Synthesis of 2-alkylidene isochromans via cyclocarbonylative Sonogashira reactions

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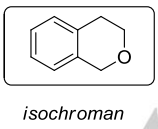
Abstract: In this study we use a tandem carbonylative Sonogashira reaction – cyclisation process to construct alkylidene functionalised isochromans in high yields and with complete stereoselectivity (only *Z* isomers are formed). The reaction is performed in the absence of CuI co-catalyst, with a small amount of $PdCl_2(PPh_3)_2$ (0.2-0.5 mol-%) and aryl iodides bearing both electron donating and electron withdrawing substituents can be successfully employed.

Introduction

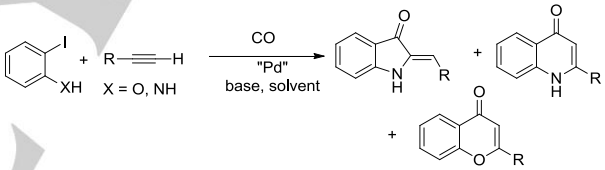
Isochromans (Figure 1) are an important class of molecules in medicinal chemistry because of their biological properties. Indeed, some of them exhibit hypotensive[1], antitumor[2], antibacterial[3] and antioxidant[4] activities and plant grow-regulating potential[5]. Some others are neuro-kinin-1-receptor antagonist[6] or have a specific effect on the dopaminergic system[7]. Moreover, isochromans can be precursors for the synthesis of isocromanones[8], tetrahydrobenzazepines[9], benzodiazepine-4-ones[10] important building blocks in organic chemistry.



isochroman

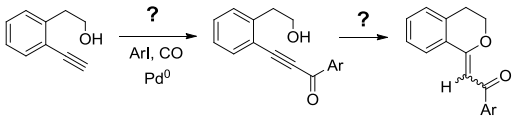
Figure 1. Isochroman structure

Several excellent methods for the formation of the isochroman skeleton are described in the literature. Many of them are basedon the oxa-Pictet-Spengler reaction[11-15] which consist of the condensation of a *β*-arylethanol derivatives with a carbonyl compound to form a hemiacetal; this intermediate undergoes cyclization to give the isochroman ring. The reaction is often promoted by acid catalysts such as H_2SO_4, HCl, *p*toluensulfonic acid, acetic acid, oleic acid, $AlCl_3$, $TiCl_4$, $ZnCl_2$, but also zeolites[16], and bismuth triflate[17] have been shown to be effective. A different approach was reported by Florio[18] et al. and is based on the sequence of lithiation–acid-catalysed cyclization of *N*-alkyl-(*o*tolyl)aziridines. Later on the same group described the preparation of polysubstituted isochromans by means of a one-pot procedure based on the addition of ortho-lithiated aryloxirans to enaminones.[19]. Ramana and co-workers[20-21] reported the application of the [2+2+2] – alkyne-diyne cyclotrimerization to the preparation of enantiopure isochromans catalysed by rhodium species. Functionalised diynes were used also in a Heck carbopalladation-cyclisation sequence[22] for the synthesis of highly substituted isochromans. Finally, palladium catalysts have been employed in cyclisation reactions [23-26] of benzyl or homobenzyl alcohols derivatives.
Recently, a few examples of synthesis of heterocyclic derivatives such as isoquinolones, isoindolinones[27], flavones, chromones[28] and benzofuranes[29] based on palladium catalysed Sonogashira reactions were described in the literature. In particular, 2-iodophenols or 2-iodoaniline were reacted with terminal acetylenes under carbon monoxide atmosphere, generating acetylenic ketones which underwent cyclisation affording the heterocyclic derivatives as depicted in Scheme 1.



Scheme 1. Sonogashira reaction for the synthesis of heterocyclic compounds

Intrigued by this data and prompted by our recent results on the Sonogashira carbonylative reaction[30], we decided to investigate the possibility to apply a carbonylative Sonogashira reaction-cyclisation sequence to the synthesis of isochromans. Indeed, starting from a suitable substrate, this tandem process could afford 2-alkylidene isochromans (Scheme 2) whose preparation is seldom reported in the literature [31].



Scheme 2. Possible synthesis of isochroman via cyclocarbonylative Sonogashira reaction

Results and Discussion

2-(2-Ethynylphenyl)ethanol **1** was chosen as model substrate and prepared according to the method described in Scheme 3.

