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Copper-catalyzed tandem reaction of 2-alkynylanilines with benzoquinones: efficient access to 3-indolylquinones†

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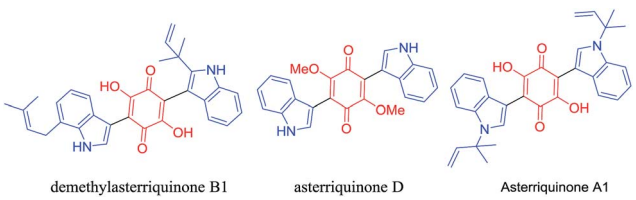
A simple, mild, catalytic and efficient method for the straightforward synthesis of an interesting class of 2-aryl/alkyl-substituted-3-indolyl quinones in good to high yields is reported for the first time. This atom-efficient method proceeds *via* copper-catalyzed one-pot sequential intramolecular hydroamination (C–N bond formation) of 2-alkynylanilines followed by oxidative C–C coupling with benzoquinones.

Introduction

Indole scaffolds represent one of the privileged structural motifs in biologically active natural products and drug molecules which have vital medicinal value.[1] Among the family of indole derivatives, 3-indolylquinones, mainly bis(indolyl) quinone, are a significant structural unit in many natural products because of their numerous biological activities.[2] Among these indolylquinones, asterriquinones show the most potential as pharmacophores, and could be used in a wide range of biological activities, including the inhibition of human immunodeficiency virus reverse transcriptase[3] (Fig. 1). These asterriquinones mostly possess a symmetrical benzoquinone unit containing two oppositely N1-prenylated tryptophanyl moieties which are isolated from *Aspergillus terreus*, *Chaetomium* sp., and *Pseudomassaria* sp.[4] It is worth mentioning demethylasterriquinone B1, described as a non-peptidyl mimetic of insulin with excellent antidiabetic activity in recent studies.[5]



demethylasterriquinone B1 asterriquinone D Asterriquinone A1

Fig. 1 Biologically active asterriquinone derivatives.

For the synthesis of 3-indolylquinones, in the past, several approaches have been reported from indolic starting materials as efficient methodologies. For instance, in 1911, Mohlau *et al.* described this for the first time using the reaction of benzoquinone and indole, however the product was not isolated.[6] Later, Bu'Lock reinvestigated and isolated 3-indolylquinones with a very low yield.[7] Subsequently, various catalytic routes were developed in this scenario. Yadav *et al.*[8] reported these products from indoles and benzoquinones using various Lewis acids such as $InBr_3$ and $Bi(OTf)_3$ under mild reaction conditions. Likewise, Park and co-workers synthesized 3-indolylquinones with indoles and benzoquinones using mineral acids like $Zn(OTf)_2$ and mercury reagents along with Pd(II)/$Cu(OAc)_2$.[9] In addition, 3-indolylquinones were also prepared using ultrasound activation between the indole and quinone using molecular iodine as a catalyst.[10] Very recently, Kamble *et al.*[11] developed 3-indolylquinones using the *in situ* oxidation of hydroquinone followed by C–C bonding with indole using a combination of Ag_2O in H_2O_2 and an Fe_3O_4/PVP–PWA catalytic system. These are all reported in the literature, mainly from indolic starting materials. Therefore, it is highly necessary to develop an efficient catalytic and high yielding tandem protocol that allows the quick preparation of 3-indolylquinones from simple 2-alkynylanilines and benzoquinone as raw materials in the presence of copper cyanide as a catalyst (Scheme 1).

