On the Synthesis of 9-Furylnaphtho[2,3-*b*]furan Derivatives

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A simple synthetic pathway to the unknown 9-furyl-substituted naphthofuran derivatives has been developed involving intramolecular cyclization of 2-carboxyaryldifurylmethanes and 2-formylaryldifurylmethanes.

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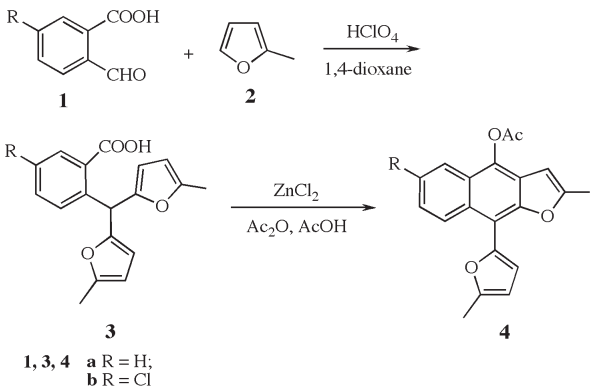
Naphthofuran derivatives have been the subject of constant interest due to a wide spectrum of physiological activities [1]. Naphthofuran backbone is a part of some natural compounds such as maturin [2], maturin acetate [3] and 14-methoxydehydrocacalohastine [4], which were isolated from *Trichilia cuneata*.

It is well-known that furan ring can easily undergo a number of modification reactions. That is why we have intended to elaborate a convenient synthesis of 9-furylnaphtho[2,3-*b*]furan derivatives, which can serve, in our opinion, as starting compounds for the synthesis of other naphthofurans, promising as biologically active compounds.

Several synthetic approaches to the naphthofuran backbone are described. Most general of them involve the following steps: a) building up the furan ring at the naphthalene core [5], b) construction of the central aromatic ring through an intramolecular acylation reaction of the corresponding 2-carboxybenzylfurans [6,7].

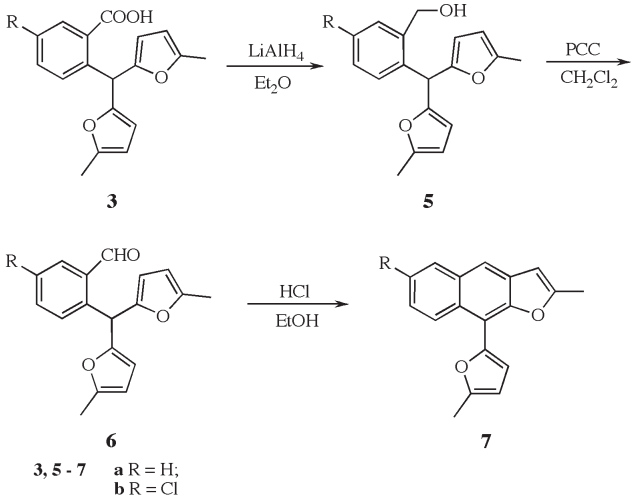
We chose the second approach for the synthesis of naphthofurans **4**, as the starting 2-carboxybenzylfurans **3** [8] had been readily available through the condensation of 2-formylbenzoic acid **1** and 2-methylfuran (**2**) in the presence of $HClO_4$ in 1,4-dioxane at 65-70 °C (Scheme 1). A standard work-up [6] led to the corresponding 9-furylnaphthofurans **4**.

Scheme 1



To obtain 4-unsubstituted 9-furylnaphthofurans we used the following approach: carboxy group in the compounds **3** was reduced with $LiAlH_4$ to give alcohols **5**, which were further oxidized into corresponding 2-formylaryldifurylmethanes **6**. The latter gave 9-furylnaphthofurans **7** under treatment with ethanolic HCl solution (Scheme 2).

Scheme 2



EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AC 200 spectrometer at 200 MHz. Chemical shifts are reported in ppm relative to the tetramethylsilane as an internal standard. IR spectra was recorded on InfraLUM FT-02. Column chromatography was carried out using silica gel KSK (50-160 mkm) manufactured by LTD Sorbpolymer.

2-Bis(5-methyl-2-furyl)methylbenzoic acid (**3a**) was synthesized and characterized earlier [8].

5-Chloro-2-bis(5-methyl-2-furyl)methylbenzoic Acid (**3b**).

The compound **3b** was synthesized analogously to **3a** starting from 5-chloro-2-formylbenzoic acid (**1b**) in 70% yield. Colorless crystals with mp 222-223 °C; ir: COOH 1695 cm^{-1}; ^{1}H nmr: δ 2.25 (s, 6H, CH_3), 5.89 (s, 4H, H_{Fur}), 6.60 (s, 1H, CH), 7.31 (d, J

= 8.3 Hz, 1H, H_{Ar}), 7.48 (dd, J = 2.3, 8.3 Hz, 1H, H_{Ar}), 8.04 (d, J = 2.3 Hz, 1H, H_{Ar})

Anal. Calcd for $C_{18}H_{15}ClO_4$: C, 65.36; H, 4.57. Found: C, 65.42; H, 4.52.

