A New Route to Annulated Furans

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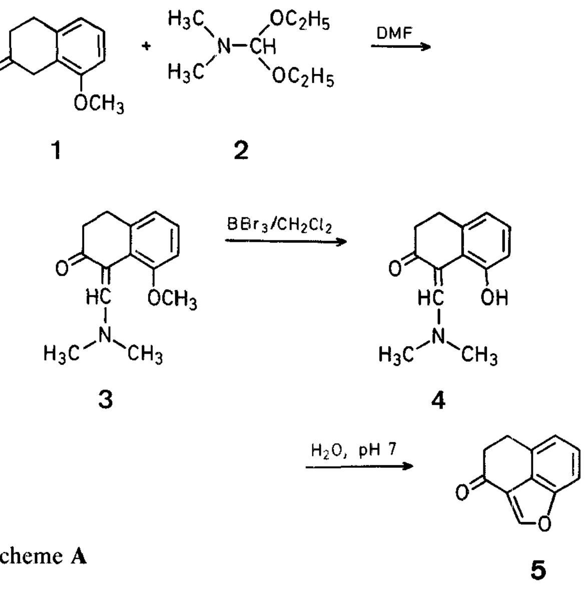
We have recently published[1,2] a new method for masking the highly susceptible furan ring of wortmannin. This method has now been successfully applied to the synthesis of annulated furans and we report here the preparation of the dihydronaphthofuran **5** (Scheme **A**) and two 3-acylbenzofurans **9** (Scheme **B**).

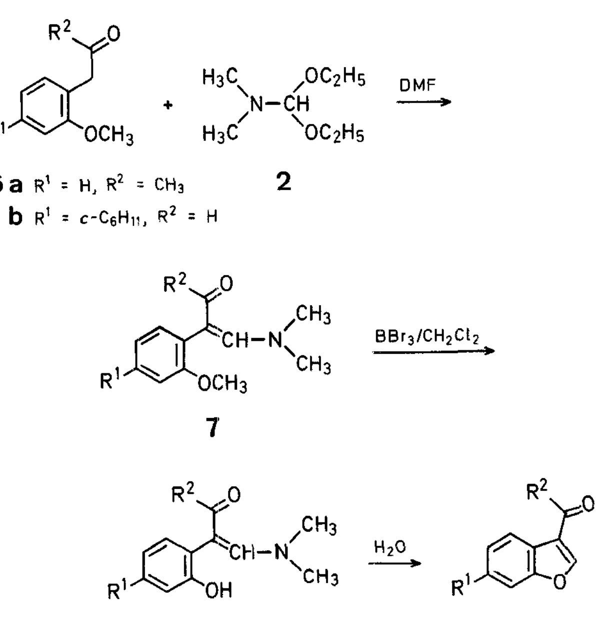


Scheme A

Reaction of 8-methoxy-2-tetralone (**1**)[3] with an excess of dimethylformamide dimethyl acetal[4,5] (**2**) at room temperature afforded the dimethylaminomethylene compound **3** in good yield. Cleavage of the methoxy group with boron tribromide in dichloromethane gave **4**. The latter is stable in crystalline form, but in solution it slowly cyclizes to the furan **5**. The best results for the cyclization were obtained in an acetone/water solution of pH 7 at room temperature. Under these conditions the reaction proceeded in over 70% yield. The steric fixation of the participating reaction centres obviously facilitates a mild and smooth reaction.

In basic or acidic medium, the enamine function is partly transformed into the corresponding enol group. The chemical shift of 8.12 ppm for the furan proton in **5** is in good agreement with the analogous proton in 11-deacetoxywortmannin[6] ($\delta = 8.22$ ppm).

The same approach is applicable to the construction of 3-acylbenzofurans, a class of compounds which is not easily accessible[7]. The synthesis of the benzofurans **9a** and **9b** is outlined in Scheme **B**.



Scheme B

Heating 1-(2-methoxyphenyl)-2-propanone (**6a**)[8] with dimethylformamide dimethylacetal (**2**) for a few hours at 80 °C furnished the dimethylaminomethylene derivative **7a** in very good yield. Cleavage with boron tribromide afforded directly the cyclized 3-acetylbenzofuran **9a**[9].

This sequence can also be applied to more susceptible substrates under essentially neutral reaction conditions as shown with the phenylacetaldehyde derivative **6b**. The latter was obtained from 4-cyclohexyl-2-methoxyphenylacetic acid[10] by diborane reduction and subsequent oxidation with chromium trioxide[11].

This furan synthesis is reminiscent of recently published work on the chromone[12] and indole[13] series of compounds.