Interestingly, the transition metal-catalyzed tandem one-pot annulation of *o*-alkynylanilines followed by *in situ* trapping with suitable electrophiles has become an extremely useful protocol for the construction of 2,3-difunctionalized indoles.[12] Previously, we reported an efficient silver catalyzed[13] domino process for the synthesis of 2,3-disubstituted indoles from alkyne imino ethers. Furthermore, the copper catalysed three-component synthesis of 2-[(2-alkyl-1*H*-indol-3-yl)methylene]malonates from *o*-alkynylanilines, triethyl orthoformate and diethyl malonoate followed by Sc-catalyzed intramolecular Friedel–Crafts reactions to the corresponding heterocyclic compounds was also reported.[14] Based on these studies, we believe that it is

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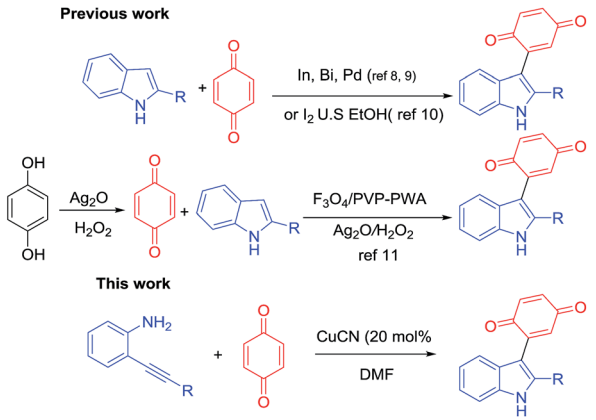


Scheme 1 Methods of synthesis of 3-indolylquinones.

possible to access 3-indolylquinones using the same protocol with benzoquinone as a good electrophile. Despite considerable progress observed in the synthesis of 3-indolylquinones, nobody has reported on the transition-metal-catalyzed heterocyclization reaction between 2-alkyanilines and quinones. Nevertheless, this combination constitutes an interesting class of 3-quinone-substituted indole scaffolds.

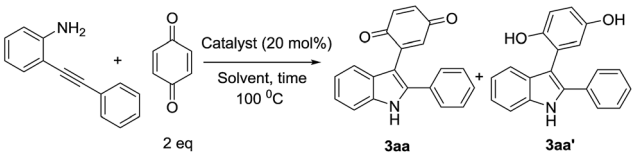
However, the cyclization of 2-alkynylanilines followed by functionalization at the C_3-position of free (N–H) indoles is a highly complex step because it often suffers from competing reactions of amines[15] and alkynes with benzoquinones which are predominantly expected to form the addition products of benzoquinone and amines under acidic conditions. However, the present study primarily exploits indole formation instead of side reactions with benzoquinone and this concept is reported for the first time in the presence of benzoquinone.

Results and discussion

We commenced optimization studies using readily available *o*-alkynylaniline **1a** and benzoquinone **2a** (1 eq.) as coupling partners. The tandem heterocyclization reaction was performed in the presence of 20 mol% CuCN as a Lewis acid catalyst at a temperature of 100 °C in DMF under an air atmosphere. Pleasingly, a new class of 3-indolyl quinone (**3aa**, 20%) and 3-indolyl hydroquinone (**3aa′**, 55%) were obtained as a mixture of products with moderate yield, after 12 h (entry 1, Table 1). Pleasantly, when the same reaction was conducted with 1.5 equivalents of **2a**, surprisingly, the yield of **3aa** was 52% and that of **3aa′** was 30%. These products (**3aa** & **3aa′**) can be distinguished by proton & carbon NMR spectroscopy: **3aa** shows two C=O signals in the carbon NMR spectrum but for **3aa′**, the corresponding C=O peaks disappear.

