Efficient Heterogeneously Palladium-Catalysed Synthesis of Stilbenes and Bibenzyls

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Abstract: An alternative heterogeneously palladium catalysed procedure for the synthesis of functional stilbenes and bibenzyls is reported. Starting from aryl bromides and using simple commercially available Pd/C catalyst at a low catalytic rate (1 mol%), stilbenes are obtained with 30-100% GC-yields and bibenzyls are produced in a one-pot *fashion* with 27-100% GC-yields. The procedure showed, however, some limitations when applied to strongly deactivated aryl bromides that could be in some extent overcome by using corresponding iodo derivatives.

Keywords: Stilbene synthesis, bibenzyl synthesis, one-pot synthesis, heterogeneous palladium catalyst.

INTRODUCTION

Stilbenes and bibenzyls are important classes of compounds that found applications in agrochemical and pharmaceutical industries. For example stilbenes derivatives like Resveratrol, Pterostilbene or other Combretastatines A4 and analogues are recognized to have beneficial health effects such as cancer-preventive, protection against coronary heart disease, neuroprotective, anti-aging and anti-inflammatory [1, 2]. Besides bibenzyls like aminoalkoxy-bibenzyls found useful applications as inhibitors of platelet aggregation or as serotonin antagonist [3, 4]. Other applications include liquid crystals for non-linear optic, polymer materials and lubricants. Additionally, stilbenes and bibenzyls are also known as substructure of several macrocycles possessing interesting biological activity like the Marchantins and Riccardins [5-8].

All of these bioactive molecules (and substructures) are naturally available through extraction from plants and fruits. However, for large availability in target compounds these methods are not suitable. On the other hand some chemical total syntheses, mainly based on Wittig and Ullmann protocols, have been reported generally for the most popular one like the Resveratrol [9-12]. However, these examples remain limited and methodologies are today not convenient as they use stoichiometric amount of reagents generating large quantities of wastes (i.e. salts mainly). Therefore, eco-friendly methods to prepare these structures are still required that can be achieved using catalytic approaches.

We previously reported a catalytic procedure for the one-pot synthesis of bibenzyl *via* the intermediate stilbene derivatives [13]. Our strategy was based on the well documented Heck C-C coupling reaction using commercially available Pd/C heterogeneous catalyst (Scheme **1**) [13, 14]; a procedure recently applied to the preparation of fragrances [15].

Continuing our effort to develop *green* syntheses of bioactive molecules, we decided to investigate the one-pot synthesis of various bibenzyls compounds through the Heck cross-coupling reaction followed by selective hydrogenation of the resulting stilbenes.

RESULTS AND DISCUSSION

As catalysts, based on our previous reports, we selected commercially available Pd/C catalysts (Aldrich 5%wt Pd and Aldrich 10%wt, Pd-Degussa type E101 NE/W) and a home-made palladium supported on zeolite Y catalyst as $[Pd(NH_3)_4]$/NaY (3.7%wt Pd) prepared following a procedure previously described in the literature [16].

As preliminary study, all catalysts were engaged in a one-pot synthesis of bibenzyls, coupling styrene with either bromobenzene or 4-bromobenzonitrile under classical reaction conditions (a. 10 mmol aryl halide, 15 mmol styrene, 15 mmol NaOAc, 1mol% Pd-catalyst, 8 mL N-methylpyrrolidone (NMP), 140°C, 24 h; b. 1 bar H_2) (Scheme **1**). Alternatively, 4-acetoxystyrene was used as the olefin. The results reported in Table **1** indicate clearly that if all catalysts are efficient to perform the first step of the synthesis, i.e; the Heck reaction, leading generally to full conversions of the aryl bromides, only the Pd/C 5%wt was effective to perform the hydrogenation of the resulting stilbenes towards the target bibenzyls with high yields.

Having these conditions in hands (a. 5 mmol aryl halide, 7 mmol styrene, 7 mmol NaOAc, 1 mol% PdC 5%wt, 4 mL NMP, 140°C, 24 h; b. 1 bar H_2) we extended the procedure to the synthesis of various stilbenes and bibenzyls starting from various aryl iodides and bromides (Scheme **2**).

