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Divergent synthesis of isoindolo[2,1-*a*]indole and indolo[1,2-*a*]indole through copper-catalysed C- and N-arylations

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ABSTRACT

A simple and efficient synthetic route to both isoindolo[2,1-*a*]indole and its structural isomer indolo[1,2-*a*]indole skeletons is presented. The key steps of the strategy are based on copper-catalysed C_{aryl}–C and C_{aryl}–N bond formation reactions, respectively. Moreover, we report the first copper-mediated intramolecular C–H functionalisation of an indole.

The indole is among the most important and ubiquitous heterocyclic frameworks in nature.[1] Its nucleus is present in plenty of biologically active molecules, among which there are several interesting dimeric alkaloid families, such as *Vocanga* and *Vinca*.[2,3] The interest in isoindolo[2,1-*a*]indoles **1**, a relatively unexplored family of heterocycle-fused indoles, has notably increased in the last years. Their high affinity for the melatonin MT3 binding site and their effectiveness against several carcinogenic tumours make them certainly appealing for medicinal chemistry.[4] Closely related to isoindolo[2,1-*a*]indoles **1** are their structural isomers indolo[1,2-*a*]indoles **2** (Scheme 1).

To the best of our knowledge, there is no general protocol to prepare the indolo[1,2-*a*]indole core **2**.[5] On the other hand, the isoindolo[2,1-*a*]indole skeleton **1** has been constructed employing different strategies, such as palladium-catalysed annulation of internal alkynes by imines,[6] intramolecular addition of 2-indolyl radicals to aromatic rings[7] and palladium-catalysed carbon–hydrogen (C–H) activation processes,[8,9] among others.

Indeed, transition metal-catalysed coupling reactions through C–H activation have attracted much attention over the last few decades.[8–10] Most of the already developed methods imply the use of expensive transition metals, such as palladium, rhodium and ruthenium.[8–11] Surprisingly, although copper was the first transition metal effecting C–H bond functionalisation,[12] it has been scarcely employed in this ambit,[13–15] and still shows important limitations. The necessity of stoichiometric amounts of copper,[14a,b] strong and/or bulky bases[13] and the reduced number of substrates that can undergo the latter processes have restrained their general use. It should be also pointed out that most of the existing methods are not suitable for the direct arylation of indoles.[14b,16]

In this context, the development of a transition metal-catalysed C–H arylation of indoles to prepare the valuable isoindolo[2,1-*a*]indole scaffold **1** would be desirable. Besides, a new and short route to synthesise scarcely studied indolo[1,2-*a*]indoles **2** is a matter of interest.

Herein, we wish to report a straightforward approach to isoindoloindole **1** and indoloindole **2** by means of a strategy based on copper-catalysed direct C- and N-arylations, and shared starting materials and intermediates.

The synthesis was started by preparing the *N*-(2-halobenzyl)indoles **3a–b** by means of a simple and quantitative N-benzylation of commercially available indole (Scheme 1).[17] With the substrate **3b** in hand, a migration of the 2-bromobenzyl group from the nitrogen to the C2 position of the indole was carried out upon heating with polyphosphoric acid (PPA), to obtain the 2-benzyl derivative **4** (58%).[18] Once the required N- and 2-substituted intermediates **3a** and **4** were synthesised, we began to study the corresponding copper-catalysed intramolecular arylation reactions.

With regard to the copper-catalysed C–H functionalisation of substrate **3a**, the use of either protic polar (H_2O, EtOH, ^{i}PrOH) or non-polar solvents (PhMe, *o*-xylene) was unsuccessful, recovering the unreacted starting material in all cases. The use of high-boiling aprotic solvents, such as *N*-methylpyrrolidinone, DMF or DMSO also afforded negligible results. However, when we stirred N-benzylated derivative **3a** along with Cu powder (10 mol %) and Na_2CO_3 (2.0 equiv) in poly(ethylene glycol)-400 (PEG-400) at 180 °C over-

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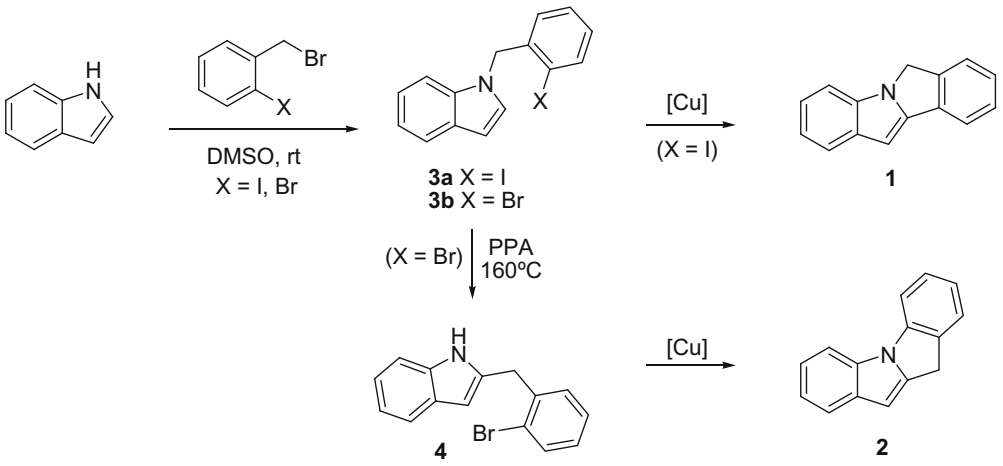