1-Dimethylaminomethylene-8-methoxy-1,2,3,4-tetrahydronaphthalen-2-one (3):

A solution of 8-methoxy-2-tetralone[3] (**1**; 100 g, 0.57 mol) in dry dimethylformamide (1 l) is stirred at 22 °C while dimethylformamide dimethyl acetal (**2**; 80 ml, 0.60 mol; from Fluka) is slowly added. After 18 h at 22 °C in a dry atmosphere the methanol produced is removed in vacuo and the residue is once more treated with dimethylformamide dimethyl acetal (**2**; 80 ml) at 22 °C for 18 h. This procedure is repeated a second time. The reaction mixture is then poured on to water and extracted three times with ethyl acetate. The organic phase is washed once with water, dried with sodium sulfate and evaporated. Crystallization of the residue from ethyl acetate affords 1-dimethylaminomethylene-8-methoxy-1,2,3,4-tetrahydronaphthalen-2-one (**3**); yield: 66.5 g; m.p. 146–147 °C. A further crop of **3** (15 g) is obtained from the mother liquor; total yield: 81.5 g (62%).

$C_{14}H_{17}NO_2$	calc.	C 72.70	H 7.41	N 6.06	O 13.83
(231.3)	found	72.4	7.4	6.1	14.1

M.S.: $m/e = 231$ (M^+).

I.R. (CH_2Cl_2): $\nu = 1650$; 1570 cm^{-1}.

U.V. (CH_3OH): $\lambda_{max} = 215$ ($\log\varepsilon = 4.21$); 278 (3.99); 351 nm (4.17).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.87$ (s, 6H); 3.76 (s, 3H); 6.65–7.3 (m, 3H); 7.97 ppm (s, 1H).

1-Dimethylaminomethylene-8-hydroxy-1,2,3,4-tetrahydronaphthalen-2-one (4):

1-Dimethylaminomethylene-8-methoxy-1,2,3,4-tetrahydronaphthalen-2-one (**3**; 37 g, 0.16 mol) is dissolved in dry dichloromethane (1 l) and stirred at 0 °C in a dry atmosphere, while boron tribromide (50 ml, 0.52 mol) is slowly added. Stirring is continued at 0 °C for 15 min. The reaction mixture is poured into 2 normal potassium hydrogen carbonate (3 l) and the aqueous phase extracted once with dichloromethane. The organic layer is washed once with saturated sodium chloride solution, dried with sodium sulfate, and evaporated. The residue is crystallized twice from ethyl acetate; yield: 6.33 g (18%); The mother liquors contain mainly the cyclized furan **5**.

$C_{13}H_{15}NO_2$	calc.	C 71.86	H 6.96	N 6.45	O 14.73
(217.3)	found	72.1	7.2	6.5	15.1

M.S.: $m/e = 217$ (M^+).

I.R. (CH_2Cl_2): $\nu = 3550$; 1660; 1580 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.88$ (s, 6H); 5.87 (b, 1H); 6.7–7.2 (m, 3H); 7.87 ppm (s, 1H).

4,5-Dihydro-3*H*-naphtho[1,8-*bc*]furan-3-one (5):

1-Dimethylaminomethylene-8-hydroxy-1,2,3,4-tetrahydronaphthalen-2-one (**4**; 10 g, 0.046 mol) in a mixture of acetone (500 ml) and a buffer solution [1 l, pH = 7, consisting of potassium dihydrogen phosphate (9.1 g) und sodium monohydrogen phosphate (18.9 g)] is allowed to stand at 22 °C for 18 h. The acetone is removed in vacuo and the aqueous solution is extracted three times with ethyl acetate. The organic phase is washed with water, dried with sodium sulfate, and evaporated. The residue is crystallized from ethyl acetate and yields initially 1.4 g of starting material. The mother liquor (6.8 g) is separated by column chromatography using silica gel (140 g). Elution with ethyl acetate/hexane (3:1) and crystallization of the pure fractions from ethyl acetate/hexane affords 4,5-dihydro-3*H*-naphtho[1,8-*bc*]furan-3-one (**5**); yield: 4.2 g. Crystallization of the mother liquors yields a further 0.74 g of **5**. For analytical purposes the product is sublimed at 80 °C/0.1 torr; yield: 72% (based on converted material); m.p. 81–83 °C.

$C_{11}H_8O_2$	calc.	C 76.73	H 4.68	O 18.6
(172.2)	found	76.9	4.8	18.4

M.S.: $m/e = 172$ (M^+).

I.R. (CH_2Cl_2): $\nu = 3140$; 1690; 1625; 1610; 1555; 1495 cm^{-1}.

U.V. (CH_3OH): $\lambda_{max} = 203$ ($\log\varepsilon = 4.63$); 232 (4.01); 284 nm (3.69).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.75$–3.50 (A_2B_2, 4H); 7.13–7.50 (m, 3H); 8.12 ppm (s, 1H).

3-Acetylbenzofuran (9a):

A solution of 1-(2-methoxyphenyl)-2-propanone[8] (**6a**; 5 g, 0.031 mol) and dimethylformamide dimethyl acetal (**2**; 8.9 g, 0.075 mol) is stirred at 80 °C for 3.5 h after which practically no starting material is left (T.L.C.). Evaporation in vacuo furnishes *1-dimethylaminomethylene-1-(2-methoxyphenyl)-2-propanone* (**7**) as a viscous oil; yield: 6.7 g; b.p. 180–190 °C/0.1 torr (Kugelrohr). Without further purification this product is dissolved in dichloromethane (40 ml) by stirring and cooled in an ice bath. A solution of boron tribromide (5 ml) in dichloromethane (10 ml) is added dropwise. After 1 h additional boron tribromide (5 ml) is added and the reaction is left for 10 min. It is then poured on to ice/sodium hydrogen carbonate and extracted with dichloromethane. The washed (water) and dried (sodium sulfate) extract gives a yellow oil (3.3 g). Distillation (Kugelrohr) gives pure 3-acetylbenzofuran[9] (**9a**); yield: 2.3 g (48%, from **6a**); b.p. 90–110 °C/0.1 torr.

