

[a] Kuban State University of Technology, Moskovskaya 2, Krasnodar, 350072, Russia.

E-mail: alexander_butin@mail.ru

[b] North-Ossetian State University, Vatutina 46, Vladikavkaz, 362025, Russia.

Received April 14, 2005

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

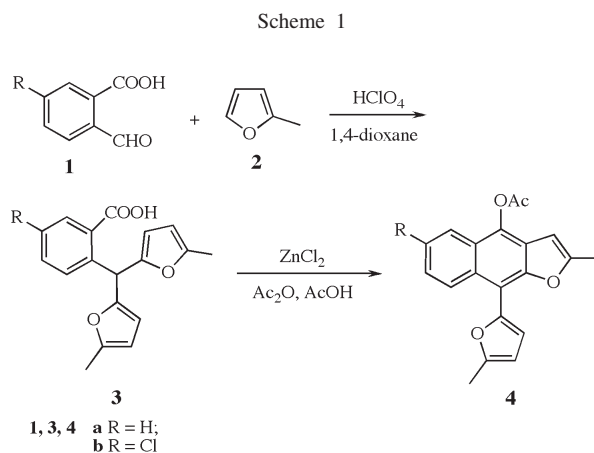
J. Heterocyclic Chem., **42**, 1429 (2005).

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-methoxydehydrocalohastine [4], which were isolated from *Trichilia cuneata*.

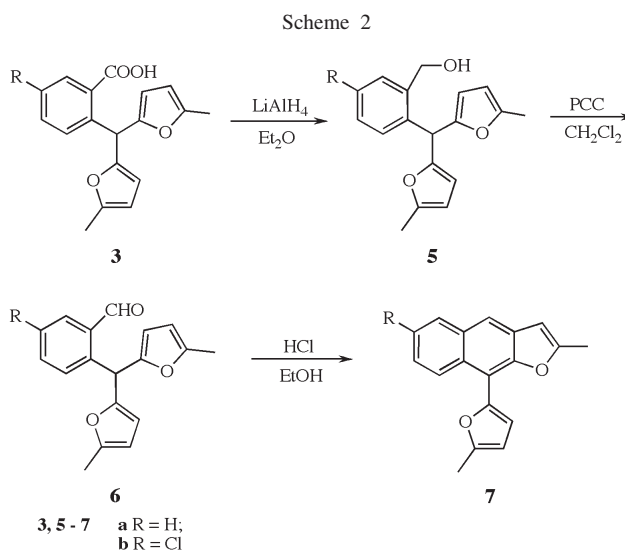
It is well-known that furan ring can easily undergo a number of modification reactions. That is why we have intended to elaborate a convenient synthesis of 9-furylnaphtho[2,3-*b*]furan derivatives, which can serve, in our opinion, as starting compounds for the synthesis of other naphthofurans, promising 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 HClO₄ in 1,4-dioxane at 65-70 °C (Scheme 1). A standard work-up [6] led to the corresponding 9-furylnaphthofurans **4**.



To obtain 4-unsubstituted 9-furylnaphthofurans we used the following approach: carboxy group in the compounds **3** was reduced with LiAlH₄ 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).



EXPERIMENTAL

Melting points are uncorrected. ¹H NMR spectra were recorded in CDCl₃ 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 Sorbopolymer.

