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Selective Synthesis of 2-Indolyl-3-oxoindolines or 2-(2-Aminophenyl)quinolines through Cu(II)- or Bi(III)-Catalyzed Tunable Dimerizations of 2-Alkynylanilines

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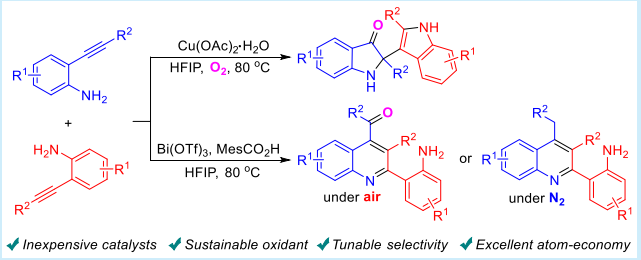
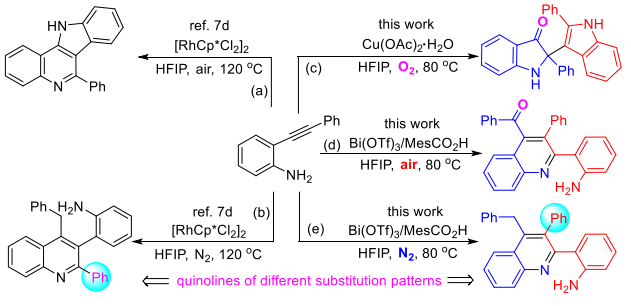
ABSTRACT: A novel and selective synthesis of 2-indolyl-3-oxoindolines or 2-(2-aminophenyl)quinolines through tunable dimerizations of 2-alkynylanilines is presented. Mechanistically, the formation of 2-indolyl-3-oxoindolines involves a $Cu(OAc)_2$/O_2-promoted intramolecular cyclization of 2-alkynylaniline to give the required indole and 3*H*-indol-3-one intermediates followed by the indolylation of 3*H*-indol-3-one. On the other hand, the formation of 2-(2-aminophenyl)quinolines is believed to go through a $Bi(OTf)_3$/$MesCO_2H$-catalyzed intermolecular N-nucleophilic addition between two 2-alkynylaniline molecules to give an enamine intermediate followed by its intramolecular C-nucleophilic addition/annulation. Notable features of these new methods include easily obtainable substrates, economical catalysts and oxidant, controllable selectivity, and high versatility toward diverse products.



2,2-Disubstituted indolin-3-one constitutes the scaffold of numerous natural products such as Austamdine, Cephalinone, LipidGreen, Aristotelon, Isatisine A, and Halichrome A,[1] fluorescence probes, and solar-cell materials.[2] Among different kinds of 2,2-disubstituted indolin-3-one derivatives, 2-indolyl-3-oxoindolines are particularly attractive. This is because they not only have unique structural features but also demonstrate potent antiviral activities.[3] To date, several reliable methods for the preparation of 2-indolyl-3-oxoindolines have been reported by Ramana, Guchhait, Jiang, Liu, and many others.[4−6]

In the past several years, we have developed some methods for the synthesis of biologically interesting heterocyclic compounds.[7] In this regard, we recently disclosed the synthesis of indolo[3,2-*c*]quinolines and 3-(2-aminophenyl)quinolines via $[RhCp^*Cl_2]_2$-catalyzed dimerization of 2-alkynylanilines under aerobic/anaerobic conditions (Schemes 1a and 1b).[7d] In continuation of our study, we have studied the reaction of 2-alkynylanilines under the catalysis of some non-noble metal catalysts. Through this study, we serendipitously developed an unrevealed selective synthesis of 2-indolyl-3-oxo-indolines or 2-(2-aminophenyl)quinolines from 2-alkynylanilines upon finely tuning the reaction conditions (Scheme 1c, 1d, and 1e). Herein, we report the results obtained in this regard.

Scheme 1. Diverse Reactions of 2-(Phenylethynyl)aniline



Initially, **1a** was treated with $Cu(OAc)_2$ in HFIP at 80 °C under air for 20 h. From this reaction, **2a** was obtained in 42% yield (Table 1, entry 1). To increase the yield, several solvents were tried, but they were inferior to HFIP in mediating this reaction (entries 2−6). Next, several other Cu(II) salts were used as catalyst (entries 7−11). Among them, $Cu(OAc)_2{\cdot}H_2O$ gave the best yield of **2a** (entry 7). Under the catalysis of $Cu(OTf)_2$ or $CuSO_4$, to our surprise, **2a** was formed only in a trace amount, while **3a** was obtained in 39% and 21% yield (entries 10 and 11). To facilitate the formation of **2a**, *m*-CPBA or TBHP was used as oxidant. In these cases, however, the yield of **2a** decreased (entries 12 and 13). When this reaction was run under O_2, gratifyingly, the yield of **2a** was improved to 61% (entry 14).

