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Facile Synthesis of Isoamericanol and Isoamericanin A

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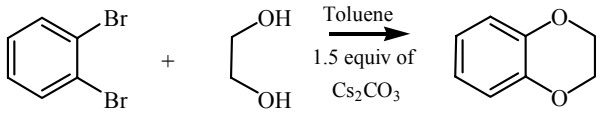
Abstract: A number of benzodioxane compounds were synthesized using the palladium-catalyzed etherification of aryl halides by employing triphenylphosphane ligands. This method was used as key step in the synthesis of isoamericanol A and isoamericanin A.

Keywords: Synthesis, isoamericanol A, isoamericanin A, benzodioxane.

Aryl ethers and oxygen heterocycles are common structures in many pharmaceutically and agriculturally important compounds[1,2]. Traditional methods for the preparation of these compounds include the Williamson ether synthesis[3], direct nucleophilic substitution reactions[4], and Ullman-type couplings of alkoxides with aryl halides[5]. These methods, however, require either highly reactive aryl halides, an excess of the alkoxide, or harsh conditions.

Recently Buchwald has reported a novel intramolecular C-O bond forming reaction[2]. According to this reference we developed a convenient method to couple benzodioxane ring from *O*-dibromoaryl and dialcohol in one step.

Table 1



1 **2** **3**

Entry	Mol ratio of Substrate **1**:**2**	$PdCl_2$ mol /%	Ph_3P mol /%	T(℃), t(h)	Solvent	Yield(%)
1	1:1	2	0	50, 24	toluene	8
2	1:1	2	2.5	50, 24	toluene	65
3	1:1	2	2.5	r.t. 50	acetone	44
4	1:1	2	2.5	r.t. 30	ether	20
5	1:1	2	2.5	reflux,24	CH_3CN	56

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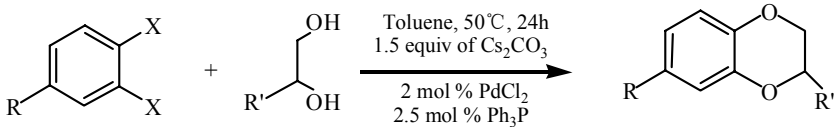
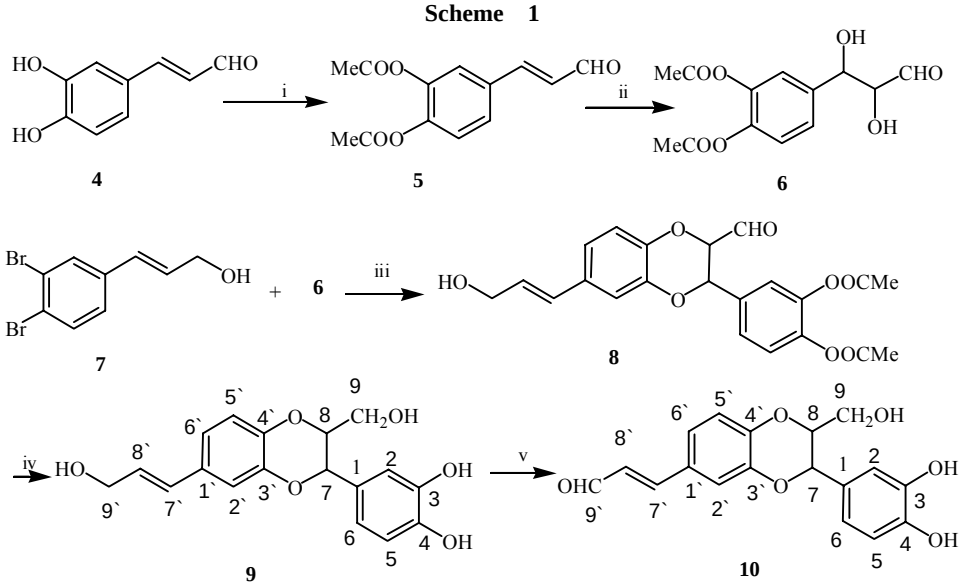
Table 2



