# Copper-Catalyzed Alkoxylation as Key Step to Convert Isatin to Oxazinoindol-2-one Derivatives

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The treatment of *N*-alkyl-5,7-dibromoisatin derivatives through the copper-catalyzed sequential processes consisting of intra/intermolecular alkoxylation/amination or double alkoxylation provided the pyrrolo[1,2,3-*de*]-1,4-benzoxazine derivatives. Moreover, the alkoxylation/arylation process proceeded in a one-pot fashion under tandem copper-palladium catalysis afording 5-(hetero)aryl substituted hetero-tricyclic systems. Biological evaluation of the synthesized compounds showed antiproliferative activity on the low micromolar range.

## Introduction

The last twenty years have seen the development of efficient and user-friendly methods for the formation of carbon–nitrogen, carbon–oxygen and carbon–carbon bonds based on transition-metals catalysis, starting from aryl halide substrates and applied to the synthesis of heterocycles.[1]

The use of copper catalysts in the C-heteroatom bond formation instead of the widespread palladium catalysis was supported by economic and environmental attributes.[2]

In particular, Ullmann-type reactions showed high efficiency and easy handling in the construction of the heterocyclic systems. The synthetic scope of the copper-mediated coupling reactions was restricted until 2000 because of the harsh reaction conditions, limited range of suitable substrates and the moderate yields obtained. Since 2004 the design and use of new simple, easily handled ligands enhances the reactivity and the applicability of copper catalysts in inter- and intramolecular amination, alkoxylation and arylations processes starting from aromatic- and vinyl halides.[2f,i] Afterwards, several "ligand-free" catalytic systems have emerged for *N*-arylation of heterocycles.[3] Moreover, green conditions can also be achieved by performing the reactions in water or mixture of water-solvent.[4]

Considering the reaction processes, the development of domino reactions that involve C-C and/or C-heteroatom bonds formation and exploit transition-metal catalyzed reactions has emerged as an attractive strategy.[5] Each reaction in the tandem catalysis may be initiated by a change in conditions (e.g. change in temperature) or by the addition of a new reagent or in some cases, also the nature of the catalyst may be changed, but compared with traditional stepwise-mediated synthetic approaches, the one-pot procedures show significant advantages. Due to the time and reagents saving in purifying the single synthetic steps, as well as the reduction of the costs of the synthetic paths, this methodology is highly atom economic and environmentally benign in a practical fashion.[6]

While the construction of the bicyclic heteroaromatic derivatives under transition-metals catalysis has been extensively reported,[7] significant efforts remain to be developed in the preparation and functionalization of hetero-tricyclic products, such as [6,5,6] membered ring systems (Fig. 1). In this work, we applied the copper-catalyzed reactions to the construction of the [6,5,6]-tricyclic isatin derivatives. The interest of this scaffold was due to the presence of this skeleton in compounds acting as aldole reductase inhibitors, useful for treatment of diabetic complications (Fig. 1 comp. **1**),[8] in compounds showing anti-inflammatory activity,[9] and in molecules acting as selective human $\beta_3$-adrenergic receptor agonists (Fig. 1, comp. **2**).[10] The tetracyclic pyrido-oxazinoindole derivatives showed affinity at the 5-HT$_{2A}$ receptor and they are studied for the activity as potential antipsychotic (Fig. 1, comp. **3**).[11] Moreover, among the cannabinoid derivatives, compound **4** (Fig. 1) exhibits anti-cancer effects in a variety of different cancerous cell lines including human prostate cancer, human glioblastoma multiform, rat glioma and B16 melanoma cells[12] and it showed antiproliferative activity through the cannabinoid receptors CB$_1$ and CB$_2$.[13] Tricyclic analogues of benzoxazine derivatives showed cardiovascular effects as antihypertensive agents,[14] inhibitory capacity against topoisomerases I and II,[15] and activity for the treatment of several bacterial infections.[16]
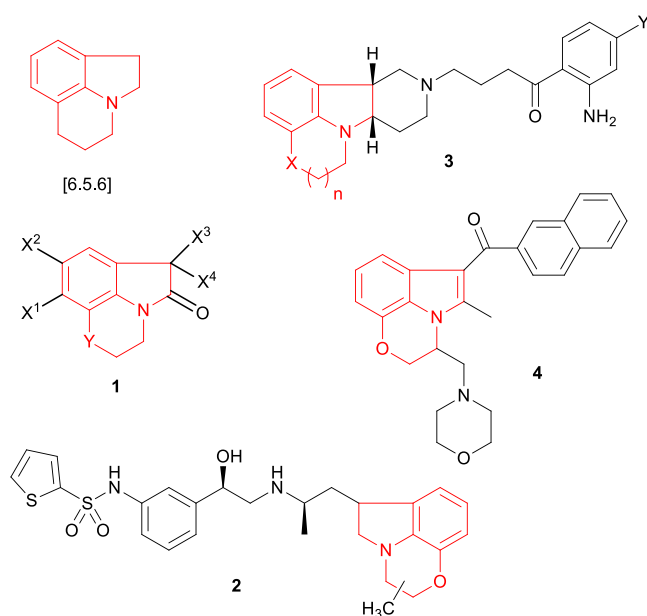
**Figure 1.** Bioactive molecules involving [6,5,6]-tricyclic skeleton

