Domino Ligand-Free Copper-Catalyzed Synthesis of Polysubstituted Indoles

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Abstract: The synthesis of polysubstituted indoles is described by the domino reaction of 2-haloanilines and 1,3-dicarbonyl compounds, 1,3-diketones, β-keto esters and β-keto amides, using copper catalysis under ligand-free conditions. The protocol provides a simple, general and atom economical process for the synthesis of substituted indoles at moderate temperature.

Key words: Cu_2O, indoles, cesium carbonate, 1,3-dicarbonyl compounds, 2-haloanilines

Indoles are probably the most common heterocycles found in nature[1] and have been referred to as ‘privileged structures’ of medicinal importance due to their high binding affinity with many receptors (Figure 1).[2] Indoles are also known as important structural constituent for the development of agrochemicals,[3] materials[4] and perfumes.[5] The development of simple, general and especially regioselective synthetic methods for the construction of substituted indole scaffold thus continues to be of tremendous interest in organic synthesis.[6]

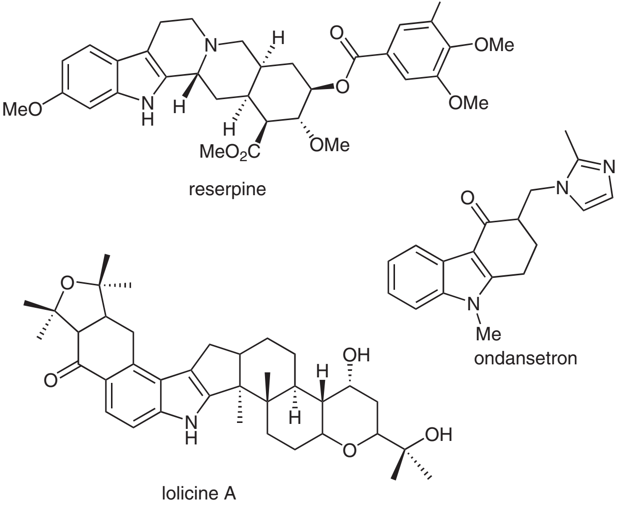
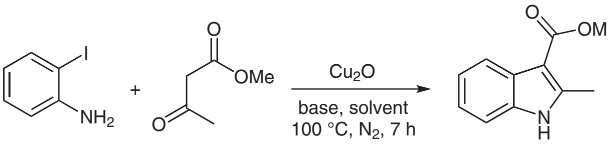


Figure 1 Examples of biologically active and naturally occurring compounds

2,3-Disubstituted indole substructures are widely distributed in nature as indole alkaloids and drugs.[7] Among the studies developed for their synthesis,[8,9] the copper-catalyzed domino reaction of 2-iodoaniline with 1,3-dicarbonyl compounds is one of the attractive processes due to the availability of a range of starting materials.[9,10] CuI–BINOL has been found to be effective for the reaction of 2-iodoanilines with β-ketoesters,[9a] while CuI–proline has been used for the reactions of 2-iodotrifluoroacetanilides with β-keto esters as well as β-keto amides.[9b,c] These reactions involve intermolecular C–C cross-coupling followed by condensation of the amine with the carbonyl group to give the indoles.[9b,c]

The use of copper oxide as an active catalyst for the cross-coupling reactions has been demonstrated in recent years.[11,12] Since copper oxides are cheap, less toxic, readi-

Table 1 Optimization of Reaction Conditions[a]



1a

Entry	Solvent	Base	Yield (%)[b]
1	DMSO	Cs_2CO_3	60
2	DMF	Cs_2CO_3	45
3	toluene	Cs_2CO_3	20
4	1,4-dioxane	Cs_2CO_3	32
5	*i*-PrOH	Cs_2CO_3	25
6	DMSO–*i*-PrOH (1:1)	Cs_2CO_3	23
7	DMSO–H_2O (1:1)	Cs_2CO_3	51
8	DMSO–H_2O (3:1)	Cs_2CO_3	81
9	DMSO–H_2O (3:1)	K_2CO_3	42
10	DMSO–H_2O (3:1)	KOH	33
11	DMSO–H_2O (3:1)	K_3PO_4	18
12	DMSO–H_2O (3:1)	Cs_2CO_3	48[c]
13	DMSO–H_2O (3:1)	Cs_2CO_3	54[d]
14	DMSO–H_2O (3:1)	Cs_2CO_3	n.d.[e]

