

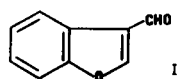
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Received October 3, 1977

Starting from the readily available 3-methylcoumarilate, 3-formylbenzo[*b*]furan was synthesized in high yield. The latter could be converted to 1-methyl-3,4-dihydrobenzo[*b*]furo[2,3-*c*]pyridine in moderate yield.

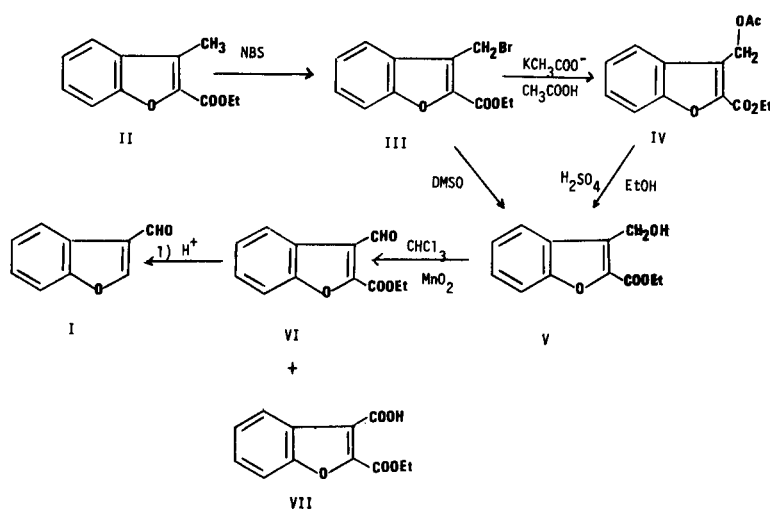
*J. Heterocyclic Chem.*, 15, 481 (1978)

As a part of a continuing program designed to expand the chemistry of benzo[*b*]furan (2), toward the synthesis of various oxa-analogs of indole alkaloids (e.g., angustidine, angustoline and nauclefine) (3-6), it became necessary to synthesize 3-formylbenzo[*b*]furan (1).

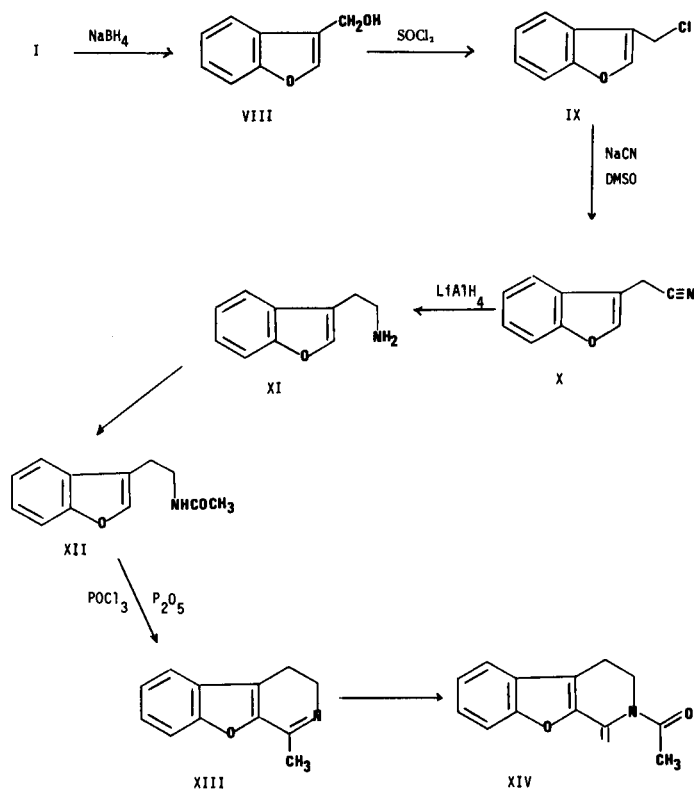


The only method reported for the preparation of compound I (7) did not have good overall yield. Recently, direct bromination of the readily available 3-methylbenzo[*b*]furan (8) to the corresponding 3-bromomethylbenzo[*b*]furan was reported (9). The latter compound seemed to be a good candidate for the preparation of the desired compound I. However, in our hands, bromination of 3-methylbenzo[*b*]furan under the specified conditions gave an untractable mixture. Finally, the desired compound I could be obtained, in high yield, starting from the readily available ethyl 3-methylcoumarilate (II) (8) (See Scheme I).

