THIENO[3,2-*b*]BENZOFURAN – SYNTHESIS AND REACTIONS

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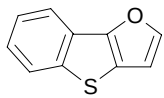
Thieno[3,2-*b*]benzofuran was synthesized starting from benzo[*b*]furan-3(2*H*)-one or benzo[*b*]furan-2-carbaldehyde. Electrophilic substitution reactions such as bromination, formylation, acetylation or nitration, take place in position 2. An electron donating group in position 2 directs further electrophilic substitution into positions 3 and 6, whereas compounds with an electron acceptor in position 2 are substituted exclusively in position 6. Metallation with butyllithium took place in position 2. The ^{1}H and ^{13}C NMR signals of the title compound were fully assigned.

Key words: Fused heterocycles; Thieno[3,2-*b*]benzofuran; Benzothieno[3,2-*b*]furan; Electrophilic substitution; Metallation.

In our previous communications we discussed the synthesis[1] and reactivity[2] of a novel heterocyclic system, [1]benzothieno[3,2-*b*]furan (**1**). We observed its lower stability in acidic media, indicating an imperfect aromaticity and a weak enol ether character. Although the isomeric thieno[3,2-*b*]benzofuran (**2**) was prepared[3], its synthesis has not been described in detail and no data on its reactivity are known. Neither compound **2** nor intermediates of its synthesis have been fully characterized by physicochemical methods. In this communication we describe novel synthetic approaches to compound **2** and discuss its reactivity in selected substitution reactions as compared with compound **1**.



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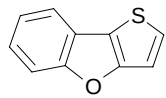

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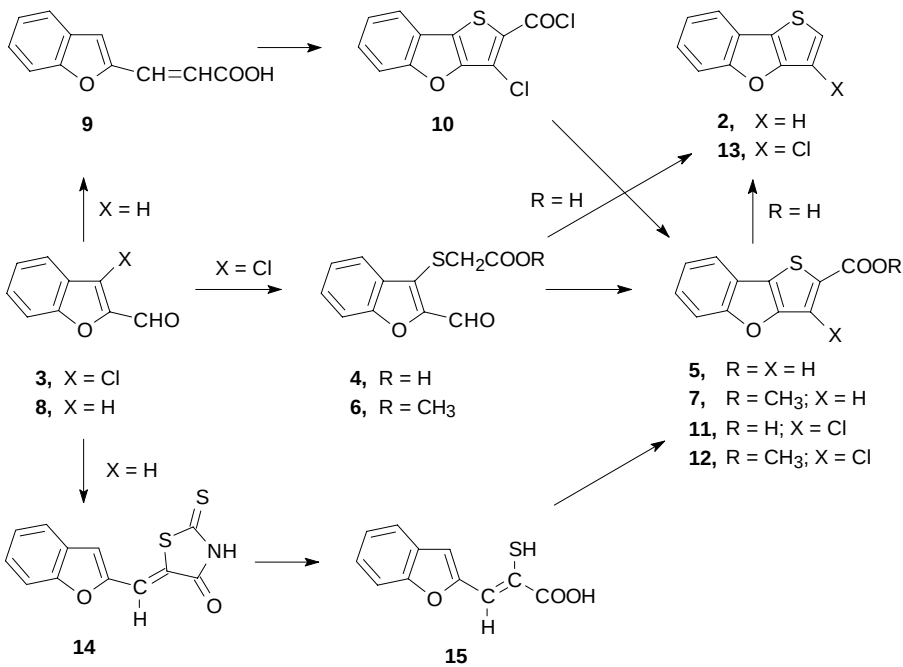
In our search for an effective synthesis of heterocycle **2** we first tried the reaction sequence starting from benzo[*b*]furan-3(2*H*)-one (Scheme 1). This compound was converted into 3-chlorobenzo[*b*]furan-2-carbaldehyde (**3**) by the Vilsmeier–Haack formylation with *N*,*N*-dimethylformamide and phosphorus oxychloride. In contrast to the published data[3], the nucleophilic substitution of chlorine atom with sulfanylacetic (thioglycolic) acid in an alkaline medium gave the desired [(2-formylbenzo[*b*]furan-3-yl)sulfanyl]acetic acid (**4**) only in a low yield (43%). Most probably, the starting

chloroaldehyde **3** is not very stable and under the reaction conditions undergoes polymerization reactions. No improvement was observed with *N*,*N*-dimethylformamide as a solvent. On treatment with sodium acetate in acetic acid[4], acid **4** cyclized to thieno[3,2-*b*]benzofuran-2-carboxylic acid (**5**) which spontaneously decarboxylated to give the desired compound **2** in 49% yield. Acid **5** was isolated from the reaction mixture as a minor product (4%). The yield of the whole reaction sequence was thus not very satisfactory and therefore we looked for a more advantageous procedure leading to compound **2**.



SCHEME 1

We modified the above procedure in that the substitution of the chlorine atom in aldehyde **3** was performed with methyl sulfanylacetate in alkaline medium instead of sulfanylacetic acid. The obtained methyl [(2-formylbenzo[*b*]furan-3-yl)sulfanyl]acetate (**6**) was easily isolable, however, the yield was again low (31%). Ester **6** was easily cyclized under catalysis with sodium methoxide to give methyl thieno[3,2-*b*]benzofuran-2-carboxylate (**7**). We have found that with an excess of methyl sulfanylacetate in alkaline medium the replacement of the chlorine atom in aldehyde **3** is followed by spontaneous cyclization of the arising formyl ester **6** to ester **7**. In this case, the thiolate anion is basic enough to start the condensation reaction of **6** to **7**. Analogous condensations leading to formation of the thiophene ring are known to proceed also smoothly[5,6]. Ester **7** was practically quantitatively hydrolyzed to the acid **5** which on standard decarboxyla-

tion by treatment with copper in quinoline at 160 °C afforded compound **2** in high yield.

