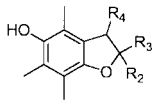
Synthesis of Novel 2-Aryl-2-methyl-2,3-dihydrobenzofurans

No-Sang Park, Young-Sik Jung, Chun Ho Park, Chul-Min Seong, and Hee-Jong Lim*

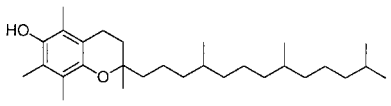
CNS Research Team, Bioorganic Division, Korea Research Institute of Chemical Technology, P.O. Box 107, Yusong, Taejon 305-600, Korea
Received November 20, 2000

Keywords : 2-Aryl-2-methyl-2,3-dihydrobenzofuran, Antioxidant, Lipid peroxidation, Claisen rearrangement.

Dihydrobenzofurans are found in many biologically important molecules.[1] Recently, 2,3-dihydrobenzofuran-5-ol **1** has been shown to possess more potent activity than vitamin E **2** in inhibition of lipid peroxidation which is ultimately associated with acute neurological and neurodegenerative diseases such as stroke, spinal cord injury, trauma, Parkinsons Disease and Alzheimer's Disease.[2] Although several studies for direct annulation from phenol and electrophile have been reported, these methods usually gave mixture of 2,3-dihydrobenzofuran isomers due to many possible cyclization routes.[3,4] 2,3-Dihydrobenzofurans are generally prepared in stepwise from allyl aryl ether *via* Claisen rearrangement to the corresponding *o*-allylphenols followed by acid catalyzed cyclization. Tandem Claisen rearrangement and cyclization reactions of allyl aryl ethers mediated by Lewis acid were also reported.[5]



2,3-Dihydrobenzofuran-5-ol, **1**

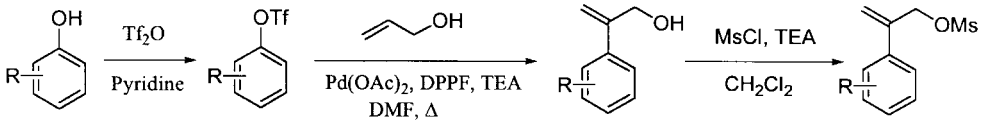


Vitamin E, **2**

We were interested in synthesizing 2-aryl-2-methyl-2,3-dihydrobenzofuran-5-ol **11** because 2,3-dihydrobenzofuran ring **1** has been postulated to have more favored stereoelectronic conformation in hydrogen abstraction by peroxyradicals than vitamin E and consequently to possess an improved antioxidant activity.[6] Furthermore, it would be valuable to provide an efficient procedure since the synthetic studies for this 2-aryl substituted benzofuran ring formation were rarely exploited.[7] In this paper, we report our preliminary result for the synthesis of 2-aryl-2-methylbenzofuran-5-ols **11** as potent radical scavenging antioxidants. The strategy for benzofuran ring formation was relied on Claisen rearrangement of aryl allyl ether followed by cyclization since various substituents could be readily introduced on aryl ring attached in 2-position of 2,3-dihydrbenzofuran-5-ol **11**.

Among the known methods to access the key intermediates 2-aryl-2-propenols **5**,[8] we utilized the palladium catalyzed Heck reaction of aryl triflate **4**.[8c] Reaction of aryl triflate **4a** and **4b** with allyl alcohol in $Pd(OAc)_2$(2.5 mol%), 1,1'-bis(diphenylphosphino)ferrocene (**DPPF**; 5 mol%) and triethylamine (2 eq.) in DMF at 100 °C afforded **5a** (68%) and **5b** (68%), respectively. Heck reaction of nitro-substituted aryl triflate (**4c** and **5d**) with a lower amount of $Pd(OAc)_2$ (1 mol%) and **DPPF** (2 mol%) was also effective to provide the corresponding 2-aryl-2-propenols (**5c** and **5d**) in moderate yields. The 2-aryl-2-propenol **5** was then converted to the corresponding mesylate **6** with methanesulfonyl chloride in dichloromethane (Scheme 1).

