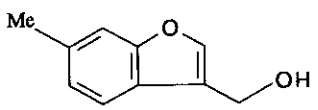
A SYNTHESIS OF 3-HYDROXYMETHYL-6-METHYLBENZOFURAN

Antonio G. González, Jaime Bermejo Barrera*, and Carlos Yanes Hernández
Centro de Productos Naturales Orgánicos Antonio González,
Consejo Superior de Investigaciones Científicas
Carretera de La Esperanza 2, 38206 La Laguna, Tenerife,
Canary Islands, Spain

Abstract--- 3-Hydroxymethyl-6-methylbenzofuran, a thymol derivative recently isolated from *Ageratina glechonophylla*, has now been synthesized.

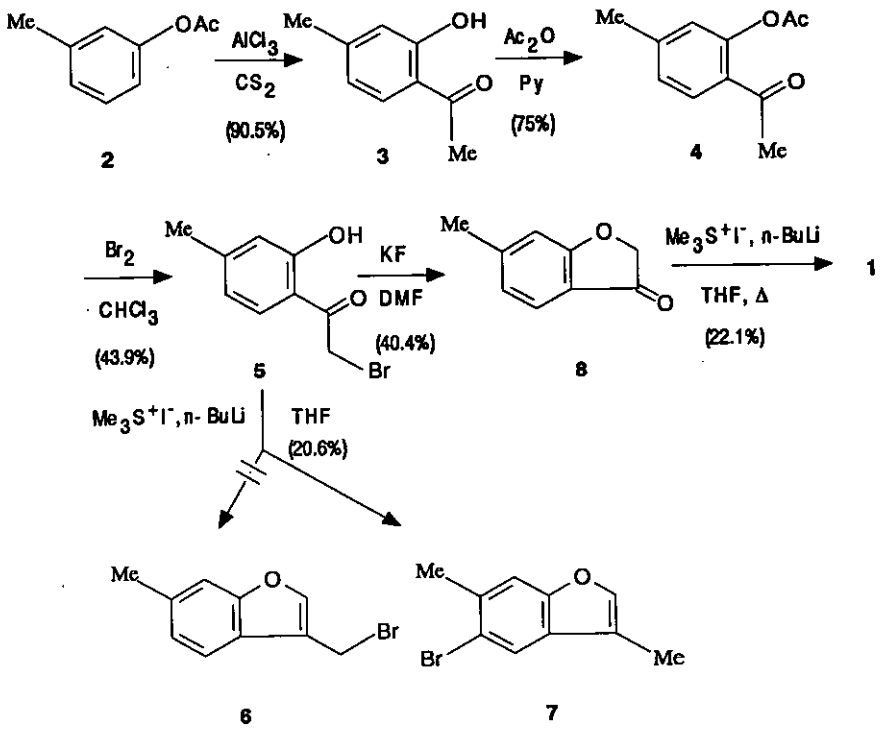
Benzofurans from the Asteraceae are known to be biologically active.[1] Compounds in the toxol and tremetone series have been associated with the causes of milk sickness[2] and an antitumoral screening carried out by the National Heart Institute reported that toxol and toxy-angelate displayed slight antitumoral activity against P-388 lymphocytic leukaemia tumours.[2] The majority of the known benzofurans exhibit a methyl ketone moiety, usually, at C-6 of the heterocyclic ring and natural compounds without this methyl ketone (such as **1**) are much less common.[3-5]

The structure assigned to 3-hydroxymethyl-6-methylbenzofuran (**1**), a benzofuran thymol derivative isolated from *Ageratina glechonophylla*,[5] had been based solely on spectroscopic evidence and the short synthesis described below has confirmed that it is correct.



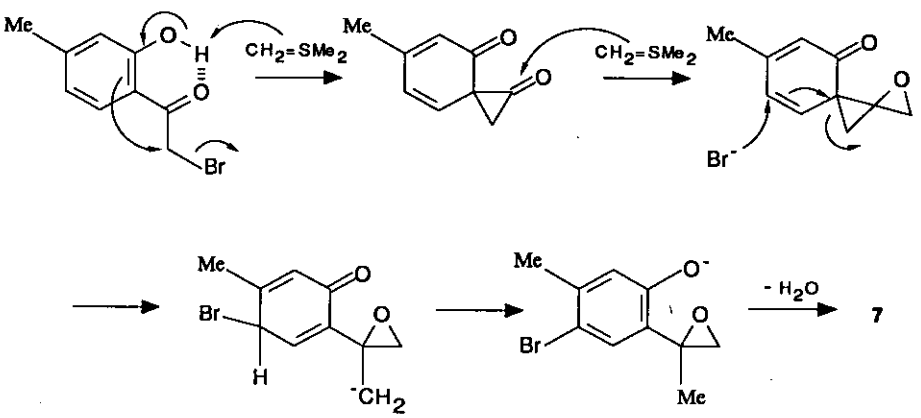
1

m-Cresol acetate (**2**) (Scheme 1) was converted to 2-hydroxy-4-methylacetophenone (**3**) by treatment with aluminium chloride in hot carbon disulphide. In order to protect the hydroxyl group, **3** was acetylated and the produced **4** was then treated[6] with bromine in chloroform to form the α-bromo derivative (**5**). Upon treatment with trimethylsulfonium methylide in tetrahydrofuran (THF)[7] **5** gave **7** instead of the desired compound, 3-bromomethyl-6-methylbenzofuran (**6**).