Since acid **5** was readily decarboxylated, it is obvious that this compound is an important intermediate in the synthesis of compound **2**. In order to find a facile synthesis of acid **5**, we tried to utilize known derivatives[7] of compound **2**. Condensation of benzo[*b*]furan-2-carbaldehyde **8** with malonic acid[8] smoothly afforded (2-benzo-[*b*]furan-3-yl)acrylic acid (**9**) which underwent Higa's cyclization[9] by treatment with thionyl chloride. Although the reaction conditions were optimized[10], the yield did not exceed 31%. The obtained 3-chlorothieno[3,2-*b*]benzofuran-2-carbonyl chloride (**10**) was hydrolyzed and methanolyzed to give 3-chlorothieno[3,2-*b*]benzofuran-2-carboxylic acid (**11**) and its methyl ester **12**, respectively. Decarboxylation of acid **11** by heating with copper in quinoline afforded the known[7] 3-chlorothieno[3,2-*b*]benzofuran (**13**).

We failed to remove the chlorine atom by reduction with zinc in acetic acid, with magnesium in propan-2-ol, by hydrogenation on palladium or by palladium-catalyzed hydrogenation transfer. Reduction with Ni(0) in the system $Zn/NiCl_2/NaI/Ph_3P$ (ref.[11]) afforded compound **2** only with low conversion (25%). Therefore, we tried to reduce the chlorine atom in ester **12**. In this case the reduction with Ni(0) proceeded well and ester **7** was obtained in high yield (90%).

Finally, we tried a method consisting in cyclization of substituted 2-sulfanylacrylic acids by the action of halogens[12–14]. Condensation of aldehyde **8** with rhodanine in the presence of sodium acetate in acetic acid afforded smoothly 5-[(benzo[*b*]furan-2-yl)methylene]-2-thioxothiazolidin-4-one (**14**). Base-catalyzed hydrolysis of the rhodanine skeleton in compound **14** proceeded readily and the resulting 3-(benzo[*b*]furan-2-yl)-2-sulfanylacrylic acid (**15**) was obtained in a good yield. Upon treatment with bromine, acid **15** was cyclized *via* intermediate sulfenyl bromide[13] to give acid **5** in 76% yield. Using this reaction sequence, compound **2** could be obtained on the preparative scale.

As we have shown previously[2], the heterocyclic system in compound **1** is substituted with a range of electrophilic reagents selectively in position 2. We compared now the reactivity of the heterocyclic systems in compounds **1** and **2**, using a series of electrophilic substitution reactions which, except acetylation[3], have not been hitherto described (Scheme 2).

Compound **2** was smoothly monobrominated with dioxane dibromide in dichloromethane, giving 2-bromothieno[3,2-*b*]benzofuran (**16**) in good yield. On the other hand, dibromination of compound **2** with excess of dioxane dibromide or bromination of compound **16** with bromine proceeded very slowly. In both cases we obtained identical product, 2,6-dibromothieno[3,2-*b*]benzofuran (**17**).

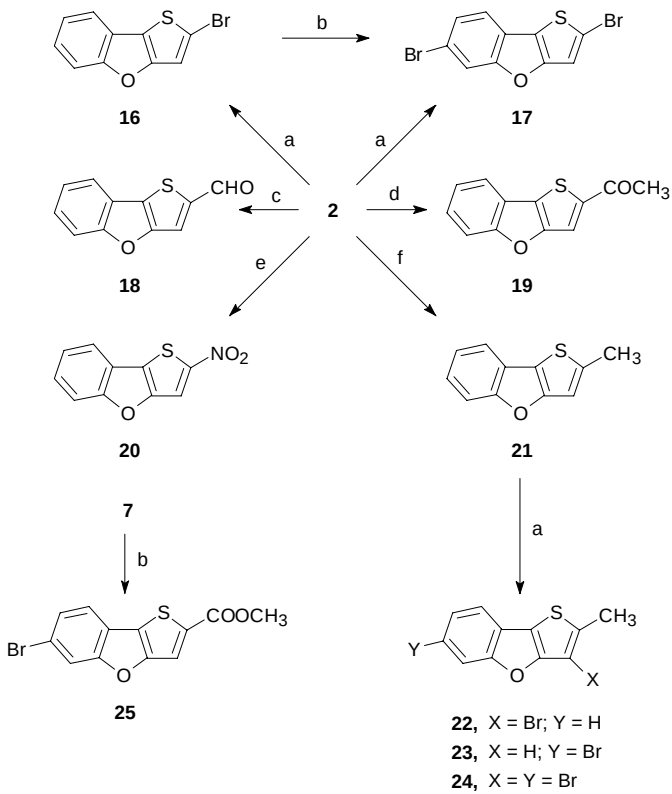
Vilsmeier–Haack formylation of compound **2** afforded thieno[3,2-*b*]benzofuran-2-carbaldehyde (**18**). Similarly to the analogous reaction of benzo[*b*]thiophene[15], the for-

mylation was very slow and a satisfactory conversion of the compound **2** was achieved only at a higher temperature (50 °C).

Acetylation of compound **2** with acetyl chloride in the presence of aluminium chloride led only to polymeric products, whereas treatment with acetic anhydride afforded the desired 2-acetylthieno[3,2-*b*]benzofuran (**19**) in the yield of 54%. With weaker Lewis acids such as zinc chloride or tin tetrachloride, no reaction was observed.

