Potentialities and Syntheses of $O$- and $N$-Heterocycles: Pd-Catalysed Cyclocarbonylative Sonogashira Reaction as a Valuable Route to Phthalans, Isochromanes and Isoindolines

Gianluigi Albano and Laura Antonella Aronica

Abstract: Oxygen and Nitrogen-heterocyclic compounds are found in a vast number of natural substrates and biologically active molecules. In particular, phthalans, isochromanes and isoindolines scaffolds are present in many classes of products such as antimiocotics, antibiotics, antioxidants, pigments and fluorophores. Therefore several procedure dedicated to the building of such heterocycles have been developed. In this review a detailed analysis of literature data regarding these nuclei is described. Particular attention has been devoted to their biological and chemical potentialities and a deep investigation on the most important synthetic methods is reported. Cyclocarbonylative Sonogashira reaction of suitable alcohols and amines has been especially considered, since it represents a valuable and atom economic route to construct alkylidene phthalans, isochromanes and isoindolines.

1. Introduction

Oxygen and nitrogen-containing heterocycles are widespread in nature and their applications in biologically active drugs, agrochemicals and functional materials are well known. So it is not surprising that among the top 25 best-selling pharmaceuticals from the year of 2015 there have been several small molecules with heterocycles moieties such as Sofosbuvir, a medication used for the treatment of hepatitis C, Rosuvastatin employed to treat high cholesterol and related conditions, Lenalidomide intended as treatment of multiple myeloma, Aliprazole, an atypical antipsychotic, Ibrutinib, used to treat mantle cell lymphoma and chronic lymphocytic leukemia and Apixaban, an anticoagulant for venous thromboembolic events. As a consequence, the interest of the scientific community in developing efficient strategies for the synthesis of these systems has been enormous and a wide range of different methodologies have been described depending on the structure of the heterocyclic target.

In this review we have taken into account three different heterocycles scaffolds depicted in Figure 1: phthalans, isochromans and isoindolines. The literature regarding each nucleus and its derivatives has been examined and organized into the following sections: biologically active molecules, chemical reactivity of substrates and principal methods for the synthesis of the heterocycle derivatives with particular attention to the synthesis of alkylidene heterocycles via palladium catalysed cyclocarbonylative Sonogashira reactions.

![Figure 1. Scaffolds of reviewed heterocycles.](image)

2. Oxygen heterocycles

2.1. Phthalans

2.1.1. Applications, reactivity and general synthetic methods

The 1,3-dihydroisobenzofuran (better known as phthalan) moiety (Figure 2) has been found in a growing number of naturally occurring compounds.\(^\text{[1]}\)
Interestingly, Larock during due to exo can be promoted T alkyne groups to alcohols oxetanes derivatives) common is Alder Pictet of 1(2H) a powerful substituents in the benzylic position

Figure 3. Chemical structure of selected bioactive phthalans: pestacin (A), citalopram (B).

Exploiting the opening of heterocyclic ring and/or the reactivity of substituents in the benzylic position, 1,3-dihydroisobenzofurans are powerful building blocks for the synthesis of several class of compounds: phthalides,[20] benzylic alcohols,[21] isochroman-3-ones[22] and complex Diels-Alder cycloadducts.[23] In addition, alkyldenedephthalans can give access to a variety of heterocycles, such as functionalized phenanthro[10,1-b]furans,[24] isoquinolin-1(2H)-ones,[25] and pyrazoles[26] (Scheme 1).

Although many procedures for phthalans preparation have been developed,[27] including reduction of phthalides,[11] hydrogenation of isobenzofurans,[12] Garratt-Braverman cyclizations,[13] exo-Pictet-Spengler reactions[14] and cycloadditions (in particular Diels-Alder[28] or [2+2+2] cyclotrimerization of alkynes[29]), the most common is based on cycloetherification of benzylic alcohols (or their derivatives) having an appropriate ortho-substituent: epoxides,[30] oxetanes,[31] quaternary ammonium salts,[32] benzylic halides or alcohols,[33] alkenes[34] and, in the specific case of 1-alkylidene-1,3-dihydroisobenzofurans synthesis, also 1,2,3-triazole rings[35] and alkyne groups.

The cyclisation of ortho-alkynyl O-benzyl-functionalized aromatics can be promoted by means of a base. Padwa et al. described 5-exo-dig cyclisation of 2-(arylethynyl)benzyl alcohols with different basic conditions.[36] Unwanted 6-endo-dig ring closure is actually due to a rearrangement of the initially formed alkyldenedephthalans during acid work-up step (Scheme 2). Interestingly, Larock et al. proposed the iodocyclization of 2-(1-alkynyl)(benzyl) alcohols with I₂ and NaHCO₃ as base: although 6-endo-dig cyclization mode is generally preferred, in the case of tertiary alcohols only (Z)-alkyldenedephthalan products were obtained, owing to the gem-dialkyl effect.[37]

Figure 2. 1,3-Dihydroisobenzofuran (phthalan) nucleus.

One of the most representative examples is pestacin (Figure 3, A), isolated in 2003 by Grant et al. from Pestalotiopsis microspora, with good antymycotic and antioxidant properties.[11] Many synthetic phthalans also revealed remarkable pharmacological activities:[20] citalopram (Figure 3, B), developed in 1989, is a selective serotonin re-uptake inhibitor (SSRI) used in the treatment of depressive syndromes and anxiety disorder.[24] Moreover, some of them have applications in the agrochemicals, colorants and perfumes industries.[3]

Synthetic routes to 1-alkylidene-1,3-dihydroisobenzofurans based on t-BuOK-promoted cycloetherification of o-alkynylbenzaldehydes[25] or o-alkynylbenzyl alcohols[33] and similar fluoride-induced reaction of silyl-protected 2-ethynylbenzyl alcohols[38] were also reported.

