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Synthesis of New Cyano-Substituted *bis*-Benzothiazolyl Arylfurans and Arylthiophenes

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Abstract: The new compounds 2-[4-(6-cyanobenzothiazol-2-yl)phenyl]-5-(6-cyano-benzothiazol-2-yl)furan (**6a**) and 2-[4-(6-Cyanobenzothiazol-2-yl)phenyl]-5-(6-cyano-benzothiazol-2-yl)thiophene (**6b**) were synthesized by multi-step reactions from the corresponding 2-furan and 2-thiophene carboxaldehydes (route A), as well as from 2-furan and 2- thiophene carboxylic acids (route B). Route B involves one less step than route A, but the overall yields of the reactions are considerably lower.

Keywords: *bis*-Benzothiazole, 6-Cyanobenzothiazole, Furan, Thiophene.

Introduction

Benzothiazoles are heterocyclic compounds with multiple applications and, although they have been known from long ago to be biologically active, [1,2,3], their varied biological features are still of great scientific interest nowadays. They show, for example, very intensive antitumor activity, especially the phenyl-substituted benzothiazoles [4-6], while condensed pyrimido[2,1-b]benzothiazoles

and benzothiazolo[2,3-b]-quinazolines exert antiviral activity [7]. Recently, Racanè at al. [8] have described the synthesis of bis-substituted amidinobenzothiazoles as potential anti-HIV agents. Substituted benzamido- and phenylacetamido-substituted 2-phenylbenzothiazoles [9,10,11], 2-substituted 6-nitro- and 6-aminobenzothiazoles [12], fluorobenzothiazoles [13] and Schiff bases derived from benzothiazoles [14] show microbiological activity.

On the other hand, bis-benzothiazoles and substituted bis-benzothiazoles are frequently fluorescent compounds and therefore convenient for fluorimetric measurements, which could serve as a potential method for detection of binding the biologically active compounds on DNA [15]. However, there is little data describing compounds containing two benzothiazole rings attached *via* a heterocyclic system, such as 2,5-benzothiazolylfuran and thiophene and its derivatives [16,17,18], as well as their vinylogues [19,20].

Results and Discussion

Cyano substituted *bis*-benzothiazolyl compounds **6a** and **6b** were synthesized starting from 2-furan- and 2-thiophenecarboxaldehydes or from 2-furan- and 2-thiophenecarboxylic acids via multistep reactions by the two routes designated A and B, respectively (Scheme 1).

In the first step of the reaction, 2-furan- or 2-thiophenecarboxaldehydes, and 2-furan- or 2-thiophenecarboxylic acids were arylated by the diazonium salts of *p*-aminobenzoic acid by the well known Meerwein arylation procedure [20,21]. In agreement with the greater aromaticity of thiophenes with respect to furans, it is evident from the arylation yields that the furan derivatives are more reactive than the corresponding thiophene derivatives. Thus, 2-furancarboxaldehyde yields 60% of **1a** [20] upon arylation; 2-furancarboxylic acid yields 58% of **2a** [20], 2-thiophenealdehyde yields 17% of **1b** [21] and 2-thiophenecarboxylic acid yields 19% of **2b**, respectively.

Benzothiazolyl compounds **3a** and **3b**, synthesized from the appropriate aldehydes and 4-amino-3-mercaptobenzonitrile [22], according to a modified condensation method [18, 23], have been converted to the corresponding chlorocarbonyl derivatives **4a** and **4b**. In the last step (route A), these chlorocarbonyl compounds were condensed with 4-amino-3mercaptobenzonitrile to obtain the *bis*-cyanobenzothiazolyl compounds **6a** and **6b** in good yields of about 75%.

The syntheses of compounds **6a** and **6b** (route B) have been carried out with 5-(4-carboxyphenyl)-2-furylcarboxylic acid (**2a**) [20] and 5-(4-carboxyphenyl)-2-thienylcarboxylic acid (**2b**). Dicarboxylic compounds **2a** and **2b** have been converted to the dichlorocarbonyl derivatives **5a** and **5b** and then these were condensed with 4-amino-3-mercaptobenzonitrile in yields of about 35%. Route B has one step less then route A, but the overall yield of the reactions is considearbly lower.