The results reported in Table **2** show that generally good to high yields were achieved under these reactions conditions for both the stilbenes and the bibenzyls whatever the functional groups present on the starting materials.

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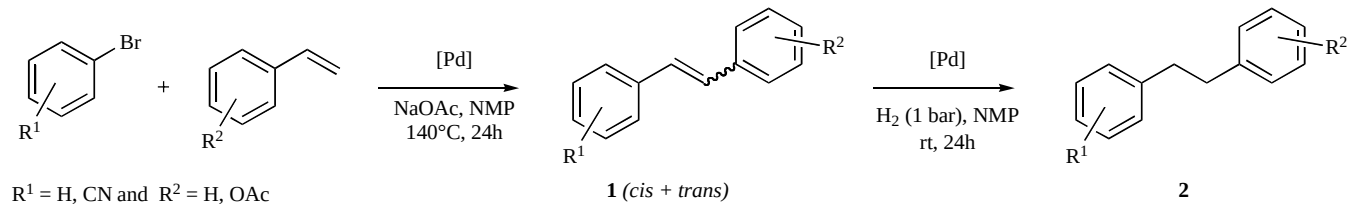
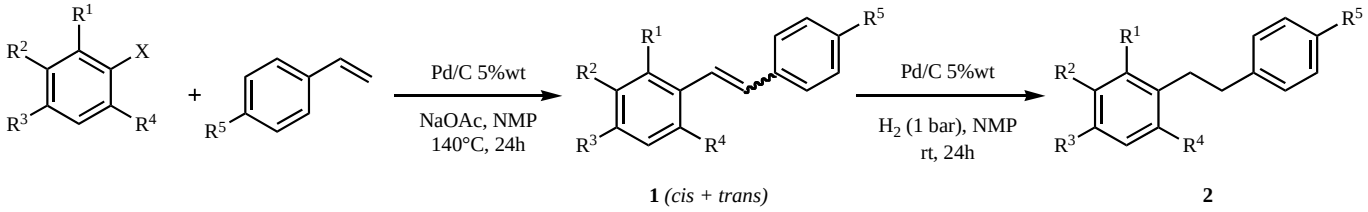


Scheme 1. Pd-catalysed synthesis of bibenzyls following a one-pot procedure.

Table 1. Optimisation of the Reaction Conditions for the Synthesis of Stilbenes and Bibenzyls (Scheme 1)

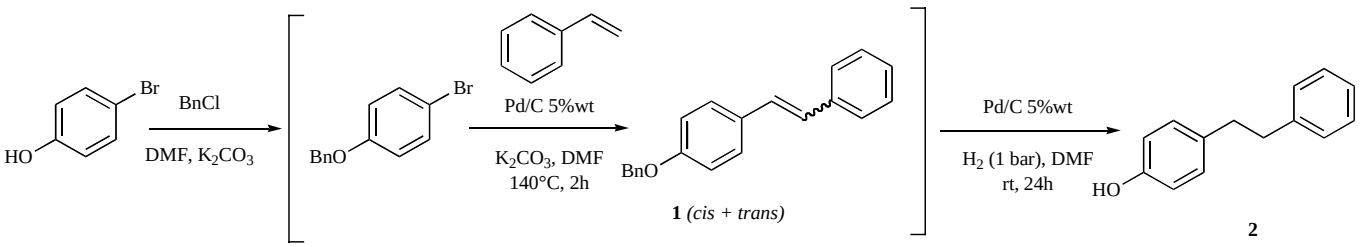
Entry	Catalyst	R^1	R^2	GC-yield 1 (%)[a]	GC-yield 2 (%)[a]
1	Pd/C 10%wt[b]	H	H	100	54
2		H	OAc	90[c]	28[c]
3		CN	H	100	61
4		CN	OAc	100[c]	46[c]
5	Pd/C 5%wt	H	H	100	100
6		H	OAc	100[c]	45[c]
7		CN	H	100	100
8		CN	OAc	100[c]	50[c]
9	$[Pd(NH_3)_4]$/NaY	H	H	100	0
10		H	OAc	86[c]	0
11		CN	H	100	0
12		CN	OAc	88[c]	0

[a]Yields were determined by GC with an internal standard (diethylene glycol di-*n*-butyl ether) (Δ_{rel} = ± 5%). [b]The Pd/C 10%wt - Degussa type E101 NE/W was not effective to perform hydrogenation of stilbenes at atmospheric pressure and room temperature as the immobilised palladium is mainly under $Pd^{(II)}$-oxidation state. However, it was effective under 10 bar hydrogen at 140°C following ref [13]. [c]Partial de-acetylation was observed under the reaction conditions leading to non-negligible amount of phenol formation (*ca*. 47-52 %).