2.1.2. Synthesis of alkyldenedephthalans by metal-catalysed 5-exo-dig cyclization of ortho-alkynyl aromatics

Metal-catalyzed cyclisation of ortho-alkynyl aromatics bearing a nucleophilic oxygen atom at the benzylic position is a more general approach to afford alkyldenedephthalans. A very intriguing synthetic methodology was proposed by Barrett et al.: alkaline earth bis(trimethylsilyl)amides [M[N(SiMe₃)₂]₂]: (M = Ca, Sr, Ba) complexes were found to act as efficient precatalysts for stereoselective hydroalkoxylation/cyclisation of 2-alkynylbenzyl alcohols to yield corresponding (E)-alkyldenedephthalans depicted in Scheme 3.[39]
Rare earth-mediated intramolecular hydroalkoxylation of alkynyl alcohols was also investigated; lanthanide bis(trimethylsilyl)amides Ln[N(SiMe3)2]2 (Ln = La, Sm, Y, Lu) and their derivatives, in fact, showed high activity and selectivity in the 5-exo-dig cyclization into 1-methylene-1,3-dihydrobenzofuran. More recently, Marks et al. extended the same protocol to some organothorium complexes.

Although many examples of cycloetherification promoted by means of transition metals (including mercury, platinum, zinc, gold and rhodium) were reported, most of them are based on copper or palladium catalysts. During the development of a new protocol for Cu(I)-catalyzed cross-coupling of alkenes with aryl iodides, Lee et al. surprisingly obtained (Z)-alkylidenephthalans when phenylacetylene was treated with 2-iodobenzyl alcohols, using Cu2O and 4,5-bis(diphenylphosphino)-9,9-dimethoxyanthracene (xantphos) as catalytic system (Scheme 4).

Moreover, copper(I) complexes bearing N-heterocyclic carbene ligands were found to be powerful catalysts in the intramolecular hydroalkoxylation of alkynols, while, Perumal et al. described a copper(I)-catalyzed synthesis of alkylidenephthalans by treatment of 2-alkynylbenzyl alcohols with Cu(OTf)2. Switching to palladium catalysis, Gabriele and coworkers reported the cycloisomerization of 2-alkynylbenzyl alcohols into corresponding (Z)-alkylidenephthalans and 1H-isochromenes by using Pd2(dcb) (1–2 mol%) as catalyst and KI (2 eq.) as additive. Substrates bearing alkyl-substituted triple bond gave preferentially 6-exo-dig ring closure, while benzyl alcohols (i.e. with an aryl-substituted triple bond) afforded 1,3-dihydroisochromenes as main product (Scheme 5).

Subsequently, they extended Pd-KI catalytic system to the oxidative carbonylation of benzyl alcohols, benzaldehydes and phenyl ketones ortho-alkynyl-substituted, which gave 1-(alkoxycarbonylmethylene)-1,3-dihydroisochromenes in good yields. More recently, the authors have exploited a similar protocol for (Z)-alkylidenephthalans synthesis from o-alkynyl aryloxiranes, through a nucleophilic ring opening–heterocyclization–oxidative carbonylation process.

Palladium species were also used for the 5-exo-dig cyclization of highly-functionalized 2-alkynylbenzyl alcohols, yielding structurally complex heterocycles such as (E)-3-(isobenzofuran-3(1H)-ylidene)indolin-2-ones or (E)-4-(isobenzofuran-1(3H)-ylidene)-1,2,3,4-tetrahydroisoquinolines.

A different synthetic route to 1-alkylidene-1,3-dihydroisochromenes was proposed by Kwon’s group and consisted in a tandem Michael-Heck reaction of 2-iodobenzyl alcohols with electron-poor alkenes, giving a β-(o-iodobenzyl)acrylate intermediate which provides alkylidenephthalan product with good (2)-stereoselectivity through intramolecular Heck coupling (Scheme 6).

However, most of the Pd-catalyzed protocols for alkylidenephthalans synthesis involved a sequential Sonogashira coupling followed by 5-exo-dig cyclization. Abbati et al. described the preparation of (Z)-1-alkylidene-methoxy-1,3-dihydroisochromenes in high yields (79–99%) by microwave-assisted treatment of o-bromobenzaldehydes and arylacetylenes with PdCl2(PPh3)2, CuI, tBuOK as base and CH2OH as both reactant and solvent (Scheme 7).

Scheme 3. (E)-Alkylidenephthalans synthesis by alkaline earth metal-catalysed hydroalkoxylation/cyclization of 2-alkynylbenzyl alcohols.

Scheme 4. Cu2O-promoted synthesis of (Z)-Alkylidenephthalans discovered by Lee et al.

Scheme 5. Cyclization of 2-alkynylbenzyl alcohols into (Z)-alkylidenephthalans and 1H-isochromenes by mean of Pd(II/KI) catalytic system.

Scheme 6. Tandem Michael-Heck reaction of 2-iodobenzyl alcohols with electron-poor alkenes proposed by Kwon’s group.