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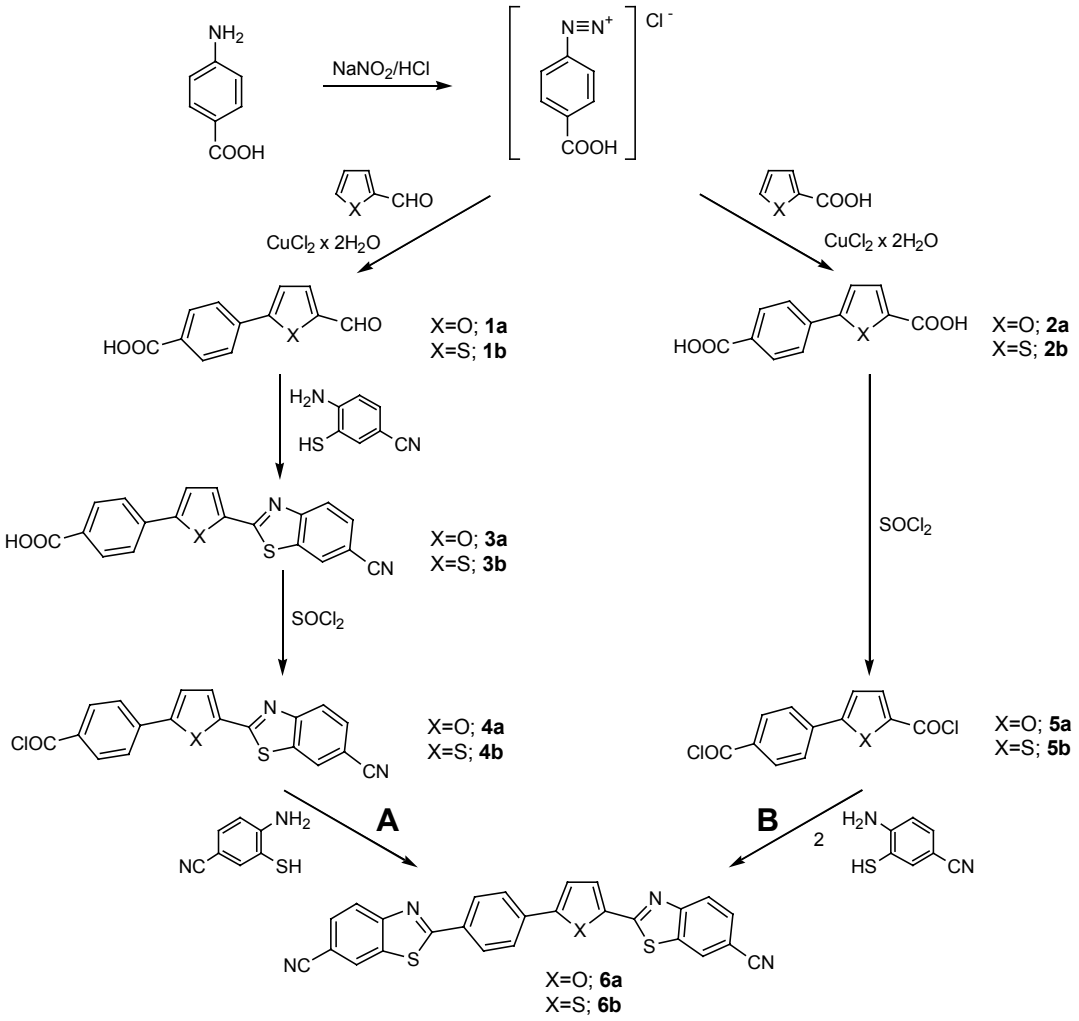
Scheme 1



Experimental

General

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

General Procedure for the Arylation of Compounds **1a**, **1b**, **2a** *and* **2b**.

A solution of *p*-aminobenzoic acid (75 mmol) in water (120 mL) and concentrated HCl (40 mL) was cooled to 5 °C and diazotized with a solution of $NaNO_2$ (91 mmol) in H_2O (35 mL). After 20 min

a solution of 75 mmol of 2-furanaldehyde for **1a** [20], 2-thiophenealdehyde for **1b** [21], 2-furan-carboxylic acid for **2a** [20] or 2-thiophenecarboxylic acid for **2b**, respectively, in acetone (50 mL) and a solution of $CuCl_2 \cdot 2H_2O$ (23 mmol) in water (25 mL) were added to the stirred reaction mixture. The reaction mixture was left to stand at room temperature for two days with occasional shaking. After dilution with water (500 mL) the precipitated crystals were filtered off and washed with abundant hot water.