Scheme 1

The mechanism shown in Scheme 2 can be proposed for the formation of **7** *via* a cyclopropanone intermediate.



Scheme 2

To overcome this problem **5** was treated with anhydrous KF in *N,N*-dimethylformamide[8] yielding **8.** Upon stirring with trimethylsulfonium methylide for thirty minutes at 0°C and subsequently for 1 h at room temperature **8** gave the desired **1** in low yield. The spectral data of the colourless oil thus obtained proved identical upon comparison with those of the natural product (**1**), confirming the structure initially proposed for the new benzofuran.[5]

EXPERIMENTAL

Materials. THF was distilled from diphenyl ketyl. All other reagents and solvents were obtained commercially and used without further purification.

Procedures. The reactions were routinely conducted under a dry nitrogen atmosphere with magnetic stirring. Organic solutions of the products were dried over anhydrous sodium sulfate and then concentrated in vacuo. The crude products were purified by preparative tlc or column chromatography on silica gel. ^{1}H-Nmr spectra were recorded on a Bruker spectrometer WP200SY (200 MHz). Ms were obtained using a direct inlet system at 70 eV, using the expression (m/z, relative intensity). Ir spectra were obtained on a Perkin-Elmer spectrophotometer mod. 257.

2-Hydroxy-4-methylacetophenone (3)--- To anhydrous aluminium chloride (5.32 g, 40 mmol) at 0°C **2** (6.0 g, 40 mmol) in carbon disulfide (15 ml) was added gradually, with stirring. The whole was heated at 140°C for 4 h with stirring and then cooled in ice-water. The reaction was quenched by HCl 0.1 N and the aqueous portion was extracted with ether, and the organic layer was next shaken with 5% sodium hydrogen carbonate, dried over anhydrous sodium sulfate, and concentrated and the oily liquid thus obtained was purified by distillation under reduced pressure (87°C/0.22 mm Hg) to give **3** (5.43 g, 90.5%) as a colourless oil. Ir ($CHCl_3$) cm^{-1}: 3000 (OH), 1625 (C=O). ^{1}H-Nmr ($CDCl_3$) δ (ppm) : 2.27 (3H, s, C<u>H</u>$_3$-Ar), 2.51 (3H, s, C<u>H</u>$_3$-C=O), 6.63 (1H, d, J = 8 Hz, <u>H</u>-Ar), 6.69 (1H, s, <u>H</u>-Ar), 7.52 (1H, d, J = 8 Hz, <u>H</u>-Ar), 12.23 (1H, s, <u>H</u>O-Ar). Ms m/z (%): 150 (M^+, 36), 135 (M^+-CH_3, 100); HRms, m/z 150.06808 ($C_9H_{10}O_2$ requires 150.06769).

2-Acetoxy-4-methylacetophenone (4)--- Compound (**3**) (4 g, 28 mmol) was dissolved in acetic anhydride (5 ml) and pyridine (3 ml), and left at room temperature overnight. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with saturated $NaHCO_3$, dilute HCl and water, then dried over anhydrous sodium sulfate and concentrated to give **4** (3.84 g, 75%) as a colourless oil. Ir ($CHCl_3$) cm^{-1} : 1750, 1670 (C=O). ^{1}H-Nmr ($CDCl_3$) δ (ppm) : 2.30 (3H, s, C<u>H</u>$_3$-COOAr), 2.34 (3H, s, C<u>H</u>$_3$-Ar), 2.48 (3H, s, C<u>H</u>$_3$-C=O), 6.88 (1H, s, <u>H</u>-Ar), 7.07 (1H, d, J = 8 Hz, <u>H</u>-Ar), 7.69 (1H, d, J = 8 Hz, <u>H</u>-Ar). Ms m/z (%): 192 (M^+, 2), 150 (M^+-CH_2=C=O, 44); HRms, m/z 192.07864 ($C_{11}H_{12}O_3$ requires 192.07883).

