Synthetic Routes to 2-(2-Benzofuranyl)benzoic Acids and their Cyclization into Benz[*b*]indeno[2,1-*d*]furan-10-ones

Jean Guillaumel, Nicole Boccara and Pierre Demerseman*

Service de Chimie de l'Institut Curie, U.R.A. 1387-P CNRS, 26 rue d'Ulm,
F-75231 Paris Cedex 05, France

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The benz[*b*]indeno[2,1-*d*]furan-10-ones **1** were prepared by the intramolecular cyclization of the 2-(2-benzofuranyl)benzoic acids, **2**, the unequivocal routes to which are described herein. Various synthetic methods to these acids were tested, as well as the methods to cyclize them.

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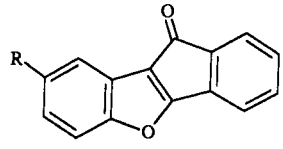
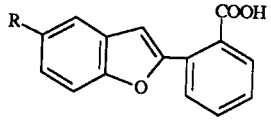
Since the virucidal properties of tilorone were discovered [1], many studies have been carried out on the pharmacomodulation of fluorenone. In this context, we have already studied the biological properties of some diethylaminoethyl ethers of bis-benzofuranyl ketones [2]. The benz[*b*]indeno[2,1-*d*]furan-10-ones (**1**) were also a pharmacological model likely to show similar properties.

Previously to this work, the 7,8-dihydroxybenz[*b*]indeno-[2,1-*d*]furan-10-one was prepared by an electrochemical synthesis [3] and the 5a,10a-dihydro-3,10a-dihydroxy-5a-methoxy-10*H*-benz[*b*]indeno[2,1-*d*]furan-10-one was detected by uv in equilibrium with a tautomeric hydroxyphenylindanedione [4]. We shall describe here the routes to the precursors of benzindenofuranones **1**, the 2-(2-benzofuranyl)benzoic acids **2a-b** and the conditions necessary for their cyclization.



1 a : R = H

b : R = OCH_3



2 a : R = H

b : R = OCH_3

Unlike their *para* isomers [5-11], the *ortho*-substituted acids **2** were, surprisingly enough, unknown in the literature. Several routes to these acids could be contemplated. We have already mentioned one of them [12]: it consists in hydrolyzing, with potassium hydroxide in methoxyethanol or ethyleneglycol, the 2-(2-benzofuranyl)-benzonitriles **4** resulting from the heterocyclization of the ether-aldehydes, **3** (Scheme 1, route A). Precise experimental conditions enabled us to induce the reaction to yield mostly the acids, **2**, thus avoiding the transposition of the intermediary amides, **5**, into 2,3-dihydro-3-phenylmethylene-1*H*-isoindole-1-ones, **6** [12]. We also demonstrated that the use of ethanol as solvent limits the hydrolysis of the nitriles, **4**, at the amides, **5**, step.

In the process of the present work, several routes to the acids **2a-b** were tested in search of a satisfactory yield.