Scheme 1. Detailed route to isoindolo[2,1-*a*]indole **1** and indolo[1,2-*a*]indole **2**.

night target isoindolo[2,1-*a*]indole **1** was isolated in a 65% yield (Table 1, entry 5). Based on this good result, the influence of the base, molecular weight of PEG and copper source in the reaction outcome were examined, as shown in Table 1. While Cs_2CO_3 and Na_2CO_3 provided the cyclised product with similar results (entries 7 and 5, 67% vs 65%, respectively), K_2CO_3 furnished it in an excellent yield of 88% (entry 2). All attempts to perform the same transformation on bromoderivative **3b** failed.

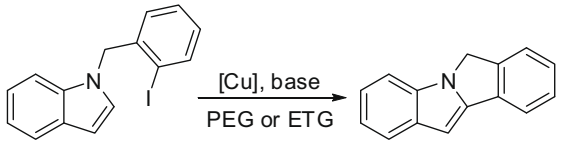
The use of other copper sources, such as CuI, CuCl and $Cu(OAc)_2$, did not improve the yield in any case (entries 1 and 8–9). The molecular weight of PEG seemed to be a crucial factor.[19] Indeed, when we changed from PEG-400 to PEG-1500, only traces of the product (entry 3) were detected. As PEG-400 apparently played the role of both solvent and ligand, we thought that its monomer ethylene glycol (ETG) could act in the same way. Although ETG was still an effective reaction medium for performing such transformation, the yield decreased to 58% (entry 6).

To the best of our knowledge, this is the first regiocontrolled copper-catalysed intramolecular C-arylation of indoles by C–H activation. Moreover, the use in this key transformation of such a sustainable solvent as PEG cannot be ignored. At this stage, we concluded that isoindolo[2,1-*a*]indole **1** can be synthesised in an excellent overall yield of 88% from commercially available, cheap indole.

Accordingly, and continuing with our scheduled studies, the previously prepared 2-(2-bromobenzyl)indole **4** was subjected to several copper-catalysed N-arylation assays, as shown in Table 2.

Based on the experience of our group in the preparation of heterocycles through copper-catalysed arylation processes in aqueous media,[20] we decided to examine the reaction outcome using a catalytic amount of a copper salt with 3.5 equiv of an aliphatic diamine in boiling water.[21] To our delight, target product **2** was isolated in moderate yields of 55% and 57% using CuBr and $Cu(OTf)_2$, respectively (Table 2, entries 3 and 4). An attempt to improve the yield by changing both the diamine and the copper source and maintaining the

Table 1
Representative assays for the C–H arylation of indole **3a**[a]

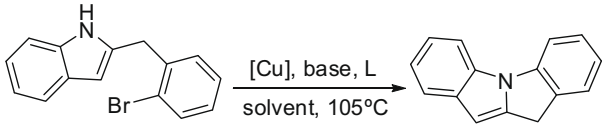


3a **1**

Entry	Copper source	Base	Solvent/ligand	**1** (%)[b]
1[c]	$Cu(OAc)_2$	Na_2CO_3	PEG-1500	Tr.
2	Cu	K_2CO_3	PEG-400	88
3	Cu	K_2CO_3	PEG-1500	Tr.
4[d]	Cu	K_2CO_3	PEG-400	67
5	Cu	Na_2CO_3	PEG-400	65
6	Cu	K_2CO_3	ETG	58
7	Cu	Cs_2CO_3	PEG-400	67
8[e]	CuCl	K_2CO_3	PEG-400	54
9[e]	CuI	K_2CO_3	PEG-400	Tr.

[a] 10 mol % of copper salt and 2.0 equiv of base were used at 180 °C, unless otherwise stated. Cu: copper bronze; PEG: poly(ethylene glycol); ETG: ethylene glycol; tr: traces of product.
[b] Yield of isolated product.
[c] A little amount of water was added to the reaction tube.
[d] The reaction was run at 160 °C.
[e] 1.5 equiv of K_2CO_3 were used.

