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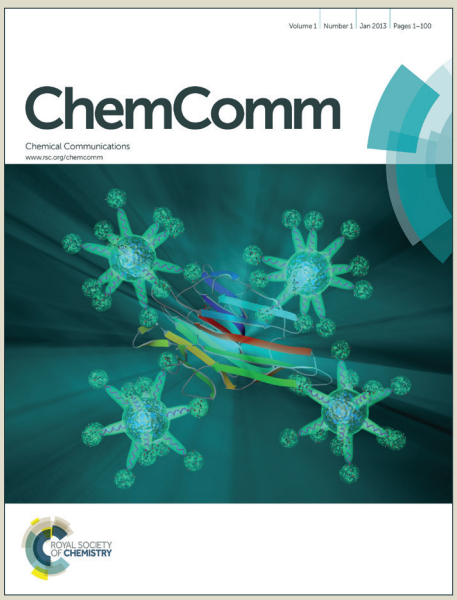

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A metal free domino synthesis of 3-aroylindoles via two sp^3 C-H activation

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A metal free synthesis of 3-aroylindole involving two sp^3 C–H activation has been achieved starting from *o*-alkynyl-*N*,*N*-dialkylamines using catalyst TBAI and oxidant TBHP.

In modern organic synthesis, C–H functionalisation strategies have brought about atom and step-economy by streamlining various arduous synthetic processes.[1] However, in this forum, much of the attention has been focused on functionalisations of sp and sp^2 C–H bonds.[2] In contrast high pK_a's (>30–35) as well as large bond dissociation energies (>104 kcal/mole) of various sp^3 C–H bonds make their selective activation a formidable challenge. The solutions to these challenges, led to the evolution of various sp^3 C–H activation strategies, one of them being the cross dehydrogenative coupling (CDC). In most cases, functionalisations of sp^3 C–H bonds α to heteroatoms are attained by CDC strategy using transition metal catalysts.[3] The heteroatoms present in precursors are invariably *N*- or *O*- that generate iminium or oxonium ion intermediates *in situ*.[3,4] These reactive intermediates are formed by a single electron transfer from the heteroatoms to the metal centre that forms a radical cation. This is then followed by a loss of hydrogen radical from the adjacent carbon generating either an iminium or an oxonium ion which is amenable for the construction of C–C or C–heteroatom bonds by an inter- or an intramolecular nucleophilic attack. For precursors like tertiary amines, a variety of transition metal catalysts in combination with organic peroxides are conducive for the formation of reactive intermediates.[3,4a-c] Noteworthy, an intramolecular nucleophilic attack at these iminium ions can generate various nitrogen containing heterocycles.[4a,5,6]

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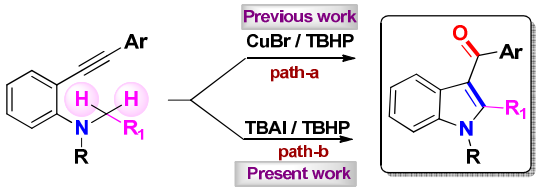
Among nitrogenous heterocycles, indole ring system finds wide applications in material chemistry and pharmaceuticals.[7] In particular, 3-aroylindoles have attracted more importance as they provide alternate routes to other functionalised indoles because of easy manipulation of its carbonyl group.[8] As an obvious consequence, development of straightforward method for the synthesis of 3-aroylindoles has been of great significance. This motivation led to our Cu catalysed synthesis of 3-aroylindole from 2-alkynyl-*N*,*N*-dialkylamine via a cascade C–C and C–O bond forming pathways following the above-mentioned intra-molecular CDC strategy (path-a, Scheme 1).[5] Exactly the same strategy has been reported by Liang group using a Pd-Cu catalytic system instead of simple Cu catalyst.[6] Prior to these reports, several other unconventional methods (via C–H activation) for their synthesis have been developed using transition metal catalysts.[8g,9]

Although transition metal catalysed processes are advantageous but are invariably associated with high cost and difficulties in removal of residual metals from the final product which limits their utility in pharmaceutical industries. Further, for a copper catalysed reaction often doubt arises whether it is the real catalyst or a co-catalyst for the traces of Pd present in commercial grade Cu salts. There are instances where the metal impurities present even in traces in commercial grade salts are the actual catalyst.[10]

