A CONVENIENT SYNTHESIS OF PTEROCARPANS

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Abstract: The first synthesis of pterocarpan (±)-**3** has been achieved in 51 % yield by a new variation of the Heck-oxyarylation of *2H*-chromene (**1**) with 2-iodophenol (**2a**) using the [$Pd(OAc)_2$ / Ph_3P / Ag_2CO_3-$CaCO_3$] catalyst system.

Introduction

Pterocarpans, possessing a 6a,11a-dihydro-6*H*-benzofuro[3,2-c][1] benzopyran skeleton, constitute the second largest group of natural isoflavanoids (1,2). Many of them are phytoalexins, which are produced in plants during infection by fungi, bacteria or viruses, and subsequently act as protective agent for plants (3). Some pterocarpans have antifungal (4), antitubercular and oestrogenic activity (5), and several of them have been reported to inhibit the HIV-1 reverse transcriptase and the cytophatic effect of HIV-1 in cell cultures (6,7). Furthermore, Nakanishi and co-workers (8,9) have demonstrated that two representatives of these natural products are the active component of a Brazilian folk medicine used against snake venoms.

Among the variety of synthetic routes to pterocarpans, the most common approach involves a cumbersome process of reduction and cyclization of the appropriate 2'-hydroxyisoflavones (10-12). In addition, 1,3-Michael-Claisen annulation forming an aromatic ring, (13,14), aldol-condensation between phenylacetates and benzaldehydes (15,16), 1,4-benzoquinone cycloaddition (17), and Heck-oxyarylation (18) of *2H*-chromenes have been utilized to obtain pterocarpans. Although the latter method is a very efficient and widely used approach for the synthesis of naturally occurring pterocarpans (18-23), it still suffers from limitations, such as the preparation of toxic 2-chloromercuriphenol derivatives upon mercuration of the corresponding phenols, and the need of a stoichiometric quantity of the expensive palladium chloride.

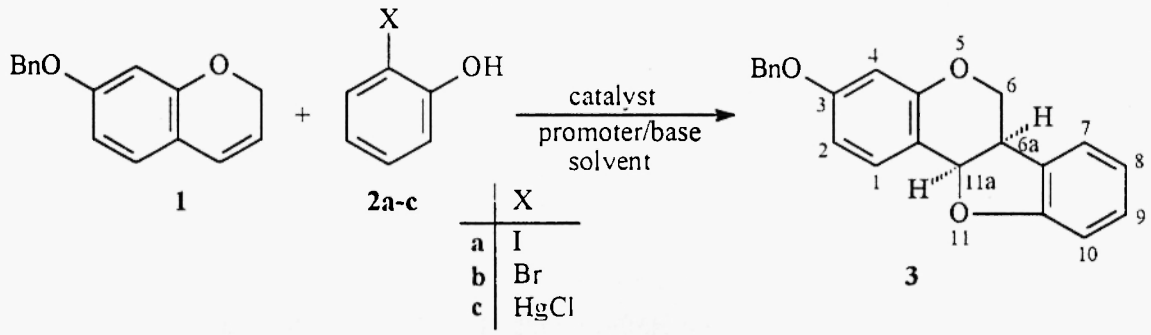
In order to avoid these limitations, we have set our sights on the extension of this method for

the most available 2-iodo, or bromophenols prepared by simple iodination or bromination of the corresponding phenols (24-26).

Results and Discussion

The Heck-reaction of 7-benzyloxy-*2H*-chromene (**1**) with 2-iodophenol (**2a**), resulting in *rac.*-3-benzyloxypterocarpan (**3**) (Scheme 1.) has been systematically studied in the presence of various catalyst systems formed by palladium chloride or acetate (with or without tertiary phosphine) in combination with an inorganic base and different solvents. The results are given in Table 1.

Scheme 1.



In order to compare the efficacy of our results with those of the traditional Heck-oxyarylation process, *rac.*-**3** was also prepared from **1** and **2c** under the conditions described by Horino and Inoue (18) (entry 1). Interestingly, no transformation of **2a** could be detected under these conditions (entry 2). If silver carbonate as a base was also present, the reaction resulted in *rac.*-**3** almost in the same yield (entry 3), as found under the conditions given in entry 1. Although the decrease of the amount of the palladium catalyst to 10 mol % has a significant influence on the reaction rate, its turnover number (TON) has valuably increased (entry 4). Comparision of entries 4 and 5 clearly reveals the influence of the phosphine ligand. Most surprisingly, any transformation of **2b** could not be detected under these conditions (entry 6), but a remarkable influence of the presence of anhydrous calcium carbonate has also been recognized (entry 7). In order to study the role of the phosphine ligand, oxyarylation was performed with different bisphosphine derivatives as well (entry 8-13). It is remarkable that no transformation of **2a** could be detected in the presence of bis(diphenylphosphino)methane, (dppm) but its coupling with **1** in the presence of bis(diphenylphosphine)ethane (dppe) resulted in *rac.*-**3** in the lowest yield (49 %) described in this study. Elongation of the carbon chain with a further methylene group only slightly influences the TON of the transformation (entry 11), but with two ones it resulted in a drastic decrease (entry 12).

Table 1. Effects of the promoter, base and solvent on the palladium-catalysed oxyarylation of **1**.

