A totally stereoselective synthesis of (*Z*)-2-arylidene-1,4-benzodioxanes using palladium–copper catalysis

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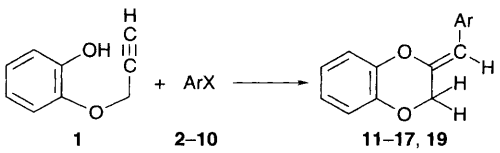
A convenient and general synthesis of (*Z*)-2-Arylidene-1,4-benzodioxanes from a mono-prop-2-ynylated catechol and aromatic halides by palladium catalysis is described.

Various 1,4-benzodioxanes (*e.g.* piperoxan, pentamoxane, idazoxan, flesinoxan *etc.*) are α-adrenoreceptor antagonists.[1] Some of these have been used as antihypertensive agents and antidepressants. Others exhibit antihyperglycemic properties.[2] Recently, a group of 1,4-benzodioxanes has been developed as inhibitors of 5-lipoxygenase which is involved in the oxygenation of arachidonic acid to the leukotrienes. Thus these compounds could be useful for the treatment of inflammatory diseases like asthma and arthritis.[3] The occurrence of the 1,4-benzodioxane structure in various naturally occurring compounds has also been reported.[4] Although a few multi-step procedures[5] are available for the synthesis of the 1,4-benzodioxane structure, a palladium-catalysed annulation strategy which has been so successfully utilised for the synthesis of carbocyclic[6] and heterocyclic compounds[7] has not yet been used to synthesise the 1,4-benzodioxane structure. In continuation of our recent studies[8] on the palladium-catalysed reactions of acetylenic substrates leading to heterocyclic compounds of biological significance, we became interested in developing a general synthesis of the 1,4-benzodioxane structure using palladium-copper catalysis. Here we report that when mono-prop-2-ynylated catechol **1** was treated with an aryl halide, **2–10** in triethylamine in the presence of bis(triphenylphosphine)palladium(II)chloride and cuprous iodide, (*Z*)-2-arylidene-1,4-benzodioxanes (**11–17**, **19**) were obtained in good yields, Scheme 1 and Table 1.

Triethylamine was used both as a solvent and a base. Bis(triphenylphosphine)palladium(II)chloride was found to be the catalyst of choice. However, cuprous iodide was found to be an essential co-catalyst. Reactions carried either with copper(I)iodide or Pd-catalyst alone led to very poor yields of product mixtures.

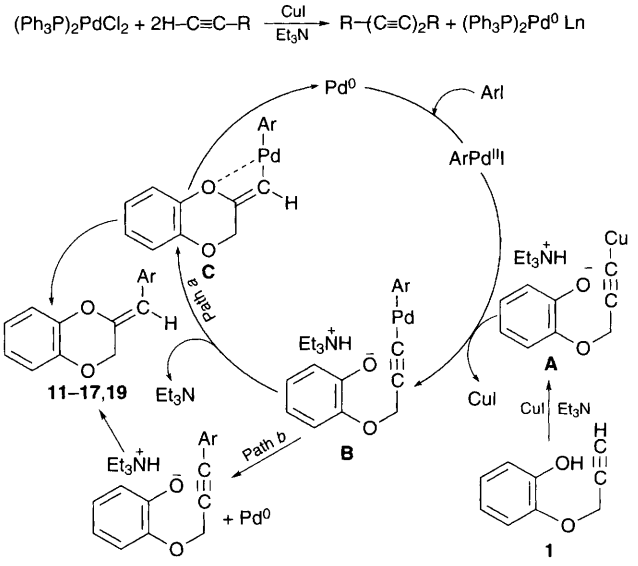
Optimum yields were obtained under condition (i) where heating at 100 °C for 16 h was necessary. Heating at a lower temperature or reactions at room temperature led to a mixture of (*Z*)-2-arylidene-1,4-benzodioxane and an acyclic condensation product (Table 1, entries 1 and 2). The acyclic product might be an intermediate in the formation of the benzodioxane derivatives. Entries 3, 4, 5 and 6 showed the compatability of the reaction with different functional groups (chloro, nitro, ester and vinyl).

This useful reaction for the building of the 1,4-benzodioxane structures was equally adaptable to both aromatic and heteroaromatic halides. The yields were found to be good except in



1 **2–10** **11–17, 19**

Scheme 1



Scheme 2

case of 5-iodo-2,4-dimethoxypyrimidine (entry 11). Modest yields in general could be attributable to the possible breakdown of the products during chromatographic purification. Electron withdrawing substituents led to some improvement in yields (entries 3 *vs.* 6). Use of a diiodo compound (entry 10) led to the bisbenzodioxanylated product **18**. The reactions were found to be completely regio- and stereo-selective and only the *exo*-(*Z*)-isomers were obtained. Assignment of the (*Z*)-configuration rests on the $^3J_{CH}$ values of the vinylic proton and the methylenic carbon.[9,†]

Mechanistically, the formation of (*Z*)-2-arylidene-1,4-benzodioxanes could be explained as shown in Scheme 2. The alkynyl palladium species **B** could undergo cyclisation to the cyclic vinyl palladium species **C** which then gives rise to the arylidene 1,4-benzodioxanes. Coordination between oxygen and palladium in **C** will ensure (*Z*)-stereochemistry of the products.[10] Alternatively, **B** → **D** transformation takes place through path **b**, the latter on stereoselective cyclisation leading to **11–19**.

