Study on the reaction mechanism of Heck-oxyarylation of 2H-chromenes

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Dedicated to Professor Henk van der Plas on his 80th birthday

Abstract
The Heck-oxyarylation reaction of deuterium labeled 2H-chromenes (12, 15) has been studied whose synthesis was achieved in four steps starting from the readily available 7-benzyloxychromane (9). Since the deuterium label was not affected in the course of the oxyarylation, the formation of the neutral achiral intermediate 7 could be ruled out as a possible reaction pathway and a reason for the lack of enantioselectivity in asymmetric Heck-oxyarylations. This also allowed the simple synthesis of 6a- and 11a-deutero-3-benzyloxypterocarpanes (13a,b).

Keywords: Pterocarpan, Heck-oxyarylation, mechanism

Introduction
Pterocarpans are naturally occurring plant products carrying a cis-fused benzofuranyl-benzopyran ring system. Many of them are phytoalexins, which are produced in plants during infections by fungi, bacteria or viruses and subsequently act as protective agents for plants1. While some pterocarpans have antifungal2 and oestrogenic activity3 others have been reported to inhibit HIV-1 in cell cultures4 and to possess significant snake or spider inhibition venom activity5.

Among the wide variety of synthetic routes to pterocarpans,6–14 one of the most commonly used approaches14 involves the Heck-oxyarylation of 2H-chromenes (1) with 2-chloromercuriophenols (2a) using equimolar amount of Li2[PdCl4] as catalyst (Scheme 1).
Recently, we have described a convenient modification of this Heck-oxyarylation step by the replacement of the toxic chloromercurophenol derivatives (2a) with 2-iodophenols (2b), which allowed to considerably decrease the amount of the expensive palladium (II) salt (from 100 mol% to 10 mol%) in the presence of triphenylphosphine and silver carbonate in acetone\textsuperscript{15} or in ionic liquids such as 1-butyl-3-methylimidazolium hexafluorophosphate [[bmim] [PF\textsubscript{6}]]\textsuperscript{16}. We have also published\textsuperscript{17} that the extension of this reaction to a practical asymmetric Heck-oxyarylation affording enantiomerically enriched pterocarpans using different chiral bidentate phosphins or (+)-\textalpha-pinene as a ligand as well as a chiral ionic liquid could not be accomplished.

**Figure 1.** Proposed sequence of Pd-catalyzed oxyarylation.
Although intramolecular Heck-oxyarylation is widely used in the synthesis of racemic pterocarpans,¹⁴,¹⁸-²² in contrast to the conventional Heck reaction,²³-²⁵ its mechanism is not fully understood.

It presumably also proceeds via the generation of active Pd(0), oxidative addition of aryl iodide (2b) or chloromercuriophenol (2a) to Pd(0), followed by regioselective syn-addition of 4 to 2H-chromenes (1) and palladium displacement by phenolic oxygen whose details are not known (Figure 1).

On the basis of data published in the literature,²⁶ the displacement step may take place via (i) cationic (5→6) (ii) neutral (5→7) or a palladium containing cyclic intermediate (5→8) as shown in Figure 2.

![Figure 2](image)

**Figure 2.** Possible pathways of the displacement step.

Since no or very moderate (ee%<10) asymmetric induction could be observed by us¹⁷ in the presence of chiral bidentate phosphine ligands, such as CHIRAPHOS, NORPHOS, TRIPHOS and R-(+)-BINAP, it could be assumed that this reaction takes place through parallel pathways and the main pathway involves an achiral intermediate 7, where the chirality introduced by chiral ligands of Pd(0) is lost.

In order to obtain unambiguous evidence about this assumption, 2H-chromenes (12,15) labeled with deuterium at C-3 or C-4 have been synthesized and their transformation to the corresponding pterocarpans were studied.

**Results and Discussion**

According to the proposed mechanism shown in Figure 1 and 2, it seemed reasonable to prepare compounds in which a D atom was introduced at C-3 or at C-4 of the 2H-chromene skeleton (1).
Scheme 2. (i) LAH/THF, Et₂O, -60 °C, (ii) CDCl₃/TBD, r.t, (iii) LAH/Et₂O, r.t, (iv) acetone, 10% HCl, 56 °C, (v) Pd(C₆H₅CN)₂Cl₂, Ag₂CO₃, Ph₃P/THP, 65 °C or [bmim] [PF₆], 100 °C or Li₂[PdCl₄] in acetone, r. t. Deuterium abundance is indicated in brackets as determined by ¹H-NMR.