Scheme 7. Synthesis of (Z)-1-alkylidene-3-methoxy-1,3-dihydroisochromenes proposed by Abbati and coworkers.
Kundu and Khan reported the reactions of 2-iodobenzyl alcohol with a slight excess of acetylenic carbonyls: through a domino Sonogashira/5-exo-dig cyclization process, they obtained (E)-alkylidenephthalans as the only products (80-96% yields, Scheme 8).[46]

A versatile protocol for tandem Sonogashira/hydroalkoxylation of functionalized 2-bromo- and 2-chlorobenzyl alcohols with several arylalkynes was developed by Buxaderas et al.[47] They obtained (Z)-alkylidenephthalans in good yields (over 50%) but a central role in the optimization of experimental conditions is played by microwave irradiation. Very recently, Pd nanoparticles dispersed in a glycerol phase have found wide application in the multi-step synthesis of various heterocycles, including (Z)-alkylidenephthalans by reaction of ortho-iodobenzyl alcohols with phenylacetylene.[48]

Gundersen and co-workers[49] reported a very intriguing work: the one-pot Sonogashira coupling/5-exo-dig cyclization reaction between 2-ethynylbenzyl alcohol which gave alkylidenephthalan mainly as the (E)-isomer. However, a very fast isomerization into the (Z)-isomer was found by acid-catalysed treatment (Scheme 9).

The reaction mechanism proposed by Aronica and coworkers involves, first of all, a Pd-catalyzed carbonylatve Sonogashira coupling between the alkynyl group and the aryl iodide (Scheme 12, step I), followed by the insertion of Pd(O) into the O-H bond of the Sonogashira product (Scheme 12, step II). Then, the obtained palladium hydride species gave syn hydropriaddition to the triple bond (Scheme 12, step III). Finally, a reductive elimination step afforded the (E)-isomer of phthalan product (Scheme 11, step IV), which equilibrated with the (Z)-isomer (Scheme 12, step V).

The reaction scope has been investigated and the most interesting results are described in Table 1. The protocol has been successfully extended to aryl iodides bearing electron-donating or electron-withdrawing substituents in the ortho and para position (Table 1). In almost all cases alkylidenephthalans were obtained quantitatively except for the reactions performed with o- and p-cyanoaroyl iodides, where significant amount of carboxylative Sonogashira products were also found (Table 1, entries 8-9).
As it is clear from Table 1, 2-ethylbenzyl alcohol was used in the reaction proceeded with good stereoselectivity toward the (Z)-isomer (Table 1, entries 1-9), while when tert-butylalcohol derivative was employed, the major isomer resulted to have (E) configuration (Table 1, entries 10-11). This unexpected result has been explained with the reduction of the global rate of the catalytic cycle due to the steric hindrance of the alcohol, resulting in a lower conversion of the (E)-isomer into (Z)-isomer (Scheme 12, step V).

Finally, a curious behavior for the reaction of 2-ethylbenzyl alcohol with 1-iodo-4-nitrobenzene has been described: in addition to the expected phthalan, almost equal amounts of aminoderivative were obtained (Scheme 13). Its formation could derive from the reduction of −NO₂ into −NH₂ due to the presence of Pd-hydride species in the catalytic cycle (Scheme 12, step II).

Table 1. Cyclocarbonylative Sonogashira reaction of ortho-ethylbenzyl alcohols with aryl iodides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Ar</th>
<th>Yield (%)</th>
<th>(after purification)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Z</td>
</tr>
<tr>
<td>1</td>
<td>H</td>
<td>Ph</td>
<td>63 (68)</td>
<td>37 (25)</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>1-naph</td>
<td>86 (87)</td>
<td>14 (10)</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>4-MeOC₆H₄</td>
<td>75 (83)</td>
<td>25 (14)</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>2-MeOC₆H₄</td>
<td>81 (81)</td>
<td>19 (14)</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>4-MeC₆H₄</td>
<td>59 (60)</td>
<td>41 (33)</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>2-MeC₆H₄</td>
<td>71 (72)</td>
<td>29 (27)</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>4-ClC₆H₄</td>
<td>61 (51)</td>
<td>39 (11)</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>2-NC₂H₄</td>
<td>83 (69)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>4-NC₂H₄</td>
<td>50 (33)</td>
<td>25 (13)</td>
</tr>
<tr>
<td>10</td>
<td>tBu</td>
<td>Ph</td>
<td>22 (15)</td>
<td>78 (57)</td>
</tr>
<tr>
<td>11</td>
<td>tBu</td>
<td>2-MeOC₆H₄</td>
<td>44 (32)</td>
<td>56 (35)</td>
</tr>
</tbody>
</table>

According to the proposed mechanism, Aronica et al. authors[60] justify this result considering that the presence of a strong electron-withdrawing −C=O group can reduced the electron density on triple bond of Sonogashira coupling products, thus slowing the syn hydopalladation step (Scheme 12, step III).

As it is clear from Table 1, when 2-ethylbenzyl alcohol was used the reaction proceeded with good stereoselectivity toward the (Z)-isomer (Table 1, entries 1-9), while when tert-butylalcohol derivative was employed, the major isomer resulted to have (E) configuration (Table 1, entries 10-11). This unexpected result has been explained with the reduction of the global rate of the catalytic cycle due to the steric hindrance of the alcohol, resulting in a lower conversion of the (E)-isomer into (Z)-isomer (Scheme 12, step V).

Finally, a curious behavior for the reaction of 2-ethylbenzyl alcohol with 1-iodo-4-nitrobenzene has been described: in addition to the expected phthalan, almost equal amounts of aminoderivative were obtained (Scheme 13). Its formation could derive from the reduction of −NO₂ into −NH₂ due to the presence of Pd-hydride species in the catalytic cycle (Scheme 12, step II).

