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## Graphical Abstract

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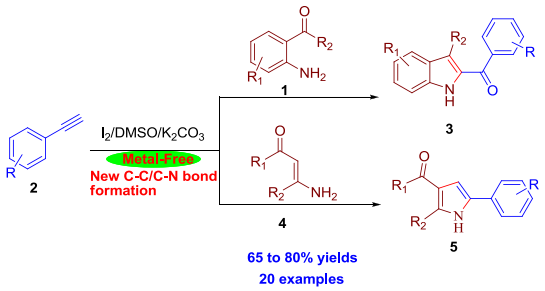

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# $I_2$-DMSO Promoted metal free Oxidative Cyclization for the Synthesis of Substituted Indoles and Pyrroles

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ABSTRACT

A series of di substituted indole and tri substituted pyrrole derivatives were synthesized efficiently by using $I_2/K_2CO_3$ in DMSO. The novel synthesis method offers the advantage of mild reaction conditions, operational simplicity, higher yields. The method is functional group tolerant and provides quick access to medicinally significant compounds in moderate to high yields.



The indole nucleus is a key shape in numerous natural products, pharmaceutical agents, and functional materials.[1] The gathering of indole derivatives have attracted great interest.[2] Amongst the family of indoles, 2,3-disubstituted indoles are an significant class of heterocycles because of their biological activities and medicinal applications.[3] They are being documented as privileged structures in medicinal chemistry because of their attraction to bind with various receptors. Various drugs and a large number of natural products bearing an indole moiety are known, e.g., fascaplysin, homofascaplysin A, B and C (Figure 1).[4-6]

In other hand, pyrroles represent an important class of heterocycles in organic chemistry. They are structural units in many natural products and pharmaceuticals and are key intermediates for the synthesis of a variety of biologically active molecules and functional materials.[7] It is the key structural fragment of heme and chlorophyll, two pigments essential for life.[8] As examples of pyrrole derived drugs, non-steroidal antiinflamatory compound tolmetin, the anticancer drug candidate tallimustine and the cholesterol-lowering agent atorvastatin calcium (Lipitor), one of the top-selling drugs worldwide (Fig. 1).[9]

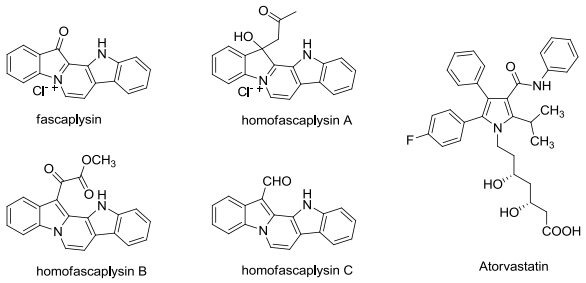



**Figure 1**: Biologically active molecules

Therefore, new methods for the synthesis of di-substituted indoles are an important and popular topic of research, particularly for acyl indole preparation due to wide applications of its carbonyl group as a versatile intermediate in the syntheses of a broad range of indole derivatives. Traditionally, Friedel–Crafts acylations,[10] Vilsmeier–Haack acylations,[11] and the reactions of indole salts with acyl chlorides[12] are usually employed for the synthesis of acyl indoles. However, some of these methods suffer from the requirement of stoichiometric metal Lewis acids, harsh

reaction conditions (often strict exclusion of moisture) and unsatisfactory selectivity. Thus, the development of new, catalytic routes to selectively accessing 3-acylindoles using readily available starting materials is highly desirable.

Inspired by previous literature,[13] herein we report a novel, efficient, and green procedure for the synthesis of 2,3-disubstituted indoles by using $I_2/K_2CO_3$ in DMSO (Scheme 1). To the best of our knowledge, this methodology has not been reported in the literature.

Initially, the condensation reaction of 2-amino acetophenone and phenyl acetylene in the presence of $I_2$ (30 mol%), $K_2CO_3$ (1 equiv) in DMSO at 70 $^oC$ was employed to prepare the desired compound **3a**. To our surprise, this condensation afford the cyclization product **3a** in 45% yield.