Based on these considerations, we planned a new synthesis of oxazinoindole-2-one derivatives exploiting different copper-catalyzed reactions and we performed preliminary assays for their antiproliferative activity.

## Results and Discussion

Considering our experiences regarding the transition-metals catalyzed amination reactions on heteroaromatic derivatives,[17] we decided to investigate the pathways toward hetero-condensed oxazinoindole scaffold starting from 5,7-dibromoisatin **5**. The presence of two bromine atoms on the substrate is the preliminary feature for a double functionalization.

Intra- and intermolecular catalysed processes such as alkoxylation/amination, double alkoxylation and alkoxylation/arylation reactions have been applied in order to provide the planned heterotricyclic system and its functionalization.

Starting from the 5,7-dibromoisatin **5**, the initial protection of the carbonyl group in position 3 as acetal (**6**)[18] was requisite to improve the subsequent step of alkylation on the nitrogen atom, perfomed using NaH as base and the unprotected 2-bromoethanol directly in DMF at 70 °C. The compound **7c** was obtained from **5** directly, in the presence of NaH and an excess of 2-bromoetanol in DMF at 70°C, by means of the nucleophilic attack of the 2-bromoethanol to yield the corresponding *N*-2-hydroxyethyl–indole-2,3-dione, followed by intramolecular addition of the –OH to the carbonyl of isatin with subsequent ring opening resulting in the unisolated spiroisatin.[19] The presence of the excess of NaH and 2-bromoethanol afforded the compound **7c** directly. The compounds **7** obtained were the suitable substrates to realize the annulation reactions (Scheme 1).



**7a** R = Et
**7b** R, R = -(CH$_2$)$_3$-
**7c** R, R = -(CH$_2$)$_2$-
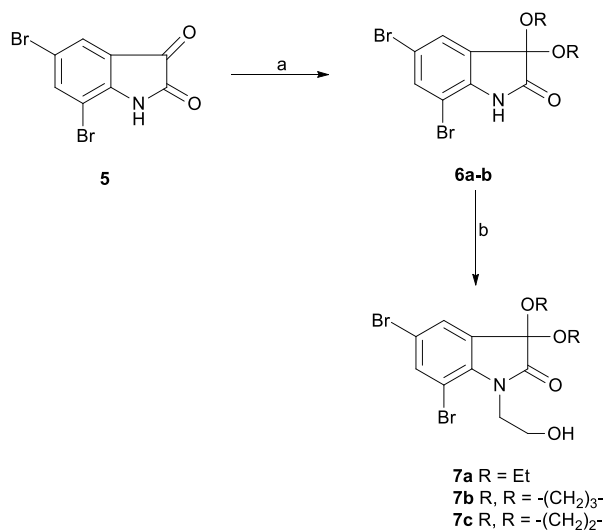
**Scheme 1.** Preparation of substrates **7**. Reagents and conditions: (a) ROH, PTSA, reflux; (b) NaH, 2-bromoethanol, DMF, 70 ˚C.

We began our investigation for the cyclization step on compound **7a** by screening different catalysts and different reaction conditions. In Table 1 we reported the optimization reactions to afford compound **8a**. The reactions under Pd-catalysis were tested with different ligands (such as DavePhos, BINAP or DPPF, entries 1, 2, 4) and bases (Cs$_2$CO$_3$, NaH, *t*-BuONa, entries 1-3) as suggested by literature

data,[20] but unreacted starting material was recovered or a complex mixture of products were formed. Searching more economic and challenging copper-catalysis, different salts and bases were tested, in the presence or in the absence of ligands (entries 5, 8 and 6, 7) and the best result for the intramolecular alkoxylation was obtained in toluene at 80 °C, using CuI as catalyst and 8-hydroxyquinoline as ligand, in the presence of NaH as base. (Table 1, entry 8 and Scheme 2). Although, in our hands, compound **8c** at the same optimal conditions was furnished in a low yield.