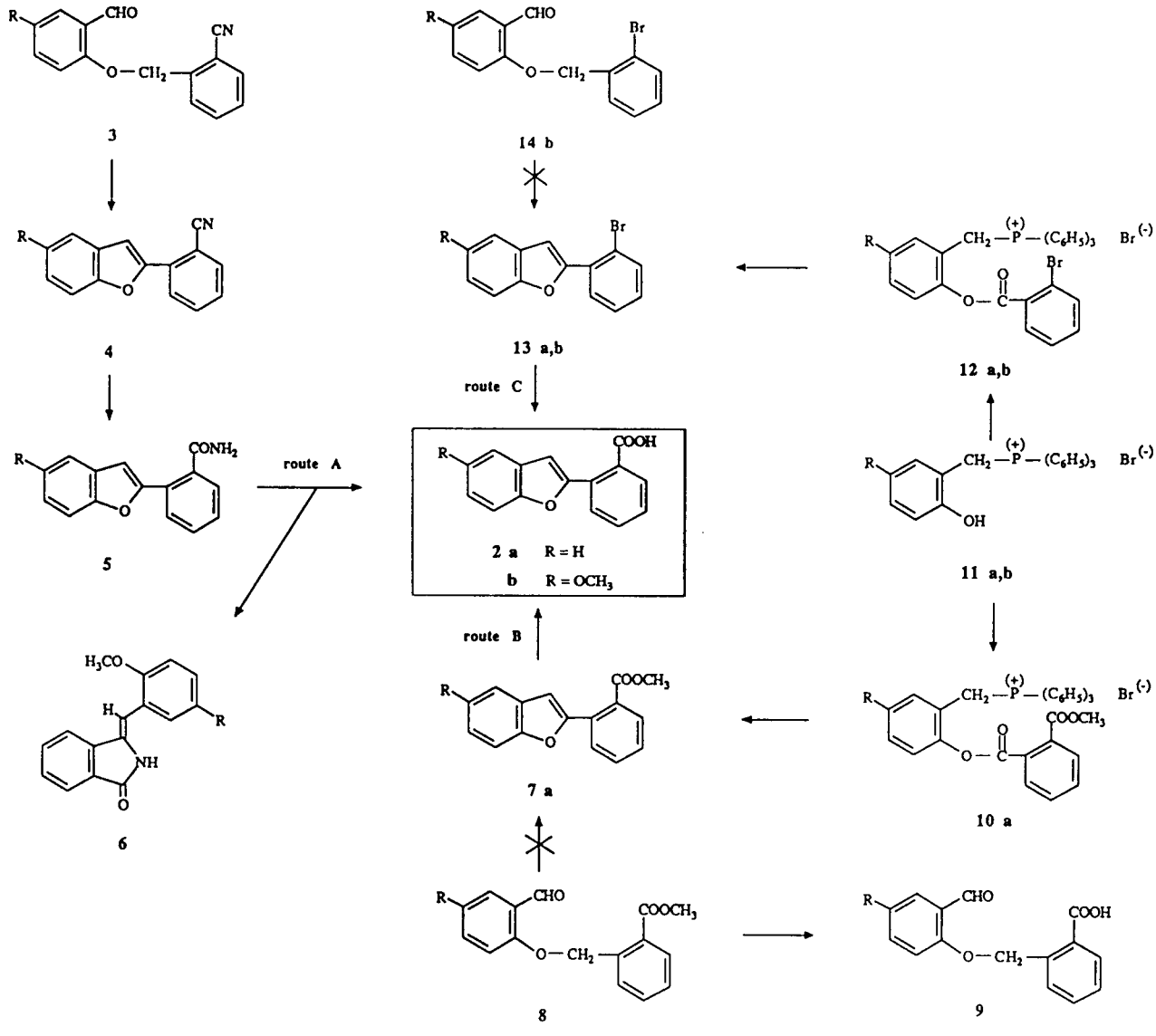
One of them consisted in hydrolyzing the precursor ester, **7**, (Scheme 1, route B). Unfortunately, the synthesis of these esters by heterocyclization of the ether-ester-aldehydes **8**, in alkaline solution was impossible as this reaction only leads to the uncyclized acids, **9**.

Nevertheless, the ester **7a** [13] could be prepared by another technique, *i.e.* intramolecular Wittig reaction, already used [14], on the phosphonium-ester salt **10a**, itself a derivative of the phenol **11a** [15]. The overall yield of acid **2a** obtained by this route amounts to 72%. This method was unsuitable for **7b**, as it was impossible to satisfactorily purify the ester **10b**.

