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Synthesis of Bisbenzamidine Derivatives in Benzo[*c*]thiophene Series*

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The synthesis of three new bisbenzamidine derivatives in benzo[*c*]thiophene series is reported. In multistep synthesis from substituted 1,4-diketone first the benzo[*c*]thiophene unit was built up and than the terminal bromine atoms were transformed to corresponding amidines.

INTRODUCTION

It has been well documented that aromatic diamidines that bind to the DNA minor groove exhibit biological activities that range from effectiveness against opportunistic infections to anticancer properties.[1] Despite the broad range of activity exhibited by diamidines, to this date only one compound of this chemical type, pentamidine (**I**) (Figure 1) has found significant clinical use.[1] Biophysical studies with 2,5-bis(4-amidinophenyl)furan (**II**) (furamidine) indicate that important contributors to the minor groove binding affinity of this type of cations are hydrogen bonding, electrostatic and van der Waals interactions, as well the radius of curvature of the observed molecule.[2,3] Based on these studies the effect of structural variations on the terminal amidino units[4–6] and the effect of replacing phenyl group(s) of furamidine with benzimidazole(s),[7–10] benzothiazole(s)[11] or pyridyl group(s)[12] were investigated. In addition to modifications of phenyl rings or the cationic center, the central furan ring was replaced with a number of others heterocyclic ring systems: thiophene,[10,13,14] pyrole,[5,8,13] pyrimidine,[15,16] pyridine,[8] homopiperazine[17] and benzopyran.[18]

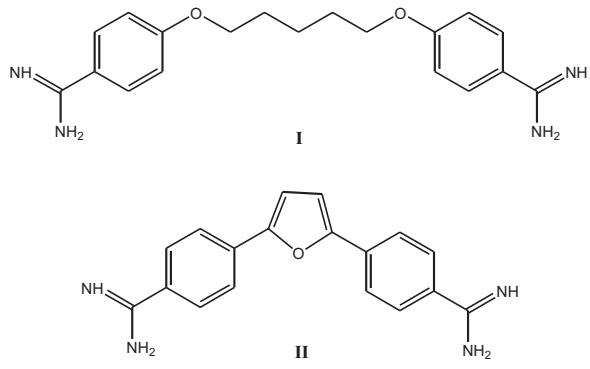

Figure 1. Pentamidine (**I**) and furamidine(**II**).

Several investigations have suggested that groups that would increase the van der Waals interactions of mi-

* Dedicated to Dr. Edward C. Kirby on the occasion of his 70th birthday.

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nor groove binders with the walls of the groove, would increase the DNA affinity of this types of molecules.[19,20] Consequently, we decided to study this effect by replacing the central furan ring in furamidine (**II**) with benzo[*c*]-thiophene unit and its nonaromatic and nonplanar analog 4,7-dihydrobenzo[*c*]thiophene. In this paper we describe the synthesis of 1,3-bis(4-amidinophenyl)-5,6-dimethylbenzo[*c*]thiophene (**7**) and its isopropyl (**8**) and 2-imidazolyl (**9**) derivatives. An attempt to synthesize nonaromatic derivative failed due its instability.

