SHORT COMMUNICATION

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Synthesis of 2-Alkylideneisochromans by Cyclocarbonylative Sonogashira Reactions

Laura Antonella Aronica,*[a] Luca Giannotti,[b] Stefano Giuntini,[a] and Anna Maria Caporusso[a]

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In this study we used a tandem carbonylative Sonogashira reaction/cyclisation process to construct alkylidene-functionalized isochromans in high yields with complete stereoselectivity (only *Z* isomers were formed). The reaction was performed in the absence of a 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 were 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 neurokinin-1-receptor antagonists[6] or have a specific effect on the dopaminergic system.[7] Moreover, isochromans can be precursors for the synthesis of isochromanones,[8] tetrahydrobenzazepines,[9] and benzodiazepine-4-ones,[10] all of which are important building blocks in organic chemistry.

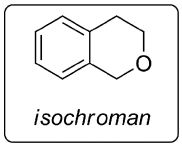
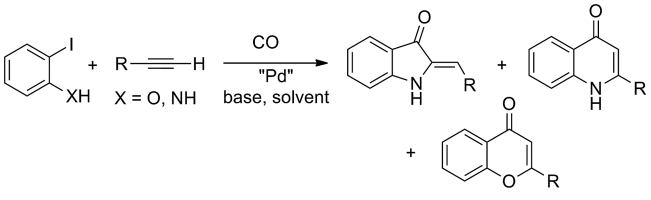


Figure 1. Isochroman structure.

Several excellent methods for the formation of the isochroman skeleton are described in the literature. Many of them are based on the oxa-Pictet–Spengler reaction,[11–15] which consists of the condensation of a β-arylethanol derivative 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*-toluenesulfonic acid, acetic acid, oleic acid, $AlCl_3$, $TiCl_4$, and $ZnCl_2$, but zeolites[16] and bismuth triflate[17] have also been shown to be effective. A different approach was reported by Florio[18] et al. and is based on the sequence of lithiation/acid-catalyzed 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 aryloxiranes to enaminones.[19] Ramana and coworkers[20,21] reported the application of [2+2+2] alkyne–diyne cyclotrimerization to the preparation of enantiopure isochromans catalyzed by a rhodium species. Functionalized diynes were also used in a Heck carbopalladation/cyclization sequence[22] for the synthesis of highly substituted isochromans. Finally, palladium catalysts have been employed in cyclization reactions[23–26] of benzyl and homobenzyl alcohols derivatives.

Recently, a few examples of the synthesis of heterocyclic derivatives such as isoquinolones, isoindolinones,[27] flavones, chromones,[28] and benzofurans[29] based on palladium-catalyzed Sonogashira reactions were described. In particular, 2-iodophenols and 2-iodoaniline were treated with terminal acetylenes under a carbon monoxide atmosphere to generate acetylenic ketones that underwent cyclization to afford the heterocyclic derivatives 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 Sono-

[a] Dipartimento di Chimica e Chimica Industriale, University of Pisa,
Via Risorgimento 35, 56123 Pisa, Italy
E-mail: laura.antonella.aronica@unipi.it
http://www.dcci.unipi.it
[b] Dipartimento di Biotecnologie, Chimica e Farmacia,
Via Aldo Moro 2, 53100 Siena, Italy

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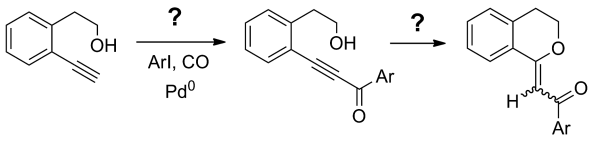
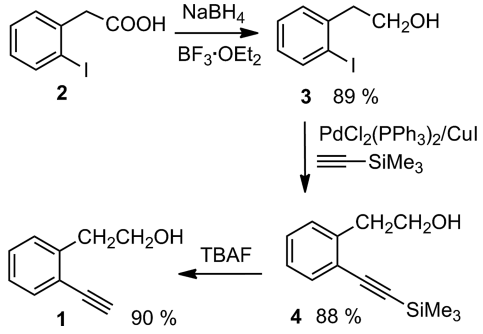
gashira reaction/cyclization sequence to the synthesis of isochromans. Indeed, starting from a suitable substrate, this tandem process afforded 2-alkylideneisochromans (Scheme 2), the preparation of which is seldom reported.[31]



Scheme 2. Possible synthesis of isochroman through cyclocarbonylative Sonogashira reaction.

