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A Convergent Synthetic Study of Biologically Active Benzofuran Derivatives

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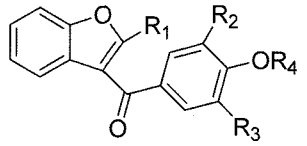
In order to construct a benzofuran library, we developed a model study of benzbromarone. Synthesis has been achieved in 53% overall yield, starting from phenol *via* the key intermediate 2-ethylbenzofuran which was afforded by intramolecular Wittig reaction.

Key words: Benzbromarone, Benzofuran library, 2-Ethylbenzofuran, Intramolecular Wittig reaction

INTRODUCTION

Benzbromarone (1) is a benzofuran derivative that has been reported to lower serum urate levels and been used as a uricosuric agent, also there are several other analogs of benzbromarone, including antihaemorrhagic agent benzarone (2), coronary vasodilator benziodazone (3) and antiarrhythmic drug amiodazone (4) etc. (Elks and Ganellin, 1990). Benzbromarone has been synthesized the first time by Buu-Hoi *et al.* in 1956 (Buu-Hoi *et al.*, 1957). Many work has been done to improve the synthesis procedure later. However a solid-phase synthesis for this type of molecule has not been reported. It's very useful to develop a less complicated and more efficient strategy for the combinatorial synthesis of the benzofuran derivatives. As a model study, we decided to develop a convergent approach for the synthesis of benzbromarone.



1:R_1=ethyl, R_2=R_3=Br, R_4=H	Benzbromarone
2:R_1=ethyl, R_2=R_3=H, R_4=H	Benzarone
3:R_1=ethyl, R_2=R_3=I, R_4=H	Benziodazone
4:R_1=butyl, R_2=R_3=I, R_4=$Et_2NCH_2CH_2$-	Amiodazone

Scheme 1. Structure of benzbromarone and its analogs

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MATERIALS AND METHODS

^{1}H-NMR and ^{13}C-NMR were recorded in the solvent indicated at 200 and 50 MHz, respectively. Chemical shifts are expressed in parts per million downfield from TMS. Flash chromatography was performed with 40-63 μm silica gel. TLC was performed on silica gel 60 plates with an F_{254} indicator and visualized under UV light or developed by immersion in a solution of 20% phosphomolybdic acid in ethanol or in a solution of 1.0% $KMnO_4$.

2-Hydroxymethyl-phenol (10)

Phenol (5 g, 0.05 mol) and formaldehyde solution (37 wt.%, 3.7 mL) were mixed in 50ml water, and zinc nitrate hexahydrate (14.9 g, 0.05 mol) was added into the solution. The pH of the solution was adjusted to 5.1 by nitric acid, and the reaction mixture was refluxed for 24 h. The aqueous solution then was extracted by ethyl acetate (3×40 mL) and washed by saturated $NaHCO_3$ solution, and brine, dried over maganesium sulfate and evaporated to dryness. The residure was recrystallized by ethyl alchol to afford 5.6 g (85%) of the title compound as a white crystal, mp.84°C.

(2-Hydroxy-benzyl)-triphenyl-phosphonium; bromide (11)

Compound **10** (5 g, 0.04 mol) and triphenylphosphine hydrobromide (13.7 g, 0.04 mol) was dissolved in 50 mL ethanol, and the solution was heated to reflux, after 2 h, the ethanol was evaporated to the dryness. The residure was recrystallized by ethyl alchol to afford 15 g (83%) of the title compound as a white crystal, mp. 243 °C.

2-Ethyl-benzofuran (5)

The salt 11 (5 g, 0.01 mol), propionic anhydride (1.4 g, 0.011 mol) were mixed together in 50 mL toluene and triethylamine (3 g, 0.01 mol) was added. The solution was refluxed for 8 h, and the solvent was evaporated to the dryness. The residure was purified by flash column chromatography (eluent, *n*-hexane/ethyl acetate = 50:1) to afford 1.4 g (90%) of the title compound as a colorless oil: Rf = 0.75 (eluant, *n*-hexane/ethyl acetate = 10:1 v/v); ^{1}H-NMR (200 MHz, $CDCl_3$) δ1.34 (3H, t, *J* = 7.8), 2.80 (2H, q, *J* = 7.8), 6.38 (1H, s), 7.16-7.21 (1H, m), 7.41-7.59 (2H, m), 7.80 (1H, d, *J* = 8.6). ^{13}C-NMR (50 MHz, $CDCl_3$) δ12.7, 21.8, 102.0, 111.5, 120.9, 123.3, 124.7, 128.8, 153.9, 158.1.