Whereas nitration of compound **1** was not very successful[2] and, moreover, the obtained 2-nitro derivative was unstable, compound **2** was successfully converted into 2-nitrothieno[3,2-*b*]benzofuran (**20**) by treatment with acetyl nitrate. In strongly acidic medium, the reaction was also accompanied by significant decomposition of the starting compound **2**.

Some heterocyclic compounds easily undergo metallation reactions[16] upon action of strong bases. Thiophene as well as benzo[*b*]thiophene are attacked by organometallic



a) dioxane dibromide; b) Br_2; c) $POCl_3$, DMF; d) Ac_2O, $AlCl_3$; e) HNO_3, Ac_2O; f) i, BuLi, ii, CH_3I

SCHEME 2

reagents in position 2. Therefore we studied an analogous reaction with the heterocycle **2**. Upon treatment with butyllithium at low temperature (–70 to –30 °C), the arising lithium derivative was trapped by reaction with methyl iodide. We have found that the reaction is regioselective and gives 2-methylthieno[3,2-*b*]benzofuran (**21**) in high yield.

It has been shown[3] that in the acetylation of methyl derivative **21** the substituent enters both position 3 and 6. The same result was obtained in bromination of compound **21** with dioxane dibromide. From the reaction mixture we isolated by thin-layer chromatography a mixture of 3-bromo-2-methylthieno[3,2-*b*]benzofuran (**22**) and 6-bromo-2-methylthieno[3,2-*b*]benzofuran (**23**) (1.3 : 1) and pure 3,6-dibromo-2-methylthieno-[3,2-*b*]benzofuran (**24**).

On the other hand, ester **7** was brominated exclusively in position 6 under formation of methyl 6-bromothieno[3,2-*b*]benzofuran-2-carboxylate (**25**) as the sole product.

We may thus summarize that under conditions of electrophilic substitution the heterocyclic system in compound **2** is more stable than in compound **1**. In analogy to other isosteric heterocyclic systems, electrophilic substitution occurs in position 2. If this position is already occupied by an electron donor substituent, the electrophilic reagent attacks position 3 or 6. On the other hand, if an electron acceptor substituent (Br, $COOCH_3$) is in position 2, the electrophile enters regioselectively position 6.

The structure of compounds **3–15** was confirmed by elemental analyses and infrared and ^{1}H NMR spectra. For compound **2**, both the ^{1}H and ^{13}C NMR signals were completely assigned (Table I). First we assigned the signals of atoms in positions 2 and 3.

TABLE I
^{1}H and ^{13}C NMR (δ, ppm; *J* in Hz) data of **2**[a]

Position	δ(H)	*J*(H,H)	δ(C)[b]	^1J(C,H)	^nJ(C,H)
2	7.35 d	*J*(2,3) = 5.2	128.2 Dd	192	5
3	7.14 d		112.1 Dd	176	2
3a	–	–	160.0 Sdd	–	14; 2
4a	–	–	159.9 Sddd	–	10; 9; 3
5	7.55 dd	*J*(5,6) = 7.2; *J*(5,7) = 1.8	113.1 Ddd	161	6; 2
6	7.30 ddd	*J*(6,7) = 7.7; *J*(6,8) = 2.2	125.0 Dd	161	8
7	7.27 ddd	*J*(7,8) = 6.7	123.7 Dd	160	7
8	7.66 dd		119.7 Ddd	158	6; 2
8a	–	–	124.5 Sm	–	not determined
8b	–	–	120.0 Sm	–	not determined

[a] Abbreviations used: s singlet, d doublet, m multiplet. [b] Capital letters denote direct coupling, small letters denote long-range coupling.

The thiophene protons H-2 and H-3 differ significantly from the benzene protons of the system in their multiplicity and lower vicinal coupling constant. They were distinguished by the heteronuclear correlation method. Analogously to benzo[*b*]thiophene[17], proton that directly interacts with carbon, whose signal is shifted downfield due to the attached sulfur atom, is bonded in position 2. The quaternary carbon atom with largest chemical shift (*i.e.* bonded to oxygen) interacting with H-2 and H-3 can be assigned as C-3a. The second quaternary carbon interacting with these protons is then C-8b. Protons H-5 and H-8, which differ in chemical shifts and multiplicities from H-6 and H-7, were distinguished on the basis of the ^3J(C,H) interaction with C-8b, possible only for H-8. Correlation experiments then assigned signals to the remaining protons and carbon atoms. Signals of the quaternary carbon atoms C-4a and C-8a differ significantly and were assigned on the basis of the ^3J(C,H) interactions with H-8 and H-5, respectively. The chemical shifts of protons and carbon atoms in the benzene part of the molecule exhibit thus similar behaviour as described for benzo[*b*]furan[18]. The values of the coupling constants J(H-2,H-3), J(C-2,H-3) and J(C-3,H-2) resemble those reported for benzo[*b*]thiophene[17,19]; the chemical shifts of C-2 and H-2 are similar whereas those for C-3 and H-3 are significantly smaller. The coupling constant J(H-2,H-3) is also the same as the corresponding constant for thieno[3,2-*b*]furan[20].

The structure of derivatives **16–25** was confirmed by elemental analyses and IR and ^{1}H NMR spectra. Proton signals were assigned using the NMR spectra of the parent heterocycle **2**, benzo[*b*]furan and analogies[2] found for the substitution derivatives of compound **1**.