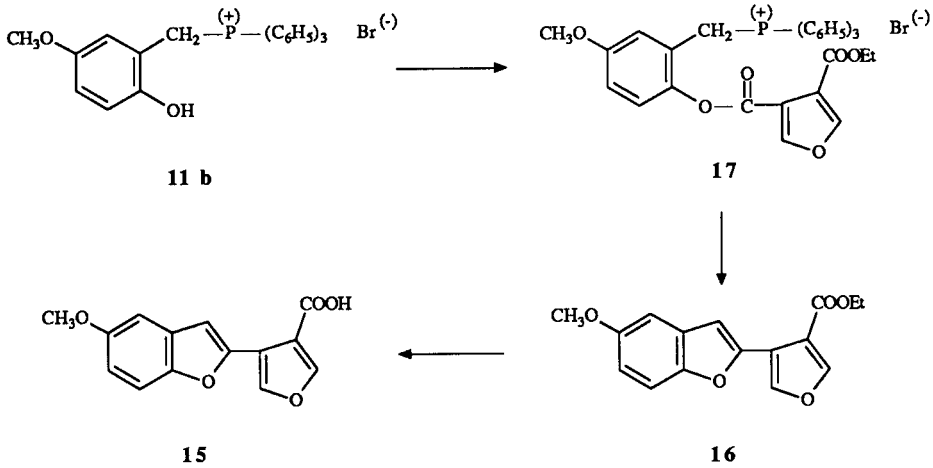
So, another reaction scheme had to be used (Scheme 1, route C) to prepare the acid **2b**. In this method, the phosphonium-phenol salt **11b** was acylated into its bromo-derivative **12b**; its heterocyclization by triethylamine can be obtained unproblematically in toluene, under reflux. The resulting brominated heterocycle **13b** was easily transformed into the acid **2b** by lithiation followed by carbonation. The overall yield in acid **2b** was then 49%. Nevertheless, this last route was not as satisfactory as route B to prepare the acid **2a**; in this case, the total yield for the three steps does not exceed 56%. It must be noted that the access to compound **13b** by cyclization of the bromoaldehyde **14b** was impossible, as the reactivity of methylene was too low [16,17].

It also appeared worthwhile to try the synthesis of another tetracyclic cyclenone, this time starting from the 4-(5-methoxy-2-benzofuranyl)-3-furoic acid **15**. This acid could be obtained in good yield using route B as above on the furoylphosphonium salt **17** (Scheme 2).

Scheme 1



Scheme 2



As routes to the acid precursors were elaborated, we further attempted to cyclize them into the corresponding cyclenones.

Several techniques were tried: (i) thermal reaction in diphenyl ether under reflux; (ii) trifluoroacetic anhydride in chloroform; (iii) gaseous hydrofluoric acid at -70°; (iv) sulfuric acid at 100°; (v) polyphosphoric acid at 100° in xylene; (vi) intramolecular Friedel-Crafts reaction in the presence of stannic chloride in benzene, aluminum chloride in carbon disulfide or chloroform, iron chloride in nitromethane.

Although the cyclization of the benzofuranylfuroic acid **15** could not be obtained by the above methods, its two analogues, **2a** and **2b**, led to the corresponding benzofuroindenones, **1a** and **1b**, but in poor yields. In the case of **2a** the best method consisted in using the Friedel-Crafts intramolecular cyclization in the presence of stannic chloride in benzene. The yield in **1a** was not more than 36% as significant resinification occurs. In the case of **2b** only 7% of the cyclenone **1b** was obtained by the same technique. This yield can be slightly increased (15%) by performing the heterocyclization in polyphosphoric acid at 100°.

Finally, since it still remains fairly difficult to obtain the benzofuroindenones **1**, this study enabled us to find routes to new intermediates useful to prepare other derivatives of biological interest.

EXPERIMENTAL

Uncorrected melting points were determined on a Kofler hot stage. The ^{1}H nmr spectra were obtained at 90 MHz using a Varian EM 390 instrument with TMS as internal standard (s = singulet, bs = broad singulet, d = doublet, dd = doublet of doublet). Mass spectra were measured at 70 eV using a Nermag R10-10C apparatus.

Methyl 2-(2-Formyl-4-methoxyphenyloxymethyl)benzoate (**8**).

