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Selectivity studies in the reaction between iodobenzene and phenylacetylene: Sonogashira coupling vs hydroarylation

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The selectivity of the coupling reaction between iodobenzene and phenylacetylene was evaluated. Several palladium catalysts, ligands and reaction conditions were tested, showing that supported catalysts, room temperature or ionic liquids (NHC precursors) favor Sonogashira coupling, while the non-supported ones, higher temperature and PPh_3 as ligand, favor hydroarylation. Neither excess of iodobenzene nor phenylboronic acids are required; and it is possible to avoid the use of PPh_3, although this lowers selectivity. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: Sonogashira reaction; C–C coupling; hydroarylation; triarylethylenes

Introduction

The palladium-catalyzed coupling reaction of alkynes with aryl halides is one of the most versatile strategies for construction of C–C bonds.[1] It can provide an efficient route to aryl alkyne derivatives following a Sonogashira reaction[2] or to triarylethylenes following hydroarylation.[3] Triarylethylenes show interesting spectroscopic and electronic properties[4] and have applications in medicinal chemistry as a core for some selective estrogen receptor modulators (SERM) like Tamoxifen® and Clomifene®, respectively used for breast cancer chemotherapy[5] and in treatment of infertility caused by polycystic ovary syndrome therapy[6] (Fig. 1).

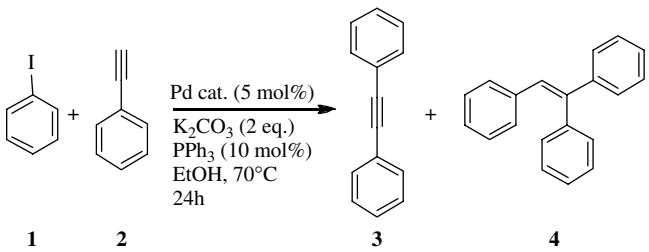
The industrial production of these compounds involves air-sensitive Grignard reagents.[7] Other approaches to the synthesis of triarylethylenes include carbometallation of alkynylsilanes,[8] McMurry reaction,[9] dehydration of 1-(*p*-alkoxyphenyl)-1,2-diphenylbutan-1-ols,[10] use of superbase-metalated propylbenzene,[11] solid support synthesis,[12] palladium-catalyzed double cross-coupling of (*E*)-vinylic dibromides with PhZnCl[13] and coupling of alkynes and boronic acids employing either rhodium,[14] nickel[15] or palladium catalysts.[16]

Cacchi's group was the first to report the synthesis of triphenylethylene by reaction of iodobenzene and phenylacetylene, employing Et_3N, $Pd(OAc)_2$, PPh_3 and HCOOH in acetonitrile. In this case, a large excess of iodobenzene was used.[17]

In the present paper we disclose our results concerning the expansion of this methodology using stoichiometric amounts of iodobenzene, exploring the selectivity based on catalyst nature, nucleofuge type (the leaving group that carries away the bonding electron pair) and physicochemical conditions of the reaction. This work can be of potential interest in order to find convenient conditions for the formation of triarylethylenes in a single step.

Results and Discussion

Our investigation used the model reaction between iodobenzene (**1**) and phenylacetylene (**2**) in the presence of K_2CO_3 and PPh_3, using ethanol as solvent (Scheme 1). To avoid the use of excess reagents, we used iodobenzene stoichiometrically. These reactions were carried out in presence of different palladium catalysts and the results are summarized according to the nature of the catalyst: supported (Table 1) and non-supported (Table 2).



Scheme 1. Model reaction between iodobenzene and phenylacetylene.

As can be seen from Table 1, the supported palladium catalysts afforded diphenylacetylene (**3**) following a Sonogashira coupling reaction. However, unreacted diphenylacetylene and iodobenzene were found. No attempts were made to optimize these results by means of copper co-catalysts, as they promote a Glaser-type homocoupling reaction of the terminal alkyne in the presence of oxidative agents or air.[19] Also, Pd–$CaCO_3$ afforded the best results in our model reaction, showing the importance of this heterogeneous catalyst[20] as a palladium reservoir.[21]

On the other hand, when non-supported catalysts were used (Table 2), triphenylethylene (**4**) was obtained and $Pd(OAc)_2$ (entry 4) was the best catalyst. Using this catalyst, it was noted that

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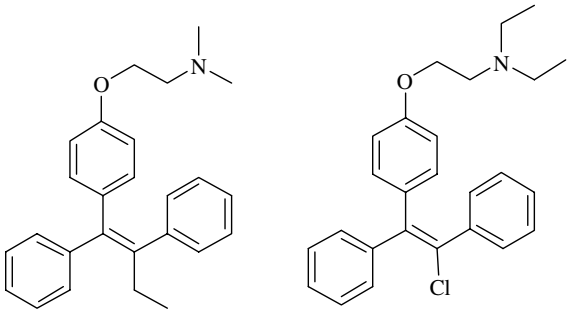


Figure 1. Structures of SERM.