**Scheme 1**: Synthesis of 2,3-disubstituted indoles from 2-amino acetophenone and phenyl acetylene


Next, we performed reactions for improving the yield of the product, various catalysts were investigated in further detail in DMSO. Our surprise, the reaction could not perform without $I_2/K_2CO_3$. Therefore, the next reaction was performed with 1.5 equiv of $I_2$. In fact, improvement in the yield from 45% to 70% was observed by increasing the amount of $I_2$ from 30 mol% to 1.5 equiv. To further optimize the reaction conditions, we investigated the effect of temperature on reaction rate as well as on yields of products. It showed that no product could be detected at room temperature even after 12 h (Table 1, entry a). The yield of product **3a** was improved and the reaction time was shortened as the temperature was increased from 70 $^oC$ to 100 $^oC$ (Table 1, entry d, 6 hrs), so the most appropriate reaction temperature is 100 $^oC$. When we employ the same reaction condition in the usual solvents (DMF, Toluene, $CH_3CN$ and DCE) and eco-friendly solvent (PEG), product **3a** was formed in low yields after long time (Table 1, entries e–i).

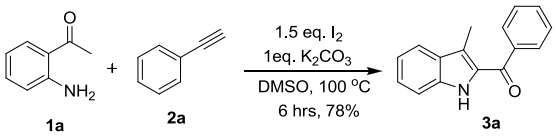
**Table 1**. Effect of catalyst and solvent in the formation of **3a**

| Entry | Solvent[a] | $I_2$ | Temp ($^o$ C) | Yield (%)[b] |
|---|---|---|---|---|
| a | DMSO | 30 mol% | RT | - |
| b | DMSO | " | 70 | 45 |
| c | DMSO | 1.5 equiv | 70 | 70 |
| d | DMSO | " | 100 [c] | 78 |
| e | DMF | " | 100 | 25 |
| f | Toulene | " | 90 | 20 |
| g | $CH_3CN$ | " | 80 | - |
| h | DCE | " | 80 | - |
| i | PEG-400 | " | 100 | 35 |

[a]The reaction was performed at 0.5 mmol scale. [b]Isolated yield. [c] Time 6 hrs

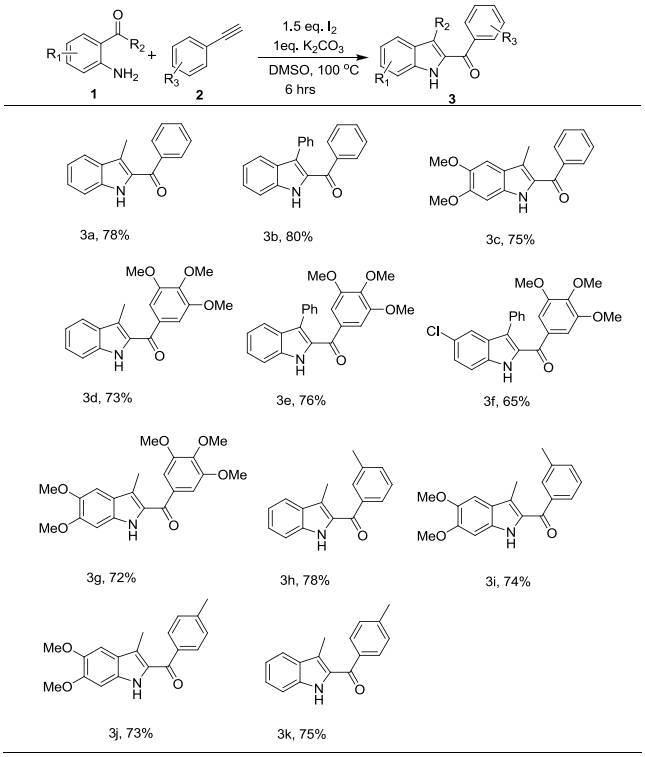
Lower yield was obtained when the reaction was conducted under an argon or $N_2$ atmosphere. After several experimental optimizations, we found best optimization conditions were $I_2$ (1.5 equiv) and $K_2CO_3$ (1 equiv) in DMSO at 100 $^o$ C for 6 h in open air (Scheme 2).