(2-Ethyl-benzofuran-3-yl)-(4-methoxy-phenyl)-methanone (12)

Compound **5** (1 g, 0.007 mol) and p-Anisoyl Chloride (1.3 g, 0.0077 mol) was dissolved in 10 mL carbon disulfide, the solution was cooled to 0°C by ice-water bath, and lewis acid tin(IV) chloride (1.8 g, 0.007 mol) was added dropwise at this temperature, after addition, the ice-water bath was removed and the solution was stirred overnight at room temperature. The reaction was quenched by adding 10 mL saturated NH_4Cl solution. The aqueous layer was extracted by ethyl acetate (3×20 mL). The combined organic layers was washed by 60 mL saturated $NaHCO_3$ and 60 mL brine, then dried over maganesium sulfate and evaporated to dryness *in vacuo*. The residure was purified by flash column chromatography(eluent, $CHCl_3$) to afford 1.8 g (90%) of the title compound as white crystal: Rf = 0.38 (eluant, $CHCl_3$), m.p. 80°C, ^{1}H-NMR (200 MHz, $CDCl_3$) δ1.37 (3H, t, *J* = 7.8), 2.91 (2H, q, *J* = 7.8), 3.85 (3H, s), 6.94 (2H, d, *J* = 8.4), 7.15-7.31 (1H, m), 7.38-7.60 (1H, m), 7.61-7.75 (1H, m), 7.85 (1H, d, *J* = 8.8), 8.00 (2H, d, *J* = 8.8), ^{13}C-NMR (50 MHz, $CDCl_3$) δ15.9, 17.8, 55.8, 111.5, 114.8, 117.3, 120.9, 122.6, 123.3, 124.7, 124.9, 128.5, 151.2, 153.9, 160.6

(2-Ethyl-benzofuran-3-yl)-(4-hydroxy-phenyl)-methanone (2)

Compound **12** (1 g, 0.004 mol) and pyridine hydrochloride (2.3 g, 0.02 mol) were mixed together and heated to 220°C. The reaction mixture melt at this temperature and was stirred at this temperature for 2 h. 25% aqueous HCl solution 20 mL was added to the reaction mixture and the aqueous layer was extracted by ethyl acetate (3×20 mL). The combined organic layers was washed by 60 mL saturated $NaHCO_3$ and 60 mL brine, then dried over maganesium sulfate and evaporated to dryness *in vacuo*. The residure was purified by flash column chromatography (eluent, $CHCl_3/CH_3OH$ = 30:1, v/v) to afford 0.95 g (100%) of the title compound as white crystal: Rf = 0.33 (eluant, $CHCl_3/CH_3OH$ = 10:1, v/v), m.p. 124°C, ^{1}H-NMR (200 MHz, $CDCl_3$) δ1.35 (3H, t, *J* = 7.8), 2.90 (2H, q, *J* = 7.8), 6.93 (2H, d, J=8.8), 7.18-7.26 (1H, m), 7.45-7.54 (1H, m), 7.61-7.68 (2H, m), 7.77 (2H, d, *J* = 8.8), ^{13}C-NMR (50M Hz, $CDCl_3$) δ15.9, 17.8, 111.5, 116.4, 117.3, 120.9, 122.9, 123.3, 124.7, 124.9, 128.9, 151.2, 153.9, 158.5

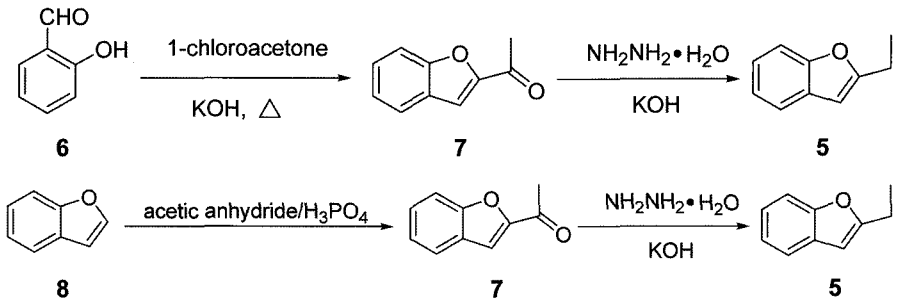
(3,5-Dibromo-4-hydroxy-phenyl)-(2-ethyl-benzofuran-3-yl)-methanone(1)

Compound **2** (0.9 g, 0.0034 mol) was dissolved in 10 mL 75% aqueous acetic acid solution. Bromine (0.82 g, 0.0051 mol) in 75% aqueous acetic acid solution 5 mL was added into the previous solution slowly at room temperature, then the solution was heated to 50°C and stirred for 2 h at this temperature. 15 mL water was added to the reaction mixture, and the aqueous layer was extracted by ethyl acetate (3×30 mL). The combined organic layers was washed by 90 mL saturated $NaHCO_3$ and 90 mL brine, then dried over maganesium sulfate and evaporated to dryness *in vacuo*. The residure was purified by flash column chromatography(eluent, *n*-hexane/ethyl acetate = 5:1, v/v) to afford 1.3 g (93%) of the title compound as white crystal: Rf = 0.54 (eluant, *n*-hexane/ethyl acetate = 3:1, v/v), m.p. 149°C, ^{1}H-NMR (200 MHz, $CDCl_3$) δ1.35 (3H, t, *J* = 7.8), 2.88 (2H, q, *J* = 7.8), 7.26-7.8 (4H, m), 7.96 (2H, s), ^{13}C-NMR (50 MHz, $CDCl_3$) δ12.7, 19.1, 111.5, 116.1, 120.8, 120.9, 123.2, 123.3, 124.7, 132.1, 133.6, 155.9, 156.3, 168.0, 190.7