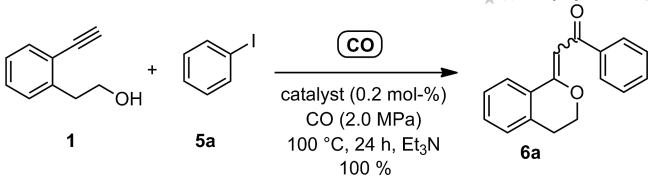
Results and Discussion

2-(2-Ethynylphenyl)ethanol (**1**) was chosen as a model substrate and was prepared according to the method described in Scheme 3. 2-Iodophenylacetic acid (**2**) was easily reduced to corresponding benzyl alcohol **3** in high yield (89%) by means of $NaBH_4/BF_3{\cdot}OEt_2$.[32] The acetylenic moiety was then introduced with a cross-coupling Sonogashira reaction with trimethysilylacetylene to yield desired product **4** (88%).[33] Finally, the trimethylsilyl group was smoothly removed by treatment of **4** with an excess amount of tetrabutylammonium fluoride (TBAF, 90%).[33]



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

A preliminary cyclocarbonylative Sonogashira reaction was performed by treating **1** with iodobenzene in triethylamine chosen as both the solvent and the base at 100 °C for 24 h with $PdCl_2(PPh_3)_2$ (0.2 mol-%) and under an atmosphere of CO (2.0 MPa, Scheme 4). To our delight, analysis of the crude mixture by NMR spectroscopy indicated the complete conversion of the reagents and the formation of 2-(isochroman-1-ylidene)-1-phenylethanone (**6a**) as the principal product, which was isolated in a chemically pure form (column chromatography) in high yield (89%). The configuration of the double bond of the olefinic moiety was then determined by analysis of the results obtained with a NOESY (nuclear Overhauser effect spectroscopy) experiment. Relevant NOE effects were detected between vinylic H^a and aromatic H^b and H^c, as shown in Figure 2, which thus indicated the exclusive formation of the *Z* isomer of isochroman **6a** with two conjugated double bonds in an *s-cis* geometry.



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

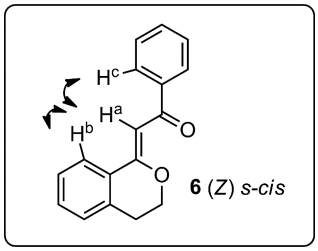


Figure 2. Isochroman structure.

Notably, according to Baldwin's rules,[34] only six-membered ring **6a** was generated during the cyclization process (6-*exo-dig*), whereas no trace amounts of the possible tetrahydrobenzoxepine derivative were detected. In addition to 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).