**Scheme 2**: Synthesis of 2,3-disubstituted indoles from 2-amino acetophenone and phenyl acetylene




With optimized reaction conditions in our hand, next we extended this method to other acetophenones such as 3-methyl, 4-methyl and 3,4,5-trimethoxy substituted phenyl acetylenes. In all cases, the corresponding indole derivatives were obtained in good yields, furthermore, we examined the reactivity of different 2-amino acetophenones. Interestingly, other 2-amino acetophenones such as 4,5-dimethoxy, 5-chloro and 2-amino benzophenones afforded the corresponding indoles in good yields. In case of halogen containing phenyl ketones, the corresponding indole was obtained relatively in lower yields (Table 2, entry 3f) than other counterpart. In all the cases, the reactions proceeded efficiently in DMSO at 100 $^o$C and the products were obtained in good yields.

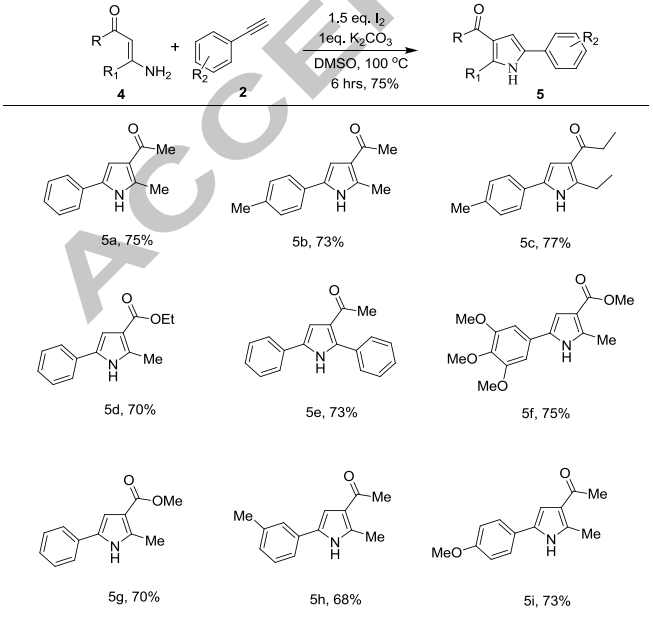
**Table 2**. Reaction screening with different phenyl acetylenes and 2-amino acetophenones.




[a]All the products were characterized by NMR, IR and mass spectroscopy.
[b]Yield refers to pure products after chromatography.

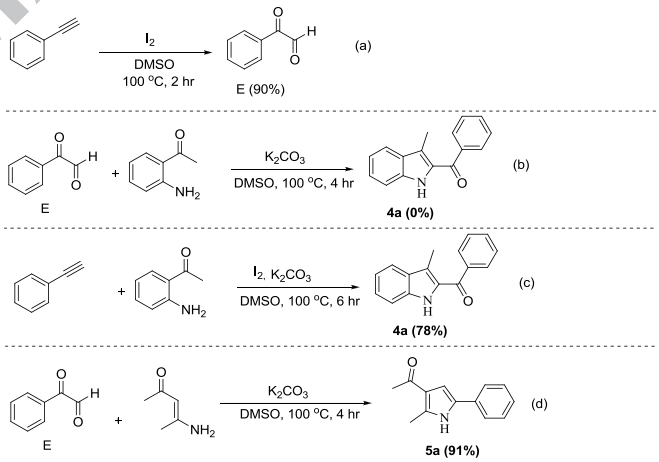
The above results provided a gateway to extend this process to other substrate like β-enamino ketones. Firstly, we performed the reaction β-enamino ketone (4) with phenyl acetylene in similar conditions. Surprisingly, the product was obtained in 75% yield. The scope of the reaction is investigated to other β-enamino ketones and substituted phenyl acetylenes. In all cases, the corresponding pyrrole derivatives were obtained in good yields (Table 3). This method also works well with β-enamino esters to furnish the respective pyrrole carboxylates (Table 3, entries d, f, and g).

**Table 3**. Reaction screening with different enamines and phenyl acetylenes.




[a]All the products were characterized by NMR, IR and mass spectroscopy.
[b]Yield refers to pure products after chromatography.

