A Convenient Synthesis of Thiopyrano[2,3-*e*]benzofuran: A New Sulfur Analogue of Angelicin

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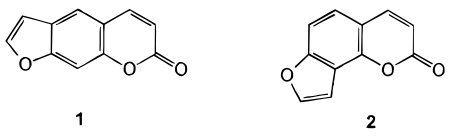
Linear furocoumarins such as psoralen (**1**) (Scheme 1) belong to an important class of photoactivatable drugs able to intercalate into DNA and to photobind with this macromolecule[1] yielding either monoadducts or interstrand cross-links[2] by one or two subsequent photocycloaddition reactions with the pyrimidine bases, particularly thymine.[3] Psoralens are used in the PUVA therapy (psoralen plus UVA) of skin diseases,[4] e.g., psoriasis, vitiligo, and mycosis fungoides, and are advanced for the decontamination of blood products[5] and photopheresis.[6] However, the linear psoralens used in photochemotherapy induce short-term side effects (erythema), and long-term risks such as mutations and skin cancer which have been associated with the ability of the bifunctional psoralens to form cross-links with DNA.[7]

Angelicin (**2**), an angular psoralen, proved to form only monoadducts with DNA owing to the geometry of the monoadduct and is therefore called a monofunctional psoralen. However, angelicin reacts more slowly with DNA partly due to lower light absorption at 365 nm.[8] Several different approaches have been followed to obtain monofunctional furocoumarins that photobind more efficiently with DNA. The introduction of methyl substituents at various positions of angelicin improves its light absorption and reactivity toward DNA, and some of the so obtained angelicins have been shown to be more efficient in clearing psoriasis and less erythematogenic than methoxsalen (8-methoxypsoralen), the most commonly used psoralen derivative, and have been shown to be less photocarcinogenic in mice.[9] Other approaches included the blockage of the photoreactive α-pyrone double bond by annelation of an additional aromatic ring,[10] or the construction of furonaphthopyrones.[11]

We have recently introduced sulfur in place of oxygen in the pyrone moiety of psoralen. This modification

Scheme 1



1 **2**

improved the dark interaction with DNA,[12] the light absorption at 365 nm and the triplet quantum yield and resulted in a greatly enhanced formation of both monoadducts and crosslinks with DNA.[13,14] This leads us to suggest that the introduction of sulfur in place of oxygen in the pyrone moiety of angelicin could give rise to a monofunctional psoralen with improved light absorption, dark interaction, and photobinding with DNA. We report here a convenient synthesis of the first angelicin containing sulfur in place of oxygen in the pyrone heterocycle.

One possible synthesis of the target thioangelicin could have made use of the recently described 4-bromobenzofuran-5-carboxaldehyde obtained by Seitz *et al.* in several steps most of which gave only moderate to low yields.[15] A more direct route would be the chloroformylation of ketone **3**.[16] A similar reaction has been applied to numerous ring-condensed cyclohexanones and particularly to 4,5,6,7-tetrahydrobenzothiophen-4-one yielding 58% of 4-chloro-6,7-dihydrobenzothiophene-5-carboxaldehyde.[17] However, according to Cagniant and Kirsch, this reaction could not be transposed to tetrahydro-4,5,6,7-benzofuran-4-one **3**[18] probably due to the fact that furanes are less aromatic and more easily alkylated than the corresponding thiophenes. Our synthesis of **9** (Scheme 2) utilizes the temperature-dependent regioselective chloroformylation of the known ketone **3** under particular reaction conditions. When ketone **3** is reacted with the Vilsmeier−Haack reagent at room temperature for 20 h, 4-chloro-6,7-dihydrobenzofuran-2-carboxaldehyde (**4b**) is obtained in 38% yield, showing that acylation proceeds very easily at the 2 position of the furan ring. During this reaction a small percentage (8%) of the 5-formyl isomer **4a** forms as a byproduct. The ratio of the formation of the two isomers changes when the temperature is increased. At 85 °C **4a** and **4b** are obtained in approximately equal amounts (22% and 18% yield, respectively) whereas at 115 °C (refluxing 1,1,2-trichloroethane), the 5-acylated isomer **4a** is obtained in 34% yield versus only 4% of **4b**. Upon heating, **4b** does not rearrange into **4a** at 115 °C but decomposes. Thus, the ratio of the formation of the two isomers **4a** and **4b** is completely reversed by increasing the temperature. Both isomers **4a** and **4b** are unstable at room temperature. They can be stored at −78 °C for several weeks but decompose within 3−4 h at 20 °C (the rate of decomposition is somewhat lower when the products are dissolved in benzene or CH_2Cl_2) to form tarry, insoluble polymers and have probably eluded synthesis for this reason. In order to limit decomposition of the isomer **4a** at 115 °C,