2-(2-Bromo-1-oxoethyl)-5-methylphenol (5)--- To a hot solution of **4** (190 mg, 0.99 mmol) in chloroform (5 ml) was added dropwise a solution of bromine (52 μl) in chloroform (2 ml) for 10 min. The reaction mixture was heated at reflux for 20 min. After cooling to room temperature, the stirring was continued for additional 15 min. The reaction mixture was concentrated to give a crude product, which was purified by chromatography on silica gel using benzene as an eluent to give **5** (100 mg, 43.9%) as a colourless oil. Ir ($CHCl_3$) cm^{-1} : 3000 (OH), 1620 (C=O). ^{1}H-Nmr ($CDCl_3$) δ (ppm) : 2.35 (3H, s, C$\underline{H}_3$-Ar), 4.40 (2H, s, BrC$\underline{H}_2$-C=O), 6.73 (1H, d, J = 8.4 Hz, $\underline{H}$-Ar), 6.80 (1H, s, $\underline{H}$-Ar), 7.60 (1H, d, J = 8.4 Hz, $\underline{H}$-Ar), 11.74 (1H, s, $\underline{H}$O-Ar). Ms m/z (%): 230 (M^+, 15).

5-Bromo-3,6-dimethylbenzofuran (7)--- A solution of n-butyllithium (1.93 ml, 4.32 mmol) in 5 ml of dry THF was added dropwise over 20 min to a stirring suspension of powdered trimethylsulfonium iodide (0.87 g, 4.9 mmol) in 20 ml of dry THF under nitrogen at 0°C. After stirring for 5 min a solution of **5** (1.0 g, 4.34 mmol) in 5 ml of dry THF was added. The stirring was continued for 30 min at 0°C and then for 1 h at room temperature. Water (50 ml) was added and the mixture was extracted with ether; the extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to leave 650 mg of a chestnut-coloured oil. Distillation under reduced pressure (80°C/0.22 mm Hg) gave 300 mg of a yellow oil, which was purified by chromatography on silica gel using a mixture of hexane and benzene (95:5) as an eluent to give **7** (200 mg, 20.6%) as a colourless oil. ^{1}H-Nmr ($CDCl_3$) δ (ppm): 2.19 (3H, d, J = 1.1 Hz, C$\underline{H}_3$-C=C), 2.49 (3H, s, C$\underline{H}_3$-Ar), 7.33 (1H, s, $\underline{H}$-Ar), 7.34 (1H, s, $\underline{H}$-C=C), 7.68 (1H, s, $\underline{H}$-Ar). Ms m/z (%): 226 (M^+, 96), 224 (M^+, 94).

6-Methylbenzofuran-3(2*H*)-one (8)--- Potassium fluoride (1.26 g, 0.022 mol) and **5** (2.5 g, 13 mmol) were stirred together in DMF (10 ml) at room temperature for 15 min. The product was extracted from the reaction mixture with ether and the ethereal extract was washed three times with equal volumes of water to remove the DMF, dried over anhydrous sodium sulfate, and evaporated to give a yellow oil, which was purified by chromatography on silica gel using benzene as an eluent to give **8** (650 mg, 40.4%) as a colourless oil. Ir ($CHCl_3$) cm^{-1} : 1700 (C=O). ^{1}H-Nmr ($CDCl_3$) δ (ppm) : 2.42 (3H, s, C$\underline{H}_3$-Ar), 4.58 (2H, s, -C$\underline{H}_2$-O-), 6.88 (1H, d, J = 10.4 Hz, $\underline{H}$-Ar), 6.93 (1H, s, $\underline{H}$-Ar), 7.54 (1H, d, J = 10.4 Hz, $\underline{H}$-Ar). Ms m/z (%): 148 (M^+, 83), 119 (M^+-CHO, 100); HRms, m/z 148.05243 ($C_9H_8O_2$ requires 148.05084).

3-Hydroxymethyl-6-methylbenzofuran (1)--- To a stirred suspension of powdered trimethylsulfonium iodide (326.5 mg, 1.60 mmol) in dry THF (10 ml) under nitrogen at 0°C, was added dropwise a solution of n-butyllithium (0.67 ml, 1.5 mmol) in THF (5 ml). After stirring for 5 min, a solution of **8** (207 mg, 1.4 mmol) in THF (5 ml) was added. The stirring was continued for 30 min at 0°C and then for 12 h at room temperature. Water (50 ml) was added and the mixture was extracted with ether; the extract was washed with water, dried over anhydrous sodium sulfate, concentrated and purified by chromatography on silica gel using a mixture of

benzene and ethyl acetate (9:1) as an eluent to give **1** (50 mg, 22.1%) as a colourless oil. Ir ($CHCl_3$) cm^{-1} : 3565 (OH). ^{1}H-Nmr ($CDCl_3$) δ (ppm) : 2.47 (3H, s, $C\underline{H}_3$-Ar), 4.81 (2H, s, -$C\underline{H}_2$-OH), 7.09 (1H, d, J = 8 Hz, $\underline{H}$-Ar), 7.29 (1H, s, $\underline{H}$-Ar), 7.53 (1H, d, J = 8 Hz, $\underline{H}$-Ar), 7.54 (1H, s, $\underline{H}$-C=C-). Ms m/z (%): 162 (M^+, 100), 147 (M^+-CH_3, 10).

ACKNOWLEDGEMENTS

This work has been partly financed by a grant from the CICYT (PB88-0049). AGG is indebted to the AIETI Foundation, Madrid.

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Received, 11th November, 1991