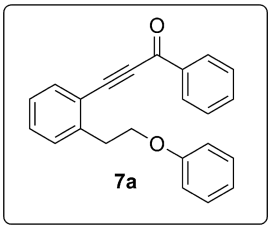
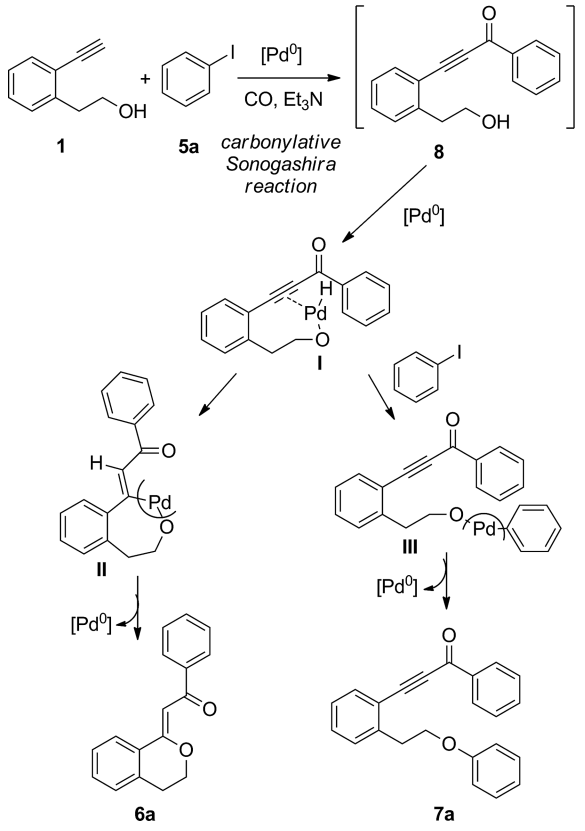


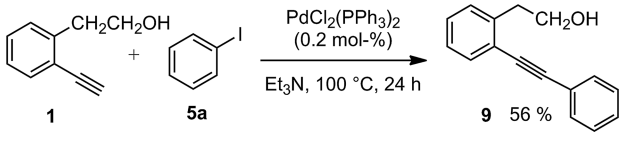
Figure 3. Structure of 3-[2-(2-phenoxyethyl)phenyl]-1-phenyl-2-yn-1-one.

A plausible mechanism for the formation of both products **6a** and **7a** is described in Scheme 5. It involves, first, the Sonogashira carbonylative reaction between iodobenzene (**5a**) and ethynyl alcohol **1**, which should form 3-[2-(2-hydroxyethyl)phenyl]-1-phenylprop-2-yn-1-one (**8**) as the intermediate of both derivatives. At this point, Pd^0 insertion into the O–H bond would generate palladium hydride specie **I**, which can undergo two different transformations. Hydropalladation 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 the arylation of benzylic or homobenzylic alcohols catalyzed by transition-metal-based species have been described.[35]



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

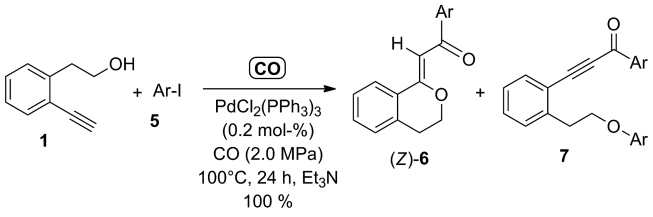
Moreover, the carbonylation of the triple bond was found to be fundamental for the cyclization process. Indeed, if a reaction between ethynyl alcohol **1** and iodobenzene (**5a**) was performed in the absence of carbon monoxide, only 2-[2-(phenylethynyl)phenyl]ethanol (**9**) was formed (56% purified 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 electron-donating and electron-withdrawing substituents in the *ortho* and *para* positions. As described in Table 1, quantitative conversion of the reagents was detected in all experiments. The reactions generated isochroman derivatives **6a**–**i** in good to excellent yields (68–89%) with complete stereoselectivity towards the formation of the *Z* isomer, regardless of the stereoelectronic features of employed aryl iodides **5**. A small decrease in the chemoselectivity was observed if the steric requirements of **5** increased, such as in the cases of α-naphthyl and *o*-tolyl derivatives (Table 1, entries 2 and 3). However, upon performing the reactions between **1** and aryl iodides **5b** and **5c** with a small excess amount of alcohol **1** with 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-%), ether byproducts **7b** and **7c** completely disappeared and improved yields (87–89% vs. 73–75%) of isochromans **6b** and **6c** were obtained (Table 1, entries 4 and 5).