Table 1. Selectivity in model reaction using supported catalysts[a]

Entry	Catalyst	Selectivity[b] (%) 3	4
1	Pd–C	44	5
2	Pd–PVP[c]	41	3
3	Pd–$CaCO_3$	50	6
4	Pd–$BaSO_4$	19	9
5	Pd–Al_2O_3	29	6

[a] Phenylacetylene, 0.45 mmol; iodobenzene, 0.90 mmol; K_2CO_3, 0.89 mmol; Pd catalyst, 5 mol%; PPh_3, 10 mol%; in 15 ml EtOH at 70 °C for 24 h. [b] Determined by GC-MS. [c] Prepared as in Li *et al.*[18]

Table 2. Selectivity in model reaction using non-supported catalysts[a]

Entry	Catalyst	*T* (°C)	Selectivity[b] (%) 3	4
1	$Pd(PPh_3)_4$	70	7	93
2	$PdCl_2$	70	1	99
3	$Pd_2(dba)_3$	70	2	98
4	$Pd(OAc)_2$	70	1	99
5	$Pd(OAc)_2$	r.t.	82	6
6	$Pd(OAc)_2$	55[c]	99	0.9

[a] Phenylacetylene, 0.45 mmol; iodobenzene, 0.90 mmol; K_2CO_3, 0.89 mmol; Pd catalyst, 5 mol%; PPh_3, 10 mol%; in 15 ml EtOH for 24 h. [b] Determined by GC. [c] Ultrasound promoted reaction.

a decrease in reaction temperature resulted in diphenylacetylene (**3**) even under ultrasound conditions (entries 5 and 6). This selectivity inversion based on reaction temperature could suggest that a tandem Sonogashira coupling followed by hydroarylation may exist in our model reaction. Also, in reactions furnishing diphenylacetylene (**3**) as by-product, traces of non-reacted iodobenzene were found.

These selectivity differences prompted us to investigate the influence of the nucleofuge in the model reaction using $Pd(OAc)_2$ as catalyst. Bromobenzene as a less reactive halide yielded **3** in 45% conversion and showed a high rate of alkyne homocoupling (1,4-diphenylbutadiyne). Less reactive chlorobenzene resulted only in alkyne homocoupling. Diazonium salts that are well-recognized as the most reactive substrates for C-C coupling[22] were also tested. However under our conditions, PhN_2BF_4 failed to afford coupled products even in presence of CuI as co-catalyst, as already observed by Bräse's[23] and Sengupta's[24] groups. As PPh_3 is reported to lower yields in Heck coupling between diazonium salts and olefins,[25] our reactions employing diazonium salts were conducted in the absence of ligands.

In order to support the selectivity differences based on the nature of the catalyst, we observed that, submitting diphenylacetylene (**3**) to our reaction conditions, 21% of **3** is converted to triphenylethylene (**4**) employing $Pd(OAc)_2$, but this conversion is decreased to 1% using Pd–C as the catalyst source.

To go further, the reaction was carried out in the absence of PPh_3 and it was observed that, although a lower selectivity to **4** was observed, the coupling reaction was made possible (Table 3, entry 1). Ionic liquids (IL), which can act as *N*-heterocyclic carbene (NHC) ligands,[26] were tested as substitutes for PPh_3 and furnished mostly **3** (entries 2 and 3), thus demonstrating the capacity of these entities to act as ligands in our model reaction, although not to triarylethylenes.

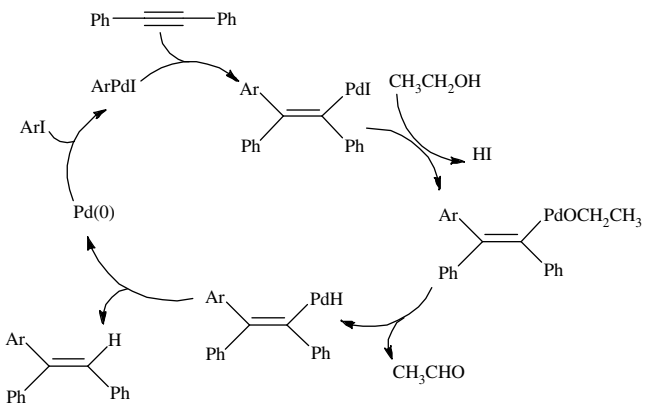
The reaction mechanism can be understood as similar to that proposed by Wu's group[27] and involves the need for a base to neutralize HI, so providing the driving force necessary to release acetaldehyde upon formation of a palladium hydride intermediate and then the hydroarylation product (Scheme 2). This proposal also agrees with Hierso's group assumptions that the palladium catalyst may act as hydrogen transfer catalyst.[28]

The importance of ethanol in this mechanistic assumption could be verified by the screening of different solvents (Table 4). Apolar solvents like dioxane and toluene (entries 4 and 5) gave poor conversions, dioxane showing alkyne homocoupling as the major product. The polar solvents induced good conversion and the polar protic solvents were the best (Table 1, entry 4 and Table 4, entry 1). We were not able to explain differences in the ratio

Table 3. Influence of ligand[a]

Entry	Ligand	Selectivity[b] (%) 3	4
1	–	12	88
2	[Hmim][Cl]	81	19
3	[Bmim][BF_4]	75	25

[a] Phenylacetylene, 0.45 mmol; iodobenzene, 0.90 mmol; K_2CO_3, 0.89 mmol; $Pd(OAc)_2$, 5%; in 15 ml EtOH at 70 °C for 24 h. [b] Determined by GC.