From this study, we observed that formed 3-indolylhydroquinone undergoes oxidation in the presence of excess benzoquinone. Hence, in the same reaction repeated with 2eq. of **2a**, the yield of **3aa** significantly improved to 80% with a trace amount of **3aa′** (entry 3). These results prompted us to examine various Lewis-acid promoted tandem heterocyclization reactions in more detail. In this context, a variety of transition-metal

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Time [h]	Yield[b]% $^{3aa\ +3aa'}$
1	CuCN	DMF	12	(20 + 55)[c]
2	CuCN	DMF	12	(52 + 30)[d]
3	CuCN	DMF	12	80 + <5
4	CuI	DMF	24	64 + trace
5	CuCl	DMF	24	68 + trace
6	$Cu(OTf)_2$	DMF	24	<5
7	$Cu(NO_2)_3$	DMF	24	ND[g]
8	$Cu(OAc)_2 \cdot H_2O$	DMF	24	58
9	$Cu(OAc)_2$	DMF	24	60
10	$InCl_3$	DMF	24	ND[g]
11	$NaAuCl_4 \cdot 3H_2O$	DMF	24	57[e]
12	$Pd(OAc)_2$	DMF	24	60[f]
13	CuCN	DCE	24	ND[g]
14	CuCN	DMSO	24	<5
15	CuCN	Toluene	24	ND[g]
16	CuCN	H_2O	24	ND[g]
17	CuCN	MeOH	24	<5
18	CuCN	ACN	24	ND[g]
19	Iodine	DMF	24	25
20	PTSA	DMF	24	ND[g]
21	$NaAuCl_4 \cdot 3H_2O$	DCM	12	78[e]
22	$Pd(OAc)_2$	DCM	12	65[f]

[a] All the reactions were performed with **1a** (38.6 mg, 0.2 mmol), **2a** (2 equiv.) at 100 °C under air. [b] All the yields are isolated yields. [c] Reaction with 1 eq. of **2a**. [d] Reaction with 1.5 equiv. of **2a**. [e] Reaction with 2 mol% gold catalyst. [f] Reaction with 5 mol% palladium catalyst. [g] ND denotes not determined.

salts such as CuI, CuCl, $Cu(OTf)_2$, $Cu(NO_2)_3$, $Cu(OAc)_2$, $Cu(OAc)_2 \cdot H_2O$, $InCl_3$, $NaAuCl_4 \cdot 3H_2O$ and $Pd(OAc)_2$, as well-known alkyne bond activators, were tested for this tandem cyclization process as shown in Table 1 (entries 4–12) using DMF as a solvent. Among them, CuCN is observed as the best catalyst to form the desired product with 80%, yield (entry 3). The obtained results from screening reactions of 2-alkynylaniline (**1a**) and benzoquinone (**2a**) with common organic solvents such as toluene, DCE, MeCN, THF, DMSO and MeOH revealed that none of the solvents (except DMF) could promote the tandem process significantly (entries 13–18, Table 1). However, $NaAuCl_4 \cdot 3H_2O$ (2 mol%) and $Pd(OAc)_2$ (5 mol%) afford 72% and 60% yields, respectively, at room temperature in 12 h, with DCM as the solvent (entry 21, 22, Table 1). After optimization of the reaction conditions, we established an efficient route to the formation of 3-indolylquinones. The optimal reaction conditions are **1a** (0.2 mmol) and **2a** (0.4 mmol) as the reactants with CuCN (0.04 mmol) and DMF (2 mL) at 100 °C for 12 h.

With the optimized reaction conditions in hand, we next explored the efficiency and generality of this tandem heterocyclization process using the reactions of several 2-(aryl/alkylethynyl) aniline derivatives with various quinones using

CuCN as an efficient Lewis acid catalyst. These results are summarized in Table 2. First, various 2-alkyl-substituted (phenyl, ethyl benzene, cyclohexyl, hydroxyl alkane, biphenyl, benzyl) ethynylanilines (**1a–f**) were reacted efficiently with benzoquinone to give the desired products **3aa–3fa** in good to excellent yields (52–90%). Contrarily, *N*-acylated 2-alkynyl aniline (**2j**) does not undergo the domino cyclization due to the low efficiency of *N*-acyl amine donation of a loan pair of electrons to the pi activated electron deficient alkyne. Halogen substitute alkynyl anilines like chlorine and fluorine have little influence under optimized reaction conditions on the formation of the corresponding products **3ga** and **3ha** in moderate yields (59% & 63%). Both alkyl and aryl substituted ethynylaniline (**1i**) produce **3ia** in 82% yield. In the case of lower yields of the final compounds, the annulated indole is the main by-product along with trace amounts of the 3-indolyl hydroquinone.