EXPERIMENTAL

Melting points were determined on a Boetius block and are uncorrected. Proton NMR spectra of compounds **3–25** were taken on a Varian Gemini-300 (300 MHz) instrument. Compound **2** was studied on a Bruker 400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) instrument at 25 °C. Deuteriochloroform was used as solvent, except for compounds **11**, **14** and **15** which were measured in hexadeuteriodimethyl sulfoxide. Chemical shifts are given in the δ-scale (ppm), coupling constants in Hz. The solvent signal served as internal standard (δ(C) 77.0). Signal multiplicities in the ^{13}C NMR spectra were determined in APT experiments. The proton-coupled spectra were measured by the "gated decoupling" method (decoupler off during the acquisition). 2D NMR experiments – COSY, HETCOR, INEPT and COLOC – were carried out using pulse sequences and programs provided by the manufacturer. Infrared spectra (ν, cm^{-1}) were recorded on a Nicolet FTIR 740 spectrometer in chloroform or in KBr (compounds **5**, **14**, **15**). Benzo[*b*]furan-3(2*H*)-one was prepared according to the literature[21], benzo[*b*]furan-2-carbaldehyde (**8**) according to ref.[22], 3-(benzo[*b*]furan-2-yl)acrylic acid (**9**) was obtained as described in ref.[8]. Preparative thin-layer chromatography was performed on Merck plates (20 × 20 cm), column chromatography on Kieselgel 60 (Merck).

Thieno[3,2-*b*]benzofuran (**2**)

A. A mixture of acid **4** (5.0 g, 21.2 mmol), freshly fused sodium acetate (20 g, 238 mmol) and glacial acetic acid (50 ml) was refluxed with stirring for 13 h and poured into an excess of cold 5%

aqueous sodium hydroxide. The alkaline solution was washed with ether (3 × 100 ml), the combined ethereal solutions were washed with water (2 × 50 ml), saturated solution of sodium chloride (50 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified by column chromatography on silica gel in hexane. Yield 1.8 g (49%) of compound **2**, m.p. 61.5–62 °C (reported[3] m.p. 63 °C). For $C_{10}H_6OS$ (174.2) calculated: 68.94% C, 3.47% H, 18.40% S; found: 68.80% C, 3.53% H, 18.41% S. IR spectrum: 3 014, 1 482, 1 449, 1 371, 1 195, 1 111, 1 086, 1 034, 838. The aqueous portion was acidified with hydrochloric acid (1 : 1) to pH 2 and washed with chloroform (2 × 30 ml), the organic phase was washed with water (2 × 30 ml), brine (30 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded 0.2 g (4%) of thieno[3,2-*b*]benzofuran-2-carboxylic acid (**5**), m.p. 249–250 °C (reported[23] m.p. 250–253 °C).

B. A mixture of acid **5** (2.4 g, 11.0 mmol), copper powder (1.3 g, 20.5 mmol) and distilled quinoline (25 ml) was heated at 165 °C for 15 min under nitrogen. After cooling, the mixture was poured into ice-cold dilute hydrochloric acid (1 : 1, 200 ml) and extracted with hexane (3 × 50 ml). The organic solution was washed with water (2 × 25 ml), saturated solution of sodium hydrogencarbonate (25 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent and crystallization of the residue from pentane afforded 1.88 g (98%) of compound **2**, m.p. 61 °C.

3-Chlorobenzo[*b*]furan-2-carbaldehyde (**3**)

Phosphorus oxychloride (167.5 g, 1.09 mmol) was added dropwise during 4 h to a stirred and externally ice-cooled suspension of benzo[*b*]furan-3(2*H*)-one (32.0 g, 0.239 mol) in dry *N*,*N*-dimethylformamide (100 ml). The cooling bath was removed and the mixture was stirred at room temperatute for 1.5 h and at 40 °C for 5 h. After addition of another portion of phosphorus oxychloride (33.5 g, 0.218 mol), the mixture was heated at 50 °C for 0.5 h, poured on ice (1 kg), the solid was collected, washed thoroughly with ice-cold water and dried. Yield 37.5 g (87%) of product **3**, m.p. 73–76 °C (reported[24] m.p. 78 °C).

[(2-Formylbenzo[*b*]furan-3-yl)sulfanyl]acetic Acid (**4**)

A stirred mixture of aldehyde **3** (20.0 g, 111 mmol), sulfanylacetic acid (15.4 g, 167 mmol), sodium carbonate (17.7 g, 167 mmol), methanol (300 ml) and water (20 ml) was refluxed for 14 h. After cooling, methanol was evaporated and the residue diluted with water (300 ml) and washed with chloroform (2 × 30 ml). The aqueous layer was acidified with hydrochloric acid (1 : 1) to pH 2 and the solid was collected and washed with water.

Crystallization from chloroform–hexane afforded acid **4** (11.15 g, 43%), m.p. 134.5–136 °C (reported[3] m.p. 127 °C). IR spectrum: 1 716, 1 679 (CO). ^{1}H NMR spectrum: 3.73 s, 2 H (CH_2); 7.42 t, 1 H, J = 7.4; 7.58 t, 1 H; 7.63 d, 1 H, J = 7.8 (H-4); 7.85 d, 1 H (H-7); 10.19 s, 1 H (CHO).

Thieno[3,2-*b*]benzofuran-2-carboxylic Acid (**5**)

A. Ester **7** (2.8 g, 12.1 mmol) was added to a solution of sodium hydroxide (1.45 g, 36.2 mmol) in 1 : 1 aqueous methanol (120 ml) and the stirred mixture was boiled for 30 min. Most of the methanol was evaporated on an evaporator and the residue was diluted with water and adjusted to pH 3 with dilute hydrochloric acid (1 : 1). The solid was collected, washed on the filter with water and air-dried. Yield 1.53 g (96%) of acid **5**, m.p. 249 °C (reported[23] m.p. 250–253 °C). IR spectrum (KBr): 1 675 (COOH). ^{1}H NMR spectrum: 7.38 t, 1 H, J = 7.6 (H-7); 7.47 t, J = 7.5 (H-6); 7.63 d, 1 H, J = 8.2 (H-5); 7.79 d, 1 H, J = 8.2 (H-8); 7.94 s, 1 H (H-3).