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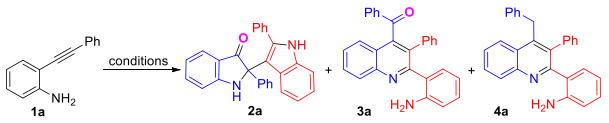
Table 1. Optimization Study for the Formation of 2a/3a/4a[a]



entry	catalyst	additive	solvent	yield (%)[b] 2a	3a	4a
1	$Cu(OAc)_2$		HFIP	42	ND	ND
2	$Cu(OAc)_2$		TFE	32	ND	ND
3	$Cu(OAc)_2$		MeOH	trace	ND	ND
4	$Cu(OAc)_2$		DCE	15	ND	ND
5	$Cu(OAc)_2$		THF	trace	ND	ND
6	$Cu(OAc)_2$		dioxane	trace	ND	ND
7	$Cu(OAc)_2{\cdot}H_2O$		HFIP	53	ND	ND
8	$CuCl_2{\cdot}2H_2O$		HFIP	22	ND	ND
9	$CuBr_2$		HFIP	trace	ND	ND
10	$Cu(OTf)_2$		HFIP	trace	39	trace
11	$CuSO_4$		HFIP	trace	21	trace
12	$Cu(OAc)_2{\cdot}H_2O$	*m*-CPBA	HFIP	28	ND	ND
13	$Cu(OAc)_2{\cdot}H_2O$	TBHP	HFIP	24	ND	ND
14	$Cu(OAc)_2{\cdot}H_2O$	O_2	HFIP	61	ND	ND
15	$Cu(OTf)_2$	TFA	HFIP	ND	36	trace
16	$Cu(OTf)_2$	$MesCO_2H$	HFIP	ND	55	trace
17	$Cu(OTf)_2$	$1\text{-}AdCO_2H$	HFIP	ND	41	trace
18[c]	$Cu(OTf)_2$	$MesCO_2H$	HFIP	ND	60	trace
19[c]	$Bi(OTf)_3$	$MesCO_2H$	HFIP	ND	72	trace
20[c]	LiOTf	$MesCO_2H$	HFIP	ND	40	trace
21[c]	$Bi(OAc)_3$	$MesCO_2H$	HFIP	ND	45	14
22[c,d]	$Bi(OTf)_3$	$MesCO_2H$	HFIP	ND	trace	64

[a]Reaction conditions: **1a** (0.3 mmol), catalyst (0.015 mmol), additive (0.3 mmol), solvent (2 mL), 80 °C, air, sealed tube, 20 h. [b]Isolated yield. [c]0.03 mmol of catalyst. [d]Under N_2.

After the optimal conditions for the formation of **2a** had been established, we moved our attention to **3a**. We realized that the formation of **3a** is synthetically and mechanistically attractive due to the following reasons: (1) This is the first example in which 2-indolyl-3-oxo-indoline and 2-(2-amino phenyl)quinoline derivatives were selectively formed from the same acyclic substrate under slightly varied reaction conditions. (2) Functionalized quinolines like **3a** are among the most useful pharmacophores of clinical drugs and most ubiquitous building blocks of natural products.[8] (3) Literature searching revealed that the synthesis of 2-(2-aminophenyl)-quinolines has only been sporadically reported, which are mostly associated with the dimerization of 2-ethynylanilines. In addition, these limited literature methods are only viable to terminal alkynes. In those cases, the more sterically handed and less reactive internal alkynes chose to undergo intramolecular cyclization to give indoles rather than dimerization.[9] To develop this intriguing reaction into a general and efficient synthesis of 2-(2-aminophenyl)quinolines from internal alkynes, several parameters possibly affecting its efficiency were screened. First, different Brønsted acids such as trifluoroacetic acid (TFA), 2,4,6-trimethylbenzoic acid ($MesCO_2H$), and 1-adamantane carboxylic acid ($1\text{-}AdCO_2H$) were used as additives (entries 15−17). It was thus found that the yield of **3a** could be improved to 55% in the presence of $MesCO_2H$. Next, the loading of catalyst was increased from 5 mol % to 10 mol %. Under this circumstance, the yield of **3a** increased to 60% (entry 18). Then, $Bi(OTf)_3$, LiOTf, or $Bi(OAc)_3$ was tried as catalyst (entries 19−21). To our pleasure, **3a** was formed in 72% yield under the catalysis of $Bi(OTf)_3$ (entry 19). When this reaction was run under an inert atmosphere (N_2) instead of air, **4a**, the 4-alkyl counterpart of **3a**, was selectively obtained in 64% yield (entry 22). Interestingly, **4a** has a different substitution pattern compared with the quinoline product obtained from $[RhCp^*Cl_2]_2$-catalyzed dimerization of the same substrate (Scheme 1e vs 1b),[7] indicating that two different dimerization pathways must have been involved.