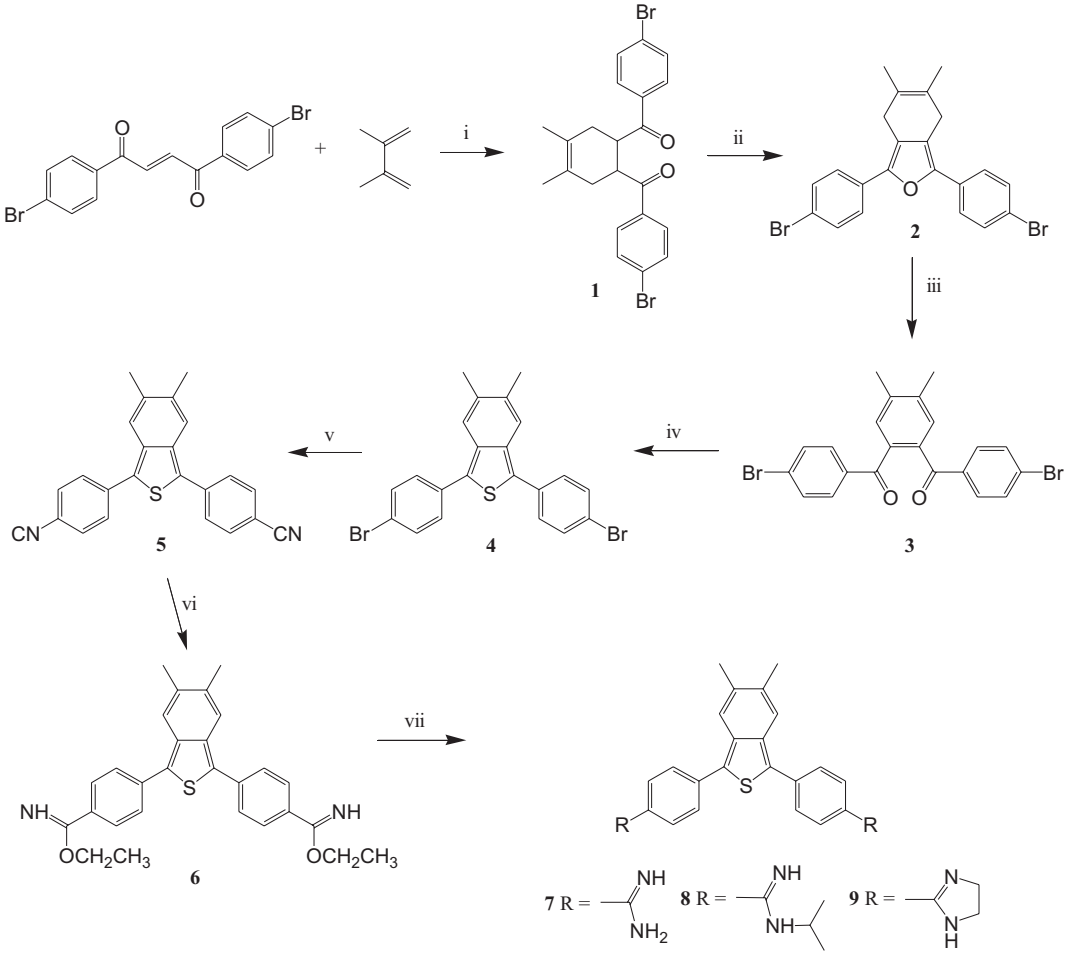
RESULTS AND DISCUSSION

The multi step synthesis employed for compounds **7–9** is outlined in Scheme 1. We started from bromo derivative and first built the central benzo[*c*]thiophene unit and then transformed terminal bromine atoms to nitrile, a key precursor for bisamidino compounds.

The starting compound 1,2-bis(4-bromobenzoyl)ethylene, prepared by Friedel-Crafts acylation from bromobenzene and fumaryl chloride,[21] in Diels-Adler cyclization with 2,3-dimethylbutadiene[22,23] formed 4,5-bis(4-bromobenzoyl)-1,2-dimethylcyclohexene (**1**) in good yield. 1,3-Bis(4-bromophenyl)-5,6-dimethyl-4,7-dihydrobenzo-[*c*]furan (**2**) was prepared by employing cyclodehydration techniques for furanization of 1,4-diketones.[23] Furan derivative **2** was oxidized with bromine and sodium acetate to obtain *o*-diacylbenzene (**3**). In reaction of diketone **3** with P_4S_{10} and sodium hydrogencarbonate in acetonitrile thiophene ring was formed leading to 1,3-bis(4-bromophenyl)-5,6-dimethylbenzo[*c*]thiophene (**4**) in good yield (85 %).

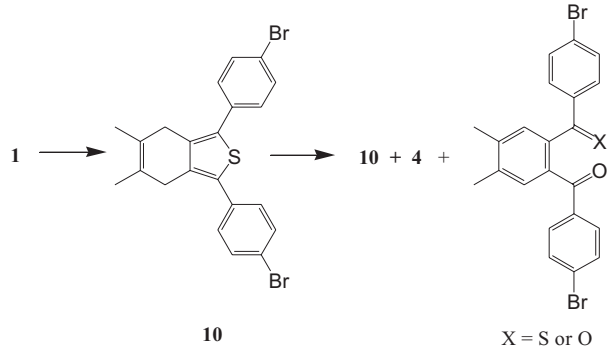
Terminal bromine atoms of compound **4** have been transformed to nitriles using CuCN in quinoline by earlier described procedures[16] to obtain 1,3-bis(4-cyanophenyl)-5,6-dimethylbenzo[*c*]thiophene (**5**) in moderate yield (63 %). The classical Pinner method[24] was used to transform the cyano into amidino group. The imidate ester hydrochloride generated as intermediate product (**6**) was used without purification and identification in next step – reaction with appropriate amines to yield desired bisamidines **7–9**.

