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## Graphical Abstract

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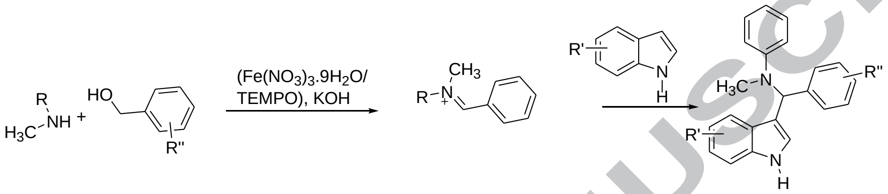

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# Iron mediated one pot three component synthesis of 3-substituted indoles via aerobic iminium ion formation

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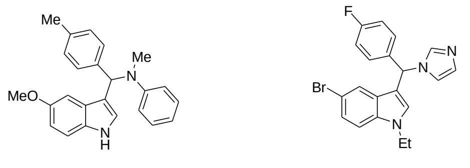
ABSTRACT

An efficient and economical method was developed for synthesis of 3 substituted indoles by highly efficient one-pot three component coupling reaction of substituted or unsubstituted benzylalcohol, *N*-methyl aniline or pyrrolidine and indoles or substituted indoles.

Synthetic organic chemists have been continuously striving for improving the efficiency of organic synthesis, especially in terms of the atom economy and cost effectiveness. In this context, one-pot strategy involving the formation of multi component reaction is highly attractive. Multi component reactions (MCRs) play an important role in atom economy and green chemistry[1]. These reactions are environmentally friendly, energy saving and produces low wastage. Multi-component reactions[2] (MCRs), which combine in one pot several simple building blocks, provide a most powerful platform to access diversity as well as complexity in a limited number of reaction steps. It is well utilized in the synthesis of medicinal compounds such as substituted indoles[3], decahydroquinolin-4-ones[4], 1,4 dihydropyridines. Strategy of multicomponent reactions have been playing a significant role in preparation of structurally diverse chemical compound. The Indole is versatile synthetic intermediates for biologically active compound which served as scaffold in a number of natural and synthetic substituted indoles. Recently Indole derivatives structural unit of many natural and synthetic unit of biologically active compound which passes various pharmacological properties.

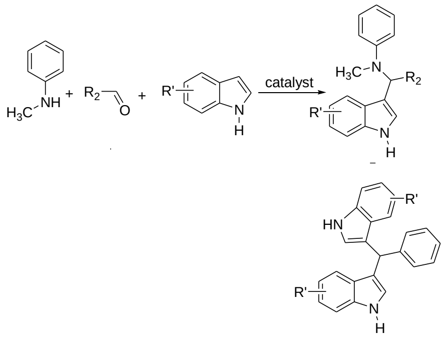
Indole derivatives multi-component are one of the most abundant components of natural products as well as synthetic compounds possessing a variety of biological, medicinal and agrochemical chemistry. The biological activity of substituted indole has attracted to explore different methods for synthesis of indoles. Their biological properties[5] have attracted many synthetic chemists to explore different methods suitable for the synthesis of substituted indoles. Though there are several methods reported in literature for formation of three component reaction. Despite several methods reported in the literature for the synthesis of substituted indoles, the development of simple, efficient, short and environmentally benign approaches for synthesis of indole derivatives is highly desirable.



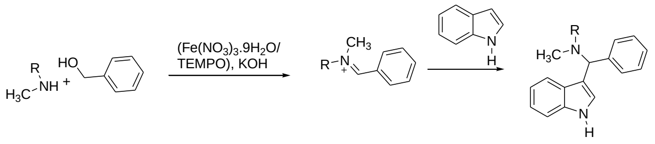
3 Amino alkylated indole    Azolylbenzyl indole

**Figure 1.** Biologically active 3 substituted indoles

Previous work:



Present work:

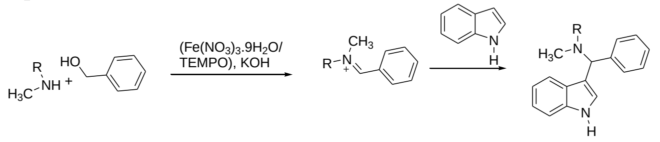


**Scheme 1**. Synthesis of 3 substituted indole.

In the earlier methods three component compounds were prepared by formation of condensation method. Which suffers the drawback of using the odorous[3d] and unstable aldehyde[3f], and also require in situ purification. Earlier methods also require large excess amounts of oxidants, which will also produce large amounts of undesired waste so developing efficient and greener methods is still an important need.