2.2. Isochromans

2.2.1. Biological properties, chemical reactivity and common synthetic methods

The 3,4-dihydro-1H-benzo[c]pyran (isochroman, Figure 4) nucleus constitutes the framework of a wide range of naturally occurring molecules. Its derivatives have been found in olive oil,[61] pine wood,[62] herbs,[63] flowers,[64] and fungi.[65] Many of them show antimicrobial and antifungal activities,[66] possess antioxidant power,[67] exhibit antiplatelet,[68] antitumoral,[69],[70] and anti-inflammatory[70] properties.

Furthermore, some synthetic 1-aryldihydroisochromans (Figure 5, A) display radical scavenger capacity[71], pseudoflectusin[72] (Figure 5, B) shows cytotoxicity against several human cancer cell lines, polysubstituted isochroman derivatives[73] (Figure 5, C) exhibit growth regulating properties on wheat and Galaxolide[74] (Figure 5, D) is one of the most used musk fragrance present in many products including surface cleaners, laundry products, air fresheners, cosmetics and perfumes.
 Indeed, isochroman can be easily submitted to oxidation affording isochromanone by means of CrO₃, ammonium salts or molecular oxygen catalysed by ferric complexes or by TEMPO derivatives. Moreover C-C bond formation at C(1) position of isochroman has been widely studied. This transformation is commonly performed through the so-called cross-dehydrogenative coupling (CDC) reaction which generally requires catalysts such as copper and iron salts, oxidants such as hydrogen peroxide, O₂, tert-butylhydroperoxide (TBHP) or 2,3-dichloro-5,6-diclanobenzoquinone (DDQ) and carbon nucleophiles. For instance, Muramatsu et al. reported several examples of arylation of the benzylic position of isochromans performed with Grignard reagents and DDQ or 2-hydroxy-2-azaadamantane as oxidants, while Todd and co-workers described efficient C-C(1) bond formation between isochroman and anisoles in the presence of DDQ and CuCl₂. Recently, successful heteroarylation with indole derivatives have been described by Cai et al. using di-tert-butylperoxide (DTBP) as the oxidant. Ketones and malonates have been introduced by Li and co-workers in the C(1) position of isochroman ring employing molecular oxygen or DDQ in the presence of indium or copper salts. Two similar approaches were developed by Manchono et al. using Cu(OTf)₂ as catalyst and 2,2,6,6-tetramethyl-1-piperidinylamine (TEMPO) oxoammonium salt as the oxidant and by Lou et al. using MnO₂ and methanesulfonic acid as oxidation system under aerobic conditions. Very recently, Huo and co-workers reported the CB₄ mediated dehydrogenative coupling of isochromans with aromatic ketones, while Wo et al. demonstrated that the nucleophilic addition of β-keto esters to isochroman can be achieved by photoredox-neutral catalysis using a commercial dyad photosensitizer. Analogously thioethers and ciano groups can be introduced in the C(1) position via a CDC strategy using DTBP or DDQ as oxidant. Amination and amidation of isochroman can be obtained with FeCl₃/TBHP or under metal-free conditions in the presence of DTBP (Scheme 14, f).

**Scheme 14. Reactivity of isochromans.**

Watson and Huang reported that alkenylation or alkynylation of isochroman can be achieved starting from its acetal via iron or copper-catalysed cross-dehydrogenative couplings. On the other hand 1-chloroisochroman can be alkylated when reacted with silyl ketene acetals in the presence of thiourea, pyridinium or polyfluoroorganocatalysts (Scheme 14, h). Finally, isochroman can be submitted to reductive ring-opening giving rise to intermediates useful for the building of several polyfunctionalised compounds. Numerous synthetic routes for the formation of the isochroman skeleton are described in the literature. Many of them are based on the oxo-Pictet-Spengler reaction which consists of the condensation of a β-arylethanol derivative with a carbonyl compound to form a hemiacetal which undergoes cyclization to give the isochroman ring (Scheme 15).

**Scheme 15. Oxo-Pictet-Spengler synthesis of isochromans.**

Depending on the nature of the starting β-arylethanols and carbonyl components (aldehydes, ketones, and their surrogates such as acetals) this condensation can be used to provide 1-substituted and 1,1-disubstituted isochromans as well as polyfunctionalized derivatives in C-3 and C-4 positions.
The reaction is generally promoted by acid catalysts that should increase the electrophilic behavior of the carbonyl compounds. Typically, H$_2$SO$_4$, HCl, TFA, perfluoroctanesulfonic acid, p-TsOH, CH$_3$COOH, oleic acid, BF$_3$·Et$_2$O, AlCl$_3$, TiCl$_4$, ZnCl$_2$, SnCl$_4$ are used, but also zeolites, bismuth trflate and trimethylsilyl triflate have been shown to be effective. Although many reports of oxa-Pictet-Spengler reaction are described in the literature, many of them suffer from drawbacks such as harsh reaction conditions, substrate specificity and use of highly toxic reagents.

Two different approaches were developed by Florio et al. and are based on the cyclization of ortho-hydroxyalkylated aziridines and on the reaction of arylepoxides with enamiones. Analogously, Kobayashi and coworkers employed epoxides for the synthesis of 1-(2-vinylphenyl)propan-2-ols which were then converted into the corresponding isochromans by treatment with HI in acetonitrile. Finally, Tamerini et al. reported a selenium-mediated strategy for the stereoselective preparation of 1- and 4-substituted isochromans.