An attempt to synthesize derivatives with modified nonaromatic, nonplanar central system, 4,7-dihydroben-



Scheme 1. Reagents and conditions: (i) MeOH, reflux; (ii) acetanhydride, H_3PO_4, 110–130 °C; (iii) Br_2, CH_3COONa, CH_3COOH, reflux; (iv) P_2S_5, $NaHCO_3$, acetonitrile, 30 °C; (v) CuCN, quinoline, reflux; (vi) HCl(g)/EtOH; (vii) NH_3, H_2N–iPr or $H_2NCH_2CH_2NH_2$.

zo[*c*]thiophene, failed. In reaction of **1** with P_2S_5 4,7-dihydrobenzo[*c*]thiophene system was formed, but compound **10** showed to be unstable and rapidly and uncontrollably oxidized to give mixture of compounds (Scheme 2).



Scheme 2.

EXPERIMENTAL

General

Solvents were distilled from appropriate drying agents shortly before use. TLC was carried out on DC-plastikfolien Kieselgel 60 F254. Melting points were determined on a Kofler hot-stage apparatus or Büchi 510 melting point apparatus and were uncorrected. IR spectra [ν_{max}/cm^{-1}] were obtained for KBr pellets on a Perkin-Elmer 882 spectrophotometer. The ^{1}H-NMR spectra were recorded on a Varian Gemini 300 spectrometer. The samples were dissolved in $CDCl_3$ or DMSO-d_6 and measured at 20 °C in 5 mm NMR tubes. Chemical shifts (δ/ppm) are referred to TMS. Digital resolution was 0.3 Hz per point in ^{1}H-one-dimensional spectra. Elemental analyses were performed by Microanalytical laboratory at the Ruđer Bošković Institute or by Atlantic Microlab Inc. Norcross, GA, USA.

*4,5-Bis(4-bromobenzoyl)-1,2-dimethylcyclohexen (**1**)*

A solution of 1,2-bis(4-bromobenzoyl)ethylene (18.75 g, 0.048 mol) and 2,3-dimethylbutadiene (7.5 g, 0.09 mol) in anhydrous methanol (15 mL) was refluxed for 7 hours. After cooling the white solid was filtered off. The crude product was recrystalized from ethanol to yield 17 g (75 %) of white crystals: m.p. 167–168 °C; IR (KBr) ν_{max}/cm^{-1}: 2908, 1673, 1585, 1401, 1207, 1005, 848, 832, 738; ^{1}H-NMR ($CDCl_3$) δ/ppm: 7.87 (d, 4H, J = 8.46 Hz, Ph-H), 7.62 (d, 4H, J = 8.46 Hz, Ph-H), 4.02 (m, 2H, CH), 2.35 + 2.30 (s+s, 2H, CH_2), 2.13 (m, 2H, CH_2), 1.60 (s, 6H, CH_3).

*1,3-Bis(4-bromophenyl)-5,6-dimethyl-4,7-dihydrobenzo[c]furan (**2**)*

Compound **1** (11 g, 0.023 mol) was dissolved in acetic anhydride (150 mL) at 110–130 °C. To this solution 85 % phosphoric acid (0.5 mL) was added and the mixture was heated under reflux for 10 min. After cooling yellow-green fluorescent solid (10.3 g, 97.5 %) was isolated and used without purification due to rapid but partial oxidation to diketone.

*1,2-Bis(4-bromobenzoyl)-4,5-dimethylbenzene (**3**)*

To a stirred solution of sodium acetate (9.6 g, 0.18 mol) in acetic acid (200 mL) compound **2** (5.8 g, 12.7 mmol) and bromine (4.6 g, 28.8 mmol) were added. The reaction mixture was refluxed for 30 min, cooled to room temperature and poured into water (400 mL). The resulting white precipitate was collected by filtration, washed with dichloromethane and dried under vacuum yielding white crystals of the product **3**: 5.1 g (85 %); m.p. 170–172 °C; IR (KBr) ν_{max}/cm^{-1}: 3085, 2923, 1663, 1581, 1308, 1292, 950, 839, 761; ^{1}H-NMR ($CDCl_3$) δ/ppm: 7.53 (s, 8H, Ph-H), 7.36 (s, 2H, Ar-H), 2.37 (s, 6H, CH_3).