Reaction of compound II with 1 mole NBS gave ethyl 3-bromomethylcoumarilate (III) (10). The latter was transformed through the similar steps of the reactions which was reported by us (11) to ethyl 3-formylcoumarilate (VI) (2). Alternatively, reaction of compound III



Scheme I



Scheme II

with dimethylsulfoxide afforded in one step ethyl 3-hydroxymethylcoumarilate (V) in high yield. Oxidation of the latter with manganese dioxide gave compound VI. Hydrolysis of compound VI in acid medium followed by decarboxylation of the intermediate acid with copper quinoleine gave the desired compound I in high overall yield.

Finally in order to be able to expand the chemistry of benzo[*b*]furan we were in need of 1-methyl-3,4-dihydro-benzo[*b*]furo[2,3-*c*]pyridine (XIII) which was synthesized starting from compound I as it is shown in Scheme II.

Reaction of compound I with sodium borohydride afforded 3-hydroxymethylbenzo[*b*]furan (VIII). Reaction of the latter with thionyl chloride and subsequent reaction of the intermediate IX with sodium cyanide gave, in high yield, 3-benzo[*b*]furylacetonitrile (X) (12,13). Reaction of compound X with lithium aluminium hydride followed by acetylation gave 3-(2-acetamidoethyl)benzo[*b*]furan (XII). Cyclization of the latter with phosphorus oxychloride afforded the desired compound XIII (14). The structure of the latter was confirmed through acetylation to 2-acetyl-1,2,3,4-tetrahydro-1-methylenebenzo[*b*]furo[2,3-*c*]pyridine (XIV).

#### EXPERIMENTAL

Melting points were taken on a Kofler hot stage microscope and are uncorrected. Nmr spectra were determined using T-60A spectrometer and chemical shifts ( $\delta$ ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian Model MAT MS-311 spectrometer at 70 eV.

##### Ethyl 3-Acetyloxymethylcoumarilate (IV).

A mixture of III (28.3 g., 0.1 mole) (10) and potassium acetate (49 g., 0.5 mole) in 500 ml. of acetic acid was refluxed for 9 hours. The solvent was evaporated under reduced pressure. To the residue water was added and extracted with chloroform. The chloroform was washed with a saturated solution of sodium bicarbonate and water. The chloroform was dried, filtered and evaporated. The residue was crystallized from petroleum ether to give 24.9 g. (95%) of IV; m.p. 48-49°; mixture melting point with an authentic sample 48-49° (2).

##### Ethyl 3-Hydroxymethylcoumarilate (V).

###### Method A.

A solution of IV (26.2 g., 0.1 mole) in 400 ml. of absolute ethanol and 8 ml. of concentrated sulfuric acid was allowed to stand at room temperature overnight. It was concentrated under reduced pressure and treated with ice-water and chloroform. The chloroform was dried, filtered and evaporated. The residue was crystallized from ether-petroleum ether to give 21.78 g. (99%) of V; m.p. 58-59°; nmr (deuteriochloroform): 7.87-7.13 (m, 4H, aromatic), 5.03 (s, 2H, CH<sub>2</sub>O), 4.43 (q, 2H, CH<sub>2</sub>), 3.57 (broad s, 1H, OH) and 1.43 (t, 3H, CH<sub>3</sub>); ms: m/e (relative intensity): 220 (M<sup>+</sup>, 25), 191 (34), 174 (11), 173 (100), 145 (22), 91 (13) and 89 (16).

Anal. Calcd. for C<sub>12</sub>H<sub>12</sub>O<sub>4</sub>: C, 65.45; H, 5.45. Found: C, 65.62; H, 5.57.

###### Method B.

A mixture of III (2.83 g., 0.01 mole) and sodium bicarbonate (0.84 g., 0.01 mole) in 8 ml. of dimethyl sulfoxide was stirred and heated at 100° for 15 hours. After cooling, water was added and extracted with chloroform. The solvent was distilled under reduced pressure, and the residue was crystallized from petroleum ether to give 2.02 g., (92%) of V; m.p. 58-59°.