A mixture of 5-methoxysalicylaldehyde (6.08 g, 40 mmoles), methyl 2-(bromomethyl)benzoate [18] (9.16 g, 40 mmoles), potassium carbonate (6.35 g, 80 mmoles) and a few crystals of sodium iodide in 45 ml of methanol was heated under reflux for 6 hours. The cooled solution was poured into water, and the precipitate obtained was filtered, washed with water and dried. Recrystallization from cyclohexane gave 9.6 g of the ether **8** in a 80% yield, mp 91-92°; ^{1}H nmr (DMSO-d_6): δ 3.73 and 3.80 (2s, 6H, OCH_3 and $COOCH_3$), 5.48 (s, 2H, CH_2), 7.20 (s, 3H, arom), 7.40-8.00 (m, 4H arom), 10.33 (s, 1H, CHO).

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 68.08; H, 5.30.

2-(2-Formyl-4-methoxyphenyloxymethyl)benzoic Acid (**9**).

A mixture of the etheraldehyde **8** (3 g, 10 mmoles) and powdered potassium hydroxide (0.64 g, 10 mmoles) in 15 ml of dimethylformamide was heated for 2 hours at 90°. The solution was then poured into water and acidified with hydrochloric acid. The gummy precipitate was extracted with ethyl acetate, and the organic layer washed with water, dried on sodium sulfate and evaporated *in vacuo*. The residue was then recrystallized from toluene. The acid **9** (1 g) was thus obtained in a 35% yield, mp 127-129°; ^{1}H nmr (DMSO-d_6): δ 3.73 (s, 3H, OCH_3), 5.50 (s, 2H, CH_2), 7.16 (s1, 3H arom), 7.30-8.00 (m, 4H, arom), 10.33 (s, 1H, COOH).

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 67.43; H, 5.10.

Phosphoniumester Salts. General Procedure.

To a suspension of phosphonium substituted phenols **11** (30 mmoles) [15] and the appropriate freshly prepared acid chloride (42 mmoles) in 25 ml of chloroform, pyridine (4.74 g, 60 mmoles) was slowly added. The mixture was then heated under reflux for 2 hours with stirring. The solution thus obtained was washed with water, dried and evaporated under vacuum. The residue was then triturated with 1,2-dimethoxyethane to induce crystallization and separated by filtration.

2-(2-Methoxycarbonylbenzoyloxy)benzyltriphenylphosphonium Bromide (**10a**).

This compound was obtained in a 90% yield, mp 200-203°; ^{1}H nmr (DMSO-d_6): δ 3.83 (s, 3H, $COOCH_3$), 5.26 (dl, 2H, CH_2-P, J = 16 Hz), 7.00-7.95 (m, 23 H arom).

Anal. Calcd. for $C_{34}H_{28}BrO_4P$: C, 66.79; H, 4.62; Br, 13.07. Found: C, 66.76; H, 4.81; Br, 12.68.

2-(2-Bromobenzoyloxy)benzyltriphenylphosphonium Bromide (**12a**).

This compound was obtained in a 75% yield, mp 189-192°; ^{1}H nmr (DMSO-d_6): δ 5.18 (dl, 2H, CH_2-*P*, J = 15 Hz), 7.00-8.00 (m, 23H arom).

Anal. Calcd. for $C_{32}H_{25}Br_2O_2P$: C, 60.78; H, 3.99; Br, 25.27. Found: C, 60.50; H, 4.05; Br, 24.95.

2-(2-Bromobenzoyloxy)-5-methoxybenzyltriphenylphosphonium Bromide (**12b**).

This compound was obtained in a 73% yield, mp 218-221°; ^{1}H nmr (DMSO-d_6): δ 3.53 (s, 3H, OCH_3), 5.20 (dl, 2H, CH_2-P, J = 15 Hz), 6.60-8.03 (m, 22 H arom).

Anal. Calcd. for $C_{33}H_{27}Br_2O_3P$: C, 59.84; H, 4.11; Br, 24.13. Found: C, 59.84; H, 4.17; Br, 23.97.

2-(4-Ethoxycarbonyl-3-furoyloxy)-5-methoxybenzyltriphenylphosphonium Bromide (**17**).

