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Copper catalyzed synthesis of highly substituted pyrrole and isoindole derivatives

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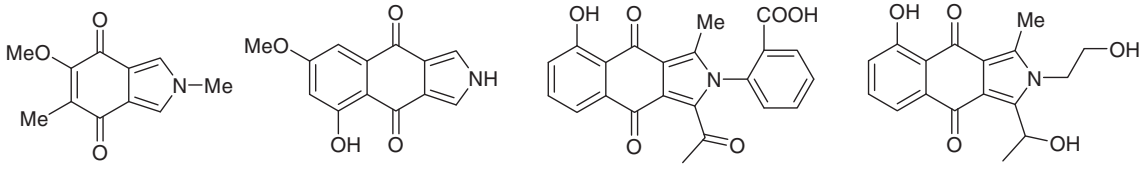
ABSTRACT

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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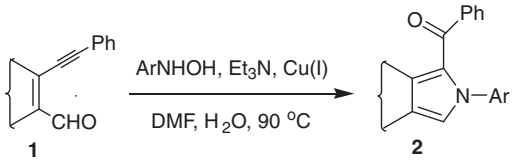
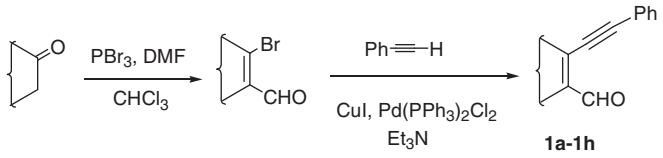


Scheme 1. Synthesis of substituted pyrrole and isoindole rings by copper-catalyzed reaction.

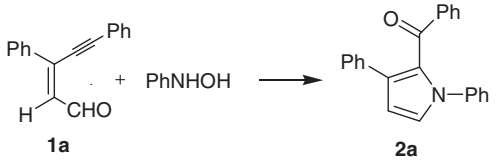


Scheme 2. Synthesis of starting materials.

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

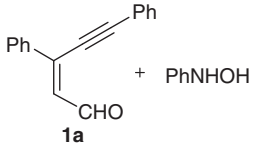
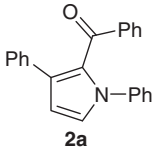
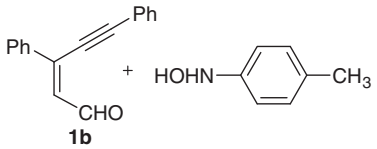
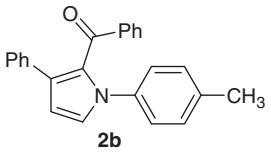
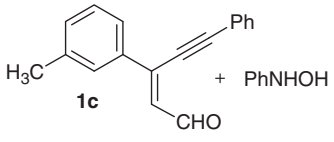
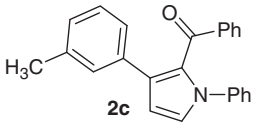
Table 1
Optimization studies[a]



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

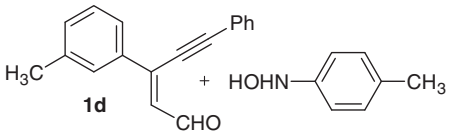
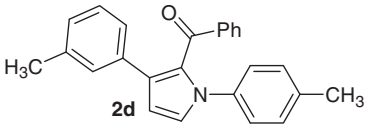
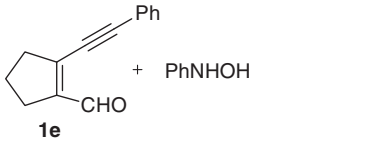
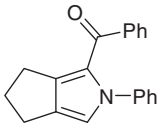
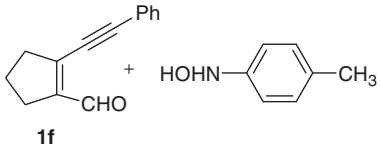
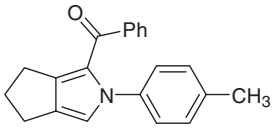
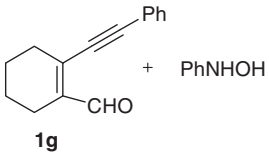
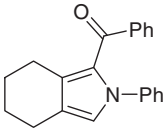
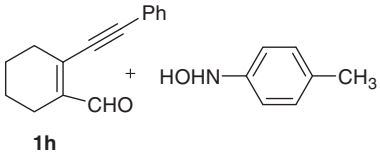
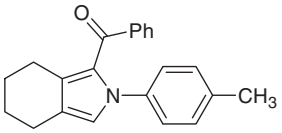
[a] All the reactions were carried out in the presence of 5 equiv H_2O, under argon atm.