B. A solution of bromine (2.2 ml of 1 M solution) in acetic acid was added at 60 °C to a stirred solution of acid **15** (0.3 g, 1.36 mmol) in glacial acetic acid (14 ml). After reflux for 15 min, the

mixture was diluted with water (15 ml) and refluxed for another 15 min. The mixture was cooled and the solid was filtered, washed with water and dried. Yield 0.27 g (91%) of acid **5**, m.p. 248–250 °C.

Methyl [(2-Formylbenzo[*b*]furan-3-yl)sulfanyl]acetate (**6**)

A mixture of methyl sulfanylacetate (0.588 g, 5.54 mmol), sodium hydrogencarbonate (0.44 g, 5.23 mmol) and *N*,*N*-dimethylformamide (10 ml) was stirred under nitrogen for 45 min. A solution of aldehyde **3** (1.0 g, 5.54 mmol) in *N*,*N*-dimethylformamide (5 ml) was added dropwise during 5 min, the mixture was stirred at 60 °C for 4 h, poured into ice-cold water (200 ml) and extracted with dichloromethane (3 × 20 ml). The organic phase was washed with water (20 ml), dried over anhydrous magnesium sulfate and the solvent was evaporated. Column chromatography of the residue on silica gel in hexane–ethyl acetate recovered the starting aldehyde **3** (0.06 g, 6%) and afforded 0.36 g (31%) of compound **6**, m.p. 61.5–62 °C. For $C_{12}H_{10}O_4S$ (250.3) calculated: 57.59% C, 4.03% H, 12.81% S; found: 57.44% C, 3.89% H, 12.67% S. IR spectrum: 1 739 ($COOCH_3$), 1 679 (CHO). ^{1}H NMR spectrum: 3.65 s, 3 H (OCH_3); 3.69 s, 2 H (CH_2); 7.43 t, 1 H, J = 8.0; 7.57 t, 1 H; 7.63 d, 1 H, J = 8.4 (H-4); 7.85 d, 1 H (H-7); 10.20 s, 1 H (CHO).

Methyl Thieno[3,2-*b*]benzofuran-2-carboxylate (**7**)

A. Methyl sulfanylacetate (17.9 g, 166 mmol) was added dropwise at room temperature under nitrogen to a stirred solution of sodium methoxide prepared by dissolving sodium (3.15 g, 137 mmol) in dry methanol (200 ml). After stirring for 5 min, aldehyde **3** (13.0 g, 72 mmol) was added in one portion and the mixture was refluxed for 17 h. After cooling, the solvent was evaporated, the residue dissolved in dichloromethane (200 ml) and the solution washed with 2% aqueous sodium hydroxide (2 × 100 ml), water (2 × 50 ml), brine (50 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent and crystallization from methanol afforded 9.20 g (55%) of ester **7**, m.p. 119–120 °C. For $C_{12}H_8O_3S$ (232.2) calculated: 62.06% C, 3.47% H, 13.80% S; found: 61.78% C, 3.46% H, 13.64% S. IR spectrum: 1 710 ($COOCH_3$). ^{1}H NMR spectrum: 3.95 s, 3 H (OCH_3); 7.36 dt, 1 H, J_1 = 7.6, J_2 = 1.5 (H-5); 7.43 dt, 1 H (H-6); 7.60 d, 1 H, J = 8.1 (H-5); 7.76 d, 1 H, J = 8.2 (H-8); 7.85 s, 1 H (H-3). ^{13}C NMR spectrum: 53.1, 113.4, 117.4, 120.8, 123.6, 124.2, 126.4, 127.1, 134.7, 158.0, 160.5, 163.7.

B. A solution of ester **6** (0.19 g, 0.76 mmol) in methanol (5 ml) was added dropwise at room temperature under nitrogen to a stirred solution of sodium methoxide prepared by dissolving sodium (0.052 g, 2.3 mmol) in methanol (20 ml). The mixture was refluxed for 10 min, cooled and the solvent was evaporated. The residue was dissolved in dichloromethane (30 ml) and the solution was washed with water (2 × 5 ml), brine (5 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent and crystallization from methanol afforded 0.15 g (85%) of ester **7**.

C. A mixture of triphenylphosphine (0.685 g, 2.61 mmol), zinc powder (1.37 g, 29.9 mmol), nickel(II) chloride hexahydrate (0.131 g, 0.55 mmol), sodium iodide (0.455 g, 3.03 mmol) and aqueous *N*,*N*-dimethylformamide (10 ml, DMF : H_2O = 25 : 1) was stirred under nitrogen for 1 h. Ester **12** (1.0 g, 3.75 mmol) was added dropwise and the mixture was heated at 70 °C for 48 h. After cooling, the solid was collected by filtration, washed with chloroform (50 ml) and the filtrate was evaporated. The residue was dissolved in chloroform (50 ml), washed with water (20 ml), brine (20 ml) and dried over anhydrous magnesium sulfate. Purification by column chromatography on silica gel in hexane–toluene (1 : 1) afforded 0.78 g (90%) of compound **7**.