##### Ethyl 3-Formylcoumarilate (VI).

A mixture of V (22 g., 0.1 mole) and manganese dioxide (220 g.) in 500 ml. of chloroform was stirred overnight. The reaction mixture was filtered. The chloroform was washed with an aqueous solution of 10% sodium bicarbonate. The chloroform was evaporated and the residue was crystallized from ether to give 17.66 g. (81%) of VI; m.p. 91-92°; mixture melting point with an authentic sample (2) 91-92°.

Acidification of the aqueous sodium bicarbonate solution gave 468 mg. (2%) of VII; m.p. 159-160° (methanol) [lit. (13) m.p. 159-160°].

##### 3-Formylbenzo[*b*]furan (I).

A solution of VI (21.8 g., 0.1 mole) in 30 ml. of six normal hydrochloric acid and 70 ml. of acetic acid was refluxed for seven hours. After cooling, the solvent was evaporated and the residue was dissolved in 100 ml. of quinoleine, copper powder (40 g.) was added and the mixture was heated in an oil bath at 170° until the evolution of the gas ceased (ca. 2 hours). After cooling, ether (300 ml.) was added and filtered. The ether was washed with dilute hydrochloric acid and water. The ether was dried, filtered and evaporated. The residue was distilled to give 11.7 g. (80%) of I; b.p. 72-74° (2 mm Hg); m.p. 38-39° [petroleum ether; lit. (7), m.p. 39°]; nmr (deuteriochloroform): 9.83 (s, 1H, CHO), 8.25 (s, 1H, H<sub>2</sub>), 8.38-8.05 (m, 1H, H<sub>4</sub>), and 7.76-7.28 (m, 3H, aromatic); ms: m/e (relative intensity) 146 (M<sup>+</sup>, 40), 145 (100), 89 (89), 63 (49), and 62 (16).

##### 3-Hydroxymethylbenzo[*b*]furan (VIII).

To a stirring solution of I (14.6 g., 0.1 mole) in 150 ml. of methanol was gradually added sodium borohydride (1.89 g., 0.05 mole). After stirring two hours at room temperature, water (500 ml.) was added and extracted with chloroform. The chloroform was washed with water, dried and evaporated. The residue was crystallized from petroleum ether to give 14.5 g., (98%) of VIII; m.p. 46-47° [lit. (7), m.p. 47°]; nmr (deuteriochloroform): 7.93-7.0 (m, 5H, aromatic), 4.50 (s, 2H, CH<sub>2</sub>O) and 4.17 (broad s, 1H, OH).

##### 3-Chloromethylbenzo[*b*]furan (IX).

To a solution of VIII (14.8 g., 0.1 mole) in 300 ml. of ether, thionyl chloride (8 ml.) was added. The mixture was allowed to stand at room temperature for 12 hours. It was filtered and evaporated. The residue was distilled to give 12.15 g. (73%) of IX; b.p. 82-84° (2 mm Hg) (10); nmr (deuteriochloroform): 7.73-7.10 (m, 5H, aromatic) and 4.68 (s, 2H, CH<sub>2</sub>); ms: m/e (relative intensity) 168 (14), 166 (45), 132 (18), 131 (100), 103 (33), 102 (20), 77 (39), and 51 (26).

Anal. Calcd. for C<sub>9</sub>H<sub>7</sub>ClO: C, 64.86; H, 4.20. Found: C, 64.98; H, 4.35.

##### 3-Benzo[*b*]furylacetonitrile (X).

To a stirring suspension of sodium cyanide (5.07 g., 0.103 mole) in 40 ml. of dry dimethyl sulfoxide compound IX (16.65 g., mole) was added dropwise at 60-70°. Stirring was continued for a further two hours at 100°. After cooling, water was added and extracted with chloroform. The chloroform was washed with water, dried and evaporated. The residue was distilled to give

13.97 g. (89%) of compound X; b.p. 120-122° (4 mm Hg); m.p. 38-39° [lit. (12) m.p. 38.5-39.5°].

