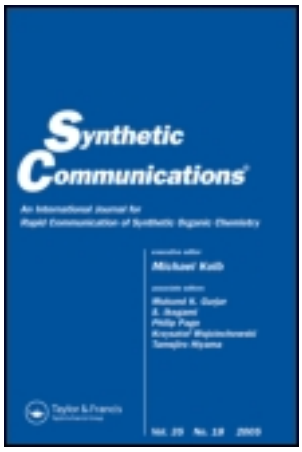

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One Step of Palladium Catalyzed Benzodioxane Ring C–O Bond Formation, Synthesis of Isoamericanol A and Isoamericanin A

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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 two natural products isoamericanol A and isoamericanin A.

Key Words: Benzodioxane; Isoamericanol A; Isoamericanin A; Palladium.

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INTRODUCTION

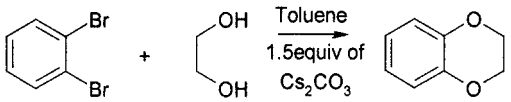
Aryl ethers and oxygen heterocycles are common structures in many pharmaceutically and agriculturally important compounds.[1,2] Traditional methods for the preparation of these compounds include the Williamson ether synthesis (for a review see Ref.[3]), direct nucleophilic substitution reactions (for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

Recently, Buchwald has reported to extend the scope and utility of the intramolecular C–O bond forming reaction.[2] From their work, we developed a convenient method to couple benzodioxane ring from *o*-dibromoaryl and dialcohol by one step.

We found in our lab that 1,2-ethanediol and *o*-dibromobenzene are difficult to be coupled to get benzodioxane at the presence of Cs_2CO_3 and catalyzed amount of $PdCl_2$ (yield $<10\%$). But once triphenylphosphane is added, the yield of benzodioxane will be improved to about 65%. Toluene is the best solution to the reaction, as show in Table 1. We are now giving further research about the mechanism of the reaction.

As shown in Table 2, different benzodioxane rings can be formed by using this method. Both aryl chlorides and bromides can be cyclized using this catalyst system. Primary as well as secondary alcohol substrates are efficiently cyclized.

Table 1. Yield of benzodioxane.



1 2 3

Entry	1 : 2	$PdCl_2$ (mol%)	Ph_3P (mol%)	T (°C), t (hr)	Solution	Yield (%) (**3**)
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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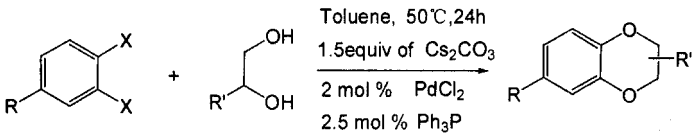
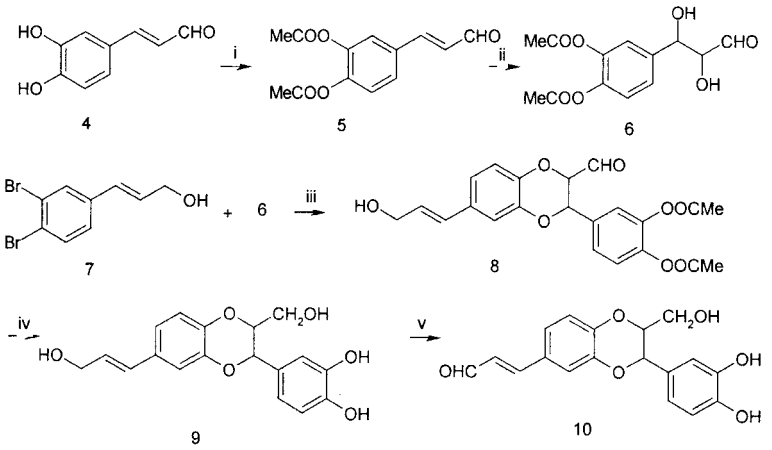
Table 2. Formation of benzodioxane ring.



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

Application of this method for the formation of benzodioxane natural products is important because those structures are widely found in nature and biologically active compound. Isoamericanol A[6] **9** and isoamericanin A[7] **10** are two benzodioxane natural products. They are reported to have CHAT activity. Herein, we report a novel and short route for the synthesis of isoamericanol A and isoamericanin A.

As shown in Sch. 1, compound **6** is easily synthesized from caffeic aldehyde **4** under the conditions reported. Under the above palladium catalyzed



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%.

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condition, compound **6** and compound **7** are coupled to obtain compound **8**. Then compound **9** and compound **10** are easily obtained by reduction and oxidation. From the melting point and the spectrum of the compounds **9** and **10**, isoamericanol A[8] and isoamericanin A,[8] we inferred compound **9** is isoamericanol A and compound **10** is isoamericanin A. We are now giving further research about the mechanism of the regioselectivity.

EXPERIMENTAL

Melting points were measured on a Kofler apparatus and were uncorrected. MS were performed on ZAB-HS spectrometer. ^{1}H-NMR spectra were recorded on a Bruker AM-500 and AM-400 instruments. Chemical shifts are referred to TMS on the "δ" scale. Standard flash chromatography were employed to purify the crude reaction mixture using 200–300 mesh silica gel under positive nitrogen pressure.