With the optimal reaction conditions in hands, the substrate generality for the synthesis of **2** was first explored. The results included in Table 2 showed that **1** bearing a methyl, methoxy, chloro, or bromo group as the R^1 unit attached on different sites of the connecting benzene ring readily underwent this oxidative dimerization reaction to afford **2b−2f** in moderate yields. In addition, **1** bearing a phenyl unit attached with either an electron-donating group (EDG) such as methyl, ethyl, *tert*-butyl, and methoxy or an electron-withdrawing group (EWG) including fluoro, chloro, or bromo on its *para*-, *meta*-, or *ortho*-position as the R^2 moiety took part in this reaction to give **2g−2o**. **1** bearing a cyclopropyl or 2-naphthyl group as the R^2 unit could afford **2p** and **2q**. With R^1 as a 4-methyl group and R^2 as a 4-chlorophenyl or 3-chlorophenyl unit, the reactions could also take place smoothly to give **2r** and **2s**. Attractively, the tolerance of various functional groups enables structural elaboration of the products. It is also worth noting that the structure of **2o** was established based on its single-crystal X-ray diffraction analysis (see the Supporting Information).

Next, the substrate scope for the preparation of **3** was studied. Thus, a range of **1** bearing various R^1 units were subjected to the optimal reaction conditions to give the desired

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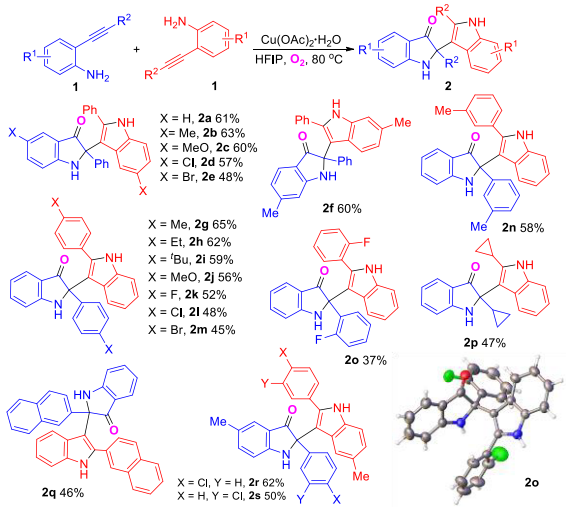
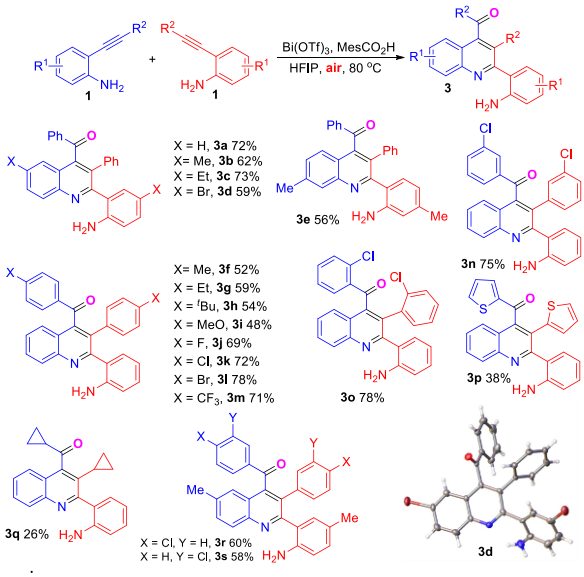
Table 2. Substrate Scope for the Synthesis of 2[a,b]



[a]Reaction conditions: **1** (0.3 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.015 mmol), HFIP (2 mL), 80 °C, O_2, sealed tube, 20 h. [b]Isolated yield.

products **3b**−**3e** in moderate to good yields (Table 3). Then, the suitability of **1** bearing diversely substituted alkynyl