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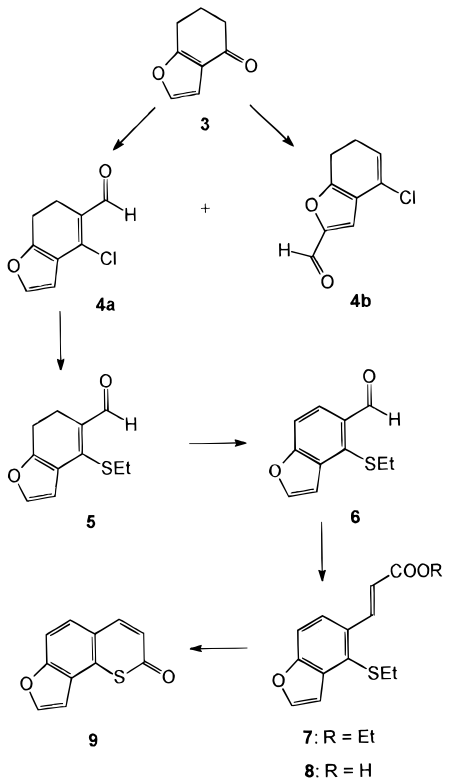
Scheme 2



the reaction time has to be shortened to 2 min by the use of a fourfold excess of the Vilsmeier−Haack reagent; a larger excess and still shorter reaction times afford lower yields. Nucleophilic substitution of the chlorine atom by the ethanethiolate anion yields 95% of the thioether **5** which also decomposes spontaneously but more slowly than **4a** at room temperature. The dihydrobenzofuran **5** is uneventfully aromatized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) into the stable 4-(ethylthio)benzofuran-5-carboxaldehyde (**6**). The reaction of the aldehyde function of **6** with the appropriate Wittig−Horner reagent allows the nearly quantitative transformation into the vinylogous ester **7** which is hydrolyzed to the corresponding acid **8**. This acid **8** is cyclized in polyphosphoric acid silyl ether (PPSE)[19] to afford thiopyrano[2,3-*e*]benzofuran **9** with a yield of 84%. The evaluation of the photochemical and photobiological activity of this compound is in progress and will be published elsewhere.

Experimental Section

General. All reagents and solvents were pure grade and were used without purification unless otherwise noted. THF was distilled from sodium and potassium. DMF was dried on 4 Å molecular sieves. The standard isolation procedure comprises pouring the reaction mixture into water, addition of CH_2Cl_2, and extraction, drying ($MgSO_4$), and evaporation of the solvent under reduced pressure. Analytical thin-layer chromatography (TLC) was done with silica plates, and 70−230 mesh silica gel was used for column chromatography. Solvent A: petroleum ether bp 60−80 °C/EtOAc 4/1; solvent B: $CHCl_3$/toluene 15/85. Melting points were determined with a Kofler hotplate melting point apparatus and are uncorrected. MS were obtained by electron impact at 70 eV and showed the correct isotopic distribution (numbers in parentheses indicate the relative peak hight). ^{1}H NMR spectra (400 MHz, in $CDCl_3$) are referenced to HMDSO. Elemental analyses were performed by the Institute of Pharmacy (Liege, Belgium).