[a] Cu_2O (10 mol%), 2-iodoaniline (1 mmol), base (1 mmol) and methyl acetoacetate (1.2 mmol) were stirred at 100 °C for 7 h in solvent.
[b] Isolated yield.
[c] Temperature: 80 °C.
[d] A 5 mol% amount of Cu_2O was used.
[e] Cu_2O was not used.

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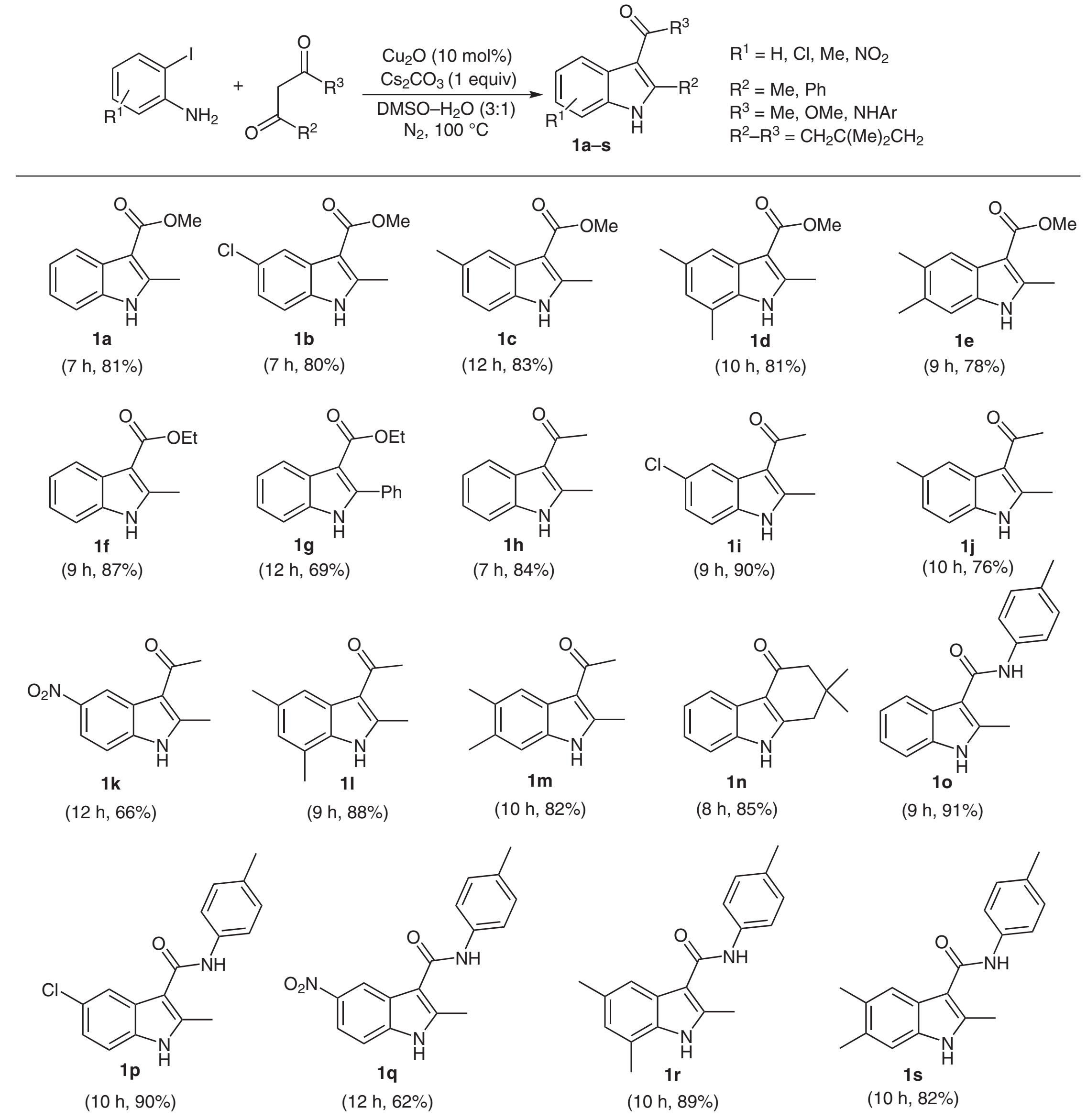
ly available and provide simplified product isolation, their further application to organic synthesis warrants investigation. Herein, we report the synthesis of polysubstituted indoles by Cu_2O-catalyzed domino reaction of 2-haloanilines with a series of 1,3-dicarbonyl compounds, 1,3-diketone, β-keto ester and β-keto amide, in a 3:1 mixture of DMSO–water at moderate temperature. The procedure is simple, general, ligand-free and atom-economical for the synthesis of polysubstituted indoles.

