SYNTHESIS OF [1]BENZOTHIENO[3,2-*b*]FURAN – A NEW FUSED BENZOHETEROCYCLIC SYSTEM

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A new heterocyclic compound has been prepared by a fourstep synthesis. The reaction of methyl thiosalicylate *I* with excess methyl chloroacetate in the presence of potassium carbonate gives methyl 3-[(methoxycarbonyl)methoxy]benzo[*b*]thiofen-2-carboxylate (*II*) which on cyclization by action of potassium *tert*-butoxide gives methyl 3-hydroxy[1]benzothieno[3,2-*b*]furan-2-carboxylate (*III*). Its base catalyzed hydrolysis and decarboxylation forms [1]benzothieno[3,2-*b*]furan-3(2*H*)-one (*IV*) whose reduction with $NaBH_4$ gives the title compound.

In an earlier communication[1] we described the effect of various basic reagents upon the course and yields of Dieckmann type condensations with the aim of finding a favourable way of synthesis of fused benzoheterocyclic compounds. These compounds belong among important intermediates in syntheses of pharmaceuticals[2,3]. In continuation of this study[1] we present here the preparation of the [1]benzothieno[3,2-*b*]furan (*IV*) which represents a not yet described parent linearly fused benzoheteroaromatic system whose derivatives are sporadically mentioned in literature[4 – 6].

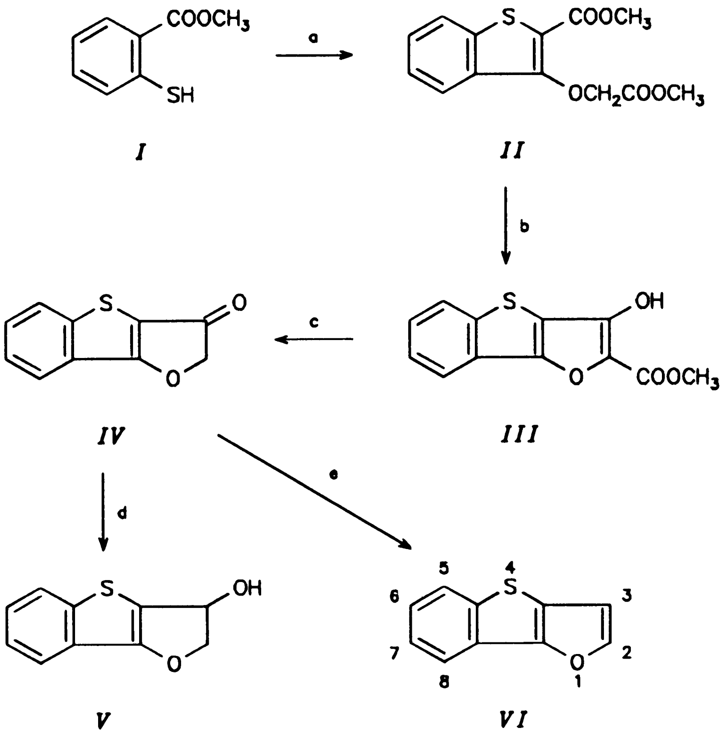
The key intermediate in the synthesis of compound *V* is methyl 3-[(methoxycarbonyl)methoxy]benzo[*b*]thiofen-2-carboxylate (*II*) which is known to be available by a multistep synthesis[7 – 9]. We have found that the diester *II* is easily formed in an one-pot process by the reaction of methyl thiosalicylate *I* with excess methyl chloroacetate in the presence of freshly annealed potassium carbonate as a base, the yield exceeding 90% (Scheme 1). Its subsequent Dieckmann condensation[1,4] by the action of potassium *tert*-butoxide is also smooth and gives a high yield (84%) of enol-ester *III*.

The hydrolysis and decarboxylation of enol-ester *III* was carried out in boiling aqueous-ethanolic solution of potassium hydroxide and subsequent acidification of the mixture with dilute hydrochloric acid. After optimizing the reaction conditions we obtained [1]benzothieno[3, 2-*b*]furan-3(2*H*)-one (*IV*) in a good yield (60 – 70%). Analogous yields were obtained from the acid catalyzed reaction, too. The distinct absorption of carbonyl group at 1 700 cm^{-1} and the absence the OH valence vibration from the

IR spectrum of compound *IV* confirm the exclusive existence of the oxo form in the solution, which agrees with the data published for analogous compounds[10].