Table 2
Selected assays for the preparation of indolo[1,2-*a*]indole **2**[a]



4 **2**

Entry	Copper source	Base	Ligand[b]	Solvent	**2**[c] (%)
1[d]	CuI	K_2CO_3	CHDA	Dioxane	44
2[e,f]	Cu_2O	K_2CO_3	DMEDA	DMF	0
3[g]	CuBr	CHDA		H_2O	55
4[g,h]	$Cu(OTf)_2$	CHDA		H_2O	57
5	CuI	K_3PO_4	CHDA	PhMe	88
6	CuI	K_3PO_4	Phe	PhMe	40
7	CuI	K_3PO_4	NMP	PhMe	27
8	CuI	K_3PO_4	P2CA	PhMe	47
9	CuI	K_3PO_4	2AP	PhMe	79
10	Cu	K_2CO_3	PEG-400		0
11[i]	CuI	K_3PO_4	CHDA	PhMe	71

[a] 10 mol % of copper salt, 10 mol % of ligand and 2.0 equiv of base in the corresponding solvent (2 mL/mmol **4**) were used, unless otherwise stated.
[b] CHDA: *trans*-1,2-diaminocyclohexane, Phe: 1,10-phenanthroline, DMEDA: *N*,*N*′-dimethylethylenediamine, NMP: *N*-methylpiperazine, P2CA: piperazine 2-carboxylic acid, 2AP: 2-aminopyridine.
[c] Yield of isolated product.
[d] The reaction was run at 110 °C.
[e] The reaction was run at 100 °C.
[f] 20 mol % of DMEDA was used.
[g] The dilution was increased to 12 mL/mmol **4** and 3.5 equiv of CHDA were used at 120 °C.
[h] 25 mol % of $Cu(OTf)_2$ was used.
[i] 2-(2-Iodobenzyl)indole was used as starting material.

water as solvent was unsuccessful. Apparently, water was not the optimal solvent for such transformation.

As CHDA seemed to be effective promoting the N-arylation reaction, we checked the combination of catalytic amounts of the latter ligand and CuI, with K_2CO_3 in dioxane (Table 2, entry 1).[22] Unfortunately, a lower yield was obtained in this case (44%). A change to DMEDA and Cu_2O in DMF only provided unreacted starting material (entry 2).

Nevertheless, a considerably better yield was obtained by mixing derivative **4** with catalytic amounts of both CuI and CHDA, K_3PO_4 in PhMe at 105 °C (88%, entry 5). Accordingly, PhMe and K_3PO_4 were chosen as a suitable solvent/base system for this transformation, and a range of experiments varying the ligand were carried out (entries 5–9). CHDA and 2AP turned out to be the best ones, providing the target tetracycle **2** in 88% and 79% yields, respectively (entries 5 and 9). When 2-(2-iodobenzyl)indole was subjected to these optimal conditions (entry 11) target product **2** was obtained in a slightly lower yield of 71%. Finally, the application of the optimised conditions for the C–H arylation reaction[23] to this C–N bond formation failed completely (entry 10), in the same way as these N-arylation conditions proved unsuccessful in the former transformation.

After all these optimisation assays leading to the conditions as shown in entry 5,[24] the synthetic route to indolo[1,2-*a*]indole **2** was completed with an acceptable overall yield of 51%.

To sum up, a divergent straightforward synthetic sequence for the access to isomeric isoindolo[2,1-*a*]indole and indolo[1,2-*a*]indole is reported, featuring as the key step two copper-catalysed arylation reactions. Moreover, it cannot be ignored that the former arylation is the first reported example of a copper-catalysed intramolecular C–H functionalisation of an indole. The extension of this approach to other indoles is now under investigation.

Acknowledgements

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Supplementary data

Typical experimental procedures, including spectroscopic and analytical data for all the new intermediates along with NMR spectra of the new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.175.

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23. *Preparation of 6H-Isoindolo[2,1-a]indole* (**1**): A screw-capped tube was charged with *N*-(2-iodobenzyl)-1*H*-indole **3a** (98.7 mg, 0.29 mmol), Cu bronze (200 mesh, 1.9 mg, 0.030 mmol) and K_2CO_3 (82.9 mg, 0.60 mmol) at room temperature and under argon. Then, PEG-400 (0.6 mL) was added and the reaction mixture was heated to 180 °C for 16 h. After cooling the reaction, it was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Then, brine was added (10 mL) to the aqueous layer, and was extracted again with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by flash chromatography (10% AcOEt/*n*-hexane) to afford the target tetracyclic product **1** as a white powder (52.3 mg, 88%). The physical data were compared with those found in the literature. See: Ref. 9c.
24. *Preparation of 10H-Indolo[2,1-a]indole* (**2**): A screw-capped tube was charged with 2-(2-bromobenzyl)-1*H*-indole **4** (80.8 mg, 0.28 mmol), CuI (5.4 mg, 0.028 mmol) and K_3PO_4 (120.1 mg, 0.56 mmol) at room temperature and under argon. Then, CHDA (3.4 μL) and dry PhMe (0.6 mL) were added and the reaction mixture was heated to 105 °C for 16 h. After cooling the reaction, it was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by flash chromatography (10% AcOEt/*n*-hexane) to afford the target tetracyclic product **2** as a white powder (51.0 mg, 88%). For physical data see Supplementary data.