For this purpose 7-benzyloxychromone (9) was reduced by lithium aluminium hydride in tetrahydrofuran at – 60 °C resulting in 7-benzyloxychromanone (10a)¹⁸ in 70% yield, whose hydrogens at C-3 could be exchanged (10a→10b) using the method published by Mioskowski et al²⁷ (Scheme 2). Since the ¹H NMR monitoring of 10a in CDCl₃ at room temperature has clearly indicated that in the presence 10 mol% triazabicyclo [4.4.0] dec-5-ene (TBD) the deuterium incorporation has reached 99% in 12h, then the target molecule (10b) could be simply isolated in 88% yield. Subsequently, 10b was reduced by lithium aluminium hydride in ether at room temperature resulting in the corresponding chromane-4-ol (11), whose dehydratation was performed by some drops of diluted hydrochloric acid in acetone at 56 °C affording the C-3 deuterium labeled 2H-chromene 12 in an overall yield 46%. The deuterium content of 12 has been determined by ¹H NMR as 75%. The Heck-oxyarylation of 12 was performed with 2a or 2b.
under the standard conditions [in case of 2a: PdCl2/LiCl, acetone, r.t.; in case of 2b: Pd(C6H4CN)2Cl2, Ag2CO3, Ph3P, THF, at 65 °C or [bmim] [PF6], at 100 °C] to result in 3-benzyloxypterocarpan (13a) in 30-40% yield whose 1H NMR spectrum has clearly indicated the presence of the C-6a deuterium with 75% abundance. Since the deuterium incorporation of the chromene ring did not change in the course of the oxyarylation, contrast to our earlier assumption, the formation of the neutral achiral intermediate 7 must have been ruled out as a possible reaction pathway. It is also noteworthy that the oxyarylation of C-4 labeled 15 possessing 100% deuterium incorporation with 2a or 2b (R’=H) took place in a similar manner to give 13b with unchanged deuterium incorporation. The 1H NMR spectra of 13a and 13b has also been found identical with those of compounds prepared by us in different synthetic route.28 Since the absence of an asymmetric Heck-oxyarylation can not be attributed to the formation of achiral intermediate 7, further efforts are required to find suitable chiral inductor and to optimize circumstances. It is also noteworthy that our efforts to increase the yield of the oxyarylation carried out in DMF or NMP in the presence of a palladacycle, such as trans-di(μ-acetato)-bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II) prepared according to the literature29 were unsuccessful. Surprisingly, no transformation could be observed in these solvents, although palladacycloles have been found highly efficient catalysts for Heck vinlylation of aryl halides under these conditions.30 Moreover the yield of the oxyarylation described in general procedure b of the experimental section could not be improved by microwave irradiation either. Work on this project is in progress in our laboratory.

Experimental Section

General Procedures. All reagents and organic compounds were purchased from Sigma Aldrich. 7-Benzylxoychromane (9), trans-di(μ-acetato)-bis[o-(di-o-tolylphosphino)benzyl]- dipalladium (II) and 2-chloromercuriophenol (2a, R’=H) were prepared according to the known procedures.29,31,32

7-Benzylxoychromanone (10a)
To a stirred solution of 9 (2 g, 7.9 mmol) in 40 ml dry THF and Et2O (1:1) at –60 °C a solution of LiAlH4 (600 mg, 15.8 mmol) in dry THF (15 ml) was added under N2 atmosphere. After 3 hours the reaction was quenched by addition of saturated aqueous NH4Cl (20 ml) and extracted with Et2O (3x20 ml). The organic layer was washed with brine, water, dried (Na2SO4), filtered and concentrated. The resulting product was purified by column chromatography on silica gel resulting in 10a of m.p.101-103 °C (1.41 g, 70%) as a colorless solid. Lit.33 m.p 102-103 °C. 1H-NMR: δ 2.69 (t, J = 6.6 Hz, 2H, 3-H), 4.44 (t, J = 6.6 Hz, 2H, 2-H), 5.03 (s, 2H, OCH2Ph), 6.44 (d, J = 2.4 Hz, 1H, 8-H), 6.61 (dd, J = 8.8, 2.4 Hz, 1H, 6-H), 7.25-7.40 (m, 5H, Ph), 7.80 (d, J = 8.8 Hz, 1H, 5-H).
7-Benzylxyo-3,3-dideutero-chromanone (10b)
To the stirred solution of TBD (33 mg, 0.24 mmol) in deuterio chloroform (8 ml) 10a (388 mg, 1.53 mmol) was added at room temperature. After 12 h the reaction mixture was quenched with 1N HCl (2 ml). The organic layer was washed with water (2x15 ml), brine (15 ml), dried (Na₂SO₄) and filtered. Evaporation of the solvent afforded 10b, whose deuterium incorporation has been found as 99% by 1H-NMR. 1H-NMR: δ 4.51 (s, 2H, 2-H), 5.09 (s, 2H, OCH₂Ph), 6.49 (d, J = 2.4 Hz, 1H, 6-H), 6.66 (dd, J = 8.8, 2.4 Hz, 1H, 6-H), 7.25-7.40 (m, 5H, Ph). 7.85 (d, J = 8.8 Hz, 1H, 5-H).