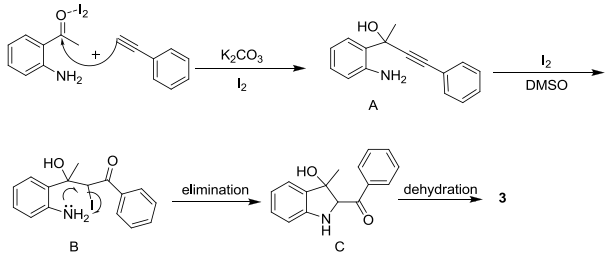
A few controlled experiments (Scheme 4) were performed in order to support our proposed mechanism. When phenylacetylene was treated with $I_2$ in presence of DMSO, the reaction exclusively produced phenylglyoxal (Scheme 4a). Phenylglyoxal (E) reacted with β-enaminoketone in presence of $I_2/K_2CO_3$ and DMSO to form pyrrole (5a) absolutely (Scheme 4d). Furthermore, in the similar conditions Phenylglyoxal (B) did not react with 2-amino acetophenone (Scheme 4b). Therefore, Scheme 4b, 4c and 4d reveals that the intermediates in the pyrrole and indole formation were different.




**Scheme 4**: Control experiments.

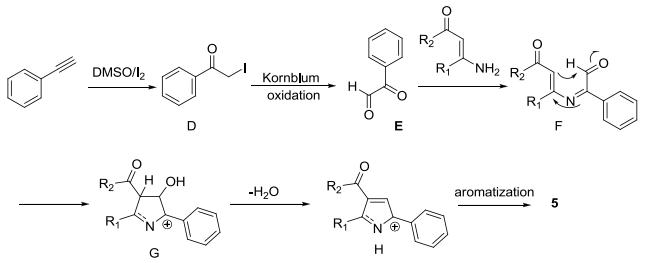
Based on the experimental results, we proposed a plausible mechanism of the Iodine/$K_2CO_3$ condensation for the formation of derivatives **3** as shown in Scheme 5. Firstly, phenyl acetylene attack on keto group on 2-amino acetophenone would give A, then Iodine/DMSO activates the alkyne group forms intermediate **B**.[13b,14] Then, displacement of iodine would furnish cyclized product C, which underwent dehydration to give the product **3**.

**Scheme 5**: A possible mechanism for the formation of **3**.




In case of pyrroles initially, the phenyl acetylene was α-iodination followed by Kornblum oxidize to (E), which could further imine formation to F. Then, F underwent cyclization/dehydration to form H. Which further aromatisation to 5 (Scheme 6).

**Scheme 6**: A possible mechanism for the formation of **5**.




In conclusion, an efficient and simple procedure to the synthesis of di substituted indoles and tri substituted pyrroles is reported. The mild reaction conditions, operational simplicity, higher yields (65–80%), short reaction time, cheap starting materials and environmental friendliness are notable features of this procedure. With no doubt, this reaction should be useful to invent a simple oxidative cyclization reaction for the synthesis of indole and pyrrole derivatives.

**Supplementary data**

Experimental details, characterization data, copies of $^{1}H$ and $^{13}C$ NMR spectrum of products can be found, in the online version, at http:// dx.doi.org/

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15. *General experimental procedure:* A mixture of 2-amino acetophenone (**1 or 4**) (1 mmol, 1 eq.), phenyl acetylene (**2)** (1 mmol, 1 eq.), $I_2$ (1.5 eq.) and $K_2CO_3$ (1 eq.) in DMSO (4mL) was stirred at 100 ˚C for 6hrs in open air. After completion of the reaction, as indicated by TLC, the solvent was diluted with water and extracted with ethyl acetate (10 x 3 times). After solvent was removed in *vacuo*. The resulting residue was subjected to column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to afford the product **3 or 5.**[13b]

Highlights

1. Synthesis of indole and pyrrole derivatives through oxidative cyclization process.
2. A metal free approach for oxidative cyclization process,
3. Iodine/DMSO has successfully been utilized to oxidize phenyl acetylene group.
4. Efficient and regieoselective construction of pyrrole and indole derivatives.