**Table1**

Optimization of reaction conditions[a]:



| Entry | $Fe(NO_3)_3.9H_2O$ (Mole %) | Solvent | Temp | Base[b] (mole %) | Yield (%)[c] |
|---|---|---|---|---|---|
| 1 | 10 | Toluene | rt | KOH (10) | 30 |
| 2 | 10 | Toluene | 50 °C | KOH (10) | 55 |
| 3 | 20 | Toluene | 80 °C | KOH (10) | 85 |
| 4 | 50 | Toluene | 80 °C | KOH (20) | 83 |
| 5 | 10 | Toluene | 80 °C | KOH (50) | 84 |
| 6 | 10 | Toluene | 80 °C | t-BuOK (10) | 81 |
| 7 | 10 | Benzene | 80 °C | $K_2CO_3$ (10) | n.d. |
| 8 | 10 | Benzene | 80 °C | $Et_3N$ (10) | n.d. |
| 9 | 10 | Benzene | 80 °C | t-BuOK (10) | 76 |
| 10 | 10 | Dioxane | 80 °C | t-BuOK(10) | 78 |
| 11 | 10 | Dioxane | 80 °C | KOH(10) | 81 |
| 12 | 10 | Xylene | 80 °C | KOH (10) | 83 |
| 13 | 10 | Xylene | 80 °C | $Et_3N$ (10) | n.d. |
| 14 | 10 | DMF | 80 °C | KOH (10) | n.d. |
| 15 | 10 | $CH_3CN$ | 80 °C | KOH (10) | n.d. |
| 16 | 10 | THF | 80 °C | KOH (10) | n.d. |
| 17 | 10 | DMSO | 80 °C | KOH (10) | n.d. |
| 18 | 10 | $CH_2Cl_2$ | 80 °C | KOH (10) | n.d. |
| 19 | 10 | $CH_3CN+H_2O$<br>(4:1)<br>80°C | 80 °C | KOH (10) | n.d. |

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[a] All reactions were run with **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.2 mmol) $Fe(NO_3)_3.9H_2O$ (10 mol %), and the base in toluene (0.5 mL) and solvent (3 mL) was heated under air in a 10 mL of sealed tube for 24 -30 h and then added by indole and monitored by TLC at room temperature.

[b] 0.1 mmol of TEMPO was used along with base in all the cases.

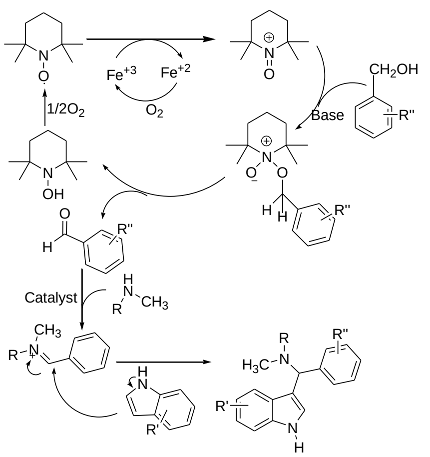
[c] Isolated yield of 4a; n.d.= not detected.

Reaction was carried out in sealed tube.

We initiated our studies of three-component reaction with *N*-methyl aniline (1a) (1 mmol), benzyl alcohol (2a) (1.2 mmol), and indole (3a) (1 mmol) was taken as a model substrate to optimize the reaction condition. Treatment of benzyl alcohol (2a) (1.2 mmol), and *N*-methyl aniline (1a mmol) with 50 mole % of KOH in 0.5 ml of toluene in the presence 10/10 mol% of ($Fe(NO_3)_2.9H_2O$/ TEMPO) for 24-30 h to yield imine which was again treated with indole, it gives desired novel 3 substituted indole as a single product. It was found that base played crucial role in the reaction as from table 1 (entry 1), reaction was initially tested at room temperature with catalytic amount of KOH added but only a low yield 30% was detected. Reaction yield can be improved when it is heated at higher temperature yield 4a 85% should be achieved at 80 °C using KOH as base (Table 1, entry 3).

During the course of reaction we attempted similar transformation in various solvent such as $CH_2Cl_2$, DMSO, DMF, THF, acetonitrile, benzene, toluene, dioxane among these solvent benzene, toluene, dioxane and xylene (Table 1, entries 1-1-6 and 9-12) were found to be most efficient reaction media to give the product in good yield (76-85) %.

Furthermore catalyst condition were optimized by using different variation of catalyst, catalyst loading and time period of reaction screening showed that 10 mol % of CsOH, and *t*-BuOK were used in place potassium hydroxide reaction. The yield was very good when potassium hydroxide is used as base table 1 (entries 1-3) to facile this reaction. After optimization of reaction condition different alcohols aliphatic and aromatic alcohol, saturated and unsaturated alcohol reaction works well in aromatic alcohols proceed in all condition except in aliphatic and unsaturated alcohols and gives corresponding product in good yields. Reaction proceeds well in both electron donating and electron withdrawing group for present protocol reaction. The result prompted us to investigate scope and generality of this methodology yielding 3 substituted indoles. Pyrrolidine and *N*-methyl aniline gave better results when compared with piperidine and morpholine as shown in the table 2.