To further investigate the substrate scope, we turned our attention to examine various unsymmetrical benzoquinones such as methyl, phenyl and methoxy benzoquinone (**2b–2e**) and symmetrical benzoquinones such as 2,6-ditertiary butyl and 2,5-dibromo benzoquinone (**2g** and **2h**). The tandem coupling of 2-alkynyl aniline with aliphatic substituted unsymmetrical benzoquinones (methyl, methoxy) affords a mixture of isomers with a 1 : 1 ratio of **3ac** and **3ad** in 80% and 82% yields, respectively. However, phenyl substituted unsymmetrical benzoquinone (**2b**) under the present reaction conditions exclusively gives the regio selective and more substituted side coupling product as shown in Table 2. Thus, these unprecedented results motivated us to work on different 2-alkynyl anilines with 2-phenyl benzoquinones under the present conditions and good to excellent yields were attained (**3ab–3cb**) and the results are shown in Table 2. Additionally, reactions with 1,4-naphthoquinone show moderate yields (**3ae**, 60%). Furthermore, the structure of compound **3fa** was unambiguously confirmed by X-ray analysis (CCDC 1844842†).

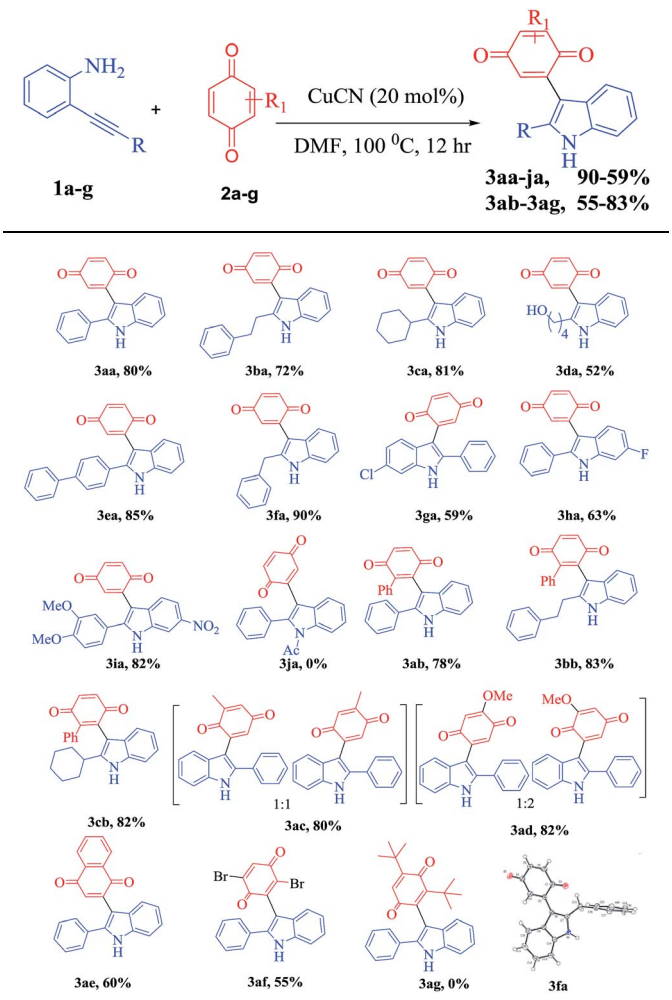
However, due to the highly bulky nature of 2,6-ditertiary butyl substituted symmetrical benzoquinones (**2ag**), they produce only the indole derivative without undergoing C–C bond formation. On the other hand, 2,5-dibromo benzoquinone achieves a 55% yield of **3af** as shown in Table 2, along with the intermediate indole.