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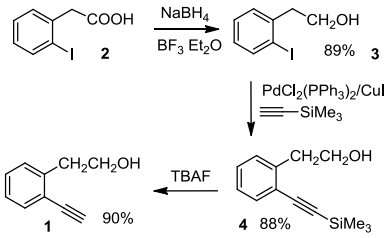
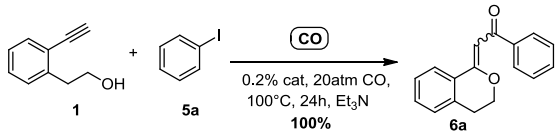


Scheme 3. Synthetic sequence for the preparation of 2-(2-ethynylphenyl)ethanol **1**

2-Iodophenylacetic acid **2** was easily reduced to the corresponding benzyl alcohol **3** in high yield (89 %) by means of $NaBH_4$ / $BF_3{\cdot}Et_2O$[32]. The acetylenic moiety was then introduced with a cross coupling Sonogashira reaction with trimethysilyl acetylene yielding the desired product **4** 2-(2-((trimethylsilyl)ethynyl)phenyl)ethanol (88 %)[33]. Finally, the trimethylsilyl group was smoothly removed by treatment of **4** with excess tetrabutylamonium fluoride (90 %)[33].



Scheme 4. Preliminary carbonylative reaction between 2-(2-ethynylphenyl)ethanol and iodobenzene

A preliminary cyclocarbonylative Sonogashira reaction was performed reacting 2-(2-ethynylphenyl)ethanol with iodobenzene in triethylamine chosen both as a solvent ad as a base, at 100 °C, for 24 h, with $PdCl_2(PPh_3)_2$ (0.2 mol- %) and under 20 atmosphere of CO (Scheme 4). To our delight, NMR analysis of the crude mixture indicated the complete conversion of the reagents and the formation of 2-(isochroman-1-yliden)-1-phenyletanone **6a** as principal product which was isolated chemically pure (column chromatography) in high yield (89 %). The configuration of the double bond of the olefinic moiety was then determined by the analysis of the results obtained with a NOESY (Nuclear Overhouser Effect SpectroscopY) experiment. Relevant NOE effects were detected between the vinylic proton $\mathbf{H_a}$ and the aromatic hydrogens $\mathbf{H_b}$ and $\mathbf{H_c}$ as shown in Figure 2, thus indicating the exclusive formation of the *Z* isomer of the isochroman **6a** with the two conjugated double bonds in a *S-cis* geometry.

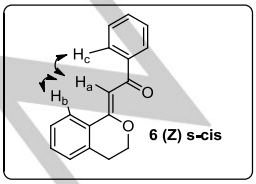


Figure 2. Isochroman structure

It is worth noting that, according to Baldwin's rules[34], only the 6-membered ring **6a** was generated during the cyclization process (6-*exo-Dig*) while no traces of the possible tetrahydrobenzoxepine derivative were detected.
In addition to the isochroman derivative **6a**, a small amount (5% purified yield) of 3-(2-(2-phenoxyethyl)phenyl)-1-phenyl-2-yn-1-one **7a** was isolated (Figure 3).

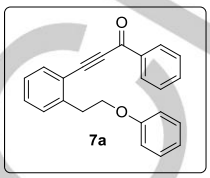
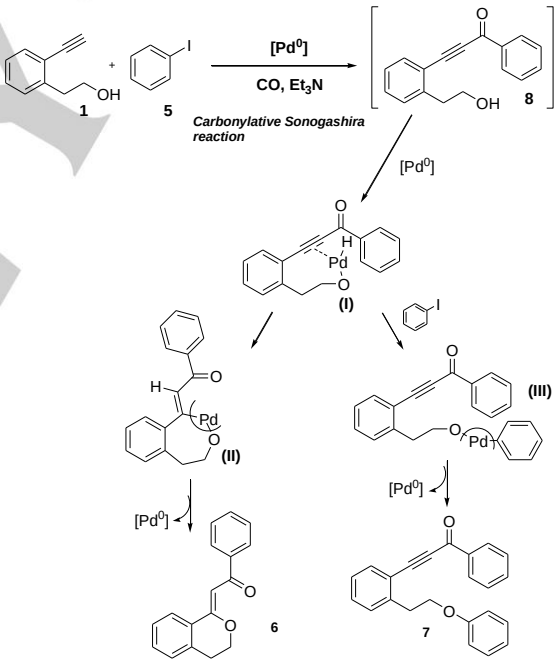


Figure 3. Structure of 3-(2-(2-phenoxyethyl)phenyl)-1-phenyl-2-yn-1-one

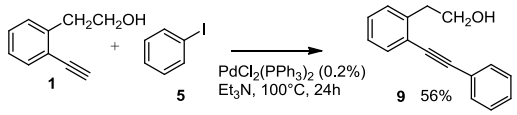
A plausible mechanism for the formation of both products **6a** and **7a** is described in Scheme 5. It involves, first of all, the Sonogashira carbonylative reaction between iodobenzene **5** and ethynyl alcohol **1** that should form 3-(2-(2-hydroxyethyl)phenyl)-1-phenylprop-2-yn-1-one **8** as intermediate of both derivatives**.**