Entry	X	Catalyst (mol % Pd)	Promoter[a] (mol %)	Base (mol %)	Solvent[b]	Reaction time (h)	Yield[c] %	TON[d]
1	HgCl	$PdCl_2$ (100)	LiCl (200)	–	A	14	36	0.36
2	I	$PdCl_2$ (100)	LiCl (200)	–	A	24	–	–
3	I	$PdCl_2$ (100)	LiCl (200)	Ag_2CO_3 (300)	A	8	34	0.33
4	I	$Pd(OAc)_2$ (10)	LiCl (20)	Ag_2CO_3 (300)	A	36	27	4.68
5	I	$Pd(OAc)_2$ (10)	Ph_3P (20)	Ag_2CO_3 (300)	A	14	42	4.18
6	Br	$Pd(OAc)_2$ (10)	Ph_3P (20)	Ag_2CO_3 (300)	A	24	–	–
7	I	$Pd(OAc)_2$ (10)	Ph_3P (20)	Ag_2CO_3 (300) $CaCO_3$ (600)	A	48	51	5.07
8	I	$Pd(OAc)_2$ (10)	dppm (10)	Ag_2CO_3 (300)	A	24	–	–
9	I	$Pd(OAc)_2$ (10)	dppe (10)	Ag_2CO_3 (300)	A	22	49	4.87
10	I	$Pd(OAc)_2$ (10)	dppe (10)	Ag_2CO_3 (300)	A	26	48	4.78
11	I	$Pd(OAc)_2$ (10)	dppp (10)	Ag_2CO_3 (300)	A	20	44	4.38
12	I	$Pd(OAc)_2$ (10)	dppb (10)	Ag_2CO_3 (300)	A	24	16	1.59
13	I	$Pd(OAc)_2$ (10)	dppb (10)	Ag_2CO_3 (300)	B	24	24	2.39
14	I	$Pd(Ph_3P)_2Cl_2$ (10)	–	Ag_2CO_3 (300) $CaCO_3$ (600)	A	26	33	3.28

a) bis(diphenylphosphine)methane (dppm), bis(diphenylphosphine)ethane (dppe), bis(diphenylphosphine)propane (dppp), bis(diphenylphosphine)butane (dppb); b) acetone (A), THF (B); c) isolated yield; d) mmol product/mmol Pd

This effect could be somewhat moderated by the exchange of the solvent (entry 13). It is noteworthy that the presence of calcium carbonate does not influence the TON of the reaction when bis(diphenlyphosphine)ehtane was used as the promoter (entry 10, and see also entries 6 and 7). Finally, **2a** was also subjected to Heck-oxyarylation with **1** using dichlorobis-(triphenylphosphine)palladium (II), as a highly stable form of palladium (II), but *rac.*-**3** could be obtained

only in a moderate yield (entry 14).

In conclusion, we have developed an efficient procedure for the synthesis of pterocarpans, and this methodology provides a good option to extend the development of an asymmetric variant, by using chiral bisphosphine-palladium complexes. Work on this project is now in progress in our laboratory.

Experimental

7-Benzyloxy-*2H*-chromene (**1**) and *o*-chloromercuriphenol (**2c**) were prepared according to known procedures (19,27). Melting points were determined in open capillary tubes and are uncorrected. 200-MHz ^{1}H-NMR spectra were recorded with a Bruker WP 200 SY instrument with TMS as internal standard. Precoated silica gel plates (Kieselgel 60 F 254, 0.25 mm Merck) were applied for analytical and preparative TLC. All reagents and organic compounds used in this study were purchased from Sigma-Aldrich.

(±)-3-Benzyloxypterocarpan [(±)-3]

a) Palladium chloride (114 mg, 0.62 mmol) and lithium chloride (112 mg, 1.28 mmol) were strirred in dry acetone (5 ml) for 15 min, 7-benzyloxy-*2H*-chromene (**1**) (145 mg, 0.62 mmol) was added, stirred again for 15 min, followed by dilution of the mixture with dry acetone (15 ml) and addition of *o*-chloromercuriphenol (**2c**) (203 mg, 0.62 mmol). Stirring was continued for 14 hours and then the reaction mixture was poured into brine (50 ml), extracted with benzene, dried, and concentrated *in vacuo* to give a viscous crude product (230 mg), whose purification by means of preparative TLC (dichloromethane:n-hexane = 1:1) resulted in (±)-**3** (73 mg, 36 %) as colourless prisms, m.p. 146-148 °C (MeOH).

b) To a stirred solution of **1** (100 mg, 0.42 mmol) in dry acetone or THF (6 ml), 2-iodophenol (85 mg, 0.42 mmol), silver carbonate (350 mg, 1.26 mmol) and the promoter were added as given in Table 1. at room temperature, and then the reaction mixture was refluxed (see Table 1). After filtration, the solution was evaporated, and *rac.*-**3** was isolated as given above.

^{1}H-NMR ($CDCl_3$): δ = 3.61-3.66 (m, 1H, C6-H_{ax}), 3.70 (t, J=10.5 Hz, 1H, C6a-H), 4.31 (dd, J=4.5 Hz and 10 Hz, 1H, C6-H_{eq}), 5.08 (s, 2H, OCH_2Ph), 5.52 (d, H=6.5 Hz, 1H, C11a-H), 6.58 (d, J=2.5 Hz, 1H, C4-H), 6.74 (dd, J=2.5 Hz and 8 Hz, 1H, C2-H), 6.84-6.98 (m, 2H, C7- and C10-H), 7.17-7.50 (m, 8H, C1- ,C8-, C9-H and Ph-H).

Anal. Cald. for $C_{22}H_{18}O_3$ (330.38): C 79.98, H 5.49; found C 79.78, H 5.50.

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