Visible-light-induced preparation of Functionalized Indoles

The use of low energy visible-light irradiation for the construction of synthetically and biologically important heterocyclic molecules by simple utilization of readily available starting substrates has emerged as powerful and sustainable approach in organic synthesis. Indole scaffold is an important structural component of numerous natural products, pharmaceuticals, bioactive compounds, and organic materials. In the light of their importance, many powerful approaches have been developed for the synthesis of the indole moieties, including classical Fischer indole synthesis (Fig. 1A (a)).

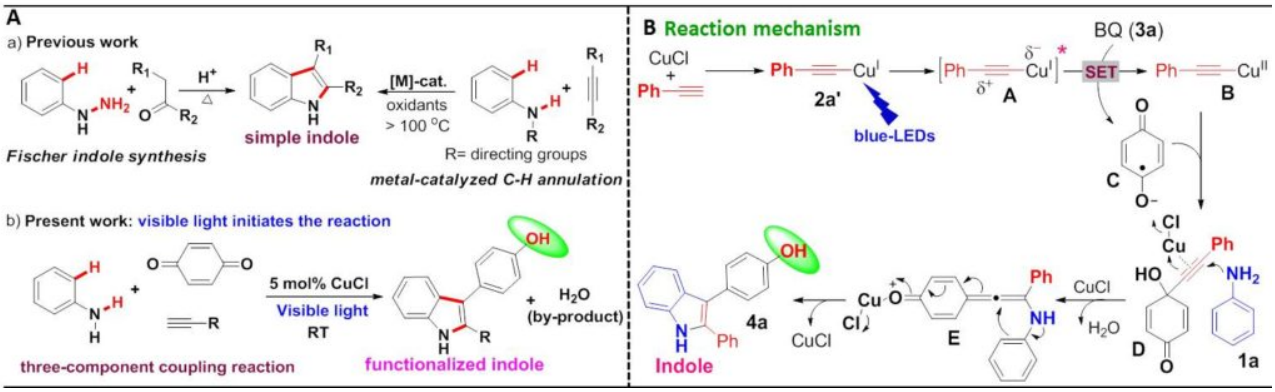

Fig. 1. (A) Comparison of the literature reported thermal process and the current visible-light-induced CuCl catalyzed process for the preparation of indoles. (B) Plausible reaction mechanism.

Recently, the precious transition metal catalytic system (Pd-, Ru- or Rh- complex) have been successfully shown to facilitate the intermolecular C-H annulation of arylamine and internal alkynes (via directing-group-assisted) for the preparation of indoles (Fig. 1A (a)). Hence, these methods suffer from some limitations, such as; a) usage of stoichiometric oxidants and thus leading to the generation of undesired wastes, b) high reaction temperature is almost always required, c) only works with internal alkynes, and d) generation of non-functionalized indoles as a mixture of region-isomers. In this study, we describe a visible-light-induced three-component coupling (TCC) of aniline, alkynes and benzoquinone to assemble the functionalized indoles through C-H annulation at room temperature *via* a simple and inexpensive process (5% CuCl, without the use of external oxidants) (Fig. 1A (b)). Installation of a phenol functional group on the indole ring is more attractive because the phenol motif involves many organic reactions and it has stronger ?-binding affinity than bare phenyl ring toward estrogen receptor (ER).

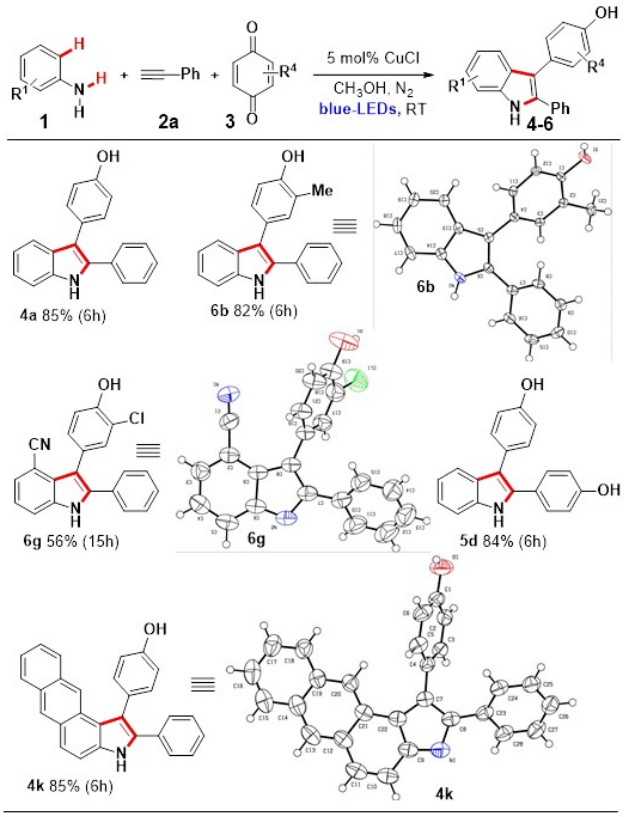

Fig. 2. Preparation of functionalized indoles.

The present study demonstrates with substrates covering a very wide range of functional groups, including; halides, methoxy, alkyl, ester, nitro, cyano, acetanilide, etc., (Fig. 2). Moreover, the current method could be readily scaled up to a preparative (1~2 grams) scale; and indole (5d) has good binding affinities to estrogen receptor (ER). Importantly, copper-catalyzed oxidative C-H annulation reactions involving terminal alkynes often heavily suffer on homocoupling by-product formation. However, the present three component C-H annulation reactions, no alkyne homocoupling product was observed. Remarkably, terminal alkynes that are unsuccessful coupling partners for rhodium-, palladium-, nickel-, and ruthenium-catalyzed indole synthesis, proved to be amenable to the current system.

Mechanistic control studies shows that photoexcited Cu(I)-phenylacetylide (A) would undergo single electron transfer (SET) to benzoquinone, and thus would have formed benzoquinone radical anion (C), and Cu(II)-phenylacetylide (B) (Fig. 1B). Based on cyclic voltammetry (CV), the redox potential of copper(I) phenylacetylide (2a') was determined to be -2.048 V_{SCE} in CH_3CN. A bandgap energy of E^{00} = 2.52 eV was deetermined from the intersection of copper(I) phenylacetylide (2a') emission and excitation spectra. This redox potential is higher than that (-0.47 V_{SCE}) for

1,4-benzoquinone. Therefore, one electron transfer from photo-excited triplet copper(I) phenylacetylide to benzoquinone is exothermic, and can occur spontaneously. From synthetic point of view, the C-H annulation method represents a sustainable and atom economical approach to construction of complex indoles (as a single regioisomer) from easily accessible starting materials in presence of inexpensive catalyst (CuCl) under low-energy visible-light-irradiation.

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Publication

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