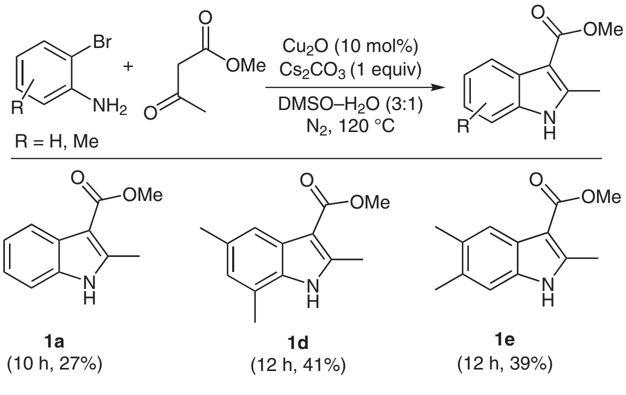
First, the optimization of the reaction conditions was carried out with 2-iodoaniline and methyl acetoacetate as the model substrates (Table 1). The reaction occurred smoothly to afford the desired 2,3-disubstituted indole **1a** in 81% conversion when the substrates were stirred with 10 mol% of Cu_2O and one equivalent of Cs_2CO_3 for seven hours at 100 °C in a 3:1 mixture of DMSO and water under a nitrogen atmosphere. Using DMSO, DMF, toluene, 1,4-dioxane and 2-propanol as the solvent afforded **1a** in 25–61% conversion. Either lowering or increasing the DMSO to water ratio led to **1a** in 51% conversion. In the screened set of bases (K_2CO_3, KOH, K_3PO_4 and Cs_2CO_3), Cs_2CO_3 was found to be superior to others affording the best results. Replacing Cs_2CO_3 with K_2CO_3, KOH and K_3PO_4 as the base provided **1a** in 18–42% conversion. Lowering the reaction temperature (80 °C) or the catalyst loading to 5 mol% led to production of **1a** in 48% and 54% yield, respectively. A control experiment confirmed that, without the copper reagent, no indole formation occurred.

Next, the scope of the procedure was studied for other substrates (Scheme 1). The reactions of 2-iodoanilines having 4-chloro, 4-nitro, 4-methyl, 4,5-dimethyl and 4,6-dimethyl substituents were investigated with 1,3-dicarbonyl compounds, pentane-2,5-dione, 5,5-dimethylcyclo-



Scheme 1 Reaction of 1,3-dicarbonyl compounds with substituted aryl iodides. *Reagents and conditions*: Cu_2O (10 mol%), 2-iodoaniline (1 mmol), Cs_2CO_3 (1 mmol) and 1,3-diketone or β-ketoester or β-ketoamide (1.2 mmol) were stirred at 100 °C in a DMSO–H_2O mixture (3:1, 1 mL) under a nitrogen atmosphere. Isolated yields are shown.

hexane-1,3-dione, ethyl acetoacetate, methyl acetoacetate and 3-oxo-*N*-*p*-tolylbutanamide. All the substrates readily participated in reaction to give the corresponding polysubstituted indoles **1b**–**s** in 7–12 hours with 62–91% yield. The reactions were selective and no by-product was obtained. These results clearly suggest that the protocol is simple and general for the regiospecific synthesis of polysubstituted indoles in high yield.