3-Chlorothieno[3,2-*b*]benzofuran-2-carbonyl Chloride (**10**)

A mixture of acid **9** (ref.[8]) (52.4 g, 0.278 mmol), pyridinium chloride (8.0 g, 0.07 mol) and thionyl chloride (265 g, 2.23 mol) was stirred and heated at 130 °C in an oil bath for 25 h. After cooling, the formed suspension was diluted with chloroform (350 ml) and the solvent was evaporated to dryness. Crystallization from benzene–hexane gave 23.6 g (31%) of compound **10**, m.p. 182–184 °C (reported[7] m.p. 183 °C).

3-Chlorothieno[3,2-*b*]benzofuran-2-carboxylic Acid (**11**)

The title acid was prepared according to the literature[7] in 92% yield, m.p. 310–312 °C (reported[7] m.p. 312 °C). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 7.47 t, 1 H, J = 7.7 (H-7); 7.51 t, 1 H, J = 7.7 (H-6); 7.83 d, 1 H, J = 8.2 (H-5); 8.19 d, 1 H, J = 7.6 (H-8).

Methyl 3-Chlorothieno[3,2-*b*]benzofuran-2-carboxylate (**12**)

A mixture of chloride **10** (3.5 g, 12.9 mmol) and dry methanol (100 ml) was refluxed for 2 h, cooled and the deposited crystals were collected on filter and washed with methanol. Yield 3.27 g (95%) of ester **12**, m.p. 143–144 °C. For $C_{12}H_7ClO_3S$ (266.7) calculated: 54.04% C, 2.65% H, 13.29% Cl, 12.02% S; found: 53.88% C, 2.55% H, 13.11% Cl, 11.86% S. IR spectrum: 1 717 ($COOCH_3$). ^{1}H NMR spectrum: 3.98 s, 3 H (OCH_3); 7.38 dt, 1 H, J_1 = 7.8, J_2 = 1.1 (H-7); 7.48 dt, 1 H (H-6); 7.68 d, 1 H, J = 7.7 (H-5); 7.76 dd, 1 H, J_1 = 8.2, J_2 = 1.1 (H-8).

3-Chlorothieno[3,2-*b*]benzofuran (**13**)

A mixture of acid **11** (0.5 g, 1.98 mmol), copper powder (0.3 g, 4.7 mmol) and quinoline (20 ml) was heated at 130–150 °C for 1 h. The mixture was cooled and poured into ice-cold dilute hydrochloric acid (1 : 1, 200 ml). The product was taken up in ether (3 × 50 ml), the extract was washed with water (2 × 25 ml) and saturated solution of sodium hydrogen carbonate and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded 0.42 g (100%) of compound **13**, m.p. 68–68.5 °C (reported[7] m.p. 67 °C). IR spectrum: 3 116, 1 447, 1 300, 1 176, 1 084, 991, 823, 808. ^{1}H NMR spectrum: 7.20 s, 1 H (H-2); 7.33 dt, 1 H, J_1 = 7.5, J_2 = 1.1 (H-7); 7.38 dt, 1 H, J_1 = 7.5, J_2 = 1.6 (H-6); 7.62 dd, 1 H, J_1 = 7.6, J_2 = 1.1 (H-5); 7.68 dd, 1 H, J_1 = 7.5, J_2 = 1.6 (H-8).

5-[(Benzo[*b*]furan-2-yl)methylene]-2-thioxothiazolidin-4-one (**14**)

A mixture of aldehyde **8** (2.0 g, 13.7 mmol), rhodanine (1.83 g, 13.7 mmol), freshly fused sodium acetate (3.30 g, 40.2 mmol) and glacial acetic acid (30 ml) was refluxed for 45 min. After cooling, the suspension was poured into water (75 ml), the solid was filtered and washed with water. Crystallization from toluene afforded 3.30 g (90%) of compound **14**, m.p. 255–257 °C (subl.). For $C_{12}H_7NO_2S_2$ (261.3) calculated: 55.16% C, 2.70% H, 5.36% N, 24.54% S; found: 54.99% C, 2.84% H, 5.22% N, 24.66% S. IR spectrum (KBr): 1 694 (CO). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 7.34 t, 1 H, J = 7.1 (H-7); 7.48 t, 1 H, J = 7.7 (H-6); 7.59 s, 1 H; 7.65 s, 1 H; 7.72 d, 1 H, J = 7.7 (H-5); 7.78 d, 1 H, J = 7.7 (H-8).

3-(Benzo[*b*]furan-2-yl)-2-sulfanylacrylic Acid (**15**)

A stirred mixture of compound **14** (0.5 g, 1.91 mmol), sodium hydroxide (2.4 g, 60 mmol) and water (15 ml) was refluxed under nitrogen for 1.5 h, the clear solution was cooled and poured into dilute hydrochloric acid (1 : 1, 75 ml) and the solid was collected and washed with water. Yield 1.95 g

(89%) of acid **15**, m.p. 175–177 °C. For $C_{11}H_8O_3S$ (220.2) calculated: 59.99% C, 3.66% H, 14.56% S; found: 59.69% C, 3.74% H, 14.11% S. IR spectrum (KBr): 2 564 (SH), 1 668 (COOH). ^{1}H NMR spectrum (hexadeuteriomedimethyl sulfoxide): 7.31 s, 1 H (H-3); 7.41 m, 2 H, *J* = 7.7 (H-5 and H-6); 7.61 d, 1 H, *J* = 7.7 (H-5); 7.46 s, 1 H (–CH=); 7.77 d, 1 H (H-8).

