Facile synthesis of 2-arylbenzo[b]furans through unusual acid catalysed 1,2-elimination

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2-Arylbenzo[b]furans have been synthesized in good to excellent yields through unusual acid catalysed 1,2-elimination of 2-aryl-2-aryl-3-hydroxybenzo[b]furans isolated as an intermediate for the first time. Their structure has been confirmed by X-ray crystallography.

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Benzofuran ring occurs widely and is the pivotal structure element of many natural and synthetic substances which show pharmacological properties. Many 2 or 3-aryl substituted benzofurans have found utility as antihypertensive, antiinflammatory, antifungal and antihyperlipidemic agents. Some 2, 3-diaarylbenzofurans and fused benzofuran ring derivatives have also been shown to possess antifeedant and mixed estrogen agonist and antagonist activities. In our pursuit for a simple and facile synthesis of 2, 3-diaryl-2H-1-benzopyrans, a novel class of potent antiestrogens through McMurry coupling reaction, we have found a highly efficient route to 2-arylbenzo[b]furans from readily available ortho hydroxylated aromatic carbonyl compounds and α-bromo-deoxybenzoinzs in good to excellent yields. This route offers very mild reaction conditions from readily accessible reagents.

The condensation of salicylaldehyde with substituted or unsubstituted α-bromo-deoxybenzoins in presence of NaH in DMF or NaOH in THF/HMPA resulted in the precipitation of an off white crystalline compound in 60-70% yield presumed to be the expected ether, 2-[2'-formylphenoxyl]-1,2-diarylethanone A. However, when the compound was subjected to McMurry coupling reaction it formed 2-aryl-2-aryl-3-hydroxybenzo[b]furan D in >80% yield instead of the desired 2, 3-diarylbenzopyran B (Scheme 1). The spectral data of the isolated intermediate and the formation of 2-arylbenzo[b]furan D in good yields under acidic conditions pointed towards a 2,3-disubstituted benzofuran derivative in which the aryl and aroyl groups could be present on C-2 and C-3 carbons and a hydroxyl group on C-3 carbon. The final structure and position of aryl and aroyl substituents were confirmed by X-ray analysis as 2-aryl-2-aryl-3-hydroxybenzo[b]furan C as shown in the ORTEP diagram (Figure 1).

A detailed literature survey does not mention formation of any intermediate of this type in any of the syntheses reported for 2-arylbenzo[b]furans.

Similar reactivity was also observed with 2-hydroxy aromatic ketones and α-bromo-deoxybenzoins forming the expected 2-aryl-2-aryl-3-alkyl-3-hydroxybenzo[b]furan E which on refluxing with dil. hydrochloric acid or any Lewis acid such as TiCl4 or SnCl4 formed the 2-aryl-3-alkylbenzo[b]furan F in >80% yield. However, if an aldehyde or a ketone with a protected carbonyl group was subjected to the same condensation, it initially formed the ether G which underwent acid catalysed deprotection, aldolisation and elimination to give 2-arylbenzo[b]furan D. From the ORTEP diagram it can be seen that the hydroxyl and aroyl groups are antitans to each other. Under acidic conditions, protonation at the 3-hydroxyl group

Figure 1—ORTEP diagram of 2-aryl-2-(4-methoxy phenyl)-3-hydroxybenzo[b]furan
results in the removal of a water molecule generating a carbocation, which possibly coordinates with the aryl group forming a cyclic transition complex. Addition of water results in the facile elimination of the aryl group as a carboxylate to give 2-arylbenzo[b]furans (Scheme II).

**Experimental Section**

**General.** Melting points were taken in open glass capillary and are uncorrected. IR spectra were taken on Shimadzu FTIR using KBr disk. Proton NMR spectra were recorded on a dpx200 and dnx300 spectrometer and $^{13}$C NMR spectra were recorded on a dnx300 spectrometer using CDCl$_3$ as solvent and trimethylsilane as the internal standard. El-MS were recorded on JEOL (Japan)/SX-102 and FAB mass were recorded on JEOL (Japan)/D-300 instrument. Microanalyses were performed on DF200 Carlo Erba instrument. X-ray crystallographic data were collected on Bruker P4 diffractometer. Dry solvents were prepared using standard methods.