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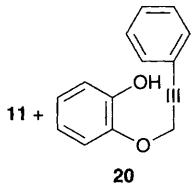
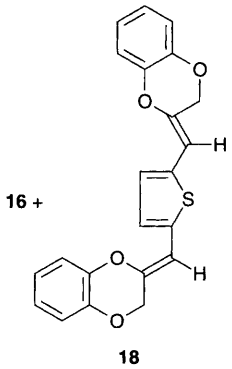
Footnote

† The $^3J_{CH}$ values of more than 7 or less than 5 Hz were attributed to (*E*)- or (*Z*)-isomers respectively. In the case of compounds **11**, **13**, **14** and **17**, $^3J_{CH}$ = 4.83, 4.95, 4.49 and 4.41 Hz respectively.

Table 1 Synthesis of (*Z*)-2-arylidene-1,4-benzodioxanes[a]

Entry	ArX	Conditions[b]	Product[c]	Yield[d] (%)
1	PhI **2**	ii	11+  **11** + **20**	56 (1:7)
2	PhI	iii	**11** + 20[e]	46
3	PhI	i	**11**	44
4	*m*-ClC_6H_4 I **3**	i	**12**	58
5	*o*-MeO_2-CC_6H_4I **4**	i	**13**	48
6	*o*-$O_2NC_6H_4$I **5**	i	**14**	56
7	PhCH = CH (*Z*) Br **6**	i	**15**	40
8	2-thienyl I **7**	i	**16**	51
9	5-formyl-2-thienyl Br **8**	i	**17**	51
10	5-iodo-2-thienyl I **9**	i	16 +  **18**	50 (1:4)
11	2,4-dimethoxy-5-pyrimidinyl I **10**	120 °C, 16 h	**19**	27

[a] Typical rection, synthesis of **17**; a mixture of 5-bromothiophene-2-carboxaldehyde **8** (1.5 mmol), $(PPh_3)_2PdCl_2$ (0.05 mmol) and CuI (0.11 mmol) was stirred in triethylamine for 20 min. under dry argon. The acetylenic compound **1** (2.55 mmol) was then added very slowly and the mixture was further stirred at room temperature for 20 h and then heated at 100 °C for 16 h. After usual work-up and purification by chromatography on neutral alumina, with 25% petroleum ether (bp 60–80 °C)– chloroform as eluent, **17** was obtained in 51% yield. [b] 3.5 mol% $(PPh_3)_2PdCl_2$ and 7 mol% $Cu^{I}I$ (based on aromatic halides) were used. Conditions (i): stirred at room temperature (28–30 °C) for 20 h and then heated at 100 °C for 16 h; (ii): room temperature (28–30 °C) for 48 h; (iii): stirred at room temperature for 20 h and then heated at 65 °C for 16 h. [c] The products had satisfactory spectroscopic and analytical data. Compound **18**, *m/z* = 376 (M^+, 100%). For **17**, mp 64–66 °C; δ_H (200 MHz, $CDCl_3$), 4.60 (2 H, s, OCH_2), 5.92 (1 H, s, =CH), 6.92–7.03 (3 H, m, ArH), 7.11 (1 H, d, ArH), 7.18–7.25 (1 H, m, ArH), 7.62 (1 H, d, ArH), 9.86 (1 H, s, CHO); ^{13}C NMR (50 MHz, $CDCl_3$) 64.81 (OCH_2, $^1J_{CH}$ 150.22, $^3J_{CH}$ 4.41 Hz), 100.66 (C=CH, $^1J_{CH}$ 163.5 Hz, $^3J_{CH}$ unresolved), 116.89–146.39 (aromatics), 136.14 (*C*=CH, $^2J_{CH}$ unressolved), 182.93 (*C*HO) [d] The yields (based on the aromatic halides) are isolated yields of chromatographically pure materials. [e] The acyclic compound **20** was converted to (*Z*)-2-benzylidene-1,4-benzodioxane **11** in Et_3N at 100 °C for 16 h, proving compound **20** to be an intermediate towards the synthesis of (*Z*)-2-arylidene-1,4-benzodioxanes. The presence of $Cu^{I}I$ alone or $(PPh_3)_2PdCl_2$ + $Cu^{I}I$ in Et_3N did not make much difference in the yields of the cyclisation process. Cyclisation according to the mechanism suggested by Luo *et al.*[7] will give rise to the (*E*)-product. The addition of ArPdX to the triple bond seems less probable due to the requirement of $Cu^{I}I$ as co-catalyst.

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