2-Methyl-9-(5-methyl-2-furyl)naphtho[2,3-*b*]furan-4-yl Acetate (**4a**).

A mixture of 2-bis(5-methyl-2-furyl)methylbenzoic acid (**3a**) (4.0 g; 13.5 mmol), acetic acid (10 mL), acetic anhydride (10 mL) and $ZnCl_2$ as catalyst was stirred under reflux for 3 hours. The reaction was monitored with TLC, and, after completion, the mixture was poured into water (100 mL), neutralized with $NaHCO_3$, and extracted with CH_2Cl_2 (3 x 80 mL). The organic layer was separated, dried with Na_2SO_4, and treated with active charcoal. The solvent was removed under reduced pressure, and the residue purified on silica gel with hexane – CH_2Cl_2 (4:1) as an eluent to give 1.34 g (31% yield) of the title compound as colorless crystals. Mp 145-147 °C (CH_2Cl_2/hexane); ir: CH_3COO 1753 cm^{-1}; ^1H nmr: δ 2.50 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 6.27 (d, J = 3.1 Hz, 1H, 4-H_{Fur}), 6.40 (s, 1H, 3-H), 6.88 (d, J = 3.1 Hz, 1H, 3-H_{Fur}), 7.47-7.54 (m, 2H, 6-H, 7-H), 7.95-8.00 (m, 1H, 5-H), 8.54-8,59 (m, 1H, 8-H).

Anal. Calcd. for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 75.10; H, 5.10.

6-Chloro-2-methyl-9-(5-methyl-2-furyl)naphtho[2,3-*b*]furan-4-yl Acetate (**4b**).

Compound **4b**; was synthesized analogously to **4a** starting from compound **3b** in 30.5% yield as colorless crystals with mp 140-143 °C; ir: CH_3COO 1751 cm^{-1}; ^1H nmr: δ 2.50 (s, 3H, CH_3), 2,52 (s, 3H, CH_3), 2,55 (s, 3H, CH_3), 6.27 (d, J = 3.1 Hz, 1H, 4- H_{Fur}), 6.38 (s, 1H, 3-H), 6.89 (d, J = 3.1 Hz, 1H, 3-H_{Fur}), 7.42 (dd, J = 2.1, 9.3 Hz, 1H, 7-H), 7.94 (d, J = 2.1 Hz, 1H, 5-H), 8,54 (d, J = 9.3 Hz, 1H, 8-H).

Anal. Calcd. for $C_{20}H_{15}ClO_4$: C, 67.71; H, 4.26. Found: C, 67.78; H, 4.20.

2-Bis(5-methyl-2-furyl)methylphenylmethanol (**5a**).

To stirred suspension of 2-bis(5-methyl-2-furyl)methylbenzoic acid (**3a**) (15 g, 50.7 mmol) in anhydrous Et_2O (150 mL) $LiAlH_4$ (3.9 g, 101.4 mmol) was added portionwise under cooling (-3 – 0 °C). The reaction was controlled with TLC, and after 5 hours the mixture was poured into ice water and carefully neutralized with 6 *M* hydrochloric acid. The product was extracted with Et_2O (3 x 200 mL), dried with Na_2SO_4, treated with active charcoal. The solvent was removed in vacuo, the residue was recrystallized from hexane to give 13.1 g (92% yield) of the title compound as colorless crystals with mp 65-67 °C; ir: OH br 3296 cm^{-1}; ^1H nmr: δ 1.61 (br s, 1H, OH), 2.26 (s, 6H, CH_3), 4.75 (s, 2H, CH_2), 5.74 (s, 1H, CH), 5.85 (d, J = 3.2 Hz, 1H, 3- H_{Fur}), 5.89 (d, J = 3.2 Hz, 1H, 4- H_{Fur}), 7.19-7.31 (m, 3H, H_{Ar}), 7.40-7.45 (m, 1H, H_{Ar}).

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.50; H, 6.19.

5-Chloro-2-bis(5-methyl-2-furyl)methylphenylmethanol (**5b**).

Compound **5b**; was synthesized analogously to **5a** starting from compound **3b** in 98% yield as colorless crystals with mp 71-73 °C; ir: OH br 3252 cm^{-1}; ^1H nmr: δ 1.70 (br s, 1H, OH), 2.25 (s, 6H, CH_3), 4.72 (s, 2H, CH_2), 5.62 (s, 1H, CH), 5.84 (d, J = 3.2 Hz, 2H, 3-H_{Fur}), 5.89 (d, J = 3.2 Hz, 2H, 4-H_{Fur}), 7.10 (d, J = 8.3 Hz, 1H, H_{Ar}), 7.25 (dd, J = 1.8, 8.3 Hz, 1H, H_{Ar}), 7.46 (d, J = 1.8 Hz, 1H, H_{Ar}).