Entry	R	X	R′	Yield (%)
1	H	Br	H	65
2	H	Cl	H	63
3	CN	Br	H	60
4	$COOCH_3$	Br	H	61
5	H	Br	Me	60

Scheme 1



Reagents and conditions: i. Ac_2O, Py, >99%; ii. H_2O_2, 94%; iii. Cs_2CO_3, Ph_3P, $PdCl_2$, 63%; iv. LAH, 88%; V. MnO_2/SiO_2, 81%

We found that 1,2-ethanediol and *O*-dibromobenzene are difficult to be coupled to get benzodioxane only in the presence of Cs_2CO_3 and catalytic amount of $PdCl_2$ (yield<10%), but when triphenylphosphane is added, the yield of benzodioxane will be improved to about 65%. Toluene is the best solvent for the reaction, as show in **Table 1**.

As shown in **Table 2**, different benzodioxane rings can be formed using this method. Both aryl chlorides and bromides can be cyclized using this catalyst system. The reaction with primary as well as secondary alcohol substrates are easy to carry out.

This benzodioxane reaction formation can be applied for the synthesis of biological active natural product with benzodioxane ring. Isoamericanol A[6] **9** and isoamericanin A[7] **10** are two benzodioxanes of natural products isolated from *phytocaccaceae* and *Juniperns chinesis*. Herein, we report a novel and short route for their synthesis.

As shown in **Scheme 1**, compound **6** is easily synthesized from caffeic aldehyde **4**. Compound **6** was coupled with compound **7** and catalyzed by palladium to obtain

compound **8**, then **9** and **10** are easily obtained by reduction and oxidation. The melting point and the spectra of the compound **9**, **10** accorded with isoamericanol A[6] and Isoamericanin A[7] respectively. The further research about the mechanism of the regioselectivity is going in our lab.

Reference and Notes

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6. Y. Fukuyama, T. Hasegawa, M. Toda, M. Kodama, H. Okazaki, *Chem. Pharm. Bull.*, **1992**, *40*(1), 252.
   9: white powder, m.p.: 155-157℃, ^{1}H-NMR(500MHz, DMSO-d_6, δ ppm) 6.96(d, 1H, *J*=2Hz, H-2′), 6.93(dd, 1H, *J*=2, 8Hz, H-6′), 6.87(d, 1H, *J*=8Hz, H-7′), 6.70(dd, 1H, *J*=8, 2Hz, H-6), 6.42(d, 1H, *J*=16Hz, H-7), 6.20(dt, 1H, *J*=16, 5Hz, H-8′), 4.81(d, 1H, *J*=8Hz, H-7), 4.07(t, 1H, *J*=12.3Hz, 5Hz, H-9′), 4.03(m, 1H, H-8), 3.51 and 3.32(dd, 2H, *J*=12.3, 5Hz, H-9). HRFABMS (*m/z*) 330.1143 (M^+ $C_{18}H_{18}O_6$) calcd. 330.1111, EI-MS (*m/z*)) 330, 166, 148, 123.
   All the spectra data are in good agreement with those of isoamericanol A in literature reported [6].
7. T. hasegawa, Y. Fukuyama, Y. Asakawa, *Chem. Lett*., **1987**, 329.
   10: yellow powder, m.p. 173-176℃; HRMS(*m/z*) 328.0931 (M^+ $C_{18}H_{16}O_6$) calcd. 328.0933, ^{1}H-NMR(400MHz, DMSO-d_6, δ ppm) 9.53(d, 1H, *J*=7.6Hz,-CHO),7.52(d, 1H, *J*=16Hz, H-7′), 6.70-7.30(m, 5H, Ar-H), 6.67(dd, 1H, *J*=16, 8Hz, H-8′), 4.85(d, 1H, *J*=8Hz, H-7), 4.14(m, 1H, H-8), 3.35 and 3.57(dd, 2H, *J*=12.3, 5Hz, H-9).
   All the spectra data are in good agreement with those of isoamericanin A in literature reported [7].

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