At this stage, to gain an understanding of the detailed mechanism of this reaction, several control experiments were carried out, as demonstrated in Scheme 2. Initially, we believed that the reaction proceeds *via* a 2-substituted indole derivative (through an aminocuprate step), which then adds to benzoquinone in a 1,4-fashion to generate the 3-indolyl hydroquinones followed by oxidation. To get a better understanding, a couple of control experiments were performed in which 2-phenylindole (1 equiv.) was treated with benzoquinone (2 equiv.) in the presence or absence of the Cu catalyst at 100 °C in DMF. In the presence of the Cu catalyst, the product **3aa** is obtained in 82% quantitative yield after 12 h whereas in the absence of the Cu catalyst, the present reaction does not proceed and no products are observed even after 24 h in DMF at 100 °C.

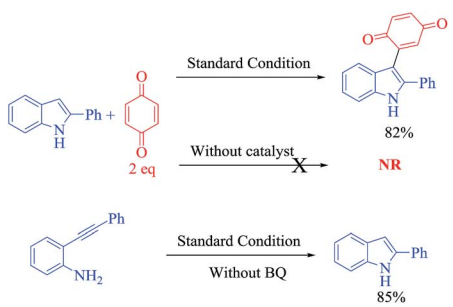
In addition, we also investigated the standard reaction conditions in the absence of benzoquinone and surprisingly, a quantitative amount of anticipated products formed after 24 h.

Based on these control experiments, a plausible mechanism for the formation of 3-indolyl quinones was proposed as shown

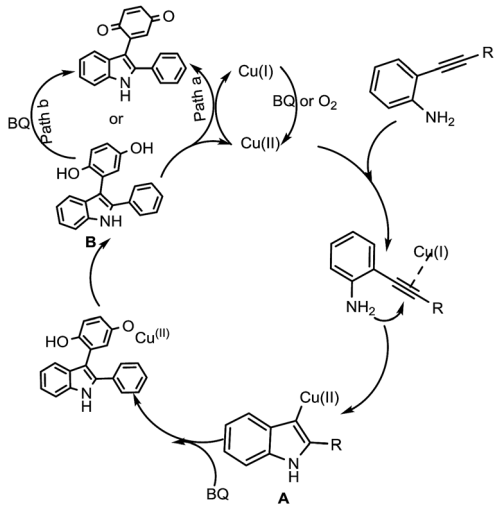
Table 2 Tandem cyclization of 2-alkynyl anilines with benzoquinones[a]



[a] The reaction was carried out with 1 (0.2 mmol), 2 (0.4 mmol) and CuCN (20 mol%) in DMF (2 mL) at 100 °C, 12 h.



Scheme 2 Control experiments.



Scheme 3 Proposed mechanism.

in Scheme 3. At first, copper(I) gets oxidised in the presence of oxygen or benzoquinone to form Cu(II), which reacts with 2-alkynyl anilines to afford a vinyl cuprate intermediate (A). This subsequently undergoes a 1,2-migratory reaction with benzoquinone, which inserts into the C–Cu bond to produce the intermediate 3-indolyl hydroquinone (B).

The formed intermediate 3-indolyl hydroquinone (B) has two possible ways to get oxidised to the final product, 3-indolyl quinone; path B,[8b] which involves oxidation in the presence of excess benzoquinone, or path A,[16] where Cu(II) is reduced to Cu(I) in the presence of 3-indolyl hydroquinone, finally to access the desired product **3aa**.

Conclusions

In summary, we report a novel catalytic method for the synthesis of 3-indolylquinones from 2-ethynylanilines and benzoquinones through a tandem-type cyclization followed by a C–C bond formation sequence. The use of a copper catalyst enabled the process to be performed efficiently under mild reaction conditions. In addition, aromatic unsymmetrical benzoquinones give regio-selective substituted 3-indolylquinones with moderate to good yields. Outstandingly, we are extending this protocol to the construction of other heterocyclic compounds, the details of which will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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