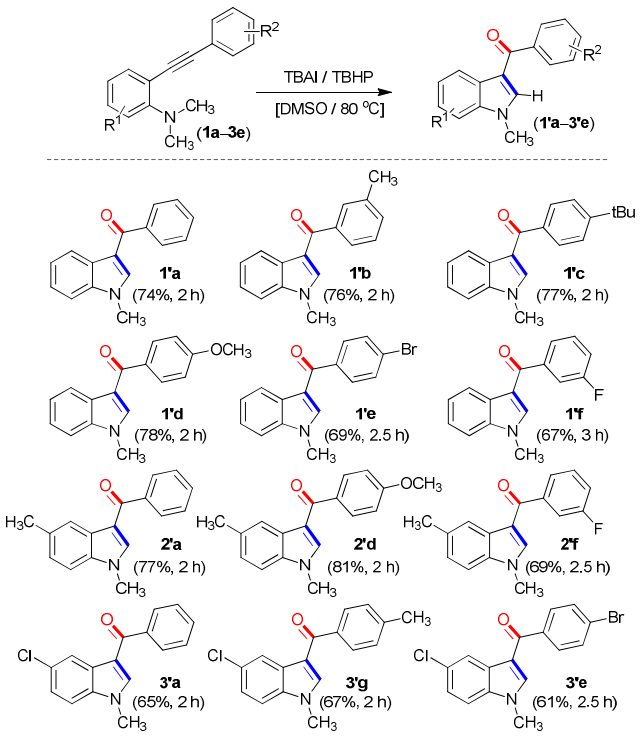


Scheme 1 Synthesis of 3-aroylindole via sp^3 C–H activation.

To overcome some of the disadvantages associated with metal catalysts recently photo-catalysts[11] and molecular iodine or organo-

iodide[12] such as tetrabutylammonium iodide (TBAI) in combination with external oxidant are appropriate substitutes.[11,12] The use of designer ligands and at times metals are unavoidable in any photo-catalytic process, thereby making the overall method expensive when applied to large scale reactions. Thus, we envisaged that instead of using metal catalysts the domino transformation of 2-alkynyl-*N*,*N*-dialkylamines to 3-aroyl indoles could be realised under a metal free condition using TBAI. With this inspiration in mind our initial investigation began by treating *N*,*N*-dimethyl-2-(2-phenylethynyl)benzenamine (**1a**) (1 equiv.) with TBAI (20 mol%) and 70% aq. TBHP (3 equiv.) at 80 °C. To our delight aroylindole (**1′a**) was isolated in 52% yield (entry 1, Table S1, ESI†). To the best of our knowledge this is the first metal free synthesis of 3-aroylindole involving two sp^3 C–H activation (path-b, Scheme 1).

Scheme 2 Substrate scope of 3-aroylindoles.[a,b]

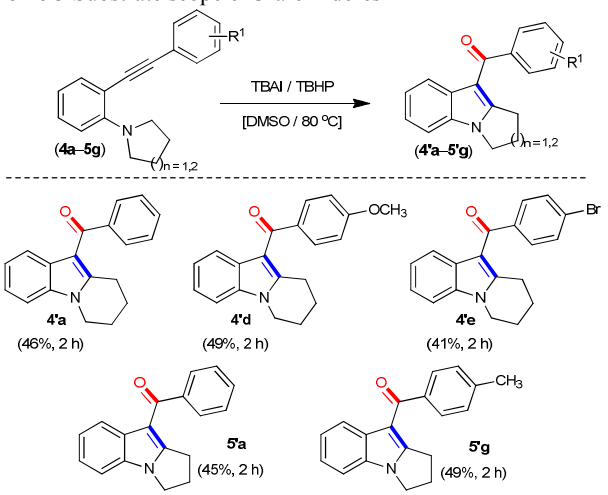


[a]Reaction conditions: *o*-alkynyl-*N*, *N*-dialkylamine (0.25 mmol), TBAI (0.05 mmol), TBHP (1.25 mmol) DMSO (1 mL) at 80 °C. [b]Isolated yields.

Encouraged by this metal-free cascade synthesis of 3-aroyl indole, other reaction parameters such as catalysts, oxidants and solvents were varied to attain best possible yield. Increasing the amount of TBHP from 3 equiv. to 4 equiv. and 5 equiv. resulted in an improved yield of 59% and 74% respectively (entries 2–3, Table S1, ESI†). Instead of TBAI, the use of other halogen analogues such as KI, I_2, and tetrabutylammonium bromide (TBAB) were found to be less effective (entries 4–6, Table S1, ESI†). A decane solution of TBHP (5–6 M) (5 equiv.) in lieu of its aqueous solution (70%) gave a comparable yield of 69%, however, other peroxides such as di-*tert*-butyl peroxide (DTBP) or aq. H_2O_2 (50%) failed to give satisfactory yield of the product (entries 7–9, Table S1, ESI†). Further, the use of other solvents such as DMF (62%), toluene (46%), 1,4-dioxane (54%), DCE (37%) were found to be less productive than DMSO (entries 10–13, Table S1, ESI†). The yield dropped to 56% when the catalyst loading was reduced to 15 mol% (entry 14, Table S1, ESI†). Neither TBAI nor TBHP alone were capable of triggering this domino transformation, suggesting an essential requirement of their combination (entries 15–16, Table S1, ESI†). Thus, catalyst TBAI (20 mol%), aqueous TBHP (5 equiv.) in DMSO at 80 °C were found to be the ideal conditions for this transformation (entry 3, Table S1, ESI†).