Scheme 2. Catalytic cycle.

Table 4. Influence of solvent[a]

Entry	Solvent	Selectivity[b] (%) 3	4
1	Ethylene glycol	97	3
2	H_2O–acetone (1 : 1)[2d]	17	62
3	DMF	84	–
4	1,4-Dioxane[c]	21	–
5	Toluene	9	12

[a] Phenylacetylene, 0.45 mmol; iodobenzene, 0.90 mmol; K_2CO_3, 0.89 mmol; Pd catalyst, 5 mol%; PPh_3, 10 mol%; in 15 ml of solvent at 70 °C for 24 h. [b] Determined by GC. [c] 1,4-Diphenylbutadiyne was detected in 41%.

3 : 4 based on the solvent nature. Acetonitrile[18] and methanol[27] have already been reported to be good solvents for hydroarylation reactions.

Experimental

GC analyses were performed on HP 5890 equipped with an FID detector using an STB-1 capillary column (30 m × 0.32 mm × 0.25 µm) from Supelco. Hydrogen was used as the carrier gas and the intion split ratio was 1 : 100. The temperature program was 10 °C/min from 150 to 250 °C and finally 5 min at 250 °C. Injector and detector temperatures were 250 °C.

GC/MS analyses were carried out on a Agilent 6850 GC coupled to a quadrupole Agilent 5973 Network operating in electron ionization mode at 70 eV. Helium was used as carrier gas and the injection split ratio was 1 : 100. Separation was achieved on an HP-1 capillary column (30 m × 0.32 mm × 0.25 µm) using the following temperature program: 15 °C/min from 180 to 280 °C. Injector and detector temperatures were 250 °C and the ion source temperature was 150 °C.

NMR spectra were recorded on a Fourier Transform Bruker AMX-200 spectrometer operating at 200 MHz (^{1}H) and 50 MHz (^{13}C), in the specified solvents. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane. Proton and carbon spectra were typically obtained at room temperature. TLC analyses were conducted on pre-coated Merck Kiesel-Gel 60 F254 plates and visualized using a UV lamp. Preparative TLC was done using the same conditions. Pd-PVP solution was prepared in accordance with a previously described method.[18] All the other reagents were obtained from commercial sources and used without purification.

General procedure for the production of diphenylacetylene (3) and triphenylethylene (4)

In a 50 ml reaction flask were added K_2CO_3 (123 mg, 0.89 mmol), PPh_3 (12 mg, 10 mol%), palladium catalyst (5 mol% for solid catalysts or 2.5 ml for Pd-PVP solution[6]), absolute EtOH (15 ml), phenylacetylene (0.05 ml, 0.45 mmol) and iodobenzene (0.1 ml, 0.90 mmol). The mixture was stirred at 70 °C under argon atmosphere for 24 h. After that period, diethyl ether (30 ml) was added and the reaction mixture was filtered through celite. The filtrate was extracted with brine (3 × 20 ml), dried over Na_2SO_4 and the solvent was removed under vacuum. The products were either analyzed by GC/MS or purified by preparative TLC using toluene : hexane 10% as eluent.

*Diphenylacetylene (**3**)*

Light yellow solid. M.p.: 59 °C (58–60 °C[29]). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.25–7.26 (m, 6H), 7.44–7.46 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 88.3, 122.3, 127.2, 127.3, 130.6. MS (70 eV, EI), *m/z* (%): 178 (M^+, 100), 152 (10), 89 (9), 76 (12), 28 (19).

*Triphenylethylene (**4**)*

Light yellow solid. M.p.: 71 °C (71–72 °C[30]). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.87 (s, 1H), 6.91–6.95 (m, 2H), 7.01 (m, 3H), 7.10–7.12 (m, 2H), 7.21 (m, 8H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 126.4, 127.1, 127.2, 127.6, 127.8, 127.9, 128.3, 129.2, 130.0, 131.2, 137.0, 140.0, 142.2, 143.0. MS (70 eV, EI), *m/z* (%): 256 (M^+, 100), 239 (20), 178 (42), 165 (16).

Conclusion

In conclusion, we were able to direct the selectivity of the coupling reaction between iodobenzene and phenylacetylene based on the nature of the catalyst, ligand type and reaction conditions. Supported catalysts, smooth conditions or ionic liquids favor Sonogashira coupling, while the non-supported ones, hard conditions and PPh_3 favor a tandem reaction of Sonogashira coupling followed by hydroarylation. As a further advantage, the present methodology does not employ excess iodobenzene nor expensive phenylboronic acids. The procedure employs no PPh_3 and readily available and non-toxic ethanol. Further work is underway on different substrates and on the use of phosphine-free systems using or not using $bmim^+$ ionic liquids as additives.

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