Anal. Calcd for $C_{18}H_{17}ClO_3$: C, 68.25; H, 5.41. Found: C, 68.31; H, 5.39.

2-Bis(5-methyl-2-furyl)methylbenzaldehyde (**6a**).

A solution of 2-bis(5-methyl-2-furyl)methylphenylmethanol (**5a**) (10 g, 35.5 mmol) in dry CH_2Cl_2 (100 mL) was added dropwise to the suspension of pyridinium chlorochromate (15 g, 70.0 mmol) in dry CH_2Cl_2 (100 mL). The mixture was stirred for 6 hours at rt. At the end of the reaction (TLC control) the precipitate was collected by filtration and washed with hot CH_2Cl_2 (3 x 100 mL). The filtrate was concentrated *in vacuo*, and the oily residue was purified chromatographically on silica gel eluting with hexane - CH_2Cl_2 (10:1). The eluate was concentrated to the volume of 50 mL and left to crystallize overnight. The compound **6a** (7 g, 70% yield) was isolated as colorless crystals with mp 63-65 °C; ir: CHO 1695 cm^{-1}; ^1H nmr: δ 2.25 (s, 6H, CH_3), 5.87 (s, 4H, H_{Fur}), 6.46 (s, 1H, CH), 7.31-7.33 (m, 1H, H_{Ar}), 7.42-7.54 (m, 1H, H_{Ar}), 7.85-7.88 (m, 1H, H_{Ar}), 10.27 (s, 1H, CHO).

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.13; H, 5.75. Found: C, 77.20; H, 5.58.

5-Chloro-2-bis(5-methyl-2-furyl)methylbenzaldehyde (**6b**).

Aldehyde **6b**; was synthesized analogously to **6a** starting from the alcohol **5b** in 60.4% yield as colorless crystals with mp 75-77 °C; ir: CHO 1693 cm^{-1}; ^1H nmr: δ 2.25 (s, 6H, CH_3), 5.89 (s, 4H, H_{Fur}), 6.34 (s, 1H, CH), 7.26 (d, J = 8.3 Hz, 1H, H_{Ar}), 7.84 (dd, J = 2.1, 8.3 Hz, 1H, H_{Ar}), 7.84 (d, J = 2.1 Hz, 1H, H_{Ar}), 10.23 (s, 1H, CHO).

Anal. Calcd for $C_{18}H_{15}ClO_3$: C, 68.68; H, 4.80. Found: C, 68.73; H, 4.85.

2-Methyl-9-(5-methyl-2-furyl)naphtho[2,3-*b*]furan (**7a**).

A solution of **6a** (2 g, 7.14 mmol) in EtOH (10 mL) was treated with ethanolic HCl solution (100 g HCl (gas) in 200 g ethanol, 5 mL). The mixture was kept at 50 °C for 1 hour. At the end of the reaction (TLC control) the mixture was poured into water (100 mL), neutralized with $NaHCO_3$, and extracted with CH_2Cl_2 (3 x 80 mL). The organic layer was separated, dried with Na_2SO_4, treated with active charcoal. The solvent was removed under reduced pressure, and the oily residue purified on silica gel eluting with hexane – benzene (3:1) to give 0.7 g (37.4% yield) of the compound **7a** as colorless crystals with mp 59-61 °C (hexane); ^1H nmr: δ 2.52 (s, 3H, CH_3), 2,54 (s, 3H, CH_3), 6.28 (d, J = 3.1 Hz, 1H, 4-H_{Fur}), 6.50 (s, 1H, 3-H), 6.93 (d, J = 3.1 Hz, 1H, 3-H_{Fur}), 7.39-7.52 (m, 2H, 6-H, 7-H), 7.89 (s, 1H, 4-H), 7.90-7.95 (m, 1H, 5-H), 8.57-8,61 (m, 1H, 8-H).

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.49; H, 5.43.

6-Chloro-2-methyl-9-(5-methyl-2-furyl)naphtho[2,3-*b*]furan (**7b**).

Naphthofuran **7b**; was synthesized analogously to **7a** starting from the aldehyde **6b** in 37% yield as colorless crystals with mp 94-96 °C; ^1H nmr: δ 2.51 (s, 3H, CH_3), 2,54 (s, 3H, CH_3), 6.29 (d, J = 3.1 Hz, 1H, 4-H_{Fur}), 6.50 (s, 1H, 3-H), 6.95 (d, J = 3.1 Hz, 1H, 3-H_{Fur}), 7.40 (dd, J = 2.1, 9.3 Hz, 1H, 7-H), 7.78 (s, 1H, 4-H), 7.89 (d, J = 2.1 Hz, 1H, 5-H), 8,55 (d, J = 9.3 Hz, 1H, 8-H).

Anal. Calcd for $C_{18}H_{13}ClO_2$: C, 72.85; H, 4.42. Found: C, 72.80; H, 4.48.

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