I.R. (CH_2Cl_2): $\nu = 1680$; 1560 cm^{-1}.

U.V. (CH_3OH): $\lambda_{max} = 224$ ($\log\varepsilon = 4.51$); 242 (3.79); 262 nm (3.84).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.5$ (s, 3H); 7.2–7.5 (m, 3H); 8.12–8.3 ppm (m, 2H).

4-Cyclohexyl-2-methoxyphenylacetaldehyde (6b):

Chromic anhydride (5.4 g, 0.051 mol) is added in small portions to a stirred solution of pyridine (8.1 g, 0.102 mol) in dry dichloromethane (120 ml). After 15 min a solution of 2-(4-cyclohexyl-2-methoxyphenyl)-ethanol[11] (2.0 g, 0.0085 mol) in dichloromethane (10 ml) is added and stirring is continued at room temperature for 15 min. The mixture is then filtered and washed twice with 2 normal hydrochloric acid (150 ml), 2 normal potassium carbonate solution (150 ml), and water. The dichloromethane extract is dried with sodium sulfate and evaporated to give the title compound; yield: 1.8 g (91%). An analytical probe is distilled at 150 °C/0.2 torr.

$C_{15}H_{20}O_2$	calc.	C 77.55	H 8.68	O 13.77
(232.3)	found	77.3	8.7	14.0

I.R. (CH_2Cl_2): $\nu = 1720$; 1620; 1580 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.0$–2.2 (m, 10H); 2.2–2.7 (m, 1H); 3.6 (d, 2H, $J = 2$ Hz); 3.8 (s, 3H); 6.7–7.2 ppm (m, 3H).

3-Dimethylamino-2-(4-cyclohexyl-2-methoxyphenyl)-propanone (7b):

The phenylacetaldehyde **6b** (6.45 g, 0.0278 mol) is dissolved in dimethylformamide (50 ml) under nitrogen and dimethylformamide dimethylacetal (5 ml, 0.0375 mol) added. After 14 h at 20 °C, the solution is partly evaporated (removal of the methanol formed) and another portion of the acetal (5 ml) is added. After an additional 15 h, this procedure is repeated once again. The reaction mixture is poured on to water (100 ml), extracted twice with ethyl acetate (100 ml), dried with sodium sulfate, and the solvent removed in vacuo to yield an oil (7.4 g) which is chromatographed on silica gel (ethyl acetate as eluent) to afford pure **7b** as an oil; yield: 4.0 g (50%).

$C_{18}H_{25}NO_2$	calc.	C 75.22	H 8.77	N 4.87
(287.4)	found	74.9	8.7	5.0

I.R. (CH_2Cl_2): ν = 2600; 1610; 1520 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.0–2.0 (m, 10H); 2.2–2.7 (m, 1H); 2.8 (m, 6H); 3.8 (s, 3H); 6.6–7.1 ppm (m, 4H).

6-Cyclohexylbenzofuran-3-carboxaldehyde (9b):

3-Dimethylamino-3-(4-cyclohexyl-2-methoxyphenyl)-propanone (**7b**; 4 g, 0.013 mol) is dissolved in dry dichloromethane (100 ml) in a nitrogen atmosphere. Boron tribromide (8.5 ml, 0.088 mol) is added dropwise by means of a hypodermic syringe, while stirring and cooling (0 °C). After 15 min at 0 °C, the solution is poured on to 2 normal sodium hydrogen carbonate solution (500 ml) and extracted with dichloromethane. The organic layer is washed several times with saturated sodium chloride solution, dried with sodium sulfate, and evaporated. The residue is allowed to stand in an acetone-buffer solution (100 ml, pH = 7) at 22 °C for 18 h. The acetone is removed in vacuo and the aqueous solution extracted three times with dichloromethane. The organic phase is washed with water, dried with sodium sulfate, and evaporated to dryness; yield: 3.15 g. Filtration through silica gel (ethyl acetate as eluent) affords pure **9b**; yield: 2.9 g (92%); m.p. 102–104 °C (from ether/light petroleum ether).

$C_{15}H_{16}O_2$	calc.	C 78.92	H 7.06
(228.3)	found	79.0	7.2

I.R. (CH_2Cl_2): ν = 1685; 1560 cm^{-1}.

U.V. (CH_3OH): λ_{max} = 230 (logε = 4.35); 266 nm (3.84).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.0–2.1 (b, 10H); 2.2–2.7 (m, 1H); 7.15–7.45 (m, 2H); 8.0–8.2 (m, 2H); 10.5 ppm (s, 1H).

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