**7a-c**

**8a** R = Et
**8b** R, R = -(CH$_2$)$_3$-
**8c** R, R = -(CH$_2$)$_2$-
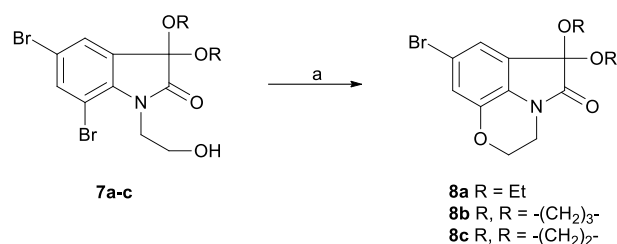
**Scheme 2.** Intramolecular alkoxylation reaction. Reagents and conditions: (a) **7a-c** (1 mmol), CuI (5 mol%), 8-OH-quinoline (10 mol%), NaH (2 eq), toluene, 110 ˚C, **8a-c** (25-70%).

**Table 1.** Optimization of the annulation reaction conditions for compound **7a**.

| | Catalyst (%mol) | Solvent | Ligand (%mol) | Base (equiv.) | Yield (%) |
|---|---|---|---|---|---|
| 1 | Pd(OAc)$_2$ (2) | toluene | DavePhos (5) | Cs$_2$CO$_3$ (1.5) | - |
| 2 | Pd$_2$(dba)$_3$ (2) | toluene | BINAP (5) | NaH (1.5) | - |
| 3 | Pd$_2$(dba)$_3$ (2) | toluene | DavePhos (5) | tBuONa (1.5) | mix |
| 4 | Pd(OAc)$_2$ (2) | toluene | DPPF (4) | tBuONa (1.5) | mix |
| 5 | CuI (10) | toluene | Phenanthroline (20) | Cs$_2$CO$_3$ (2) | 20 |
| 6 | Cu(OAc)$_2$ (10) | toluene | - | NaH (2) | 60 |
| 7 | CuI (5) | toluene | - | NaH (2) | 50 |
| 8 | CuI (5) | toluene | 8-OH-quinoline (10) | NaH (2) | 70 |

In order to obtain new original functionalization of the scaffold, we envisaged to include a panel of nucleophiles at position 5. For the intermolecular reactions which involve the formation of C-N or C-O bonds, the presence of polar solvents and different ligands were necessary. Also, different reaction conditions were applied. For aryl-anilines (**9b,c,l,m**), the reactions were performed using 10 mol% of CuI as catalyst and 20 mol% pyrrole-2-carboxylic acid as ligand, utilizing DMSO as solvent at 120 °C and of K$_2$CO$_3$ as base (reaction conditions A). For other nucleophiles the coupling was achieved with 50 mol% of CuCl as catalyst, 10 mol% 2,2,6,6-tetramethyl-3,5-heptanedione as ligand and NMP as solvent at 120 °C, in the presence of Cs$_2$CO$_3$ as base (reaction conditions B) (Scheme 2 and Table 2).

In the case of substrate **8b**, the reaction conditions to perform the coupling step must be chosen carefully, in order to avoid the formation of the side-product **10**, arising from the opening of the oxindole ring. In fact, in some cases, and in particular with apolar solvents such as toluene and nucleophiles such as pyrazole, besides the coupling product, also compound **10** was observed. With 4-methylphenol as nucleophile, only compound **10** was obtained (Scheme 3). In order to be certain for the formation of product **10**, a hydrolysis of this compound was performed in the presence of LiOH, providing the acid **11** which was fully characterized.
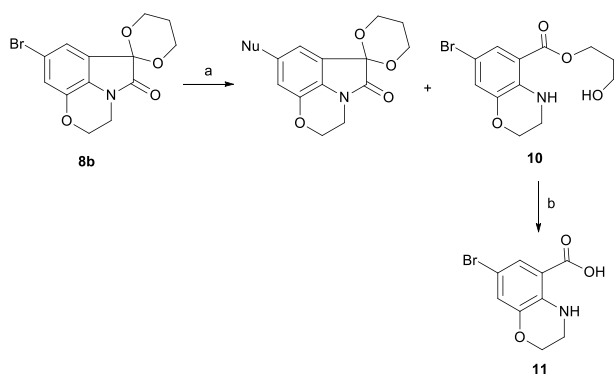
**Scheme 3**. Functionalization of compound **8b**. Reagents and conditions: (a) NuH, apolar solvent; (b) LiOH, THF, H$_2$O, 80 ˚C.