### 2.2.2. Palladium catalysed synthesis of alkylideneisochromans via cyclocarbonylative Sonogashira reaction

The synthesis of isochromans has also been accomplished via palladium catalysed cyclisation reactions of suitable substrates (Scheme 16). White and coworkers used benzyl alcohols (Scheme 16, a) and a Pd(II)/bis-sulfoxide catalyst to obtain 3-vinylisochroman derivatives in good yields (65-76%). Later on the same group reported the synthesis of 1-functionalised isochromans promoted by Pd(OAc)$_2$ and a sulfoxide-based ligand (Scheme 16, b). Han et al. described the first palladium-catalysed heteroannulation of 1,3-dienes and 2-iodobenzylcnic alcohol; this protocol provides an efficient way to optically active chiral isochromans (Scheme 16, c). In 2011 Perumal et al. reported the first detailed study on the synthesis of 4-arylisochromans (Scheme 16, d) starting from (2-bromobenzoxylxy)prop-1-ynyl-4-methylbenzene derivatives promoted by Pd(PPh$_3$)$_2$. This cyclisation reaction occurs with high regio- and stereoselectivity leading to one isomer in high yields.

1-Methylene-functionaionalised isochromans were obtained also by Yu and coworkers through a Pd(II) catalysed hydroxyl-directed C-H olefination of homobenzylcnic alcohols (Scheme 16, e). Also in this case, the cyclisation process took place with complete stereoselectivity affording the E-isochroman derivatives exclusively.

As already discussed (see section 2.1.3) Sonogashira cyclocarbonylative reaction demonstrated to be a valuable route for the synthesis of carbonylmethylene-1,3-dihydrobenzofurans from 2-ethynylbenzylcnic alcohols and arylic acids. Aronica et al. applied this methodology to the preparation of alkylidenoisochromans.

The starting material, 2-(2-ethylphenyl)ethanol was easily generated through a synthetic sequence which involved: i) reduction of 2-iodophenylacetic acid to the corresponding benzyl alcohol; ii) cross coupling reaction with trimethylsilylacetylene and iii) final desilylation with TBAF.

At the beginning of their study, Aronica and co-workers performed a cyclocarbonylative Sonogashira reaction using 2-(2-ethylphenyl)ethanol with iodobenzene under the experimental conditions optimized for dihydrobenzofurans. (Scheme 17).

Scheme 17. Preliminary cyclocarbonylative reaction between 2-(2-ethylphenyl)ethanol and iodobenzene.

After 24 h, the complete conversion of the reagents was reported and the formation of 2-(isochroman-1-yliden)-1-phenylcetone as principal product was observed. The reaction resulted completely stereoselective since the exclusive synthesis of the Z isomer with two double bonds in an s-cis geometry was detected (Scheme 17).

In agreement with Baldwin’s rules, only the 6-membered isochroman ring was generated (6-exo-dig cyclisation) while no traces of the possible tetrahydrobenzoxepine derivative were detected. Nevertheless, together with the methyleneisochroman derivative, a small amount of an opened by-product was isolated. It resulted to be 3-(2-(2-phenoxyethyl)phenyl)-1-phenyl-2-yn-1-one, shown in Figure 6.

Figure 6. Structure of 3-(2-(2-phenoxyethyl)phenyl)-1-phenyl-2-yn-1-one.
The formation of both products was explained with the proposed mechanism (Scheme 18) which involved, first of all, the Sonogashira carbylationative reaction between iodobenzene and ethynyl alcohol that should form 3-(2-(2-hydroxyethyl)phenyl)-1-phenylprop-2-yn-1-one as intermediate of both products. At this point, Pd(0) insertion into the O-H bond would generate the palladium hydride species I which can undergo two different transformations: i) hydropalladation reaction to the triple bond (Scheme 18, II) followed by reductive elimination which should afford isochroman; ii) a direct insertion of palladium into the C-I bond of iodobenzene (Scheme 5, III) with subsequent reductive elimination of Pd2, generating the benzylether.

![Scheme 18. Plausible mechanism for the formation of isochroman and ether.](image)

The importance of the carbylation step in the cyclisation process was demonstrated by reacting 2-(2-ethylnaphthalen-1-yl)ethanol and iodobenzene under nitrogen atmosphere. In this case only 2-(2-phenylethynyl)phenyl)ethanol was formed (Scheme 19).

![Scheme 19. Sonogashira reaction between 2-(2-ethylnaphthalen-1-yl)ethanol and iodobenzene.](image)

The cyclocarbonylation process was successfully extended to iodoaryl substrates possessing both electron donating and electron withdrawing substituents in ortho or para position (Table 2). In all cases, the reactions generated the isochroman derivatives with good to excellent yields (68-89 %) and with complete stereoselectivity towards the formation of the (Z)-isomer, regardless the stereoelectronic features of Ar-I. A particular behaviour was observed when 4-iodonitrobenzene was tested. Indeed, in this case, the reaction afforded (Z)-1-(4-aminophenyl)-2-(isochroman-1-ylidene) ethanone exclusively (Scheme 20 path I). The structure of this product was confirmed by means of a cyclocarbonylative reaction performed between the ethynylalcohol and 4-idoaniline (Scheme 20 path II). In this case the exclusive formation of amino derivative was detected and the product was isolated chemically pure with a good yield (53 %).