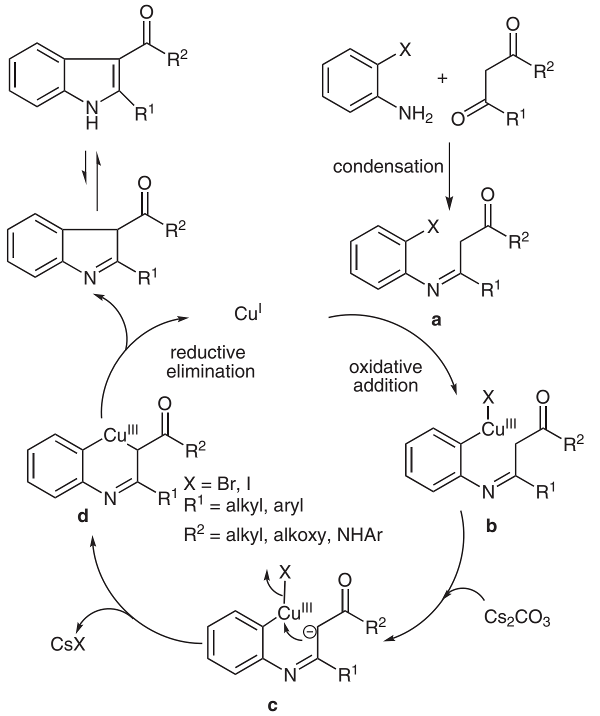


Scheme 2 Reactions of 2-bromoanilines and methyl acetoacetate. *Reagents and conditions*: Cu_2O (10 mol%), 2-bromoaniline (1 mmol), Cs_2CO_3 (1 mmol), and methyl acetoacetate (1.2 mmol) were stirred at 120 °C in a DMSO–H_2O mixture (3:1, 1 mL) under a nitrogen atmosphere. Isolated yields are shown.

Finally, the reactions of 2-bromoanilines with methyl acetoacetate were studied (Scheme 2). These reactions required slightly higher temperature to afford the products in 27–41% yield. Thus, 2-bromoaniline underwent reaction at 120 °C in 10 hours to give **1a** in 27% yield. Likewise, 2-bromoaniline having 4,5-dimethyl and 4,6-dimethyl substituents provided the respective substituted indoles **1d** and **1e** in 12 hours with 41% and 39% yield, respectively.

The proposed catalytic cycle is shown in Scheme 3. The reaction of iodobenzene with methyl acetoacetate was investigated using 10 mol% of Cu_2O and no intermolecular C–C cross-coupling was observed. On the other hand, aniline readily underwent condensation with methyl acetoacetate to give the imine derivative in quantitative yield. These results suggest that the present protocol involves condensation followed by intramolecular C–C cross-coupling to afford the indoles. Thus, the condensation of 2-haloaniline with carbonyl compound can give imine derivative **a** that might undergo oxidative addition with Cu(I) to give the intermediate **b**. The latter with base could generate intermediate **c** which may transform into **d** by nucleophilic substitution. The intermediate **d** could complete the catalytic cycle by reductive elimination to generate the indole.

In conclusion, the synthesis of polysubstituted indoles has been reported using the cheap, readily available, commercial Cu_2O as catalyst under ligand-free conditions. The protocol is simple, general and atom economical for the regiospecific synthesis of polysubstituted indoles in high yield.



Scheme 3 The possible mechanistic pathway

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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