This compound was obtained in a 72% yield, mp 193-196°; ^{1}H nmr (DMSO-d_6): δ 1.23 (t, 3H, CH_2-CH_3), 3.06 (s, 3H, OCH_3), 4.16 (q, 2H, CH_2-CH_3), 5.23 (dl, 2H, CH_2-P, J = 15 Hz), 6.63 (m, 1H, H_3), 6.93 (m, 1H, H_5, J = 9 Hz), 7.20 (d, 1H, H_6).

Anal. Calcd. for $C_{34}H_{30}BrO_6P$: C, 63.27; H, 4.68; Br, 12.38. Found: C, 63.60; H, 4.91; Br, 11.99.

Cyclization of Phosphoniumester Salts. General Procedure.

A suspension of phosphonium ester **10a**, **12a-b** or **17** (25 mmoles) in 100 ml of anhydrous toluene was refluxed for 1 hour with stirring in the presence of triethylamine (3.8 g, 37.5 mmoles). The triethylammonium salt was then eliminated by filtration and the concentrated mother-liquors chromatographed on 100 g of silica gel (eluent:toluene).

Methyl 2-(2-Benzofuranyl)benzoate (**7a**) [13].

This compound, previously reported without physical data [13] was obtained in 85% yield as a light yellow oil $n_D^{25} = 1.6320$; ^1H nmr (deuteriochloroform): δ 3.75 (s, 3H, OCH_3), 6.86 (s, 1H, $H_{3'}$), 7.06-7.83 (m, 8H arom); ms: m/z (relative intensity) 252 (M^+, 100), 221 (30), 165 (20).

2-(2-Bromophenyl)benzofuran (**13a**).

This compound was obtained from pentane in a 93% yield, mp 36-37°; ^1H nmr (DMSO-d_6): δ 7.16-8.03 (m, 9H arom).

Anal. Calcd. for $C_{14}H_9BrO$: C, 61.56; H, 3.32; Br, 29.26. Found: C, 61.53; H, 3.34; Br, 29.29.

2-(2-Bromophenyl)-5-methoxybenzofuran (**13b**).

This compound was obtained in a 89% yield, mp 82-83° (petroleum ether); ^1H nmr (DMSO-d_6): δ 3.83 (s, 3H, OCH_3), 6.96 (dd, 1H, H_6, J = 2.5 Hz, J = 9 Hz), 7.20 (d, 1H, H_4, J = 2.5 Hz), 7.26-8.00 (m, 6H arom).

Anal. Calcd. for $C_{15}H_{11}BrO_2$: C, 59.43; H, 3.66; Br, 26.36. Found: C, 59.51; H, 3.55; Br, 26.45.

Ethyl 4-(5-Methoxy-2-benzofuranyl)-3-furoate (**16**).

This compound was obtained in a 80% yield, mp 79-80°; ^1H nmr (deuteriochloroform): δ 1.36 (t, 3H, CH_2-CH_3), 3.83 (s, 3H, OCH_3), 4.33 (q, 2H, CH_2-CH_3), 6.85 (dd, 1H, $H_{6'}$, J = 2.5 Hz, J = 9 Hz), 7.00 (d, 1H, $H_{4'}$, J = 2.5 Hz), 7.33 (d, 1H, $H_{7'}$, J = 9 Hz), 7.56 (s, 1H, $H_{3'}$), 7.95 and 8.06 (2d, 2H, H_2 and H_5, J = 0.9 Hz).

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 67.02; H, 5.12.

Hydrolysis of Esters. General Procedure.

Esters were easily hydrolysed by heating them for 2 hours in the presence of 0.05 *N* sodium hydroxide (1.2 equivalents) in water. The acid precipitates by acidification and was filtered under vacuum and dried.

(2-Benzofuranyl)benzoic Acid (**2a**).

This compound, recrystallized from toluene, was obtained in a 94% yield, mp 131-132° (lit [12], mp 131-132°).

4-(5-Methoxybenzofuranyl)-3-furoic Acid (**15**).

