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TOTAL SYNTHESIS OF AN ANTIOXIDANT ISOLATED FROM YEAST *VIA* PALLADIUM-CATALYZED COUPLING AND ITS APPLICATION FOR RELATED COMPOUNDS

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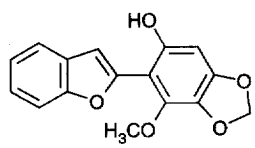
Abstract: A total synthesis of an antioxidant (**1**) having a benzofuran skeleton was achieved in four steps *via* the palladium(0)-catalyzed cross-coupling reaction. We also prepared several related compounds bearing a variety of aromatic or heterocyclic rings. Some of these compounds demonstrate more potent than **1** for antioxidative activity using guinea pig liver microsomes.

Benzofuran derivative (**1**) was isolated from various yeasts as an antioxidant[1] and its structure was determined by degradation studies[2,3]. Compound **1** was also highly active in tests including the inhibition of hemolysis of red cells. Wagner *et al.* reported the first total synthesis of **1** using the Hoesch reaction[4]. McKittrick and Stevenson prepared **1** with developing elegant benzofuran ring construction by way of the intramolecular Wittig reaction[5]. However, these methods were low yielding and limited applicability only to the synthesis of arylbenzofurans. In order to develop a facile, versatile and efficient methodology for assembling **1** and related compounds, we focused our attention on palladium(0)-catalyzed cross-coupling reaction between organometallic reagents (organoboranes[6] and organostannanes[7]) and organic electrophiles. This reaction is a powerful tool for carbon-carbon bond formation.

Herein we disclose a total synthesis of **1** *via* the palladium-catalyzed coupling reaction. We also synthesized related benzodioxole derivatives having various aromatic or heterocyclic rings and evaluated their antioxidative activity.



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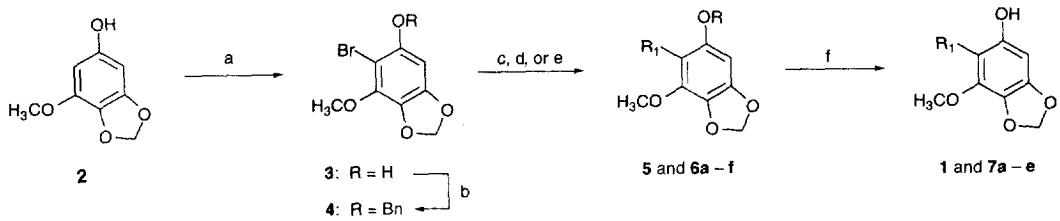
Synthesis: Scheme 1 illustrates our synthetic route. Regioselective bromination of the known benzodioxole derivative (**2**)[5] furnished bromobenzodioxole (**3**), a key intermediate for the synthesis of benzodioxole derivatives. Attempt on direct coupling between **3** and benzo[*b*]furan-2-boronic acid in the presence of $Pd_2(dba)_3$ and P(*o*-tol)$_3$ (method A) gave only trace amounts of **1**. This problem was overcome by protection of **3** with benzyl group to give **4**. With **4** and benzofuranboronic acid in hand, palladium-catalyzed coupling gave protected arylbenzofuran (**5**)[8] in an excellent yield, which upon deprotection under the normal conditions afforded **1** in a 62% overall yield from **2**. Physicochemical data of the synthetic product are in good agreement with those reported values[1,5].



reagents: a) Br_2, AcOH, CH_2Cl_2; b) BnBr, NaH, DMF; c) Benzo[*b*]furan-2-boronic acid, *i*-Pr_2NEt, $Pd_2(dba)_3$, P(*o*-tol)$_3$, DMF (method A); d) $ArB(OH)_2$, *n*-Bu_4NBr, K_2CO_3, $Pd(OAc)_2$, H_2O (mehod B); e) $HetSn(n\text{-}Bu)_3$, $Pd(PPh_3)_4$, HMPA (method C); f) H_2, Pd-C, EtOAc

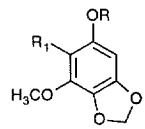
Scheme 1

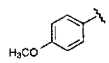
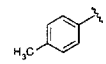
This efficient methodology was applied to the synthesis of novel benzodioxole analogs. In the synthesis of the various aromatic derivatives (**7a-d**), method A was low yielding and considerable amounts of starting materials remained. Modification of the reaction conditions (base, ligand, solvent, temperature) afforded high yields of the coupling products (**6a-d**). Coupling reaction in aqueous media in the presence of *n*-Bu_4NBr, K_2CO_3, and $Pd(OAc)_2$ (method B)[9] gave the desired products (**6a-d**) in excellent yields (81-100%). Subsequent hydrogenation of the resulting coupled products on Pd-C catalyst yielded the aromatic derivatives (**7a-d**)[10]. On the other hand, in the case of the heterocyclic derivatives Suzuki reaction failed to provide any coupled product. To our delight, tributylstannyl heterocyclic analogues reacted smoothly with **4** using $Pd(PPh_3)_4$ (method C) to give the desired products (**6e**, **f**[11]) almost quantitatively. Cleavage of the benzyl ether in thienyl derivative (**6e**) by the catalytic hydrogenation gave a small mount of the target product (**7e**)[12]. Attempted deprotection under acidic conditions was led to complete recovery of **6e**. Under these deprotective conditions, furanyl derivative (**6f**) was predominantly decomposed or polymerized to give no desired compound.