2-[4-Methoxybenzoyl]-2-phenyl-3-hydroxy-benzo[b]furan C. 2-Hydroxybenzaldehyde (0.122 g, 1 mmole) was added to a stirred solution of NaOH (0.044 g, 1.1 mmole) and THF : HMPA (1:1, 4 mL) and the mixture was allowed to reflux for 30 min. Thereafter, 2-bromo-1-[4-methoxyphenyl]-2-phenyl ethanone (0.336 g, 1.1 mmole) in dry THF (2 mL) was added dropwise and the solution refluxed for further 8 hr. On completion of the reaction (monitored
by T.L.C.) it was cooled and quenched with water. It was extracted with solvent ether (3 × 50 mL) and washed with KOH (5% aqueous solution, 3 × 10 mL), water (2 × 5 mL) and dried (NaSO4). Excess of solvent was removed under vacuum. The residual oil was triturated with ethyl acetate and cooled to give a crystalline solid C. It was filtered and recrystallised from benzene/hexane, m.p. 164°C; yield 70% (0.242 g); IR (KBr): 3452 (OH, νC=O), 1664 (CO) cm⁻¹; ¹H NMR (300 MHz, CDCl3): δ 1.38 (d, 1H, OH, J = 7.2 Hz, exchangeable with D2O shake), 3.80 (s, 3H, OCH3), 6.18 (d, 1H, vicinal to OH, J = 7.2 Hz), 6.98-7.56 (m, 9H, ArH) and 8.0 (d, 2H, J = 8.7 Hz); ¹³C NMR (75 MHz, CDCl3): δ 55.3, 75.7, 98.9, 110.4, 113.2, 122.0, 125.6, 126.3, 127.2, 127.7, 130.5, 131.5, 133.3, 134.9, 157.8, 163.6 and 195.2 (CO); MS (FAB): m/z 347 (M+), 329 (M-17), 194, 135 (100%); Anal Calcd for C22H18O4: C, 76.30; H, 5.20%. Found: C, 76.71; H, 5.28%.

**X-ray analysis:** Crystal data: C₂₂H₁₈O₄, MW = 346.36, monoclinic, space group P2₁/n, a = 7.730(1), b = 16.997(2), c = 13.244(2) Å; β = 100.56(1)°, V = 1710.6(4) Å³, Z = 4, Dm = 1.345 g cm⁻³, μ = 0.092 mm⁻¹ (Mo-Kα, λ = 0.71073), F(000) = 728.0, T = 293(2) K, crystal size 0.28 × 0.23 × 0.13 mm, 4534 reflections measured, 3333 unique, (Rint = 0.036). Unit cell determination and intensity data were collected on a Bruker P4 diffractometer. Structure solution by direct methods, full-matrix least-squares refinement on F², anisotropic displacement parameters, riding hydrogen atoms, no absorption correction at convergence (Δρmax = 0.000) gave R = 0.0742 on F values of 1713 reflections with I > 2σ(I), S = 1.030 for all data and 237 parameters. Final difference map between Fobs and Fcalc shows a density peak of 0.35 e Å⁻³.


2-[4-Methoxybenzoyl]-2-phenyl-3-hydroxy-3-methylbenzo[b]furan E. This compound was prepared following the same procedure as described for C using 2- hydroxycacetophenone and 2-bromo-1-[4-methoxyphenyl]-2-phenyl ethanone. After work-up, the residue was purified by column chromatography on silica gel using ethyl acetate : hexane (1:20) as the eluting system to give the product E, m.p. 145°C; yield 65%; IR (KBr): 3344 (OH), 1645 (CO cm⁻¹); ¹H NMR (200 MHz, CDCl3): δ 1.22 (s, 3H, CH₃), 3.80 (s, 3H, OCH₃), 5.33 (s, 1H, OH, exchangeable with D₂O), 6.80 (d, 2H, ArH, J = 8.7 Hz), 6.98-7.56 (m, 9H, ArH) and 8.0 (d, 2H, ArH, J = 8.7 Hz); EI-MS m/z 390 (M⁺), 135 (100%).

2-[2-(1,3-Dioxolan-2-yl)-phenoxy]-1-[4-methoxyphenyl]-2-phenyl ethanone G. This compound was prepared using 1,3-dioxolan-2-yl phenol and 2-bromo-1-[4-methoxyphenyl]-2-phenyl ethanone following the procedure as described for C and E. The
crude residue obtained was purified by column chro-
matography on silica gel using ethyl acetate : hexane
(1:20) as the eluting system to give pure compound
G, m.p. 136 - 38°C; yield 55%; IR (KBr): 1674 (CO),
1076 (C-O) cm⁻¹; ¹H NMR (CDCl₃): δ 3.63 (s, 3H,
OCH₃), 3.85 - 3.95 (m, 4H, -CH₂-CH₂-), 6.08 and 6.10
(s, s, 1H each), 6.69 (d, 2H, ArH, J = 8.7 Hz), 6.79 -
7.44 (m, 9H, ArH), 7.95 (d, 2H, ArH, J = 8.7 Hz); EI-
MS: m/z 390 (M⁺), 135 (100%).

General procedure for the synthesis of 2-
arylbenzo[b]furans D or F from C, E or G using
mineral acid (10% aq. HCl) or Lewis acids (SnCl₄,
TiCl₄). Compounds C, E or G (1 mmole) were di-
solved in dioxan (5 mL), aq. HCl (10%, 5 mL) was
added and the mixture refluxed for 10 hr. The reaction
mixture was quenched with water, extracted with sol-
vent ether (3 x 10 mL) and washed with water (3 x 5
mL). It was dried (Na₂SO₄) and after removal of the
excess solvent, the residue was recrystallised from
hexane to give compounds D (m.p. 122°C, lit.
121°C)¹² or F, yield 80%. All the spectral data corre-
sponded to the authentic 2-phenylbenzo[b]furan¹².

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