4-Chloro-6,7-dihydrobenzofuran-5-carboxaldehyde (4a). DMF (6 mL, 77.6 mmol) was dissolved in 25 mL of 1,1,2-trichloroethane and cooled to 0 °C. A solution of 6 mL (66 mmol) of phosphorus oxychloride in 6 mL of 1,1,2-trichloroethane was added dropwise while the temperature was kept at 0 °C. The mixture was stirred for 10 min and then rapidly heated to reflux. Immediately after the boiling began, 2.7 g (19.8 mmol) of 4,5,6,7-tetrahydro-4-benzofuranone in 6 mL of 1,1,2-trichloroethane were added at once. The mixture was stirred for 2 min at reflux temperature and immediately cooled to 10 °C. About 20 mL of 1,1,2-trichloroethane and 60 mL of 4 N sodium acetate were added, and the mixture was stirred for 20 min. The organic layer was decanted, evaporated under reduced pressure, and flash-chromatographed (solvent A) to yield 1.225 g (34%) of yellow plates which darkened within 3 h on standing at rt but could be stored in a frozen benzene solution at −78 °C for several weeks. mp 70 °C dec. ^{1}H NMR δ 10.08 (s, 1H), 7.31 (d, 1H, J = 2.0 Hz), 6.54 (d, 1H, J = 2.0 Hz), 2.83 (s, 4H); MS, m/z 182 (M^+). R_f (solvent A): 0.39. Due to the instability of this compound, elemental analysis could not be performed.

4-Chloro-6,7-dihydrobenzofuran-2-carboxaldehyde (4b). DMF (6 mL, 77.6 mmol) was dissolved in 25 mL of 1,1,2-trichloroethane and cooled to 0 °C. A solution of 6 mL (66 mmol) of phosphorus oxychloride in 6 mL of 1,1,2-trichloroethane was added dropwise while the temperature was kept at 0 °C. A 2.7 g (19.8 mmol) amount of 4,5,6,7-tetrahydro-4-benzofuranone in 6 mL of 1,1,2-trichloroethane was added at once and the mixture was stirred for 20 h at rt. About 20 mL of 1,1,2-trichloroethane and 60 mL of 4 N sodium acetate were added, and the mixture was stirred for 20 min. The organic layer was decanted, evaporated under reduced pressure, and flash-chromatographed (solvent A) to yield 1.370 g (38%) of yellow plates which darkened within 2 h on standing at rt but could be stored in a frozen benzene solution at −78 °C for several weeks. ^{1}H NMR δ 10.03 (s, 1H), 7.07 (s, 1H), 5.67 (t, 1H, J = 4.5 Hz), 2.81 (t, 2H, J = 9.3 Hz), 2.54 (m, 2H, J = 9.3 Hz, J = 4.5 Hz); MS, m/z 182 (65, M^+), 153 (22), 125 (73), 91 (100). R_f (solvent A): 0.29. This compound decomposes rapidly at room temperature but can be stored in a frozen benzene solution (−78 °C) for several days.

4-(Ethylthio)-6,7-dihydrobenzofuran-5-carboxaldehyde (5). To an ice cooled solution of 1 g (5.48 mmol) of 4-chloro-5,6-dihydrobenzofuran-5-carboxaldehyde (**4a**) in 15 mL of acetonitrile were added 1.2 g (8.68 mmol) of K_2CO_3, and 0.53 mL (445 mg, 7.16 mmol) of ethanethiol. The mixture was stirred at 0 °C for 15 min and then allowed to warm up to rt. Stirring was continued for 2 h after which standard isolation afforded **5**, which was sufficiently pure to be used in the next step but could be purified by column chromatography (solvent B) to yield 1.08 g (95%) of a yellow oil which decomposed at rt. ^{1}H NMR δ 9.96 (s, 1H), 7.25 (d, 1H, J = 2.0 Hz), 6.50 (d, 1H, J = 2.0 Hz), 2.73 (m, 6H), 1.26 (t, 3H, J = 7.3 Hz); MS, m/z 208 (96, M^+), 206 (31), 179 (89), 149 (71). Due to the instability of this compound, a satisfactory elemental analysis could not be perfomed.

4-(Ethylthio)benzofuran-5-carboxaldehyde (6). A solution of 1.2 g (5.76 mmol) of freshly prepared 4-(ethylthio)-5,6-dihydrobenzofuran-5-carboxaldehyde (**5**) and 1.4 g (6.17 mmol) of DDQ in 30 mL of benzene was refluxed for 30 min. The reaction medium was poured into 1 N NaOH, decanted, washed with brine, and dried. Flash chromatography of the resulting mixture (solvent B) yielded 1.18 g (99%) of a yellow oil. R_f (solvent B): 0.27. ^{1}H NMR δ 10.74 (s, 1H), 7.85 (d, 1H, J = 8.6 Hz), 7.66 (d, 1H, J = 2.1 Hz), 7.44 (d,1H, J = 8.6 Hz), 7.01 (d, 1H, J = 2.1 Hz), 2.82 (q, 2H, J = 7.3 Hz), 1.10 (t, 3H, J = 7.3 Hz); MS, m/z 206 (91, M^+), 188 (65), 177 (97), 144 (68).