The reduction of ketone *IV* with sodium borohydride smoothly produces the respective alcohol *V* which can be isolated by alkaline treatment of the reaction mixture. In the presence of acidic reagents, however, it is spontaneously dehydrated to give [1]benzothieno[3,2-*b*]furan (*VI*). This new heterocyclic compound is a low-melting crystalline solid with limited stability at room temperature and practically unlimited stability at −18 °C. Its UV spectrum shows two bands of separated maxima at 245 and 281 nm with slight shoulders whose character reminds of the excitation of benzene system.

In a following communication we are going to present the results obtained from the verification of reactivity of the parent tricyclic heterocycle *VI*.



a) $ClCH_2COOCH_3$, K_2CO_3; b) *t*-BuOK, THF; c) 1.NaOH, 2.HCl;
d) $NaBH_4$, MeOH; e) 1.$NaBH_4$, MeOH, 2.HCl

SCHEME 1

EXPERIMENTAL

The temperature data were not corrected. The melting points were determined with a Boetius block. The IR spectra (cm^{-1}) were measured with a Perkin–Elmer 325 and Nicolet 740 apparatus in chloroform. The ^{1}H NMR spectra (δ, ppm; *J*, Hz) were measured with a Bruker 400 apparatus in deuteriochloroform, using tetramethylsilane as the internal standard. The UV spectra (nm) were measured in 2,2,4-trimethylpentane using a Specord M40 apparatus. The MS were measured with a JEOL DX 300 apparatus (the electron energy 70 eV).

Methyl 3-[(Methoxycarbonyl)methoxy]benzo[*b*]thiofen-2-carboxylate (*II*)

A mixture of methyl thiosalicylate *I* (100.0 g, 0.60 mol), methyl chloroacetate (260.0 g, 2.4 mol), anhydrous potassium carbonate (330 g, 2.4 mol), and acetone (1 200 ml) was stirred and refluxed 20 h. After cooling the solid was removed by filtration and washed with acetone (2 × 50 ml) and the acetone filtrate was evaporated. The residue was recrystallized from methanol to give 160.0 g (95%) product *II*, m.p. 96 – 97 °C (ref.[9] gives m.p. 98 – 99 °C).

Methyl 3-Hydroxy[1]benzothieno[3,2-*b*]furan-2-carboxylate (*III*)

A solution of 1.44 M potassium *tert*-butoxide (450 ml) in THF was added dropwise to a stirred solution of ester *II* (18.0 g, 64 mmol) in benzene (450 ml) under nitrogen at 0 °C during 20 min. The mixture was refluxed 4 h, decomposed with ice water (200 ml), and washed with chloroform (50 ml). After acidifying the aqueous solution with 5% hydrochloric acid, the solid was collected by filtration, washed with water, and recrystallized from methanol to give 13.4 g (84%) compound *III*, m.p. 124 – 125 °C (refs[1,4] give m.p. 124 – 125 °C).

[1]Benzothieno[3,2-*b*]furan-3(2*H*)-one (*IV*)

A mixture of enolester *III* (17.0 g, 69 mmol), sodium hydroxide (33.0 g, 825 mmol), and 50% aqueous ethanol (220 ml) was stirred and refluxed 2 h, diluted with ice water (1 000 ml), and the aqueous solution was acidified with dilute hydrochloric acid (350 ml, 1 : 5). After 1 h, the crystals were collected by filtration and washed with water. The recrystallization from ethanol gave 8.6 g (66%) compound *IV*, m.p. 133 – 134 °C. For $C_{10}H_6O_2S$ (190.2) calculated: 63.14% C, 3.18% H, 16.85% S; found: 63.02% C, 3.29% H, 16.44% S. IR spectrum: 3 012, 1 700, 1 603, 1 568, 1 520, 1 484, 1 423, 1 267, 1 054, 973, 915. ^{1}H NMR spectrum: 5.13 s, 2 H (CH$_2$); 7.47 dt, 1 H, *J* = 9.8 and *J* = 0.8 (H-6); 7.56 dt, 1 H, *J* = 1.2 (H-7); 7.83 dd, 1 H, *J* = 8.2 and *J* = 0.8 (H-8); 7.95 dd, 1 H, *J* = 8.2 (H-5).