Scheme 5. Hypothesis of mechanism for the formation of isochroman **6** and ether **7**

At this point, Pd(0) insertion into the O-H bond would generate the palladium hydride specie **I** which can undergo two different transformations. Hydropalladation reaction to the triple bond (Scheme 5, **II**) followed by reductive elimination could afford isochroman **6a** with regeneration of the palladium catalyst. On the other hand, the presence of ether **7a** can be explained with a direct insertion of palladium into the C-I bond of iodobenzene (Scheme 5, **III**) with subsequent reductive elimination of Pd^0. As

a matter of fact, a few examples of arylation of benzylic or homobenzylic alcohols catalysed by transition metal based species are described in the literature[35].
Moreover, the carbonylation of the triple bond resulted fundamental for the cyclisation process to take pace. Indeed, when a reaction between the ethynyl alcohol **1** and iodobenzene **5** was performed in the absence of carbon monoxide, only 2-(2-(phenylethynyl)phenyl)ethanol **9** was formed (56 % purified yield, Scheme 6).



Scheme 6. Sonogashira reaction between 2-(2-ethynylphenyl)ethanol and iodobenzene

The cyclocarbonylative Sonogashira reaction was then extended to several aryl iodides **5** possessing both electron donating and electron withdrawing substituents in ortho or para position. As described in Table 1, a quantitative conversion of the reagents was detected in all experiments. The reactions generated the isochroman derivatives **6a-i** with good to excellent yields (68-89 %) and with complete stereoselectivity towards the formation of the (*Z*)-isomer, regardless the stereoelectronic features of the employed aryliodides **5.** A small reduction of chemoselectivity was observed when the steric requirements of **5** increased such as in the cases of *α*naphtyl and *o*tolyl derivatives (Table 5, entries 2 and 3). However, when the reactions between 2-(2-ethynylphenyl)ethanol **1** and aryl iodides **5b** and **5c** were performed with a small excess of alcohol **1** respect to the iodoarenes (2.5 mmol vs. 2 mmol) and in the presence of a slightly higher amount of the catalyst (0.5 instead of 0.2 mol- %), the ether by-products **7b** and **7c** completely disappeared and improved yields (87-89 vs. 73-75) of the isochromans **6b** and **6c** were obtained (Table 5, entries 4 and 5).

Moreover, when the reaction was carried out with 2-iodobenzonitrile **5i**, i.e. in the presence of a strong electron withdrawing group in the ortho position, a small amount (16 %, Figure 4) of 2-((2-(2-hydroxyethyl)phenyl)ethynyl) benzonitrile (**10**) was isolated.

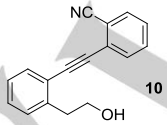
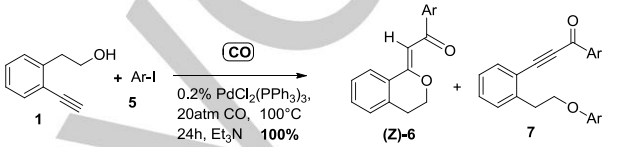


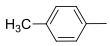
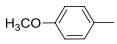
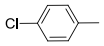
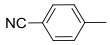
Figure 4. By-product of Sonogashira cyclocarbonylation of 2-iodobenzonitrile.

This result can be explained with a competitive non carbonylative Sonogashira reaction that determined the formation of the direct coupling product **10.** According to the results previously observed in the noncarbonylative experiment (Scheme 6), **10** did not cyclise because of the absence of the CO moiety. Finally, when 4-iodonitrobenzene was tested in the cyclocarbonylative reaction, an unexpected result was obtained.

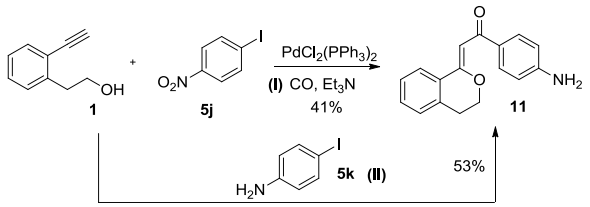
Indeed, the reaction afforded (*Z*)-1-(4-aminophenyl)-2-(isochroman-1-ylidene) ethanone **11** exclusively (Scheme 7 path I). The structure of this product was confirmed by means of a cyclocarbonylative reaction performed between the ethynylalcohol **1** and 4-iodoaniline **5k** (Scheme 7 path II). In this case the chemoselective formation of amino derivative **11** was detected and the product was isolated chemically pure with a good yield (53 %). These results indicated that the Sonogashira cyclocarbonylative process can take place successfully even in the presence of a free NH_2 group, while NO_2 moiety is reduced in situ.