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



Entry	5	Ar	(*Z*)-6	Yield[b] [%]	7	Yield[b] [%]
1	**a**	Ph	**a**	*89*	**a**	5
2	**b**	1-naphthyl	**b**	75	**b**	7
3	**c**	2-MeC_6H_4	**c**	73	**c**	8
4[c]	**b**	1-naphthyl	**b**	87	–	–
5[c]	**c**	2-MeC_6H_4	**c**	89	–	–
6	**d**	4-MeC_6H_4	**d**	81	–	–
7	**e**	2-$MeOC_6H_4$	**e**	75	–	–
8	**f**	4-$MeOC_6H_4$	**f**	80	–	–
9	**g**	4-ClC_6H_4	**g**	83	–	–
10	**h**	4-NCC_6H_4	**h**	72	–	–
11	**i**	2-NCC_6H_4	**i**	68	–	–

[a] Reactions were performed with **1** (2 mmol), **5** (2 mmol), Et_3N (5 mL), and $PdCl_2(PPh_3)_3$ (0.004 mmol) at 100 °C for 24 h under an atmosphere of CO (2.0 MPa). [b] Yield of isolated product after purification by silica gel column chromatography. [c] Reaction was performed with **1** (2.5 mmol) and $PdCl_2(PPh_3)_2$ (0.5 mol-%).

Moreover, upon performing the reaction with 2-iodobenzonitrile (**5i**), that is, 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.

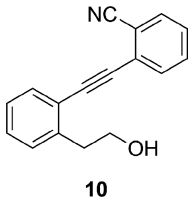
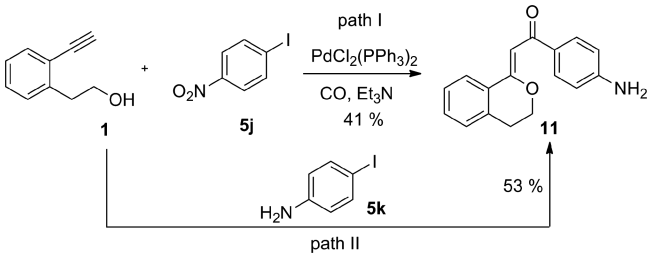


Figure 4. Byproduct of the Sonogashira cyclocarbonylation of 2-iodobenzonitrile.

This result can be explained with a competitive noncarbonylative Sonogashira reaction that determined the formation of direct coupling product **10**. According to the results previously observed in the noncarbonylative experiment (Scheme 6), **10** did not cyclize because of the absence of the CO moiety.

Finally, upon testing 4-iodonitrobenzene 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 **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 in chemically pure form in a good yield (53%). These results indicate that the Sonogashira cyclocarbonylative process can take place successfully even in the presence of a free NH_2 group, whereas the NO_2 moiety is reduced in situ.



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

Conclusions

We developed a new approach for the synthesis of alkylideneisochromans through a Pd-catalyzed copper-free cyclocarbonylative coupling reaction. This tandem process involves a 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 possessing electron-withdrawing and electron-donating groups can be successfully employed.

Experimental Section

Typical Procedure for the Synthesis of (*Z*)-2-(Isochroman-1-ylidene)-1-phenyletanone (6a): A Pyrex Schlenk tube was charged with 2-(2-ethynylphenyl)ethanol (0.292 g, 2 mmol), iodobenzene (0.22 mL, 2 mmol), and Et_3N (5 mL). This solution was introduced by a steel siphon into the autoclave, previously charged with $PdCl_2(PPh_3)_2$ (2.91 mg, 0.004 mmol) and placed under vacuum (13.3 Pa). The reactor was pressurized with CO (2.0 MPa), and the mixture was stirred for 24 h at 100 °C. After removal of the excess amount of CO (fume hood), the mixture was diluted with CH_2Cl_2, filtered through Celite, and concentrated under vacuum. The crude product was purified by column chromatography (silica gel 60, 230–400 mesh, $CHCl_3$) to yield **6a** (0.446 g, 1.78 mmol, 89%) and 3-[2-(2-phenoxyethyl)phenyl]-1-phenyl-2-yn-1-one (**7a**; 0.034 g, 0.1 mmol, 5%).

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures, spectroscopic data, and copies of the ^1H NMR and ^{13}C NMR spectra

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