![Scheme 20. Sonogashira cyclocarbonylative reaction between 2-(2-ethylnaphthalen-1-yl)ethanol and 4-iodonitrobenzene or 4-idoaniline.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Yield (%, isolated)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>1-Naphthyl</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>2-MeC6H4</td>
<td>89</td>
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<tr>
<td>4</td>
<td>4-MeC6H4</td>
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<td>5</td>
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<td>6</td>
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<tr>
<td>8</td>
<td>4-NCMe2</td>
<td>72</td>
</tr>
<tr>
<td>9</td>
<td>2-NCC6H4</td>
<td>68</td>
</tr>
</tbody>
</table>

The in situ reduction of nitro group has been already described for the cyclocarbonylative Sonogashira reaction of ethynylbenzylalcohols (Scheme 13), indicating a very similar reaction mechanism for both processes.

3. Nitrogen heterocycles

3.1. Isoindolines

3.1.1 Biological properties, chemical reactivity

Isoindoline (Figure 7) can be considered the hydrogenated analogue of isoindole, whose scaffold is widespread in naturally occurring compounds such as alkaloids and antibiotics. On the contrary, isoindoline nucleus is almost absent in nature but is present in a large variety of biologically active synthetic derivatives. For instance, some of them act as inhibitor of dipeptidyl peptidases, a drug target for type II diabetes.
N-Acylisoindolines (Figure 8, A) showed high activity in the inhibition of heat shock protein 90 (HSP90), a molecular chaperon responsible for the correct folding and proper conformation of many signaling proteins, especially some oncogenic ones.

Similar compounds (Figure 8, B) were reported to act as efficient pyruvate dehydrogenase kinase (PDK) inhibitors by entering in the ATP-binding pocket of the enzyme. This is particularly interesting since different PDKs are up-regulated in obesity, diabetes, heart failure, ischemia, and cancer. Shultz and co-workers synthesized a novel series of isoindolines-based hydroxamates which were able to inhibit cellular proliferation of human colon cancer cells (Figure 8, C). Benzoylisoindolines D (Figure 8) were discovered as potent and selective inhibitors of glycine transporter-1 (GlyT1), a mediator of glycine uptake probably involved in the pathophysiology of schizophrenia.

Some synthetic polysubstituted isoindolines (Figure 8, E) derivatives were able to bind to the human dopamine receptor, thus suggesting a potential application as antipsychotic agents. Danoprevir (Figure 9), discovered in 2013, is a novel small-molecule inhibitor of the hepatitis C virus NS3/4A protease, a clinical candidate based on its favorable potency profile against multiple HCV genotypes.

Mancilla Percino et al. described the synthesis of two series of N-alkylated isoindolines (Figure 10) that were tested as inhibitors of cyclooxygenase 1 and 2, and possessed antitumoral properties against cervical cancer cells. The same compounds resulted to be effective as brain and cardiac Ca\textsuperscript{2+} channel blockers, potentially active for epilepsy treatment and for the correct performance of atrial and ventricular myocytes.

The isoindoline class of nitroxides are stable free radical species which are finding increased use in a wide range of applications. Compared with the more common nitroxides containing piperidine or pyrrolidine units, isoindoline ones contain a fused aromatic moiety which imparts rigidity to the ring system, making it less susceptible to opening side reactions. One of the most common use for nitroxides is as sensitive probes for the study of processes involving reactive free radical species using EPR spectroscopy. In this field, the first class of isoindoline nitroxides were developed by Bottle and co-workers in 1999 and are depicted in Figure 11.

Subsequently, isoindolines nitroxides bearing a stilbene fluorophore, a benzophenone moiety, anthracene structural cores, porphyrin groups and fullerene have been synthesized and tested as free radical traps, antioxidants, therapeutic agents and other biomedical researches.
Finally, isoindoline diylidene derivatives are the nucleus of several pigments which cover the range from greenish yellow, to orange, red and brown (Figure 12). \[109\]

**Figure 12.** Isoindoline-based pigments.

From the point of view of chemical reactivity isoindolines can be submitted to many chemical transformation both on the nitrogen atom and on the carbon atoms of the pyrrolidine moiety.

For instance, Pd-catalyzed hydroamination of isoindoline has provided N-benzylated derivative,\[^{110}\] while isoindoline has been N-alkylated with a cyclopropyl group through a reaction of copper-mediated cyclopropanation with cyclopropyboronic acid,\[^{111}\] (Scheme 21, a). Analogously, a naphtalene ring has been added on the nitrogen atom using the corresponding acid under microwave irradiation,\[^{112}\] (Scheme 21, b).

Besides the typical protection of NH with Boc, isoindoline can be N-alkylated via aerobic oxidative amidation of aromatic aldehydes,\[^{113}\] (Scheme 21, c).

![Scheme 21. Synthetic applications of isoindolines.](image)

C-alkylation of isoindoline has been achieved using Meyers methodology, a three steps sequence consisting in the conversion of the isoindoline into a formamidine derivative, metallation and C-alkylation followed by deprotection of nitrogen with LiAlH\(_4\),\[^{114}\] (Scheme 21, d). Moreover, isoindoline can be precursors of isoidoles (Scheme 21, e) via palladium-catalysed dehydrogenation,\[^{115}\] and of 4,5,6,7-tetrahydroisoindoles by means of Pd(OH)\(_2\) promoted reduction\[^{116}\] (Scheme 21, f).

Recently, Galletti et al.\[^{117}\] have reported a chemo-enzymated aerobic oxidation of isoindoline that generate isoindolinone selectively (Scheme 21, g).