Scheme 2. Pd-catalysed synthesis of stilbenes and bibenzyls.

Nevertheless, when using the 4-bromophenol as aryl halide poor conversions were achieved in the Heck coupling reaction (Table **2**, entry 9). This disappointing result could be overcome by protecting the phenol function as the benzylether derivative. After hydrogenation, the corresponding 4-phenethylphenol was obtained quantitatively (Table **2**, entry 10). Interestingly, we demonstrated that the overall procedure (i.e. a). benzylation of the phenol using benzylchloride (BnCl), b). Heck coupling, c). hydrogenation/hydrogenolysis) could be performed as a one-pot reaction affording the expected compound in good isolated yield (86 %) (Scheme **3**). Performing thus the synthesis resulted in higher reaction rate in the coupling step as the Heck reaction was quantitative after 2 h while it required *ca*. 24 h when



Scheme 3. Efficient one-pot synthesis of 4-phenethylphenol.

Table 2. Synthesis of Stilbenes and Bibenzyls (Scheme 2)

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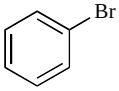
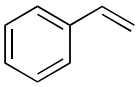
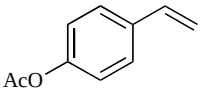
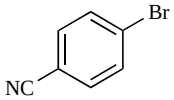
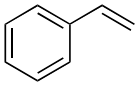
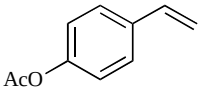
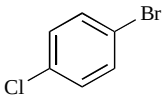
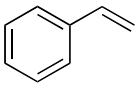
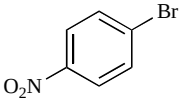
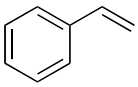
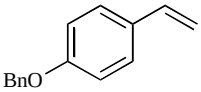
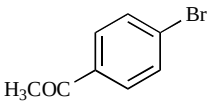
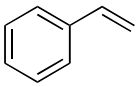
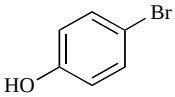
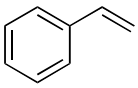
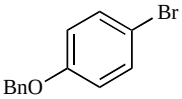
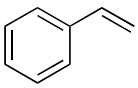
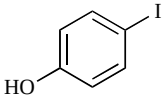
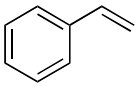
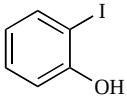
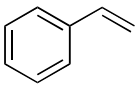
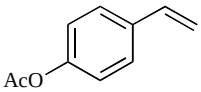
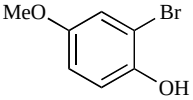
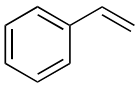
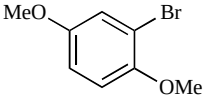
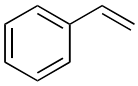
1			100	100 [93]
2			100	45
3			100	100 [84]
4			100	50
5			100	100 [92]
6			100	100 [56][b]
7			100	100[c]
8			100	100 [86]
9			40	-
10			100	100 [86][d]
11			50	-
12			100	75
13			100	45
14			37	-
15			34	-

(Table 2). Contd…..