The 4-hydroxy-2,3,6-trimethylphenyl acetate **8** was prepared from 2,3,5-trimethylhydroquinone **7** by bisacetylation and selective deacetylation of less hindered 4-acetyl group by modification of known procedure.[9] The allyl aryl ether **9** was prepared from sodium salt of phenol **8** and mesylate **6** in DMF at 40 °C in high yield. We investigated Claisen rearrangement of allyl aryl ether to form *o*-allylphenol **10**. Thermal rearrangement in dimethylaniline resulted in desired product in poor yield. BCl_3 catalyzed rearrangement afforded to *o*-allylphenol **10** in high yield.[10] A typical procedure for this rearrangement was described as follow: to a solution of allyl aryl ether **9** in dichloromethane was added dropwise a solution of BCl_3 (*ca* 2 eq) at room temperature until starting ether was disappeared by TLC monitoring. The resulting solution was poured into a vigorously stirred cold saturated $NaHCO_3$ solution, extracted with dichloromethane, dried and concentrated *in vacuo*. The crude *o*-allylphenol **9** was used for cyclization without purification since it was unstable and extensive decomposition was observed on chromatographic separation. Therefore, *o*-allyl phenol **9** was immedi-



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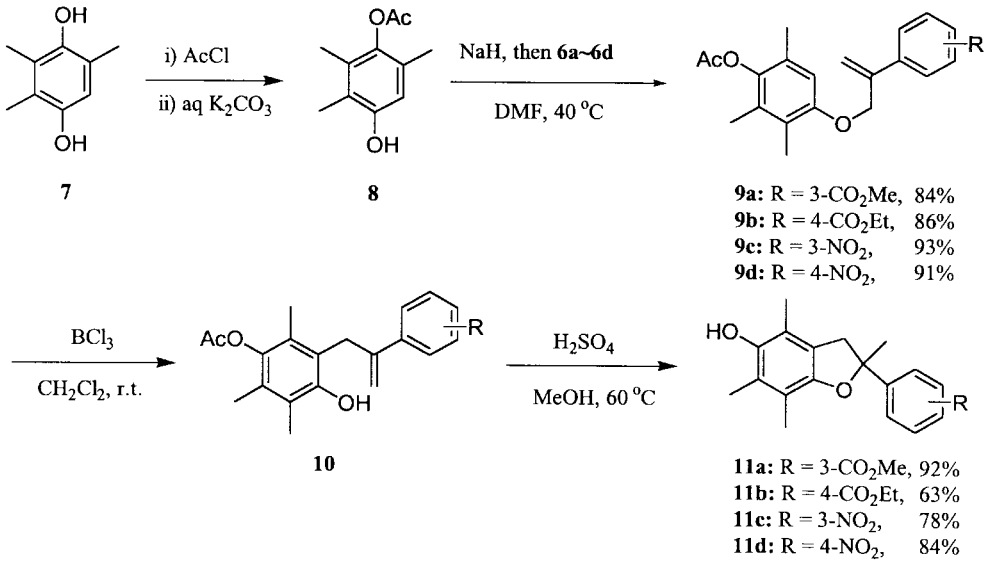
4a: R = 3-CO_2Me, 96%
4b: R = 4-CO_2Et, 96%
4c: R = 3-NO_2, 98%
4d: R = 4-NO_2, 98%

5a: R = 3-CO_2Me, 68%
5b: R = 4-CO_2Me, 68%
5c: R = 3-NO_2, 64%
5d: R = 4-NO_2, 71%

6a: R = 3-CO_2Me
6b: R = 4-CO_2Et
6c: 3-NO_2
6d: 4-NO_2

Scheme 1



Scheme 2

ately treated with sulfuric acid in methanol at 60 °C to afford desired 2-aryl-2-methyl2,3-dihydrobenzofuran-5-ol **11** in high yield (Scheme 2).[11]

In conclusion, we have developed an efficient procedure for the synthesis of 2-aryl-2-methyl-2,3-dihydrobenzofuran-5-ol utilizing Claisen rearrangement of allyl aryl ether and subsequent cyclization.

Acknowledgment. We are grateful to the Ministry of Science and Technology for financial support for this work.

References and Notes

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11. All new compounds were characterized by spectroscopic analysis. Spectral data for the selected 2-aryl-2-methyl-2,3-dihydrobenzofuran-5-ol **11a** as follows: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.75 (s, 3H), 2.05 (s, 3H), 2.14 (s, 3H), 2.27 (s, 3H), 3.29 (s, 2H), 3.89 (s, 3H), 4.91 (bs, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.69 (d, J = 7.6Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 8.15 (s, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 12.0, 12.2, 12.8, 29.5, 44.6, 52.1, 52.1, 87.5, 115.8, 117.4, 121.9, 122, 0, 125.8, 128.0, 129.2, 130.0, 145.9, 148.0, 150.6, 167.1; EI MS m/z 326 (M).