This compound was obtained in a 98% yield, mp 210-212°; ^1H nmr (DMSO-d_6): δ 3.83 (s, 3H, OCH_3), 6.88 (dd, 1H, H_4, J = 2.7 Hz, J = 9 Hz), 7.21 (d, 1H, $H_{4'}$, J = 2.7 Hz), 7.46 (d, 1H, $H_{7'}$, J = 9 Hz), 7.60 (s, 1H, $H_{3'}$), 8.33 and 8.50 (2d, 2H, H_2 and H_5, J = 0.9 Hz).

Anal. Calcd. for $C_{14}H_{10}O_5$: C, 65.12; H, 3.90. Found: C, 65.26; H, 4.10.

Transformation of Bromo Compounds, **13**, into Acids **2**. General Procedure.

A commercial solution of *n*-butyllithium (2.5 *M* in *n*-hexane, 12 mmoles) was added at -70°, in 15 minutes with stirring, to a solution of the bromo-derivative (10 mmoles) in tetrahydrofuran (35 ml). The reaction mixture was kept at this temperature for 1 hour. The solution of lithium derivative was then slowly poured onto previously ground dry ice (125 g) and left overnight. After dissolution of the lithium salt in water, the acid was precipitated by acidification and extracted with ether. The residue remaining after evaporation of the solvent was then recrystallized.

2-(2-Benzofuranyl)benzoic Acid (**2a**).

This compound, recrystallized from toluene, was obtained in a 80% yield, mp 131-132° (lit [12], mp 132°).

2-(5-Methoxy-2-benzofuranyl)benzoic Acid (**2b**).

This compound, recrystallized from toluene, was obtained in a 76% yield, mp 155-157° (lit [12], mp 156°).

Benz[*b*]indeno[2,1-*d*]furan-10-one (**1a**).

To a solution of **2a** (0.95 g, 4 mmoles) in anhydrous benzene (10 ml) thionyl chloride (0.95 g, 8 mmoles) was added, and the mixture was refluxed for 1 hour. After cooling, the excess reagent was evaporated *in vacuo* and the residual acid chloride dissolved in anhydrous benzene. Stannic chloride (1.3 g, 5 mmoles) in 5 ml of benzene was added to the stirred solution at 0° and the mixture stirred for a further 5 hours at ambient temperature. After pouring onto dilute hydrochloric acid, the product was extracted in dichloromethane. The organic phase was washed with water and dried. After evaporation of the solvent, chromatography of the residue on silica gel, eluting with toluene, yielded indenone **1a**. This compound, recrystallized from cyclohexane-toluene (1/1), was obtained in a 36% yield, mp 159-160°; ^1H nmr (DMSO-d_6): δ 7.30-7.80 (m, 8H arom); ms: m/z (relative intensity) 220 (M^+ 100), 163 (42).

Anal. Calcd. for $C_{15}H_8O_2$: C, 81.81; H, 3.66. Found: C, 81.87; H, 3.90.

2-Methoxybenz[*b*]indeno[2,1-*d*]furan-10-one (**1b**).

A mixture of acid **2b** (1 g), polyphosphoric acid (4 g) and xylene (25 ml) was heated for three hours at 100°. The cooled mixture was poured into water. The organic layer was washed, dried and evaporated *in vacuo*. The compound **1b**, purified by chromatography on silica gel (eluent: dichloromethane) was obtained in a 15% yield, mp 161-162°, after recrystallization from cyclohexane-toluene 1/1; ^1H nmr (DMSO-d_6): δ 3.83 (s, 3H, OCH_3), 6.86 (dd, 1H, H_3, J = 2.5 Hz, J = 9 Hz), 7.10 (d, 1H, H_1, J = 2.5 Hz), 7.20 to 7.50 (m, 4H arom), 7.56 (d, 1H, H_4); ms: m/z (relative intensity) 250 (M^+, 95), 220 (20), 207 (100), 179 (25), 150 (30), 125 (25).

Anal. Calcd. for $C_{16}H_{10}O_3$: C, 76.79; H, 4.03. Found: C, 76.66; H, 4.16.

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