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Copper catalyzed synthesis of highly substituted pyrrole and isoindole derivatives

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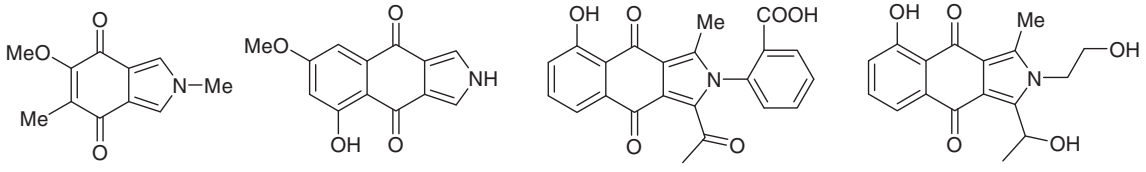
ABSTRACT

We have developed an efficient synthesis of highly substituted pyrrole and isoindole derivatives using copper(I) catalyst. This methodology is helpful for the synthesis of some quinones bearing annealed *N*-heterocyclic natural products.

The pyrrole and isoindole moieties have become attractive targets in organic and medicinal chemistry. Among numerous heterocycles, the pyrrole moiety has always been one of the most prominent since it is found in natural products[1] and electrically conducting materials such as polypyrroles.[2] In particular, substituted pyrroles are highly biologically active and have proven to display antibacterial,[3] antiviral (also anti-HIV-1),[4] antiinflammatory,[5] and antioxidant[6] activities as well as inhibitor of cytokine-mediated diseases.[7] On the other hand, isoindoles can also be potential precursors of porphyrin analogs or pyrroles with extended conjugation and therefore, should find important applications in materials science.[8] Moreover, isoindoles have been widely used for their high level of reactivity in cycloaddition reactions[9] and, more recently, isoindoles and their derivatives have become attractive candidates for organic light-emitting devices (OLEDs) due to their high fluorescent and electroluminescent properties.[10] However, they are rather unstable and their preparatory methods are still limited, especially in a catalytic fashion, which creates a demand for new and straightforward methodologies to access these substrates. These heterocyclic frameworks are an integral part of the structure of some biologically active compounds as well as that of natural products such as *Reniera* indole, which have been isolated from the blue sponge *Reniera* sp.[11] azamonosporascone. This fungus (azamonosporascone) has been found to be



Reniera indole *Azamonosporascone* *Bhimamycin C* *Bhimamycin D*

Figure 1. Some biologically active natural products.

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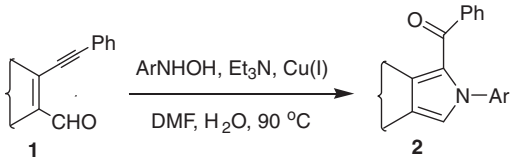
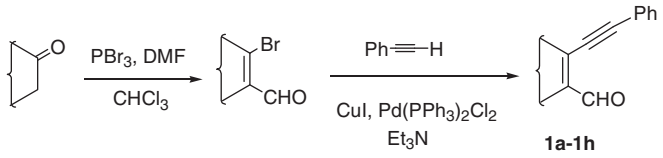


Scheme 1. Synthesis of substituted pyrrole and isoindole rings by copper-catalyzed reaction.

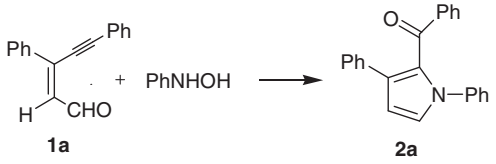


Scheme 2. Synthesis of starting materials.

responsible for crop losses of musk melon and watermelon,[12] bhimamycin C, and bhimamycin D (Fig. 1) which display bioactivities against human ovarian cancer cell lines and are also EP_4 receptor agonists in the treatment of pain.[13]

As a consequence, many synthetic methods are known from early days for the construction of the pyrrole and isoindole moieties. The most frequently used methods include the classical cyclocondensation of primary amines with 1,4-dicarbonyl compounds (Paal–Knorr synthesis), the reaction between an α-amino ketone and a β-ketoester or β-diketone (Knorr pyrrole synthesis), the condensation between an α-halo ketone, a β-ketoester, and a primary amine or ammonia (Hantzsch procedure), and various cycloaddition strategies. However, these methods have some limitations with respect to the desired regioselectivity and substitution patterns. Many methods for the synthesis of pyrrole[14] and isoindole[15] have been developed recently, including the one-pot methodology developed by our group.[16] In spite of recent advances, particularly in transition metal mediated multi-component reactions, a more flexible and generalized methodology

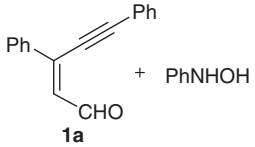
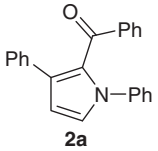
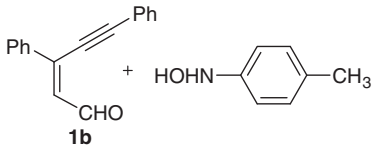
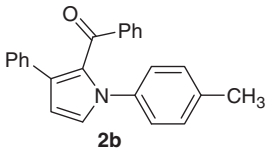
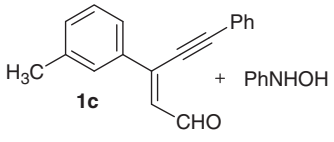
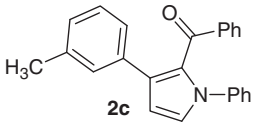
Table 1
Optimization studies[a]



Entry	Catalyst (10 mol %)	Base (1 equiv)	Solvent	Temp (°C)	Yield (%)
1	CuCl	Et_3N	DMF	85–90	78
2	CuCl	Et_3N	DMF	65–70	46
3	CuBr	Et_3N	DMF	85–90	20
4	CuI	Et_3N	DMF	85–90	10
5	CuCl	K_2CO_3	CH_3CN	85	0
6	CuCl	Et_3N	CH_3CN	85	10
7	CuBr	Et_3N	Toluene	95	0
8	CuCl	Na_2CO_3	Toluene	95	0
9	CuCl	K_2CO_3	DMF	85–90	0

[a] All the reactions were carried out in the presence of 5 equiv H_2O, under argon atm.

Table 2
Copper-catalyzed synthesis of pyrroles and isoindoles[a]

Entry	Substrates	Products	Yield (%)
1			82
2			78
3			77

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