Compounds **5** and **6** were synthesized by the reported procedure.[8]

Compound 8. To a solution of 115 mg **7** and 110 mg **6** in 100 mL dry toluene, catalytic amount of $PdCl_2$ and Ph_3P were added. After stirred for 20 min at r.t., the solution was added to 192 mg Cs_2CO_3. At 50°C, the mixture stirred for 24 hr more. The mixture was filtered, evaporated, and purified by flash-chromatography (ethyl acetate : petroleum ether = 1 : 1) to obtain white powder 102 mg, 63% yield; m.p.: 127–129°C. ^{1}H-NMR (400 MHz, DMSO-d_6, ppm) δ 9.72 (d, 1H, 7.6 Hz, –CHO), 6.62. (d, 1H, 16 Hz, H-7′), 6.70–7.30 (m, 5H, Ar-H), 6.25 (dd, 1H, 16 Hz, 8 Hz, H-8′), 5.70 (d, 1H, 8 Hz, H-7), 5.44 (m, 1H, H-8), 4.20 (dd, 2H, 12.3 Hz, 5 Hz, H-9). HRFABMS (m/z) 412.3952 (M^+ $C_{22}H_{20}O_8$) requires 412.3949.

Isoamericanol A 9. Isoamericanol A were synthesized by the reported procedure.[8] Isoamericanol A: white powder, m.p.: 155–157°C, ^{1}H-NMR (500 MHz, DMSO-d_6, ppm) δ 6.96 (d, 1H, 2 Hz, H-2′), 6.93 (dd, 1H, 8 Hz, 2 Hz, H-6′), 6.87 (d, 1H, 8 Hz, H-7′), 6.70 (dd, 1H, 8 Hz, 2 Hz, H-6), 6.42 (d, 1H, 16 Hz, H-7), 6.20 (dt, 1H, 16 Hz, 5 Hz, H-8′), 4.81 (d, 1H, Hz), 4.07 (t, 1H, H-9′), 4.03 (m, 1H, H-8), 3.51 and 3.32 (dd, 2H, 12.3 Hz, 5 Hz, H-9). HRFABMS (m/z) 330.1143 (M^+ $C_{18}H_{18}O_6$) requires 330.1111, EIMS (m/z) 330, 166, 148, 123.

All the spectra data are in good agreement with those of literature report.[8]

Isoamericanin A 10. Isoamericanin A were synthesized by the reported procedure. Isoamericanin A: yellow powder, m.p.: 173–176°C; HRMS (m/z) 328.0931 (M^+ $C_{18}H_{16}O_6$) requires 328.0933, ^{1}H-NMR (400 MHz, DMSO-d_6, ppm) δ 9.53 (d, 1H, 7.6 Hz, –CHO), 7.52 (d, 1H, 16 Hz, H-7′), 6.70–7.30 (m, 5H, Ar-H), 6.67 (dd, 1H, 16 Hz, 8 Hz, H-8′), 4.85 (d, 1H, 8 Hz, H-7), 4.14 (m, 1H, H-8), 3.35 and 3.57 (dd, 2H, 12.3 Hz, 5 Hz, H-9).

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All the spectra data are in good agreement with those of literature report.[8]

REFERENCES

1. Gu, W.X.; Jing, X.B.; Pan, X.F.; Chan, A.C.S.; Yang, T.K. First asymmetric synthesis of chiral 1,4-benzodioxane lignans. Tetrahedron Lett. **2000**, *41*, 6079.
2. Kuwabe, S.; Torraca, K.E.; Buchwald, S.L. Palladium-catalyzed intramolecular C—O bond formation. J. Am. Chem. Soc. **2001**, *123*, 12202.
3. Feuer, H.; Hooz, J. Williamson ether synthesis. In *Chemistry of the Ether Linkage*; Patai, S., Ed.; Wiley Interscience: New York, 1967; chapter III, 445.
4. Paradisi, C. Nucleophilic substitution reactions. In *Comprehensive Organic Synthesis*; Trost, B.M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, chapter II, 423.
5. Lindley, J. Copper assisted nucleophilic substitution of aryl halogen. Tetrahedron **1984**, *40*, 1433.
6. Fukuyama, Y.; Hasegawa, T.; Toda, M.; Kodama, M.; Okazaki, H. Structures of americanol A and isoamericanol A having a neurotrophic property from the seeds of *Phytolacca americana*. Chem. Pharm. Bull. **1992**, *40* (1), 252.
7. Hasegawa, T.; Fukuyama, Y.; Asakawa, Y. Neolignans from the leaves of *Phytolacca americana*. Chem. Lett. **1987**, *182* (2), 329.
8. She, X.; Gu, W.; Wu, T.; Pan, X. A convenient stereoselective synthesis of isoamericanol and isoamericanin A. Synthetic Commun. **1999**, *29* (15), 2625–2628.

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