*1,3-Bis(4-bromophenyl)-5,6-dimethylbenzo[c]thiophene (**4**)*

To a solution of compound **3** (6 g, 12.7 mmol) in dry acetonitrile (400 mL) P_4S_{10} (17.2 g, 38.7 mmol) and $NaHCO_3$ (12.8 g, 0.15 mol) were added. The reaction mixture was stirred for 3.5 hours at 30 °C. The resulting yellow solid was filtered off and recrystallized from hot chloroform yielding 5.1 g (85 %) of yellow crystals: m.p. >240 °C; IR (KBr) ν_{max}/cm^{-1}: 2911, 1515, 1480, 1070, 1009, 816; ^{1}H-NMR ($CDCl_3$) δ/ppm: 7.61 (d, 4H, J = 7.95 Hz, Ph-H), 7.53 (d, 6H, J = 8.20 Hz, Ph-H, H-4, H-7), 2.32 (s, 6H, CH_3). *Anal*. calcd. for $C_{22}H_{16}Br_2S$ (M_r = 472.24): C 55.95, H 3.42 %; found C 56.16, H 3.30 %.

*1,3-Bis(4-cyanophenyl)-5,6-dimethylbenzo[c]thiophene (**5**)*

A mixture of 1,3-bis(4-bromophenyl)-5,6-dimethylbenzo[*c*]thiophene (**4**) (2.3 g, 4.8 mmol) and CuCN (1.12 g, 12.5 mmol) in quinoline (40 mL) was refluxed for 3.5 hours under nitrogen. After cooling the reaction mixture was poured into diethyl ether (200 mL). The resulting white precipitate was collected by filtration, washed with diethyl ether and water, and extracted with chloroform in Soxlet apparatus. Eluate was passed through a short alumina colon to remove traces of copper, and solvent was evapored in vacuum to yielding 1.12 g (63.3 %) of orange powder: m.p. >240 °C; IR (KBr) ν_{max}/cm^{-1}: 2914, 2200, 1599, 1515, 1169, 831; ^{1}H-NMR ($CDCl_3$) δ/ppm: 7.80 (s, 8H, Ph-H), 7.61 (s, 2H, H-4, H-7), 2,38 (s, 6H, CH_3). *Anal*. calcd. for $C_{24}H_{16}N_2S$ (M_r = 364.46): C 79.09, H 4.42, N 7.69 %; found C 78.95, H 4.38, N 7.70 %.

*1,3-Bis(4-amidinophenyl)-5,6-dimethylbenzo[c]thiophene dihydrochloride (**7**)*

A stirred suspension of bisnitrile **5** (0.54 g, 1.5 mmol) in dry dichloromethane (200 mL) and absolute ethanol (100 mL) was chilled to 0–5 °C, and was saturated with HCl (g). The flask was stoppered, and contents were stirred at room temperature until an IR spectrum indicated the disappearance of the nitrile peak. The solvent was partially evaporated and dry ether was added to the residue. The resulting solid was collected by filtration and washed with dry ether. Diimidate ester **6** was suspended in absolute ethanol (100 mL), chilled to 0–5 °C and saturated with NH_3 (g). The flask was stop-

pered and the contents were stirred at room temparature for 3 days. About half of the solvent was evaporated and the residue was treated with dry ether. The resulting solid was filtered off, washed with ether and dried in vacuum. The free base was suspended in absolute ethanol saturated with HCl (50 mL), and the mixture was stirred at room temperature for 16 h. Addition of ether gave a red precipitate which was filtered off and dried in vacuum at 80 °C for 24 h. Yield 0.12 g (15.2 %) of red powder; m.p. >290 °C; IR (KBr) ν_{max}/cm^{-1}: 3374 (bs), 3110 (bs) 1680, 1602, 1503, 1481, 841, 681; ^{1}H-NMR ($CDCl_3$) δ/ppm: 9.30 (bs, 6H, N-H), 7.98 (s, 8H, Ph-H), 7.68 (s, 2H, H-4,H-7), 2.33 (s, 6H, CH_3). *Anal*. calcd. for $C_{24}H_{22}N_4S \cdot 2HCl \cdot 3.5H_2O$ (M_r = 534.51): C 53.93, H 5.84, N 10.48 %; found C 53.92, H 5.68, N 10.48 %.