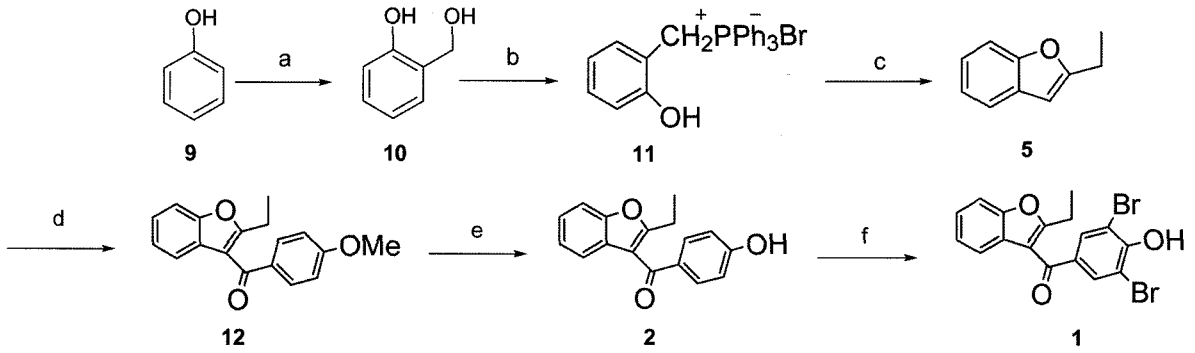
RESULTS AND DISCUSSION

2-ethylbenzofuran (5) is the key intermediate of the synthesis of the benzbromarone. The usual method for the synthesis of 2-ethylbenzofuran uses the salicylaldehyde (6) as the starting material, heating together with 1-chloroacetone (4) under base condition to give 2-acetylbenzofuran (7), followed Wolff-Kishner reduction to afford 2-ethylbenzofuran (5) (Buu-Hoi *et al.*, 1964). The other method uses benzofuran (8) as starting material which reacts with acetic anhydride/H_3PO_4 to give the 2-acetylbenzofuran (7) which is reduced to give 2-ethylbenzofuran (5) also by Wolff-Kishner reduction.

We used the important industrial chemicals phenol (9) and formaldehyde as the starting material. Aqueous solutions of phenol and formaldehyde were refluxed with zinc nitrate hexahydrate for 24 h to afford 2-hydroxymethyl phenol (10) selectively in the yield of 85% (Morozumi and Komiyama, 1991). Compound 10 was treated with triphenylphosphine hydrobromide in ethanol under its reflux temperature, to give the salt (2-Hydroxybenzyl)triphenylphosphonium bromide (11) in 83% yield (Hercouet and Le Corre, 1981). The salt 11, propionic anhydride and triethylamine were mixed together and refluxed for 8 h in toluene to give the most important intermediate 2-ethyl



Scheme 2. Known method for synthesis of 2-ethylbenzofuran



Scheme 3. Our method for synthesis of benzbromarone. (a) HCHO, $Zn(NO_3)_2 \cdot 6H_2O$, H_2O, reflux, 24 h; (b) $PPh_3 \cdot HBr$, EtOH, reflux, 2h; (c)propionic anhydride, Et_3N, toluene, reflux, 8 h; (d) *p*-anisoyl chloride, tin(IV) chloride, CS_2, 0°C-r.t., overnight; (e) pyridine hydrochloride (excess), 220°C, 2h; (f) Br_2,75% aqueous acetic acid solution, 50°C, 2 h.

benzofuran (5) in 90% yield (Hercouet and Le Corre, 1979). Our method approach to 2-ethyl benzofuran avoid the strong base condition and Wolff-Kishner reduction which were needed in the known method. Compound **5** can be acylated by p-Anisoyl Chloride in 3-position at room temperature using Lewis acid tin(IV) chloride as catalyst and carbon disulfide as the solvent to give the intermediate 12 in 90% yield. Here, We used the tin(IV) chloride which can efficiently avoided the benzofuran ring opening and reduced the ropy byproducts to make the reaction mixture easier to work up (Zhang and Hua, 2002). The demethylation was finished by mixing excess pyridine hydrochloride with compound 12 together and heating at 220°C for 2 h to give benzarone (2) (100% yield). Bromonation with bromine dissolved in the aqueous solution of acetic acid at 50°C, gave the final product benzbromarone (1) in 93% yield.

The chemistry method we developed can be applied to synthesize both benzbromarone (1) and other analogs. Considering the phenol derivatives and acyl anhydride or acyl chloride commercially available and easily synthetically accessible, this method will allow us to generate other diversified benzofuran-based compounds. Furthermore, our further research of solid phase synthesis of benzbromarone (1) will enable us to construct a library of benzofuran compounds soon.

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