Results and Discussion: Antioxidative activity of benzodioxole derivatives was evaluated by using the lipid peroxidation of guinea pig liver microsomes enzymatically induced with CCl_4[13]. In CCl_4-stimulated lipid peroxidation, the reactive trichloromethyl free radical (CCl_3•) was produced by a metabolic activation involving

the NADPH-cytochrome P-450 system[14]. Table summarizes the 50% inhibitory concentration (IC_{50}) for each compound against the lipid peroxidation. α-Tocopherol and *n*-propyl gallate were also tested as reference compounds and their IC_{50} values were 280 μM and 50 μM, respectively.

Table: Antioxidative Activity for Benzodioxole Derivatives.



No.	R_1	R	Method	Yield[a] (%)	IC_{50}[b] (μM)
1		H	A	100	98
7a		H	B	81	83
7b		H	B	84	56
7c		H	B	100	65
7d		H	B	100	107
7e		H	C	93	44
6f		Bn	C	96	n.t.[c]

a) Isolated yields of the palladium-catalyzed reactions.
b) IC_{50} values of reference compounds: α-tocopherol = 280 μM, *n*-propyl gallate = 50 μM.
c) n.t. = not tested.

Modification of the ring at 5-position influenced antioxidative activity and all compounds tested were more active than tocopherol. Interestingly, among these synthesized benzodioxole derivatives, most of them exhibited higher activity than the natural product (**1**). We examined the effect of the aromatic rings at 5-position. Comparison of *para*-substituents of the phenyl moiety revealed that the relative activity profile was methoxy (**7b**) > methyl (**7c**) >> hydride (**7a**) >> phenyl (**7d**). Conversion of benzofuran to thiophene resulted in significant increase of activity (**1** *vs.* **7e**). These highly active compounds (**7b** and **7e**) showed equal potency to *n*-propyl gallate.

In conclusion, we have developed a facile and versatile synthesis of a natural antioxidant (**1**) by using palladium-catalyzed reaction; this reaction is demonstrated to be applicable to synthesis of novel related compounds. We also have evaluated their antioxidative activity. In this study, it was found that thienyl derivative (**7e**) and methoxyphenyl derivative (**7b**) exhibited about 2 times more potent activity than **1** and also similar activity to *n*-propyl gallate. Further structure-activity relationships studies on benzodioxole analogs are in progress.

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8 **5**: ^{1}H NMR (400 MHz, $CDCl_3$) 3.95 (s, 3H), 5.01 (s, 2H), 5.95(s, 2H), 6.39 (s, 1H), 6.83 (s, 1H), 6.8–7.6 (m, 9H).

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10 **7a**: ^{1}H NMR (400 MHz, $CDCl_3$) 3.83 (s, 3H), 4.78 (brs, 1H), 5.91 (s, 2H), 6.31 (s, 1H), 7.32–7.34 (m, 2H), 7.37–7.41 (m, 1H), 7.46–7.50 (m, 2H).
7b: ^{1}H NMR (400 MHz, $CDCl_3$) 3.83 (s, 3H), 3.85 (s, 3H), 4.79 (brs, 1H), 5.90 (s, 2H), 6.30 (s, 1H), 7.00–7.02 (m, 2H), 7.23–7.25 (m, 2H).
7c: ^{1}H NMR (400 MHz, $CDCl_3$) 2.40 (s, 3H), 3.83 (s, 3H), 4.80 (brs, 1H), 5.90 (s, 2H), 6.30 (s, 1H), 7.20–7.22 (m, 2H), 7.28–7.30 (m, 2H).
7d: ^{1}H NMR (400 MHz, $CDCl_3$) 3.87 (s, 3H), 4.86 (brs, 1H), 5.91 (s, 2H), 6.33 (s, 1H), 7.35–7.41 (m, 3H,), 7.44–7.48 (m, 2H), 7.63–7.65 (m, 2H), 7.68–7.71 (m, 2H).

11 **6f**: ^{1}H NMR (400 MHz, $CDCl_3$) 3.91 (s, 3H), 4.96 (s, 2H), 5.92 (s, 2H), 6.36 (s, 1H), 6.47–6.48 (m, 1H), 7.27–7.33 (m, 6H), 7.52 (m, 1H).

12 **7e**: ^{1}H NMR (400 MHz, $CDCl_3$) 3.91 (s, 3H), 5.21 (brs, 1H), 5.91 (s, 2H), 6.31 (s, 1H), 7.06 (dd, J = 0.8, 3.5 Hz, 1H), 7.15 (dd, J = 3.5, 5.0 Hz, 1H), 7.48 (dd, J = 0.8, 5.0 Hz, 1H).

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