*1,3-Bis(4-*N*-isopropylamidinophenyl)-5,6-dimethylbenzo[*c*]thiophene dihydrochloride (**8**)*

Freshly distilled isopropyl amine (1.4 g, 23.7 mmol) was added to a suspension of imidate ester hydrochloride prepared from **5** (0.4 g, 1.1 mmol) in absolute ethanol (50 mL) and stirred under nitrogen at room temperature for 3 days. The solvent was partially evaporated and dry ether was added. The resulting solid was collected by filtration, washed with ether and dried in vacuum. The free base was suspended in absolute ethanol (50 mL) saturated with HCl (g). The reaction mixture was refluxed for 2 h and then stirred at room temperature for 16 h. The mixture was treated with dry ether and the resulting solid was filtered off, dried in vacuum at 80 °C for 8 h, to yield 0.285 g (44 %) of yellow powder, m.p. > 297 °C (decomposition); IR ν_{max}/ cm^{-1}: 3442 (bs), 3038, 1671, 1517, 1128, 1118, 841, 796, 723, 696; ^{1}H-NMR (DMSO-d_6) δ/ppm: 9.66, 9.54 and 9.18 (bs, 6H, N-H), 7.96–7.88 (dd, 8H, J = 8.32 Hz, Ph-H), 7.65 (s, 2H, H-4, H-7), 4.09 (m, 2H, CH), 2.32 (s, 6H, CH_3), 1.29 (d, 12H, J = 6.32 Hz, CH_3). *Anal*. calcd. for $C_{30}H_{34}N_4S \cdot 2HCl \cdot 1.5H_2O$ (M_r = 582.61): C 61.84, H 6.75, N 9.62 %; found C 61.41, H 6.62, N 9.45 %.

*1,3-Bis[(4-imidazolin-2-yl)phenyl]-5,6-dimethylbenzo-[c]thiophene dihydrochloride (**9**)*

A mixture of ethylenediamine (0.207 g, 3.44 mmol) and bis imidate ester hydrochloride from **5** (0.6 g, 1.65 mmol) in absolute ethanol (50 ml) was refluxed under nitrogen for 24 h. The solvent was partially evaporated, and treated with dry ether. The resulting solid was collected by filtration, washed with ether and dried in vacuum. The free base was suspended in absolute ethanol (50 mL) and saturated with HCl (g). The reaction mixture was refluxed for 2 h and then stirred at room temperature for 16 h. The mixture was treated with dry ether and the resulting solid was filtered off, dried in vacuum at 80 °C for 8 h, to yield 0.378 g (41 %) of orange powder: m.p. > 290 °C; IR ν_{max}/ cm^{-1}: 3419 (bs), 3093 (bs), 2964, 1607, 1516, 1366, 1285, 1033, 842, 658; ^{1}H NMR (DMSO-d_6) δ/ppm: 10.62 (s, 2H, N-H), 8.08–7.97 (dd, 8H, Ph-H), 7.70 (s, 2H, H-4, H-7), 4.02 (s, 8H, CH_2), 2.32 (s, 6H, CH_3). *Anal*. calcd. for $C_{28}H_{26}N_4S \cdot 2HCl \cdot 2H_2O$ (M_r = 559.54): C 60.10, H 5.77, N 10.01 %; found C 59.85, H 5.75, N 10.11 %.

*1,3-Bis(4-bromophenyl)-5,6-dimethyl-4,7-dihydrobenzo[*c*]thiophene (**10**)*

To a solution of compound **1** (0.95 g, 2 mmol) in dry acetonitrile, P_4S_{10} (2.7 g, 6.1 mmol) and $NaHCO_3$ (2.0 g, 24 mmol) were added. The mixture was stirred at 30 °C for 4 h. The mixture was treated with water (50 mL) and the resulting solid was collected by filtration to yield 0.815 g (86 %) of yellow crystals: m.p. 228–230 °C; ^{1}H-NMR ($CDCl_3$) δ/ppm: 7.62 (d, 4H, J = 8.63 Hz, Ph-H), 7.57 (d, 4H, J = 8.64 Hz, Ph-H), 3.36 (s, 4H, CH_2), 1.88 (s, 6H, CH_3).

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SAŽETAK

Sinteza bisbenzamidinskih derivata u benzo[*c*]tiofenskoj seriji

Mirjana Kožul, Ivana Stolić, Biserka Žinić i Miroslav Bajić

Opisana je sinteza tri nova bisbenzamidinska derivata u benzo[*c*]tiofenskoj seriji. U višestupnjevitoj sintezi iz supstituiranoga 1,4-diketona prvo je izgrađena centralna benzo[*c*]tiofenska jedinica, a zatim su terminalni atomi broma prevedeni u odgovarajuće amidine.