We were also interested in the insertion of aryl derivatives at the position 5 obtained through an arylation process catalyzed by Pd(0). In this case, the alkoxylation/arylation sequence was achieved in a one-pot procedure affording 5-(hetero)aryl derivatives. Applying the tandem copper-palladium catalysis, the sequential transformation of the substrate occurred straightway and the isolation of the intermediate product **8** was not necessary. The overall yield of tandem reactions was comparable with the performance of the two step reactions, including the isolation of the intermediate compound **8** (Scheme 4).
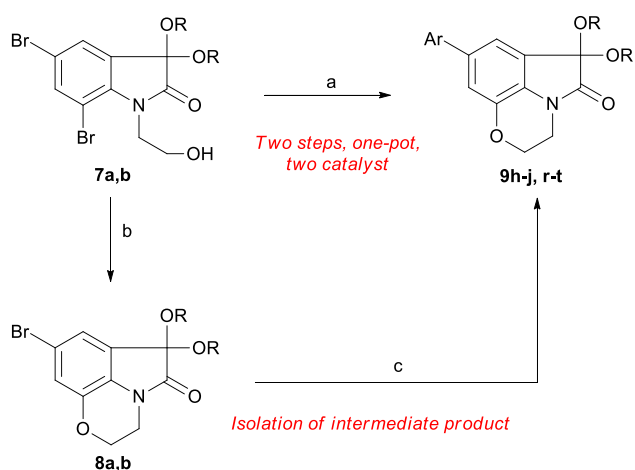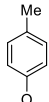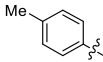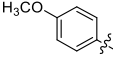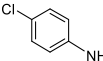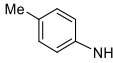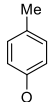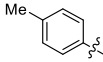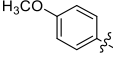


**Scheme 4**. One-pot alkoxylation/arylation reactions. Reagents and conditions: (a) **7a** (1 mmol), Cu(OAc)$_2$ (10 mol%), NaH (2 eq), toluene, 110 ˚C, ii) Pd(OAc)$_2$ (10 mol%), PPh$_3$ (10 mol%), ArB(OH)$_2$ (1.5 eq), K$_2$CO$_3$ (2 eq), toluene, 110 ˚C, **9h** (68%) (b) **7a** or **7b** (1 mmol), CuI (5 mol%), 8-OH-quinoline (10 mol%), NaH (2 eq), toluene, 110 ˚C, **8a** (70%), **8b** (50%); (c) **8a** or **8b** (1 mmol), Pd(OAc)$_2$ (10 mol%), PPh$_3$ (10 mol%), ArB(OH)$_2$ (1.5 eq), K$_2$CO$_3$ (2 eq), toluene, 110 ˚C, **9h-j, r-t** (69-81%).

**Table 2**. Functionalization of oxazinoindoles.
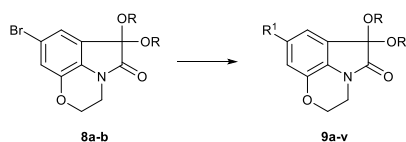


| Entry | R | R$^1$ | Yield (%) |
|-------|-----|--------------|-----------|
| **9a**[a] | Et | PhCH$_2$NH | 50 |
| **9b**[b] | Et | (4-Cl-C$_6$H$_4$)NH | 58 |
| **9c**[b] | Et | (4-Me-C$_6$H$_4$)NH | 56 |
| **9d**[a] | Et | pyrazol-1-yl | 38 |

| cmpd | R | nucleophile | yield |
|------|-----|-------------|-------|
| **9e**[c] | Et |  | 48 |
| **9f**[a] | Et |  | 37 |
| **9g**[a] | Et |  | 45 |
| **9h**[e] | Et |  | 68 |
| **9i**[e] | Et |  | 69 |
| **9j**[e] | Et |  | 81 |
| **9k**[a] | -(CH₂)₃- | PhCH₂NH | 50 |
| **9l**[b] | -(CH₂)₃- |  | 40 |
| **9m**[b] | -(CH₂)₃- |  | 60 |
| **9n**[a] | -(CH₂)₃- |  | 35 |
| **9o**[c] | -(CH₂)₃- |  | 71 |
| **9p**[a] | -(CH₂)₃- |  | 38 |
| **9q** | -(CH₂)₃- |  | _n. o._[d] |
| **9r**[e] | -(CH₂)₃- |  | 75 |
| **9s**[e] | -(CH₂)₃- |  | 77 |
| **9t**[e] | -(CH₂)₃- |  | 71 |