5-[(Ethoxycarbonyl)vinyl]-4-(ethylthio)benzofuran (7). A solution of 420 mg of $Ba(OH)_2 \cdot 0.8H_2O$,[20] 690 mg (3.34 mmol) of 4-(ethylthio)benzofuran-5-carboxaldehyde (**6**), 0.828 mL (936 mg, 4.17 mmol) of triethyl phosphonoacetate, and 0.08 mL of water in 15 mL of THF was refluxed with stirring for 1 h. After cooling, 2 N HCl and CH_2Cl_2 were added, and the organic layer was decanted and dried ($MgSO_4$) and the solvent evaporated. Flash chromatography on a short column (toluene) yielded 910 mg (99%) of a slightly yellow oil. ^{1}H NMR δ 8.53 (d, 1H, J =

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16.0 Hz), 7.59 (d, 1H, J = 2.2 Hz), 7.54 (d, 1H, J = 8.6 Hz), 7.39 (d, 1H, J = 8.6 Hz), 6.95 (d, 1H, J = 2.2 Hz), 6.35 (d, 1H, J = 16.0 Hz), 4.24 (q, 2H, J = 7.1 Hz), 2.75 (q, 2H, J = 7.3 Hz), 1.30 (t, 3H, J = 7.1 Hz), 1.07 (t, 3H, J = 7.3 Hz); MS, m/z 276 (63, M^+), 247 (92), 231 (75), 215 (100).

5-(Carboxyvinyl)-4-(ethylthio)benzofuran (8). To a solution of 340 mg (6 mmol) of KOH in 9 mL of 50% aqueous ethanol were added 830 mg (3 mmol) of 5-[(ethoxycarbonyl)vinyl]-4-(ethylthio)benzofuran (**7**), and the solution was refluxed for 40 min. After cooling, the solution was washed with ether and the aqueous layer was acidified with 6 N HCl. The precipitate was washed with 10 mL of water and dried at 80 °C to yield 663 mg (89%) of 5-(carboxyvinyl)-4-(ethylthio)benzofuran (**8**) which was used in the next step without further purification: mp 178−180 °C.

4*H*-Thiopyrano[2,3-*e*]benzofuran-4-one (9). PPSE was prepared by refluxing a mixture of 9.33 g (65.7 mmol) of P_2O_5 and 17.74 mL (13.55 g, 83.5 mmol) of HMDSO in 50 mL of $CHCl_3$ for 1 h. The solvent was evaporated under reduced pressure, and the mixture was heated to 150 °C on an oil bath. 5-(Carboxyvinyl)-4-(ethylthio)benzofuran (**7**) (500 mg, 2.01 mmol) was added, and the mixture was stirred at 150 °C for 2 h 30 min. The mixture was allowed to cool, 50 mL of $CHCl_3$ were added, and stirring was continued until a homogenous mixture was obtained. This solution was washed with water and 1 N $NaHCO_3$ and dried. After evaporation of the solvent, the residue was column chromatographed (solvent B) and recrystallized in ethanol to yield 343 mg (84%) of pale yellow needles: mp 128 °C. R_f (solvent B): 0.24. ^{1}H NMR δ 7.81 (d, 1H, J = 10.6 Hz), 7.74 (d, 1H, J = 2.2 Hz), 7.51 (s, 2H), 6.92 (d, 1H, J = 2.2 Hz), 6.52 (d, 1H, J = 10.6 Hz); MS, m/z 202 (72, M), 174 (100), 145 (92). UV-vis (ethanol) λ_{max}= 241, ϵ = 2.63 × 10^4; λ_{max}= 266, ϵ = 2.89 × 10^4; λ_{max}= 322, ϵ = 7.17 × 10^3. Anal. Calcd for $C_{11}H_6O_2S$: C, 65.33; H, 2.99; S, 15.85. Found: C, 65.65; H, 3.03; S, 15.66.

Supporting Information Available: ^{1}H NMR spectra of **6** and **7** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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