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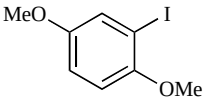
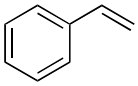
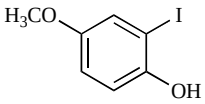
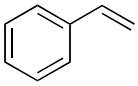
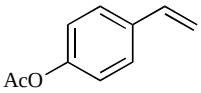
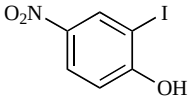
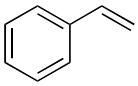
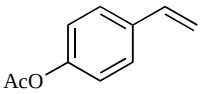
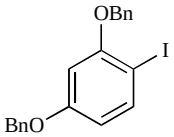
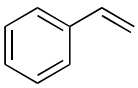
16			64	-
17			89	60
18			80	35
19			100	80
20			100	48
21			30	27[d]

[a]Yields were determined by GC with an internal standard (diethylene glycol di-*n*-butyl ether) (Δ_{rel} = ± 5%). When available, [isolated yields] are reported. [b]Under hydrogenation conditions, the nitro group is reduced to the corresponding amino derivative. [c]Under hydrogenation conditions, both the benzyl group is hydrogenolysed and the nitro group is reduced giving the 4-(4-aminophenethyl)phenol whose purification failed. [d]Under hydrogenation conditions, the benzyl group is hydrogenolysed leading to the direct formation of phenol derivative.

starting from isolated 4-benzyloxybromobenzene. This was reasonably attributed to the presence of KCl in the reaction medium that is known to promote the Heck coupling reactions [17]. Proceeding thus, the 4-phenethylphenol was obtained with 86% isolated yield. Unexpectedly, the use of the free-OH 4-iodophenol as aryl halide did not improve the procedure as poor conversion was achieved (Table **2**, entry 11) whereas good yield was obtained when using the unprotected 2-iodophenol (Table **2**, entry 12).

While successful this methodology shows, nevertheless, some limitations when engaging in highly deactivated arylbromides as generally no or poor conversions were observed (some conversion was observed in few cases; Table **2**, entries 14-15). For these cases it was necessary to use costly and not commercially available iodo-derivatives to achieve better results (Table **2**, entries 16 and 21). But also in these examples, good results were achieved only when activating groups were present on the aromatic ring (Table **2**, entries 19-20 *versus* Table **2**, entry 21).

CONCLUSIONS

In conclusion we reported in this communication an alternative route to the synthesis of functional stilbenes and bibenzyls. Starting from aryl bromides and using simple commercially available Pd/C catalyst good yields in target compounds were achieved. However, the procedure showed some limitations when applied to functional aryl bromides that could be in some extent overcame by using corresponding iodo derivatives.

Current investigations focus on improving the activity of the heterogeneous catalysts to achieve the one-pot syntheses of stilbenes and bibenzyls bearing electro-donating groups. Alternatively we develop new methodology to face the lack of availability of functional styrenes.

EXPERIMENTAL

All preparations, manipulations and reactions were carried out under argon, including the transfer of the catalysts to the reaction vessel. All glassware was base- and acid-washed and oven dried.

The NaY zeolite (LZ-Z-52) was purchased from Sigma-Aldrich Chemicals and was dried before use at 120°C for 48h under 5.10^{-2}mmHg before palladium loading. The palladium content determination of the catalysts prepared with this support was performed by AAS spectroscopy from a solution obtained by treatment of the catalysts with a mixture of HBF_4, HNO_3 and HCl in a Teflon reactor at 180°C.

The Pd/C catalyst (5%wt Pd and Aldrich 10%wt Pd on dry basis {52% water} from Degussa type E101 NE/W) was purchased from Aldrich Chemicals and used as supplied.

All organics and solvents were used as received from the suppliers (Sigma-Aldrich, Alfa Aesar, Acros Organics) after deaerating by an argon flow.

NMR spectra were recorded with a Bruker AM 400 spectrometer (^{1}H NMR were referenced to the residual protio-solvent: $CDCl_3$, δ=7.25 ppm; ^{13}C NMR were referenced to the C-signal of the deutero solvent: $CDCl_3$, δ=77ppm).

Gas-liquid chromatograms were performed on a HP 6890 series chromatograph equipped with a FID detector and a HP-1 column (cross-linked methylsiloxane, 30m x 0.25mm x 0.25µm film thickness) using N_2 as carrier gas. Alternatively, a Shimadzu GC-MS-QP2010S equipped with a Sulpelco SLB-5MS column (95% methylpolysiloxane + 5% phenylpolysiloxane, 30m x 0.25mm x 0.25µm) with He as carrier gas was used.