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

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

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrates	Products	Yield (%)
4	 **1d**	 **2d**	69
5	 **1e**	 **2e**	81
6	 **1f**	 **2f**	78
7	 **1g**	 **2g**	72
8	 **1h**	 **2h**	67

[a] Reagents and conditions: **1a–1h** (1 equiv), ArNHOH (1.2 equiv), CuCl (10 mol %), Et_3N (1 equiv), H_2O (5 equiv), DMF (5 mL), 85–90 °C.

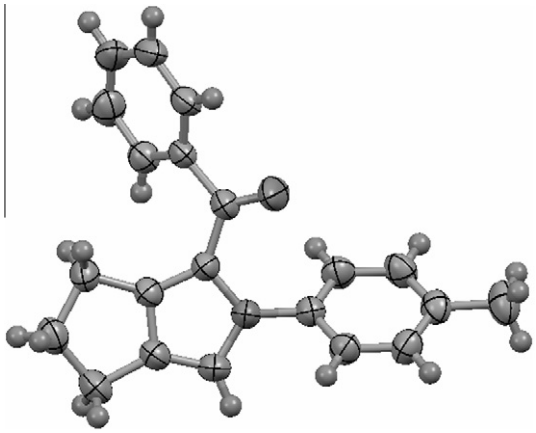
that is tolerant of a large number of functional groups is still needed. Considering their potential biological relevance herein we report a synthetic approach to highly substituted pyrroles and isoindoles using **1** (Scheme 1).

The convergent approach involved the preparation of precursors **1a–1h**, which were efficiently synthesized from bromovinylaldehydes by Sonogashira coupling[17] as per Scheme 2.

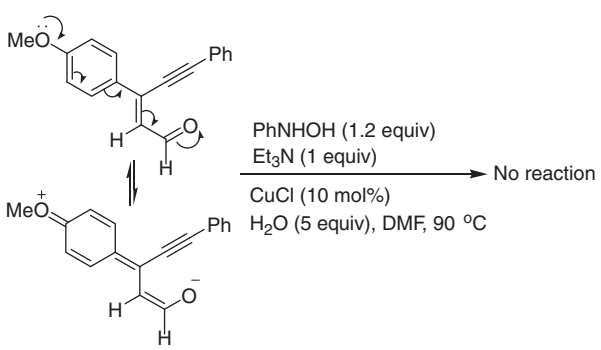
The initial experiment was carried out by heating a mixture of compound **1a** (1 equiv), phenylhydroxylamine (1.2 equiv), H_2O (5 equiv), Et_3N (1 equiv), and CuCl (cat.) in DMF at 85–90 °C under argon atmosphere for 2 h (Table 1, entry 1). A pyrrole ring resulted from the substrate **1a**, but when the reaction was carried out in an open flask or in the absence of water the product yield was very low along with other side products. By lowering the temperature to 60 °C, very low yields were obtained (Table 1, entries 2 and 3). The reaction was then attempted by changing the catalyst, base, and solvent to optimize the reaction conditions. The results are summarized in Table 1. Finally, we concluded that our optimized condition was CuCl (10 mol %), 5 equiv H_2O, 1 equiv Et_3N in 4–5 mL DMF, heated at 85–90 °C for 2 h. We next examined the scope of this reaction with different 3-(1-alkynyl)-2-alkene-1-als (**1a–1h**) with ArNHOH to obtain the pyrrole or isoindole ring in compounds **2a–2h** in moderate to good yield[18] which are shown in Table 2. The crystal structure of isoindole **2f**[19] is shown in Scheme 3 which confirms the product structure.