After achieving the optimised conditions, this methodology was applied to different *o*-alkynyl-*N*,*N*-dialkylamines to afford their respective 3-aroylindoles. As shown in Scheme 2 and 3, a series of aroylindoles could be obtained in moderate to excellent yields from their aminoalkyne precursors. At first, effects of substituents on the aryl ring of the alkynes were examined. The electron-donating substituents viz. *m*-Me (**1b**), *p*-tBu (**1c**) and *p*-OMe (**1d**) when present in the aryl ring of the alkyne had a positive impact on the products (**1′b–1′d**) yields (in the range of 76–78%). However, when the aryl ring contains electron-withdrawing groups such as *p*-Br (**1e**) and *m*-F (**1f**), the reactions proceeded sluggishly to afford their corresponding aroylindoles (**1′e**) and (**1′f**) in slightly lesser yields (in the range 67–69%). When the amine bearing aryl ring of the *o*-alkynylamines are substituted with weakly electron-donating groups such as *p*-Me and the other aryl ring being unsubtituted (**2a**) or substituted with an electron-withdrawing group (**2f**), good yields of the products were achieved. An excellent yield of 81% was obtained when both the rings contain electron-donating groups as found for (**2′d**). A moderately electron-withdrawing group such as *p*-Cl present in the aryl ring bearing the tertiary amine group resulted in comparatively lesser yields regardless of the nature of the substituents on the other ring as exemplified for (**3′a**), (**3′g**) and (**3′e**). The scope of this methodology was next extended to annular tertiary amines. The *o*-alkynyl amines precursors with a six- or a five-membered ring provided their corresponding aroylindoles under the optimised reaction condition as has been demonstrated by the synthesis of (**4′a**), (**4′d**), (**4′e**) (**5′a**) and (**5′g**). However, the yields were moderate which may be due to the ring strain associated with the resulting fused aroylindoles. The structure of the aroylindole (**5′g**) was confirmed by X-ray crystallography (Figure S1, see ESI†).

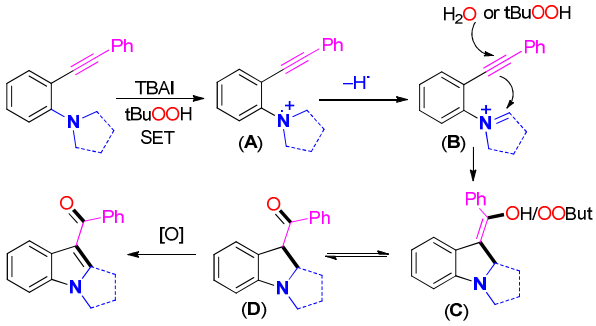
Scheme 3 Substrate scope of 3-arolindoles[a,b]



[a]Reaction conditions: *o*-alkynyl-*N*, *N*-dialkylamine (0.25 mmol), TBAI (0.05 mmol), TBHP (1.25 mmol) DMSO (1 mL) at 80 °C. [b]Isolated yields.

Based on literature reports[12a,n,o] and trends in the yields of product obtained for substituted substrates a plausible mechanism has been proposed for this transformation. An aminyl radical cation (**A**) is formed by a single electron transfer (SET) process from the nitrogen atom of the *o*-alkynyl-*N*,*N*-dialkylamine. Abstraction of a hydrogen radical α to the nitrogen atom gives an imminium intermediate (**B**).

The intermediate (**B**) then undergoes annulation by an intramolecular nucleophilic attack of the alkynyl group at the imminium carbon with simultaneous attack of water or TBHP at the alkenyl carbon to give intermediate species (**C**).[5,6] The reaction of substrate (**1a**) under the reaction condition in the presence of 20 equivalent of $H_2{}^{18}O$ afforded aroylindole (**1′a**) without any ^{18}O incorporation indicating TBHP as the possible oxygen source. Ketonisation of (**C**) provides 3-aroylindoline (**D**) which is finally oxidised/aromatised to its 3-aroylindole.



Scheme 4 Proposed mechanism for the formation of 3-aroylindoles.

In conclusion, we have developed a metal free method for the synthesis of 3-aroylindoles from *o*-alkynyl-*N*,*N*-dialkylamine through a TBAI catalysed intramolecular oxidative coupling pathway using TBHP as oxidant. This protocol simultaneously installs C–C and C–O bonds at the expense of two sp^3 C–H bonds. The use of inexpensive and environmentally benign catalytic system and relatively lower reaction time and temperature make the present protocol practically more applicable.

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