7-Benzylxyo-4-deutero-2H-chromene (15)
To stirred solution of 10a (132 mg, 0.52 mmol) in dry Et₂O (10 ml) LiAlD₄ (28 mg, 0.66 mmol) was added at 0 °C. After 30 min. the reaction mixture was quenched with sat. aqueous NH₄Cl (20 ml) and the organic layer was separated and the water phase was extracted with Et₂O (3x10 ml). The combined organic phase was washed with brine and dried (Na₂SO₄), whose evaporation resulted in 14 as a colorless solid (132 mg). It was dissolved in acetone (5 ml) and heated in the presence of one drop 10% HCl for 3 hours. After neutralization with Et₃N, the reaction mixture was diluted with water and extracted with dichloromethane (3x5 ml). The organic layer was washed with brine and dried (Na₂SO₄). Evaporation of the solvent gave an oil (70 mg), which was purified by preparative TLC (n-hexane:ethyl acetate = 3:1) to give 15 of m.p. 59-60 °C (55 mg, 44%), as a colorless solid incorporation has been determination by 1H-NMR to be 99%. 1H-NMR: δ 4.77 (d, J = 3.2 Hz, 2H, 2-H), 5.01 (s, 2H, OCH₂Ph), 5.61 (t, J = 3.2 Hz, 1H, 3-H), 6.44 (d, J = 2.2 Hz, 1H, 8-H), 6.48 (dd, J = 8.2, 2.2 Hz, 1H, 6-H), 6.86 (d, J = 8.2 Hz, 1H, 5-H), 7.25-7.40 (m, 5H, Ph).

7-Benzylxyo-3-deutero-2H-chromene (12)
Starting from 10b (170 mg, 0.66 mmol) 12 (73 mg, 46%) was obtained by a similar procedure described for 15. On the basis of its 1H-NMR the deuterium incorporation is 75%.
1H-NMR: δ 4.78 (d, J = 1.8 Hz, 2H, 2-H), 5.02 (s, 2H, OCH₂Ph), 6.30-6.40 (m, 1H, 4-H), 6.44 (d, J = 2.4 Hz, 1H, 8-H), 6.49 (dd, J = 8.2, 2.4 Hz, 1H, 6-H), 6.86 (d, J = 8.2 Hz, 1H, 5-H), 7.30-7.45 (m, 5H, Ph).

General procedures for the Heck-oxyarylation reaction
a) Palladium chloride (89 mg, 0.48 mmol) and lithium chloride (45 mg, 1.06 mmol) were stirred in dry acetone (5 ml) for 15 min, 7-benzyloxy-2H-chromene (12 or 15) (120 mg, 0.50 mmol) was added, stirred further for 15 min, followed by dilution of the mixture with dry acetone (15 ml) and addition of o-chloromercuriophenol (2a) (181 mg, 0.55 mmol). Stirring was continued for 14 hours and then the reaction mixture was poured on brine (50 ml), extracted with dichloromethane, dried, and concentrated in vacuo to give a viscous crude product (180 mg), whose purification by column chromatography on silica gel (n-hexane:ethyl acetate = 7:1) resulted in (±)-13a or 13b respectively (60-66 mg, 36-40%) as colorless prisms, m.p. 146-148 °C (MeOH).
b) To a stirred solution of 12 or 15 (100 mg, 0.42 mmol) in dry acetone or THF (6 ml), 2-iodophenol (93 mg, 0.42 mmol), silver carbonate (350 mg, 1.26 mmol), PPh₃ as ligand (220 mg, 0.84 mmol) and Pd(C₆H₅CN)₂Cl₂ palladium catalyst (16 mg, 0.042 mmol) were added at room temperature, and then the reaction mixture was stirred at 65 °C. After filtration, the solution was evaporated, and 13a or 13b respectively (40-45%) was isolated as given above.

c) 4.2 x 10⁻³ mmol Pd(II) catalyst and 8.4 x 10⁻³ mmol PPh₃ were stirred in [bmim][PF₆] (1 g) at 80 °C for 5 min, respectively. Then 100 mg (0.42 mmol) 12 or 15, 93 mg (0.42 mmol) 2b and Ag₂CO₃ (348 mg, 1.26 mmol) were added. Stirring was continued at 100 °C for 5 hours and then the reaction mixture was cooled, extracted with toluene and concentrated in vacuo. The crude product was purified by preparative TLC (dichloromethane:n-hexane=1:2) to give rac-13a or 13b respectively (34-36 mg, 36-38%).

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