2-Bromothieno[3,2-*b*]benzofuran (**16**)

A solution of dioxane dibromide (158 mg, 0.637 mmol) in dichloromethane (2 ml) was added dropwise during 20 min to a stirred solution of compound **2** (100 mg, 0.574 mmol) in a mixture of dichloromethane (2 ml) and dioxane (2 ml) under external cooling with ice. After 5 min the mixture was neutralized with solid sodium hydrogencarbonate (0.5 g, 6.0 mmol), diluted with dichloromethane (10 ml), washed with water (10 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent and crystallization from methanol afforded 115 mg (79%) of bromo derivative **16**, m.p. 68.5–70.5 °C. For $C_{10}H_5BrOS$ (253.1) calculated: 47.45% C, 1.99% H, 31.57% Br, 12.67% S; found: 47.61% C, 2.01% H, 31.29% Br, 12.70% S. IR spectrum: 3 014, 1 523, 1 481, 1 448, 1 197, 1 109, 1060, 989. ^{1}H NMR spectrum: 7.03 s, 1 H (H-3); 7.30 t, 1 H, *J* = 6.6 (H-7); 7.34 t, 1 H, *J* = 6.1 (H-6); 7.55 d, 1 H, *J* = 7.7 (H-5); 7.62 d, 1 H, *J* = 7.1 (H-8).

2,6-Dibromothieno[3,2-*b*]benzofuran (**17**)

A. A solution of dioxane dibromide (311 mg, 1.25 mmol) in dichloromethane (2 ml) was added during 5 min to a stirred ice-cool solution of compound **2** (100 mg, 0.574 mmol) in a mixture of dichloromethane (2 ml) and dioxane (2 ml). The mixture was stirred at room temperature for 3 h and then refluxed for 2 h. The subsequent work-up procedure was the same as described for compound **16**. Column chromatography on silica gel in hexane afforded 20 mg (11%) of compound **17**, m.p. 171–172 °C, and 80 mg (16%) of bromo derivative **16**. For $C_{10}H_4Br_2OS$ (332.0) calculated: 36.18% C, 1.21% H; found: 36.02% C, 1.45% H. IR spectrum: 3 017, 1 470, 1 451, 1 411, 1 379, 1 262, 1 062, 1 048. ^{1}H NMR spectrum: 7.26 s, 1 H (H-3); 7.43 dd, 1 H, J_1 = 8.2, J_2 = 1.1 (H-7); 7.48 d, 1 H (H-5); 7.72 d, 1 H, *J* = 1.1 (H-8).

B. A solution of bromine in dichloromethane (0.7 ml of 2 M solution) was added to a solution of bromo derivative **16** (27 mg, 0.107 mmol) in dichloromethane (2 ml) and the mixture was stirred at room temperature for 120 h. An analogous work-up as described for compound **16** gave 35 mg (99%) of dibromo derivative **17**, m.p. 172–172.5 °C.

Thieno[3,2-*b*]benzofuran-2-carbaldehyde (**18**)

Phosphorus oxychloride (1.6 g, 10.4 mmol) was added dropwise during 15 min under nitrogen to *N*,*N*-dimethylformamide (5 ml) under external cooling with ice. After stirring for 20 min, compound **2** (200 mg, 1.15 mmol) was added in one portion. The mixture was heated at 50 °C for 2 h and then decomposed with saturated solution of sodium hydrogencarbonate and extracted with hexane (3 × 20 ml). The organic extract was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was chromatographed on a column of silica gel in hexane and then in hexane–ethyl acetate (2 : 1). After the recovered starting compound **2** (50 mg, 25%), the chromatography afforded 110 mg (63%, corrected for recovered **2**) of aldehyde **18**, m.p. 122–123.5 °C (hexane). For $C_{11}H_6O_2S$ (202.2) calculated: 65.33% C, 2.99% H, 15.85% S; found: 65.02% C, 3.32% H, 15.45% S. IR spectrum: 1 686 (CHO). ^{1}H NMR spectrum: 7.38 t, 1 H, *J* = 7.1 (H-7); 7.47 t, 1 H, *J* = 7.2 (H-6); 7.62 d, 1 H, *J* = 7.7 (H-5); 7.79 s, 1 H (H-3); 7.81 d, 1 H, *J* = 7.7 (H-8); 9.96 s, 1 H (CHO).

2-Acetylthieno[3,2-*b*]benzofuran (**19**)

Acetic anhydride (0.585 g, 5.74 mmol) was added dropwise to a stirred suspension of aluminium chloride (765 mg, 5.74 mmol) in dichloromethane (10 ml) under external cooling with ice. After 15 min, compound **2** (100 mg, 0.574 mmol) was added. The mixture was stirred at room temperature for 10 min and then decomposed by pouring into 5% aqueous potassium carbonate solution (100 ml). The product was extracted with chloroform (3 × 20 ml) and the organic extract was washed with water (20 ml), brine (20 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent and crystallization from methanol afforded 67 mg (54%) of compound **19**, m.p. 201–201.5 °C (reported[3] m.p. 200 °C). For $C_{12}H_8O_2S$ (216.3) calculated: 66.65% C, 3.73% H, 14.83% S; found: 66.36% C, 3.91% H, 14.61% S. IR spectrum: 1 660 (CO). ^{1}H NMR spectrum: 2.63 s, 3 H (CH_3); 7.36 t, 1 H, *J* = 7.7 (H-7); 7.44 t, 1 H, *J* = 7.7 (H-6); 7.60 d, 1 H, *J* = 8.2 (H-5); 7.74 s, 1 H, (H-3); 7.78 d, 1 H, *J* = 7.7 (H-8).