Procedure for the Preparation of the $[Pd(NH_3)_4]$/NaY Catalyst [16]

The heterogeneous $[Pd(NH_3)_4]$/NaY catalyst was prepared as follows: A 0.1 M ammonia solution of $[Pd(NH_3)_4]Cl_2$ -prepared from $PdCl_2$ and a commercial ammonia solution- was added drop wise (5 mL/g zeolite, corresponding to *ca*. 5% wt Pd in the final catalyst) to a suspension of the zeolite NaY in bi-distilled water (100 mL/g zeolite). The mixture was stirred for 24 h at rt and the exchanged zeolite was filtered off and washed until no trace of chloride was detected in the filtrate ($AgNO_3$ test). Then the zeolite was allowed to dry at room temperature to give the entrapped $[Pd(NH_3)_4]$/NaY catalyst as slightly yellow material. ICP-AES analysis: 3.7 % wt Pd.

General Procedure for Catalytic Tests

5 mmol of aryl halide, 7 mmol of olefin, 7 mmol of NaOAc and 1 mol % of Pd-catalyst were introduced in a pressure tube under argon. 4 mL of solvent NMP previously deaerated were added and the mixture was deaerated by an argon flow for 5 min. The reactor was then placed in a preheated oil bath at 140 °C for 24 h under vigorous stirring and then cooled to room temperature before the reaction mixture was analyzed by GC. At completion of the reaction, the mixture was filtered on celite, diluted with 50 mL of water and the resulting mixture was extracted with 3 x 20 mL CH_2Cl_2. The combined organic layers were washed with 15 mL of brine, dried over $MgSO_4$ and evaporated. The residue was then purified by flash chromatography on silica gel.

GLC Analysis

A homogeneous 3 mL sample of the reaction mixture was sampled and quenched with 3 mL of water in a test tube. The mixture was extracted with 2 mL of CH_2Cl_2 and the organic layer was filtered through a $MgSO_4$ pad. The resulting dry organic layer was then analysed by GLC. GLC-Rate program: 2 min at 100 °C, heating 15 °C/min up to 170 °C, 2 min at 170 °C, heating 35 °C/min up to 240 °C, 10 min at 240 °C, heating 50 °C/min up to 270 °C and 2 min at 270 °C.

Characterisations of Organic Compounds

All compounds were characterised through MS spectra obtained from GC-MS. Additionally, isolated compounds were fully characterised through ^1H and ^{13}C NMR. All isolated compounds gave spectroscopic data in agreement with the literature (**2/1**[13], **2/3**[18], **2/5**[19], **2/8**[20] and **2/11**[21]).

Example of NMR Characterisations (Table 2, entry 3)

(E)-4-styrylbenzonitrile

^1H NMR (250 MHz, $CDCl_3$): δ ppm: 7.41 (d, ^3J = 7.5 Hz, 2H), 7.34 (d, ^3J = 7.5 Hz, 2H), 7.27 – 7.09 (m, 5H), 7.01 (d, ^3J = 16.4 Hz, 1H), 6.87 (d, ^3J = 16.4, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ ppm: 141.69, 136.19, 132.35, 132.24, 128.81, 128.59, 126.91, 126.83, 126.57, 119.03, 110.31. $C_{15}H_{11}N$: 205,09 g.mol^{-1}. MS: *m/z* (%) = 205 (100) [$M^{+\cdot}$].

4-phenethylbenzonitrile

^1H NMR (250 MHz, $CDCl_3$): δ ppm: 7.51 (d, ^3J = 8.3 Hz, 2H), 7.34 (m, 3H), 7.24 (d, ^3J = 8.3 Hz, 2H), 7.22 (d, ^3J = 7.5 Hz, 2H), 2.98 (m, 4H). ^{13}C NMR (63 MHz, $CDCl_3$): δ ppm: 147.28, 140.67, 132.12, 129.39, 128.49, 126.27, 119.15, 109.76, 37.89, 37.21. $C_{15}H_{13}N$: 207,10 g.mol^{-1}. MS: *m/z* (%) = 207 (20) [$M^{+\cdot}$]; 91 (100) [$M^+ - C_8H_6N^{\cdot}$].

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