5-(4-carboxyphenyl)-2-thiophenecarboxylic acid (**2b**). Yield: 3.9 g (21%); m.p.: >300 °C (from DMF - water); IR (KBr): 1674 (COOH) cm^{-1}; ^{1}H-NMR (300 MHz; DMSO-d_6) δ: 13.22 (s, 2H, H-COOH), 8.01 (d, *J*=8.4 Hz, 2H, H-arom.), 7.88 (d, *J*=8.4 Hz, 2H, H-arom.), 7.76 (d, *J*=3.9, 1H, H-thioph.), 7.72 (d, *J*=3.9 Hz, 1H, H-thioph.); Anal. Calcd. for $C_{12}H_8O_4S$: C 58.06, H 3.25, S 12.92. Found: C 58.32, H 3.13, S 12.78.

General Procedure for the Synthesis of Benzothiazolyl Compounds **3a** *and* **3b**.

4-Amino-3-mercaptobenzonitrile (21 mmol) was added to a solution of the appropiate aldehyde **1a** or **1b** (21 mmol) in pyridine (60 mL) and the stirred reaction mixture was refluxed 4 h. The mixture was then poured into 2 M hydrochloric acid (400 mL), and after cooling overnight, the crystalline product obtained was oxidized with an ethanolic solution of $FeCl_3$ to obtain the benzothiazole compounds **3a** and **3b**, respectively.

2-(4-Carboxyphenyl)-5-(6-cyanobenzothiazol-2-yl)furan (**3a**). Yield: 5.0 g (70%); m.p.>300°C (DMF); IR (KBr): 2210 (CN), 1670 (COOH) cm^{-1}; ^{1}H-NMR (300 MHz; DMSO-d_6) δ: 13.18 (s, 1H, H-COOH), 8.78 (s, 1H, H-arom.), 8.50 (d, *J*=8.6 Hz, 1H, H-arom.), 8.07 (d, *J*=8.5 Hz, 2H, H-arom.), 8.01 (d, *J*=8.5 Hz, 2H, H-arom.), 7.97 (d, *J*=8.9 Hz, 1H, H-arom.), 7.68 (d, *J*=3.8 Hz, 1H, H-furan), 7.52 (d, *J*=3.8 Hz, 1H, H-furan); Anal. Calcd. for $C_{19}H_{10}N_2O_3S$: C 65.89, H 2.91, N 8.09 S 9.26. Found: C 65.52, H 2.82, N 8.31 S 9.13.

2-(4-Carboxyphenyl)-5-(6-cyanobenzothiazol-2-yl)thiophene (**3b**). Yield: 4.5 g (62%); m.p.>300°C (from DMF - ethanol); IR (KBr): 2224 (CN), 1687 (COOH) cm^{-1}; ^{1}H-NMR (300 MHz; TFA) δ: 8.33 (s, 1H, H-arom.), 8.11 (d, *J*=4.2 Hz, 1H, H-thioph.), 8.06 (d, *J*=8.1 Hz, 2H, H-arom.), 7.99 (d, *J*=8.7 Hz, 1H, H-arom.), 7.91 (d, *J*=8.4 Hz, 1H, H-arom.), 7.68 (d, *J*=8.1 Hz, 2H, H-arom.), 7.56 (d, *J*=4.2 Hz, 1H, H-thioph.); Anal. Calcd. for $C_{19}H_{10}N_2O_2S_2$: C 62.97, H 2.78, N 7.73 S 17.70. Found: C 62.95, H 2.82, N 8.01 S 17.58.

General Procedure for the Synthesis of Chlorocarbonyl Compounds **4a**, **4b**, **5a** *and* **5b**.

Heating of a mixture of compounds **3a** or **3b** (11.5 mmol) with thionyl chloride (230 mmol) or of compounds **2a** or **2b** (18 mmol) with thionyl chloride (344 mmol) for 4 h on an oil bath at 85 °C

afforded the corresponding monochlorocarbonyl compound **4a** and **4b** or the dichlorocarbonyl compound **5a** and **5b**.

2-(4-Chlorocarbonylphenyl)-5-(6-cyanobenzothiazol-2-yl)furan (**4a**). Yield: 3.1 g (74%); m.p.>300°C ($CHCl_3$); IR (KBr): 2210 (CN), 1760 (COCl) 1720 (COCl) cm^{-1}; ^{1}H-NMR (300 MHz; DMSO-d_6) δ: 8.78 (s, 1H, H-arom.), 8.20 (d, *J*=8.5 Hz, 1H, H-arom.), 8.07 (d, *J*=8.2 Hz, 2H, H-arom.), 8.00 (d, *J*=8.5 Hz, 2H, H-arom.), 7.96 (d, *J*=9.0 Hz, 1H, H-arom.), 7.68 (d, *J*=3.8 Hz, 1H, H-furan), 7.51 (d, *J*=3.8 Hz, 1H, H-furan).