[1]Benzothieno[3,2-*b*]furan (*VI*)

Sodium borohydride (1.5 g, 40 mmol) was added in 5 portions to a solution of ketone *IV* (5.0 g, 26.2 mmol) in methanol (50 ml) at 0 °C during 15 min. The solution was stirred at 0 °C 1 h, diluted with ice water (100 ml), and acidified to pH 4 with 5% hydrochloric acid. The mixture was washed with ether (5 × 30 ml) and the combined extracts were washed with saturated sodium hydrogencarbonate solution and with salt brine. After drying with anhydrous magnesium sulfate the ether was evaporated and the residue was purified by flash chromatography (silica gel, hexane) to give 3.5 g (76%) compound *VI*, m.p. 36 – 37 °C (hexane). For $C_{10}H_6OS$ (174.2) calculated: 68.94% C, 3.47% H, 18.40% S; found: 68.54% C, 3.42% H, 17.73% S. IR spectrum: 3 152, 3 129, 3 084, 3 012, 2 927, 2 859, 1 493, 1 485, 1 426, 1 411, 1 346, 1 300, 1 264, 1 150, 1 128, 1 077, 1 048, 1 031, 1 014, 952, 889. ^{1}H NMR spectrum: 6.78 d, 1 H, *J* = 2.0 (H-3); 7.28 dt, 1 H, *J* = 8.2 and *J* = 1.2

(H-6); 7.38 dt, 1 H, J = 8.0 and J = 1.0 (H-7); 7.62 d, 1 H (H-2); 7.78 d, 1 H, J = 8.1 (H-8); 7.86 d, 1 H (H-5). Mass spectrum, *m/z* (%): 176 (6), 175 (12), 174 (M$^+$, 100), 146 (15), 145 (M – CHO, 22), 137 (8), 125 (10), 123 (11), 111 (14), 109 (12), 102 (28), 97 (22), 95 (20), 85 (23), 83 (23), 76 (12), 71 (19), 69 (42), 67 (12), 57 (35), 55 (32), 49 (8). UV spectrum, λ_{max} (log ε): 238 (4.27), 245 (4.34), 249 (4.29), 254 (4.28), 281 (4.12), 298 (3.86), 307 (3.23).

2,3-Dihydro[1]benzothieno[3,2-*b*]furan-3-ol (*V*)

Ketone *IV* (1.0 g, 5.3 mmol) was reduced in the same way as that in the synthesis of heterocycle *VI*. The reaction mixture was poured in 5% sodium hydroxide solution (100 ml), washed with ether (3 × 30 ml), the extract was dried with anhydrous magnesium sulfate, and the solvent was evaporated to give 0.91 g (89%) compound *V*, m.p. 125 – 127 °C. For $C_{10}H_8O_2S$ (192.2) calculated: 62.48% C, 4.19% H, 16.68% S; found: 62.48% C, 4.19% H, 16.86% S. IR spectrum: 3 584, 3 498, 3 068, 3 017, 2 955, 2 879, 1 589, 1 479, 1 405, 1 171, 1 086, 1 051, 946, 913, 771. ^{1}H NMR spectrum: 2.32 s, 1 H (OH); 4.84 dd, 1 H, ^2J = 11.6, $^3J_{cis}$ = 2.1 (H-2); 5.00 dd, 1 H, $^3J_{trans}$ = 6.6 (H-2); 5.47 m, 1 H (H-3); 7.34 dd, 1 H (H-6); 7.37 dd, 1 H (H-7); 7.68 dd, 1 H (H-8); 7.73 dd, 1 H (H-5).

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