In view of the absence of any supporting evidence, at this point, we are unable to produce any mechanistic explanation other than the account of the formation of the observed products.

When we used 3-(4-methoxyphenyl)-5-phenylpent-2-en-4-ynal as a starting material we did not get any pyrrole product



Scheme 3. Crystal structure of isoindole **2f** with 50% probability.



Scheme 4. Reaction with 3-(4-methoxyphenyl)-5-phenylpent-2-en-4-ynal.

(Scheme 4). This may be due to the conjugation of the lone electron pair of the oxygen with the aldehyde group.

In conclusion, we have developed a new methodology for the synthesis of highly substituted pyrrole and isoindole rings by reaction of substituted 3-(1-alkynyl)-2-alkene-1-als with arylhydroxylamines under Cu(I) catalysis. This reaction is also helpful for the synthesis of some quinones bearing annelated *N*-heterocyclic natural products.

Acknowledgments

S.N. thanks CSIR, New Delhi for the fellowship. D.S.T. is also thanked for providing funds for the project and creating 400 MHz NMR facility under the IRPHA program.

Supplementary data

Supplementary data (detailed experimental procedures and spectral data for the compounds **2a–2h**) associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.070.

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18. *General procedure for the copper catalyzed cyclization*: Compound **1** (1 equiv) and phenylhydroxylamine (1.2 equiv) were placed in a two-neck round bottom flask and flashed with argon. DMF (5 mL) was added to the reaction mixture. Then Et_3N (1 equiv), CuCl (10 mol %), and H_2O (5 equiv) were added and the reaction mixture was heated at 85–90 °C for 2 h. After cooling, the reaction mixture was diluted with cold water and extracted with ether (30 mL × 3) and the combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography. *Spectral data of representative compounds*: (1,3-Diphenyl-1*H*-pyrrol-2-yl)-phenylmethanone (**2a**): red solid; yield: 82%; mp 116–118 °C; R_f = 0.3 (silica gel, petroleum ether:EtOAc 10:1); ^{1}H NMR ($CDCl_3$, 200 MHz): 6.50 (d, 1H, J = 2.8 Hz), 7.08–7.24 (m, 10H), 7.28–7.34 (m, 4H), 7.66 (d, 2H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): 110.8, 125.4 (2C), 126.6, 127.4, 127.6, 127.9 (2C), 128.0 (2C), 128.6, 129.2 (2C), 129.3 (2C), 130.0 (2C), 132.3, 133.7, 135.3, 138.5, 140.5, 188.3; Anal. Calcd for $C_{23}H_{17}NO$: C: 85.42, H: 5.30, N: 4.33. Found: C: 85.34, H: 5.38, N: 4.25; HRMS Calcd for $C_{23}H_{18}NO^+$ [M^++H]: 324.14, found: 324.1404.
19. *Crystal data for* **2f**: CCDC No. 836651, $C_{21}H_{19}NO$, M = 301.37, triclinic, $P\bar{1}$, a = 7.7853(17) Å, b = 10.173(2) Å, c = 11.267(3) Å, α = 93.558(6), β = 104.572(6), V = 107.809(6) Å^3, Z = 2, D_{cal} (mg/m^3) = 1.231, 2260 reflections out of 3783 unique reflections with $I > 2\sigma(I)$, $1.89 < \theta < 28.52$, final R-factors R_1 = 0.0542, wR_2 = 0.2075.