2-(4-Chlorocarbonylphenyl)-5-(6-cyanobenzothiazol-2-yl)thiophene (**4b**). Yield: 2.7 g (62%); m.p.>300°C ($CHCl_3$);. IR (KBr): 2222 (CN), 1769 (COCl) 1720 (COCl) cm^{-1}; ^{1}H-NMR (300 MHz; DMSO-d_6) δ: 8.75 (s, 1H, H-arom.), 8.17 (d, *J*=8.7 Hz, 1H, H-arom.), 8.07 (d, *J*=3.9 Hz, 1H, H-thioph.), 8.03 (d, *J*=8.1 Hz, 2H, H-arom.), 7.95 (m, 3H, H-arom.), 7.86 (d, *J*=3.9 Hz, 1H, H-thioph.).

2-(4-Chlorocarbonylphenyl)-5-chlorocarbonylfuran (**5a**). Yield: 2.2 g (46%); m.p.102-106 °C (from benzene - cyclohexane); IR (KBr): 1740 (COCl) cm^{-1}; ^{1}H-NMR (300 MHz; $CDCl_3$) δ: 8.21 (d, *J*=8.7 Hz, 2H, H-arom.), 7.95 (d, *J*=8.7 Hz, 2H, H-arom.), 7.60 (d, *J*=3.8 Hz, 1H, H-furan), 7.05 (d, *J*=3.8 Hz, 1H, H-furan).

2-(4-Chlorocarbonylphenyl)-5-chlorocarbonylthiophene (**5b**). Yield: 3.7 g (81%); m.p.88-92 °C (from benzene - cyclohexane); IR (KBr): 1771 (COCl) 1736 (COCl) cm^{-1}; ^{1}H-NMR (300 MHz; $CDCl_3$) δ: 8.20 (d, *J*=8.5 Hz, 2H, H-arom.), 7.99 (d, *J*=4.1 Hz, 1H, H-thioph.), 7.80 (d, *J*=8.5 Hz, 2H, H-arom.), 7.52 (d, *J*=4.1 Hz, 1H, H-thioph.).

General Procedure for the Synthesis of bis-Benzothiazolyl Compounds **6a** *and* **6b.**

A solution of monochlorocarbonyl compounds **4a** or **4b** (5.0 mmol, route A), or of dichlorocarbonyl compounds **5a** or **5b** (2.5 mmol, route B) in dry chlorobenzene (100 mL) was stirred under a stream of nitrogen. To these solutions 4-amino-3-mercaptobenzonitrile (5.1 mmol) was added. The reaction mixture was heated under reflux under the stream of nitrogen for 70 h. After cooling, a crystalline product was obtained.

2-[4-(6-Cyanobenzothiazol-2-yl)phenyl]-5-(6-cyanobenzothiazol-2-yl)furan (**6a**). Yields: 1.73 g (75%, method **A**), 0.38 g (33%, method **B**); m.p.>300°C (DMF); IR (KBr): 2226 (CN) cm^{-1}; ^{1}H-NMR (300 MHz; TFA) δ: 9.35 (s, 1H, H-arom.), 9.27 (s, 1H, H-arom.), 9.03 (d, *J*=8.1 Hz, 2H, H-arom.), 8.96-8.80 (m, 6H, H-arom.), 8.74 (d, *J*=3.9 Hz, 1H, H-furan), 8.16 (d, *J*=3.9 Hz, 1H, H-furan). Anal. Calcd. for $C_{26}H_{12}N_4OS_2$: C 67.81, H 2.63, N 12.17 S 13.92. Found: C 67.86, H 2.54, N 12.10, S 14.02.

2-[4-(6-Cyanobenzothiazol-2-yl)phenyl]-5-(6-cyanobenzothiazol-2-yl)thiophene (**6b**). Yields: 1.95 g (82%, method **A**), 0.43 g (36%, method **B**); m.p.>300°C (DMF); IR (KBr): 2224 (CN) cm^{-1}; ^{1}H-NMR (300 MHz; TFA) δ: 8.49 (s, 1H, H-arom.), 8.38 (s, 1H, H-arom.), 8.18-8.05 (m, 4H, H-arom.), 8.01 (d, *J*=3.9 Hz, 1H, H-thioph.), 7.97-7.92 (m, 4H, H-arom.), 7.70 (d, *J*=4.0 Hz, 1H, H-thioph.); Anal. Calcd. for $C_{26}H_{12}N_4S_3$: C 65.52, H 2.54, N 11.76, S 20.18. Found: C 65.38, H 2.51, N 11.66, S 20.32.

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Sample availability: Samples of compounds **2b**, **3b**, **6a** and **6b** are available from MDPI.