**3.1.2 General synthetic methods**

A very large number of synthetic routes to isoindolines are reported in the literature: reduction of phthalimides,\[^{118}\][119] isoindolones,\[^{120}\] or isoindoles,\[^{121}\] photolysis of aromatic fused 1,2,3-triazolines,\[^{122}\] cycloaddition of dipropargylamines with alkynes,\[^{123}\][124] Diels-Alder reaction and its analogues,\[^{124}\] or formation of the benzofused five-membered N-heterocycle. Although many protocols belong to this last approach, they can be grouped into three main pathways, depicted in Scheme 22.

The first route involves reaction of aliphatic and aromatic primary amines with phthalimides,\[^{120}\] or \(\alpha\)-xylene dihalides,\[^{126}\] often base- or metal-promoted (Scheme 22, a).

The second one is based on a 5-exo-dig cyclization by C-C bond formation (Scheme 22, b), achieved through intramolecular \(\alpha\)-arylation of \(\alpha\)-amino acid esters,\[^{127}\] or cyclization of unsaturated amines or amides.\[^{126}\]

![Scheme 22. Main synthetic pathways to isoindolines by N-heterocyclization.](image)

Similar to phthall synthesis, the most common approach to isoindolines is the 5-exo-dig cyclization of benzyl amines (or their derivatives) having an ortho-substituent: hydroxymethyl groups,\[^{98}\][126] (often protected as ethers,\[^{130}\] or esters,\[^{131}\] methyl or ethyl groups,\[^{132}\] alkenes,\[^{133}\] (including tandem alkylation–cyclization)\[^{134}\] and nucleophile addition–cyclization\[^{135}\] processes) and also alkynes, with the help of a base or of a metal catalyst (Scheme 22, c).

Dominguez et al. described the 5-exo-dig cyclization of N-acetyl 2-ethynylbenzylamine with NaH affording, the corresponding alkyldieneisoindoline with 90% of yield (Scheme 23). However, this protocol suffers the presence of hindered substituents at the benzylic position.\[^{136}\]

![Scheme 23. NaH-promoted protocol for cyclization of ortho-ethynylbenzylamides proposed by Dominguez et al.](image)
Sakamoto and co-workers reported an extensive study on the TBAF-promoted cyclisation of several α-alkynylbenzylamine derivatives. Interestingly, the authors found that substrates bearing alkyl-substituted triple bond gave preferentially 6-endo-dig ring closure, affording 1,2-diaryldiquinolines as main product, while benzyl amides having a TMS- or aryl-substituted triple bond yielded only alkylideneisoindolines (Scheme 24).[27a]

Moving to transition metal catalysts, the only examples of 5-exo-dig cyclization of ortho-alkynylbenzylamine derivatives described in the literature are based on gold or palladium organometallic compounds. Catalán et al. reported the synthesis of many alkylideneisoindolines by gold(I)-catalyzed intramolecular hydroamination of enantiopure α-alkynylbenzyl carbamates bearing a fluorinated alkyl substituent at the benzylic position (Scheme 25).[137]

Switching to palladium catalysis, Mori et al. found that ortho-alkynylbenzylamine derivatives, in the presence of Pd-dba2·CHCl3 as catalyst, and N-methyltosylamide as nucleophile, yielded comparable amounts of alkylideneisoindoline and isoquinoline derivatives, generated from a parallel 6-endo-dig cyclization (Scheme 26).[138]

More interestingly, Luo and Wang reported the cyclization of many N-tosyl acetylenic amines by deprotonation with n-BuLi in THF at 0°C, followed by a domino Sonogashira/hydroamination process with the one-pot addition of a (hetero)aryl iodide, Pd(OAc)2, and PPh3. This protocol was successfully extended to N-tosyl 2-ethynylbenzylamine, which afforded the corresponding (E)-alkylideneisoindoline with 63% of yield (Scheme 27).[139]

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The first application of Palladium-catalyzed cyclocarbonylative Sonogashira reaction to the synthesis of alkylideneisoindoline ring was reported very recently by Aronica et al.[140]

2-Ethynylbenzylamine could not be used directly as substrate, since its reaction with iodobenzene did not give any isoindoline product, although a total consumption of reagents was observed (Scheme 28).

In order to overcome this problem, maybe ascribable to a possible interaction between NH2 group and palladium, the amine moiety was protected with tert-butylxycarbonyl (Boc) and tosyl (Ts) groups (Figure 13).

The first reaction of N-Boc 2-ethynylbenzylamine with iodobenzene (Scheme 29) gave the tert-butyl 2-(3-oxo-3-phenylprop-1-yn-1-yl)benzylcarbamate as main product which derived from carbonylative Sonogashira coupling of iodobenzene with the alkynyl benzylamide. Only small amounts of the desired alkylideneisoindoline were detected (19%) but the formation of the five-membered product was completely stereoselective: (E) isomer was obtained exclusively.
However, increasing the reaction time to 24h, higher chemoselectivity towards the cyclisation product was observed (86%).

When Aronica and coworkers authors switched to N-tosyl 2-ethynylbenzylamine (Table 3, entry 1), the reaction afforded 1-phenyl-2-(2-tosyloisodindolin-1-ylidene)ethanone quantitively and with complete E-stereoselectivity (72% of yield after purification).

The protocol was then successfully extended to iodoarenes characterised by different functional groups such electron donating (2-OMe, 4-OMe, 2-naphthyl) or electron withdrawing (2-Cl, 4-CN) substituents (Table 3, entries 2-6). A quantitative conversion of the reagents was detected in all cases affording the corresponding (E)-1-carbonylmethyleneisoindoline products with good yields (55-72%).