Table 1. Cyclocarbonylative reaction of 2-(2-ethynylphenyl)ethanol and aryl iodides



Entry[a]	5	Ar	(*Z*)-6	Yield[b]	7	Yield[b]
1	**a**		**a**	89	**a**	5
2	**b**		**b**	75	**b**	7
3	**c**		**c**	73	**c**	8
4[c]	**b**		**b**	87	/	/
5[c]	**c**		**c**	89	/	/
6	**d**		**d**	81	/	/
7	**e**		**e**	75	/	/
8	**f**		**f**	80	/	/
9	**g**		**g**	83	/	/
10	**h**		**h**	72	/	/
11	**i**		**i**	68	/	/

[a] Reactions were carried out with 2 mmol of 2-(2-ethynylphenyl)ethanol **1**, 2 mmol of aryl iodide **5**, 5 mL of Et_3N, 0.004 mmol of $PdCl_2(PPh_3)_3$, at 100° C, for 24 h, under 20 atm CO. [b] Yield of isolated product after purification by silica gel column chromatography. [c] Reactions performed with 2.5 mmol of 2-(2-ethynylphenyl)ethanol **1** and 0.5 mol-% of $PdCl_2(PPh_3)_2$.



Scheme 7. Sonogashira cyclocarbonylative reaction between 2-(2-ethynylphenyl)ethanol and 4-iodonitrobenzene or 4-iodoianiline

Conclusion

We have developed a new approach to the synthesis of alkylidene isochromans through a Pd-catalysed copper-free cyclocarbonylative coupling reaction. This tandem process involves carbonylative Sonogashira reaction between a suitable ethynyl alcohol and iodoarenes followed by a spontaneous cyclization process. The reaction proceeds with complete regio- and stereoselectivity towards the exclusive formation of the six-membered isochroman derivatives with a *(Z)-S-cis* configuration of the double bonds and aryl iodides characterized by electron withdrawing and electron donating functional groups can be successfully employed.

Experimental Section

Typical Procedure for the synthesis of (Z)-2-(isochroman-1-yliden)-1-phenyletanone 6a: 0.292 g (2 mmol) of 2-(2-ethynylphenyl)ethanol, 0.22 mL (2 mmol) of iodobenzene and 5 mL of Et_3N were put in a Pyrex Schlenk tube. This solution was introduced by a steel siphon in the autoclave, previously carried with 2.91 mg (0.004 mmol) of $PdCl_2(PPh_3)_2$ and placed under vacuum (0.1 Torr). The reactor was pressurized with CO (20 atm) and the mixture was stirred for 24 h at 100° C. After removal of excess CO (fume hood), the reaction mixture was diluted with CH_2Cl_2, filtered on celite and concentrated under vacuum. The crude product was purified by column chromatography (silica gel 60, 230–400 mesh, $CHCl_3$) yielding 0.446 g (1.78 mmol, 89%) of (*Z*)-2-(isochroman-1-yliden)-1-phenyletanone **6a** and 0.034 g (0.1 mmol, 5%) of 3-(2-(2-phenoxyethyl)phenyl)-1-phenyl-2-yn-1-one **7a**.
Supporting Information: Detailed experimental procedures, spectroscopic data, copies of the ^{1}H NMR and ^{13}C NMR spectra

Keywords: Synthetic methods / Cross-coupling / Carbonylation Cyclisation / Isochromans

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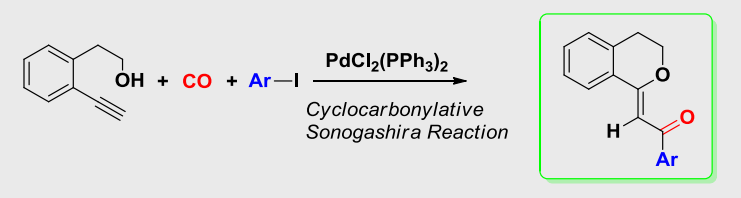
SHORT COMMUNICATION



An atom-economic palladium catalysed carbonylative Sonogashira reaction – cyclisation sequence is used for the preparation of 2-alkylidene isochromans with high yields and stereoselectivity

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Synthesis of 2-alkylidene isochromans via cyclocarbonylative Sonogashira reactions