[a] Reaction conditions A: **8** (0.35 mmol), CuCl (5 mol%), 2,2,6,6-tetramethyl-3,5-heptanedione (10 mol%), nucleophile (2 equiv.), $Cs_2CO_3$ (2 equiv.), NMP (0.5 mL), stirred overnight at 120 °C. [b] Reaction conditions B: **8** (0.47 mmol), CuI (10 mol%), pyrrole-2-carboxylic acid (20 mol%), nucleophile (2 equiv.), $K_2CO_3$ (2 equiv.), DMSO (0.7 mL), stirred overnight at 120 °C. [c] Yield obtained performing the reaction under Pd-catalysis: **8** (0.32 mmol), $Pd_2(dba)_3$-chloroform (2.5 mol%), tBuXPhos (3 mol%), morpholine (1.2 equiv.) $Cs_2CO_3$ (2 equiv.), DMF (0.5 mL), stirred overnight at 100 °C. [d] n.o. = not obtained. [e] Reaction conditions C: **8** (0.22 mmol), Pd(OAc)₂ (10 mol%), PPh₃ (10 mol%), boronic acid derivative (2 equiv), $K_2CO_3$ (2 equiv.), toluene (5.5 mL), stirred overnight at 110 °C.

Due to the interest of the scaffold, the antiproliferative activity of selected compounds was evaluated on two human tumor cell lines, A2780 (ovarian carcinoma) and MSTO-211H (biphasic mesothelioma), and expressed as $GI_{50}$ values, i.e. the concentration (µM) of compound able to induce 50% reduction in cell growth with respect to a control culture (Table 3).

**Table 3**. Cell growth inhibition of test compounds.

| | $GI_{50}$ (µM)[a] | | | $GI_{50}$ (µM)[a] | |
|------|-------|--------|------|-------|--------|
| **cmpd** | A2780 | MSTO-211H | **cmpd** | A2780 | MSTO-211H |
| **7a** | >20 | >20 | **7b** | >20 | >20 |

| | | | | | |
|---|---|---|---|---|---|
| **8a** | >20 | >20 | **8b** | >20 | >20 |
| **9a** | >20 | >20 | **9k** | >20 | >20 |
| **9b** | 8.8 | >20 | **9l** | >20 | >20 |
| **9c** | 10.2 | >20 | **9m** | >20 | >20 |
| **9d** | >20 | >20 | **9n** | >20 | >20 |
| **9e** | >20 | >20 | **9o** | >20 | >20 |
| **9f** | >20 | >20 | **9p** | >20 | >20 |
| **9g** | 17.0 | >20 | **9r** | 16.6 | >20 |
| **9i** | 3.6 | 7.2 | **9s** | 5.6 | 16.0 |
| **9j** | >20 | >20 | **9t** | >20 | >20 |

[a] Values are the mean of at least three independent experiments

Some of the test compounds showed a detectable activity on tumor cells, with A2780 cell lines as the most sensitive. In particular, the most cytotoxic derivative was **9i**, characterised by a *p*-methoxybenzene substituent linked to the tricyclic common chromophore, and indeed, for both cell lines, $GI_{50}$ values in the low micromolar range were obtained. The biological activity slightly decreased by the condensation of a fourth 1,3-dioxane ring (**9s**) that actually leaded to the doubling of the $GI_{50}$ values on both A2780 and MSTO-211H cells. The substitution of the *p*-methoxy group in **9s** with a methyl one (**9r**) produced a further decrement in biological activity that yielded to the disappearance of any significant effect on MSTO-211H cell line. Moreover, the lengthening of the spacer by the insertion of an aniline ring (**9m**) provoked the inability to exert any biological effect.

Finally, a detectable and comparable antiproliferative effect on A2780 cells was exerted by derivatives characterised by the *p*-chloro aniline or the p-methyl aniline as pendant substituent of the tricyclic condensed moiety (**9b** and **9c**, respectively), while the insertion of a *p*-methylphenol provoked a detrimental effect on biological activity (**9g**).

## Conclusions

In summary, we developed a copper-catalyzed annulation and amination or alkoxylation processes starting from 5,7-dibromoisatin as a new pathway for the synthesis of oxazinoindole-2-one derivatives. The alkoxylation/arylation process was developed as a one-pot procedure using the tandem copper-palladium catalysis, providing 5-(hetero)aryl substituted oxazinoindole-2-ones. Due to the interest of the scaffold, a preliminary biological evaluation for some of the compounds showed inhibition on the low micromolar range.

### Supporting Information Summary

General information, experimental procedure, spectroscopic data ^{1}H-NMR,^{13}C-NMR and HRMS spectra of selected compounds are provided in the Supporting Information.

**Keywords:** alkoxylation • copper-catalysis • isatin • one-pot process • oxazinoindole • tandem Cu-Pd-catalysis

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