, —CHO), 9.02 (s, 2H, $H_{thioph.}$), 8.32 (s, 2H, $H_{arom.}$). ^{13}C NMR (δ ppm) (DMSO-d_6): 186.0, 144.02, 140.2, 135.2, 133.2, 123.6. Anal. Calcd for $C_{12}H_6O_2S_2$: C, 58.54; H, 2.44. Found: C, 58.31; H, 2.38.

*2,7-Bis-[(5-amidino)-2-benzimidazolyl]-benzo-[1,2-b:4,3-b′]dithiophene Dihydrochloride (**8**)*

Compound **8** was prepared in the way described for the preparation of **4**, from **7** (0.5 g, 2.3 mmol), 3,4-diaminobenzamidine (0.61 g, 4.1 mmol), and *p*-benzoquinone (0.44 g, 4.1 mmol) in absolute EtOH (80 ml). It was obtained in a yield of 0.6 g (45.0%) dark green crystals, mp >300°C. IR (cm^{-1}) (KBr): 3340, 3076, 2924, 2852, 1673, 1624. ^1H NMR (δ ppm) (DMSO-d_6): 9.39 (s, 4H, NH), 9.06 (s, 4H, NH), 8.83 (s, 2H, $H_{thioph.}$), 8.23 (s, 2H, $H_{arom.}$), 8.18 (s, 2H, $H_{ethylenic}$), 7.87 (d, $J = 8.55$ Hz, 2H, $H_{arom.}$), 7.74 (dd, $J = 8.55$, 1.65 Hz, 2H, $H_{arom.}$). ^{13}C NMR (δ ppm) (DMSO-d_6): 169.1, 149.8, 137.8, 134.8, 134.02, 122.5, 121.8, 120.8. Anal. Calcd for $C_{26}H_{20}N_8S_2Cl_2$: C, 53.84; H, 3.45; N, 19.30; Cl, 12.23. Found: C, 53.85; H, 3.62; N, 19.06; Cl, 12.3.

*2,7-Bis-[(5-N-isopropylamidino)-2-benzimidazolyl]-benzo[1,2-b:4,3-b′]dithiophene Dihydrochloride (**9**)*

Compound **9** was prepared in the way described for the preparation of **5**, from **7** (0.87 g, 3.5 mmol), 3,4-diamino-*N*-isopropylbenzamidine (1.35 g, 7.06 mmol), and *p*-benzoquinone (0.76 g, 7.06 mmol) in absolute EtOH (50 ml). It was obtained in a yield of 1.64 g (70.0%) green cystals, mp >300°C. IR (cm^{-1}) (KBr): 3363, 3073, 2978, 1667, 1626. ^1H NMR (δ ppm) (DMSO-d_6): 9.57 (s, 2H, NH), 9.42 (s, 2H, NH), 8.99 (s, 2H, NH), 8.83 (s, 2H, $H_{thioph.}$), 8.21 (s, 2H, $H_{arom.}$), 8.16 (s, 2H, $H_{ethylenic}$), 7.88 (d, $J = 8.48$ Hz, 2H, $H_{arom.}$), 7.60 (d, $J = 8.75$ Hz, 2H, $H_{arom.}$), 4.1–4.09 (m, 2H, CH), 1.32 (d, $J = 6.3$ Hz, 12H, CH_3). ^{13}C NMR (δ ppm) (DMSO-d_6): 162.2, 149.3, 137.6, 134.6, 133.7, 123.1, 122.6, 122.4, 120.6, 44.9, 21.2. Anal. Calcd for $C_{32}H_{32}N_8S_2Cl_2{\cdot}3H_2O$: C, 53.50; H, 5.29; N, 15.60. Found: C, 53.72; H, 5.06; N, 15.79.

*2,7-Bis-[(5-imidazolinyl)-2-benzimidazolyl]-benzo[1,2-b:4,3-b′]dithiophene Dihydrochloride (**10**)*

Compound **10** was prepared in the way described for the preparation of **6**, from **7** (0.21 g, 0.85 mmol), 4-[*N*-(2-imidazolinyl)]-1,2-phenylene-diamine (0.5 g, 1.7 mmol), and *p*-benzoquinone (0.18 g, 1.7 mmol) in absolute EtOH (80 ml). It was obtained in a yield of 0.45 g (83.0%) dark green crystals, mp >300°C. IR (cm^{-1}) (KBr): 3407, 3118, 2970, 1605. ^1H NMR (δ ppm) (DMSO-d_6): 14.5 (s, 2H, NH), 10.53 (s, 4H, NH), 8.79 (s, 2H, $H_{thioph.}$), 8.39 (s, 2H, $H_{arom.}$), 8.20 (s, 2H, $H_{ethylenic}$), 7.91–7.88 (m, 4H, $H_{arom.}$), 4.06 (s, 8H, —CH_2). Anal. Calcd for $C_{30}H_{24}N_8S_2Cl_2{\cdot}2H_2O$: C, 53.97; H, 4.23; N, 16.17. Found: C, 54.05; H, 4.20; N, 15.98.

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