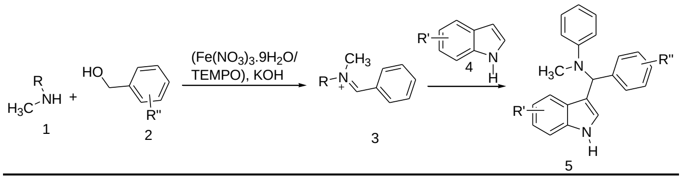


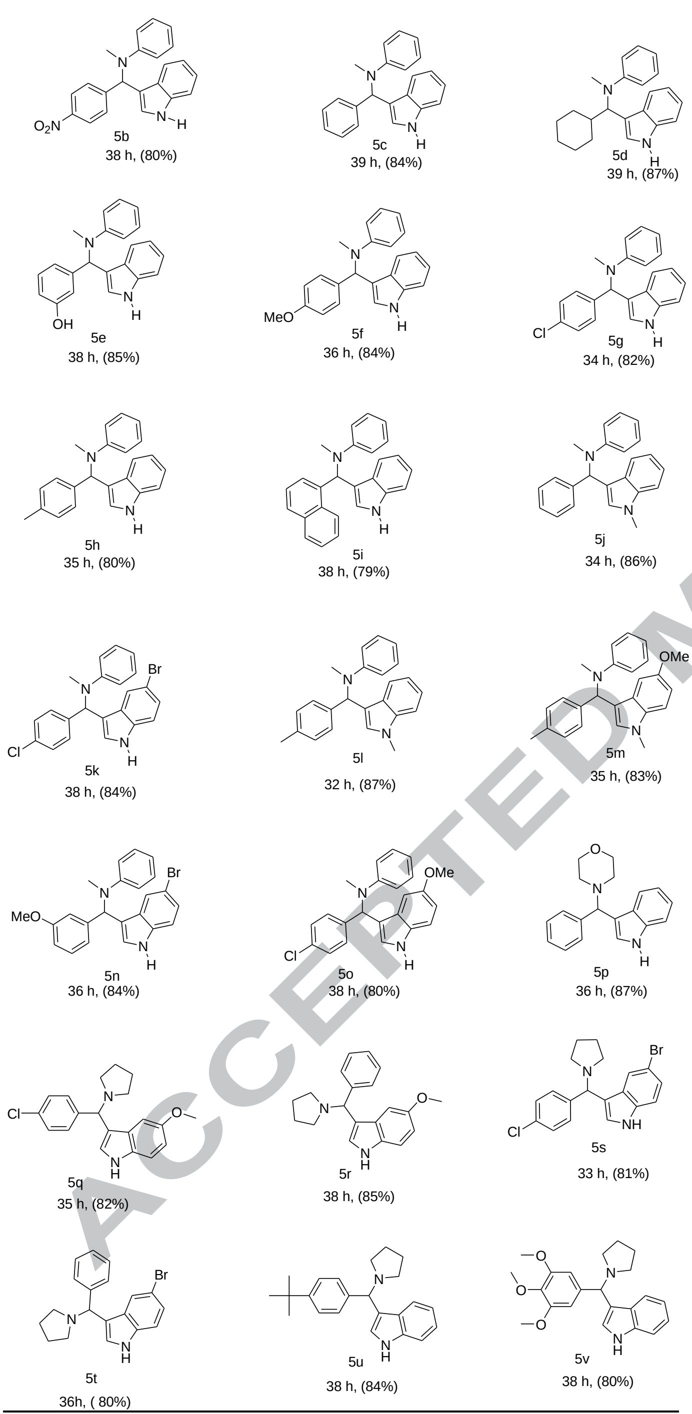
**Scheme 2**. A plausible mechanism for the formation for 3 substituted indole.

A plausible mechanism for this reaction is suggested in Scheme 2. Mechnistically it was presumed that formation of 3-substituted indole reaction was proceeded through formation of imine[7], followed by nucleophilic attack of indole to give 3 substituted indole as shown in scheme 2.

**Table 2**

Substrate scope for the preparation of 3 substituted indoles[abc]




5b 38 h, (80%)
5c 39 h, (84%)
5d 39 h, (87%)
5e 38 h, (85%)
5f 36 h, (84%)
5g 34 h, (82%)
5h 35 h, (80%)
5i 38 h, (79%)
5j 34 h, (86%)
5k 38 h, (84%)
5l 32 h, (87%)
5m 35 h, (83%)
5n 36 h, (84%)
5o 38 h, (80%)
5p 36 h, (87%)
5q 35 h, (82%)
5r 38 h, (85%)
5s 33 h, (81%)
5t 36h, ( 80%)
5u 38 h, (84%)
5v 38 h, (80%)

---

[a] For experimental procedure, see supporting information.

[b] All compounds are known and were characterized by comparison of their spectral data with those reported in the literature.[3d,3m]

[c] Yields of isolated pure compounds 4a.

In conclusion, we developed a highly efficient, short and green method for the synthesis of 3-amino-alkylated indole via one-pot three-component Mannich[3d, 3g, 3m] type reaction. The Mannich-type reactions are very important carbon–carbon bond-forming reactions in organic synthesis. It is easy and safe to handle at a large scale synthesis for preparation of the final product make this an attractive protocol by using insitu iminium ion formation.

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## Supplementary data

Supplementary data (detailed experimental procedures, product characterization, and NMR spectra of the products) associated with this article can be found, in the online version.

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