2-Nitrothieno[3,2-*b*]benzofuran (**20**)

Fuming nitric acid (52 mg, 0.833 mmol) was added dropwise to acetic anhydride (1 ml) under stirring and cooling to 0 °C. After 15 min, a solution of compound **2** (100 mg, 0.574 mmol) in acetic acid (1 ml) was added. The mixture was stirred at 0 °C for 4 h, poured into ice-cold water (50 ml) and extracted with chloroform (50 ml). The organic extract was washed with water (20 ml), saturated solution of sodium hydrogencarbonate (10 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent and crystallization from hexane gave 26 mg (21%) of nitro derivative **20**, m.p. 161–163.5 °C (sealed tube). For $C_{10}H_5NO_3S$ (219.2) calculated: 54.79% C, 2.30% H; found: 54.64% C, 2.48% H. IR spectrum: 3 026, 1 447, 1 379, 1 321, 1 298. ^{1}H NMR spectrum: 7.41 t, 1 H, *J* = 7.7 (H-7); 7.52 t, 1 H, *J* = 7.6 (H-6); 7.64 d, 1 H, *J* = 8.2 (H-5); 7.80 d, 1 H, *J* = 8.2 (H-8); 8.07 s, 1 H (H-3).

2-Methylthieno[3,2-*b*]benzofuran (**21**)

A solution of butyllithium in hexane (1.0 ml of 2 M solution, 2 mmol) was added dropwise under nitrogen at –70 °C to a stirred solution of compound **2** (150 mg, 0.861 mmol) in tetrahydrofuran (15 ml). The reaction mixture was stirred at –30 °C for 2 h, methyl iodide (0.8 g, 5.62 mmol) was then added in a single portion and stirring was continued at room temperature for 2 h. The solution was evaporated and the residue purified by column chromatography on silica gel in hexane. Yield 140 mg (86%) of compound **21**, m.p. 56–57 °C (reported[3] m.p. 57.5 °C). For $C_{11}H_8OS$ (188.2) calculated: 70.18% C, 4.28% H, 17.03% S; found: 70.01% C, 4.21% H, 16.79% S. IR spectrum: 3 012, 1 497, 1 447, 1 405, 1 191, 1 049, 935. ^{1}H NMR spectrum: 2.63 s, 3 H (CH_3); 6.90 s, 1 H (H-3); 7.31 m, 1 H (H-7); 7.33 m, 1 H (H-6); 7.59 m, 1 H (H-5); 7.65 m, 1 H (H-8).

Bromination of 2-Methylthieno[3,2-*b*]benzofuran (**21**)

A solution of dioxane dibromide (134 mg, 0.55 mmol) in dichloromethane (4 ml) was added dropwise during 5 min at 0 °C to a solution of methyl derivative **21** (95 mg, 0.521 mmol) in a mixture of dichloromethane (2 ml) and dioxane (2 ml) and the mixture was stirred at 0 °C for 1 h. The reaction mixture was worked up as described for compound **16** and the crude product was subjected to preparative thin-layer chromatography in hexane to give 43 mg (32%) of a mixture of 3-bromo-2-methylthieno[3,2-*b*]benzofuran (**22**) and 6-bromo-2-methylthieno[3,2-*b*]benzofuran (**23**) (1.3 : 1), and 5 mg (4%) of 3,6-dibromo-2-methylthieno[3,2-*b*]benzofuran (**24**). The elemental analysis of the mixture of monobromo derivatives **22** and **23** was in accord with the calculated values. For $C_{11}H_7BrOS$ (267.1) calculated: 49.46% C, 2.64% H, 29.91% Br; found: 49.41% C, 2.76% H, 29.58% Br. ^{1}H NMR

spectrum of **22**: 2.54 s, 3 H (CH_3); 7.31 m, 2 H (H-6 and H-7); 7.60 m, 2 H (H-5 and H-8). ^{1}H NMR spectrum of **23**: 2.61 s, 3 H (CH_3); 6.86 s, 1 H (H-3); 7.38 dd, 1 H, J_1 = 8.8, J_2 = 1.6 (H-7); 7.44 d, 1 H, J = 8.2 (H-5); 7.68 d, 1 H, J = 1.6 (H-8). ^{1}H NMR spectrum of **24**: 2.54 s, 3 H (CH_3); 7.43 dd, 1 H, J_1 = 8.2, J_2 = 1.7 (H-7); 7.47 d, 1 H (H-5); 7.75 d, 1 H, J = 1.7 (H-8).

Methyl 6-Bromothieno[3,2-*b*]benzofuran-2-carboxylate (**25**)

A solution of bromine (1.8 g, 11.3 mmol) in chloroform (20 ml) was added dropwise at room temperature during 5 min to a stirred solution of ester **7** (2.0 g, 8.61 mmol) in chloroform (10 ml) and the mixture was stirred for 50 h. The reaction was quenched by addition of sodium hydrogensulfite (2 g, 10.5 mmol) and the mixture was stirred until it decolorized. The solution was washed with water (10 ml) and brine (10 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was crystallized from methanol to give 1.36 g (51%) of compound **25**, m.p. 147–148 °C. For $C_{12}H_7BrO_3S$ (311.2) calculated: 46.32% C, 2.27% H, 25.68% Br, 13.30% S; found: 46.08% C, 2.34% H, 25.42% Br, 13.27% S. IR spectrum: 1 709 ($COOCH_3$). ^{1}H NMR spectrum: 3.94 s, 3 H (OCH_3); 7.47 dd, 1 H, J_1 = 8.2, J_2 = 1.1 (H-7); 7.59 dd, 1 H (H-8); 7.75 d, 1 H (H-5); 7.81 s, 1 H (H-3). ^{13}C NMR spectrum: 53.2, 116.9, 117.4, 120.2, 121.6, 122.7, 125.8, 127.6, 135.4, 158.3, 160.5, 163.4.

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