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; ¹H nmr: δ 2.25 (s, 6H, CH₃), 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 C₁₈H₁₅ClO₄: 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 ZnCl₂ 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 NaHCO₃, and extracted with CH₂Cl₂ (3 x 80 mL). The organic layer was separated, dried with Na₂SO₄, and treated with active charcoal. The solvent was removed under reduced pressure, and the residue purified on silica gel with hexane – CH₂Cl₂ (4:1) as an eluent to give 1.34 g (31% yield) of the title compound as colorless crystals. Mp 145–147 °C (CH₂Cl₂/hexane); ir: CH₃COO 1753 cm⁻¹; ¹H nmr: δ 2.50 (s, 3H, CH₃), 2.52 (s, 3H, CH₃), 2.54 (s, 3H, CH₃), 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 C₂₀H₁₆O₄: 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: CH₃COO 1751 cm⁻¹; ¹H nmr: δ 2.50 (s, 3H, CH₃), 2.52 (s, 3H, CH₃), 2.55 (s, 3H, CH₃), 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 C₂₀H₁₅ClO₄: 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 Et₂O (150 mL) LiAlH₄ (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 Et₂O (3 x 200 mL), dried with Na₂SO₄, 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, CH₃), 4.75 (s, 2H, CH₂), 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 C₁₈H₁₈O₃: 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, CH₃), 4.72 (s, 2H, CH₂), 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 C₁₈H₁₇ClO₃: 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 CH₂Cl₂ (100 mL) was added dropwise to the suspension of pyridinium chlorochromate (15 g, 70.0 mmol) in dry CH₂Cl₂ (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 CH₂Cl₂ (3 x 100 mL). The filtrate was concentrated *in vacuo*, and the oily residue was purified chromatographically on silica gel eluting with hexane – CH₂Cl₂ (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, CH₃), 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 C₁₈H₁₆O₃: 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, CH₃), 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 C₁₈H₁₅ClO₃: 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 NaHCO₃, and extracted with CH₂Cl₂ (3 x 80 mL). The organic layer was separated, dried with Na₂SO₄, 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, CH₃), 2.54 (s, 3H, CH₃), 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 C₁₈H₁₄O₂: 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, CH₃), 2.54 (s, 3H, CH₃), 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 C₁₈H₁₃ClO₂: C, 72.85; H, 4.42. Found: C, 72.80; H, 4.48.

Acknowledgements.

Financial support was provided by Bayer HealthCare AG and the Russian Foundation of Basic Research (grant 03-03-32759).

REFERENCES AND NOTES

- [1a] R. Cavier, J.-P. Buisson, J. Lemoine and R. Royer, *Eur. J. Med. Chem.* **16**, 73 (1981); [b] N. Weill-Thevent, J.-P. Buisson, R. Royer and M. Hofnung, *Mutation Research* **104**, 1 (1982); [c] D. Averbek, M. Moradi, J.-P. Buisson and R. Royer, *C. R. Acad. Sci. Ser. C* **295**, 181 (1982); [d] M. Venegas, M. Sala, J.-P. Buisson, R. Royer and I. Chourolinkov, *Cancer Research*, **44**, 1969 (1984).
- [2] F. Bohlmann, C. Zdero and M. Grenz, *Chem. Ber.*, **110**, 474 (1977).
- [3] F. Bohlmann and C. Zdero, *Phytochemistry*, **17**, 759 (1978).
- [4] F. Bohlmann, C. Zdero, J. Jakupovic, L. N. Misra, S. Banerjee, P. Singh, R. N. Baruah, M. A. Metwally, G. Schmeda-Hirschmann, L. P. D. Vincent, R. M. King and H. Robinson, *Phytochemistry*, **24**, 1249 (1985).
- [5a] B. Halton, C. S. Jones and D. Margetic, *Tetrahedron*, **57**, 3529 (2001); [b] T. V. Lee, A. A. Galan and C. B. Chapleo, *Tetrahedron Lett.*, **28**, 2301 (1987); [c] E. Ghera and R. Maurya, *Tetrahedron Lett.*, **28**, 709 (1987); [d] N. S. Narasimhan and R. S. Mali, *Tetrahedron*, **31**, 1005 (1975).
- [6a] C. L. Zani, A. B. de Oliveira and V. Snieckus, *Tetrahedron Lett.*, **28**, 6561 (1987); [b] S. M. Starling, D. S. Raslan, A. B. de Oliveira and C. L. Zani, *Synth. Commun.*, **28**, 3567 (1998); [c] S. M. Starling, D. S. Raslan, and A. B. de Oliveira, *Synth. Commun.*, **28**, 1013 (1998); [d] C. C. Lopes, R. S. C. Lopes, A. V. Pinto and P. R. R. Costa, *J. Heterocyclic Chem.*, **21**, 621 (1984).
- [7a] P. J. Perry, V. H. Pavlidis and J. A. Hadfield, *Tetrahedron*, **53**, 3195 (1997); [b] Y. Ohta, M. Doe, Y. Morimoto and T. Kinoshita, *J. Heterocyclic Chem.*, **37**, 731 (2000).
- [8] A. V. Gutnov, V. T. Abaev, A. V. Butin and A. S. Dmitriev, *J. Org. Chem.*, **66**, 8685 (2001).