### 3-(2-Aminoethyl)benzo[*b*]furan (XI).

To a stirring suspension of lithium aluminium hydride (5 g.) in 300 ml. of dry ether was added dropwise a solution of X (15.7 g., 0.1 mole) in 200 ml. of dry ether. Stirring was continued for 4 hours. Then a saturated solution of sodium sulfate (15 ml.) was added cautiously to decompose the reagent. It was filtered and evaporated. The residue was crystallized as hydrochloride from ethanol-ether to give XI as hydrochloride (18.96 g., 96%); m.p. 188-190° [lit. (13); m.p. 189-190°]; nmr (deuteriochloroform): 7.76-7.0 (m, 5H, aromatic), 3.16-2.66 (t, 4H, CH<sub>2</sub>-CH<sub>2</sub>) and 1.56 (broad s, 2H, NH<sub>2</sub>).

### 3-(2-Acetamidoethyl)benzo[*b*]furan (XII).

To a stirring suspension of XI (16.1 g., 0.1 mole) and 250 ml. of 20% sodium hydroxide solution at ice-water temperature was added dropwise 72 ml. of acetic anhydride. After further stirring for four hours at this temperature, chloroform was added. The chloroform was washed with water, dilute hydrochloric acid and water and dried, evaporation of the solvent followed by distillation gave 10.15 g., (50%) of XII; b.p. 179-180° (4 mm Hg) (14); nmr (deuteriochloroform): 7.66-7.16 (m, 5H, aromatic), 6.60 (broad s, 1H, NH), 3.53 (q, 2H, CH<sub>2</sub>N), 2.86 (t, 2H, CH<sub>2</sub>) and 1.90 (s, 3H, CH<sub>3</sub>); ms: m/e (relative intensity): 203 (M<sup>+</sup>, 26), 145 (23), 144 (100), 131 (40), 77 (22), 43 (42) and 30 (99).

*Anal.* Calcd. for C<sub>12</sub>H<sub>13</sub>NO<sub>2</sub>: C, 70.99; H, 6.40; N, 6.90. Found: C, 70.82; H, 6.25; N, 6.78.

### 1-Methyl-3,4-dihydro-benzo[*b*]furo[2,3-*c*]pyridine (XIII).

A stirring suspension of XII (2.03 g., 0.01 mole), phosphorus oxychloride (4.8 ml.) and phosphorus pentoxide (4 g.) in 60 ml. of dry toluene was refluxed for 10 hours. After cooling water was added. The mixture was made alkaline with a concentrated solution of potassium hydroxide. The organic layer was dried and filtered. The solvent was evaporated and the residue was purified by tlc (silica gel, chloroform/methanol: 99/1); to give an oil (1.02 g., 55%); nmr (deuteriochloroform): 7.66-7.16 (m, 4H, aromatic), 3.90 (unresolved t, 2H, CH<sub>2</sub>N), 2.82 (unresolved t, 2H, CH<sub>2</sub>) and 2.20 (t, 3H, CH<sub>3</sub>, J = 1.8 Hz); ms: m/e (relative intensity): 185 (M<sup>+</sup>, 100), 184 (97), 157 (28), 128 (49), 102 (27), 89 (26), 77 (38), 75 (29), 63 (69), 51 (69), 50 (38) and 39 (79). It was crystallized as hydrochloride (ethanol-ether), m.p. 167-169° [lit. (14), m.p. 167-169°].

### 2-Acetyl-1,2,3,4-tetrahydro-1-methylene-benzo[*b*]furo[2,3-*c*]pyridine (XIV).

A solution of XIII (185 mg., 1 mmole) and 10 ml. of acetic anhydride was refluxed for 7 hours. The solvent was evaporated and the compound was purified by tlc (silica gel, chloroform) to give 113.5 mg. (50%) of XIV: nmr (deuteriochloroform): 7.66-7.16 (m, 4H, aromatic), 5.70 (d, 1H, ethylenic), 5.07 (d, 1H, ethylenic), 4.10 (t, 2H, CH<sub>2</sub>N), 2.80 (t, 2H, CH<sub>2</sub>) and 2.28 (s, 3H, CH<sub>3</sub>); ms: m/e (relative intensity): 227 (53), 186 (55), 185 (100), 184 (88), 159 (48), 156 (35), 43 (65) and 30 (29).

*Anal.* Calcd. for C<sub>14</sub>H<sub>13</sub>NO<sub>2</sub>: C, 74.01; H, 5.73; N, 6.17. Found: C, 74.18; H, 5.59; N, 6.01.

### Acknowledgement.

This work was supported by a grant from the Ministry of Sciences and Higher Education Research Development Council.

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