Table 3. Cyclocarbonylative Sonogashira reactions of N-Boc and N-tosyl ortho-ethynylbenzylamines with aryl iodides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>t (h)</th>
<th>Yield (isolated, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>2</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>4-MeOC6H4</td>
<td>4</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>4-CIC6H4</td>
<td>4</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>4-NCC6H4</td>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>2-naphthyl</td>
<td>4</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>2-MeOC6H4</td>
<td>4</td>
<td>55</td>
</tr>
</tbody>
</table>

3.2. Serendipitous synthesis of 2,3-dihydro-1H-benzo[d]azepine via cyclocarbonylative Sonogashira reaction

Prompted by the good results obtained in the Sonogashira cyclocarbonylative reactions applied to the synthesis of alkylidene ptalans, isochromans and isoindolines, Aronica and coworkers tried to extend this method to the preparation of tetrahydroisoquinolines (Figure 14).[140]

The requiring starting material was easily prepared starting from 2-(2-iodophenyl)acetonitrile which was converted into the corresponding amine and then protected with the tosyl group affording N-(2-iodophenethyl)-4-methylbenzenesulfonamide. Subsequent ethynylation/desilylation steps yielded homobenzylic amide (Scheme 30).

The first Sonogashira cyclocarbonylative reaction of N-(2-ethynylphenethyl)-4-methylbenzenesulfonamide with iodo benzene was tested working under the experimental conditions optimised for isoindolines, i.e. CO (20 atm), 100°C, PdCl₂(PPh₃)₂, in a toluene/triethylamine mixture. Surprisingly the formation of a mixture of three products was detected. One resulted to be 4-methyl-N-(2-(3-oxo-3-phenyprop-1-yn-1-yl)phenethyl)benzenesulfonamide (Figure 15), generated by Sonogashira cycloamyative reactions without cyclisation step.

Figure 15. Structure of 4-methyl-N-(2-(3-oxo-3-phenyprop-1-yn-1-yl)phenethyl)benzenesulfonamide.
The other two compounds were identified after purification as two conformational isomers (s-trans and s-cis) of phenyl(3-tosyl-2,3-dihydro-1H-benzo[d]azepin-4-yl)methanone (Figure 16).

![Figure 16. Conformational isomers of phenyl(3-tosyl-2,3-dihydro-1H-benzo[d]azepin-4-yl)methanone.](image)

Even if the generation of the seven-membered ring is permitted by Baldwin’s rules\(^*\) since a 7-endo-dig cyclisation is favored compared with the 6-exo-dig one, the serendipitous formation of the dihydrobenzoazepine (Figure 17) derivatives was extremely interesting considering that these substrates could be precursors of the corresponding tetrahydrobenzoazepines which have been studied for more than 30 years due to their very important biological and pharmacological properties.\(^{[141]}\)

![Figure 17. 2,3-Dihydro-1H-benzo[d]azepine moiety.](image)

The chemoselectivity of the reaction was optimised working on Pd loading, reaction time and temperature. Dihydrobenzoazepine was exclusively formed when the reactions were performed for 6 h, at 110°C and with 0.4mol% PdCl\(_2\)(PPh\(_3\)_2). The extension of the Sonogashira cyclocarbonylative reaction to functionalised iodoarenes resulted in the quantitative conversion of the reagents. The (2,3-dihydro-1H-benzo[d]azepin-4-yl)aryl methanones were obtained chemically pure in good yield (46-65%) (Scheme 31).

![Scheme 31. Sonogashira cyclocarbonylative reaction of N-(2-ethynlyphenethyl)-4-methylbenzenesulfonylamine and aryl iodides.](image)

Finally, when 1-iodo-4-nitrobenzene was reacted with N-(2-ethynlyphenethyl)-4-methylbenzenesulfonylamine (Scheme 32), aminobenzepidine derivative was obtained as sole product, in agreement with the results already discussed for phthalans, isochromans and isoindolines.

![Scheme 32. Sonogashira cyclocarbonylative reaction of N-(2-ethynlyphenethyl)-4-methylbenzenesulfonylamine and 1-iodo-4-nitrobenzene.](image)

4. Conclusions

In this review has been focused on the biological activities, chemical reactivity and synthetic approaches to phthalans, isochromans and isoindolines have been taken into account. A particular attention has been paid to cyclocarbonylative Sonogashira reaction which can be used to afford alkylidene derivatives with good yields and stereoselectivities. Moreover instead of the expected tetrahydroisoquinolines, dihydrobenzazepines were exclusively generated when the reaction was performed with homobenzylic amide.

We hope that this review will stimulate further research on the application of cyclocarbonylative Sonogashira reactions such as the extension of this protocol to the synthesis of sulphur containing heterocycles, or the investigation on the possible use of heterogeneous palladium catalysts in order to improve the “greenness” of the process.

**Keywords:** Carbonylation • Cross-coupling • Phthalan • Isochroman • Isoindoline


This microreview covers the biological activities, chemical properties and synthetic methodologies of phthalans, isochromans and isoindolines with particular attention to the cyclocarbonylative Sonogashira reaction applied to the preparation of alkylidene derivatives.

O-, N-Heterocycles

Gianluigi Albano, Laura Antonella Aronica*

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Potentialities and Syntheses of O- and N-Heterocycles: Pd-Catalysed Cyclocarbonylative Sonogashira Reaction as a Valuable Route to Phthalans, Isochromanes and Isoindolines