Table 3. Substrate Scope for the Synthesis of 3[a,b]

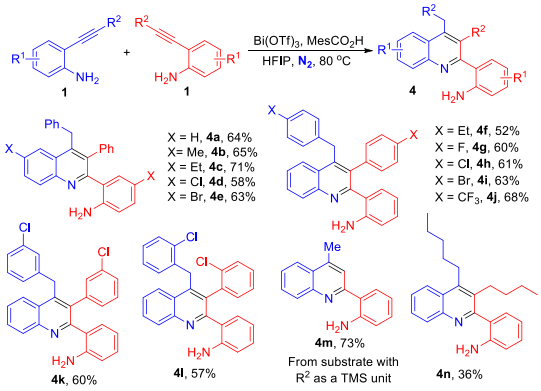


[a]Reaction conditions: **1** (0.3 mmol), $Bi(OTf)_3$ (0.03 mmol), $MesCO_2H$ (0.3 mmol), HFIP (2 mL), 80 °C, air, sealed tube, 20 h. [b]Isolated yield.

moieties was also probed. It was thus found that the R^2 unit could be a phenyl unit bearing either an EDG or an EWG to give **3f**−**3o**. In general, substrates bearing an electron-deficient R^2 unit showed higher efficiency than those bearing an electron-rich R^2 moiety (**3f**−**3i** vs **3j**−**3o**). Our further study found that substrates bearing a thienyl moiety at the alkyne terminus took part in this reaction readily to produce **3p**. Apart from aryl groups, this reaction was also suitable for substrate **1** bearing a cyclopropyl group as the R^2 unit to give product **3q**. Furthermore, the desired products **3r** and **3s** were obtained from substrates with different substituents attached on the connecting benzene and the alkyne moiety. Last but not least, the structure of **3d** was confirmed based on its single-crystal X-ray diffraction analysis (see the Supporting Information).

Third, the substrate scope for the formation of **4** was explored. The results listed in Table 4 showed that under the

Table 4. Substrate Scope for the Synthesis of 4[a,b]

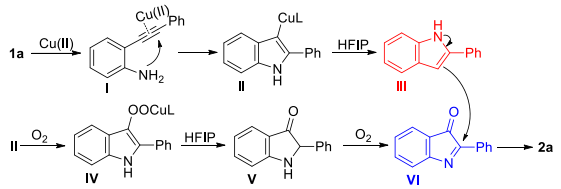


[a]Reaction conditions: **1** (0.3 mmol), $Bi(OTf)_3$ (0.03 mmol), $MesCO_2H$ (0.3 mmol), HFIP (2 mL), 80 °C, N_2, sealed tube, 20 h. [b]Isolated yield.

optimized conditions for the formation of **4a** all the selected 2-alkynylaniline substrates underwent the dimerization to give **4a**−**4n** in reasonably good yields, thus setting up a general synthesis of diversely substituted 2-(2-aminophenyl)quinoline derivatives from the inactive internal alkynes.

Based on experimental outcomes and literature reports,[5,6] a reaction pathway leading to the formation of **2a** is proposed in Scheme 2. As a first step, complexation of Cu(II) with **1a**

Scheme 2. Plausible Mechanism for the Formation of 2a



affords intermediate **I**, from which intermediate **II** is formed through an intramolecular N-cyclization. Protonation of **II** with HFIP as a proton source affords 2-phenylindole (**III**). Meanwhile, **II** could also be trapped by O_2 to give a peroxic species **IV**. Next, protonation and decomposition of **IV** give 2-phenylindolin-3-one (**V**). Under the reaction conditions, **V** takes part in an oxidative dehydrogenation to give 2-phenyl-3*H*-indol-3-one (**VI**). In the final stage of this cascade process, **III** undergoes a C-nucleophilic addition onto **VI** to give **2a**.

The mechanism as proposed in Scheme 2 is supported by the following control experiments. First, **1a** was treated with $Cu(OAc)_2{\cdot}H_2O$ in HFIP at 80 °C under nitrogen for 20 h. As a result, the proposed intermediate **III** was obtained in a yield of 82%. Then, **III** was subjected to I_2/KOH and then silica gel under air to give **VI** (Scheme 3a).[1f] Next, **III** was treated with **VI** under the promotion of $Cu(OAc)_2{\cdot}H_2O$ in HFIP at 80 °C under N_2 to give **2a** in 83% yield (Scheme 3b).

In another aspect, reaction pathways leading to the formation of **3a** and **4a** are proposed in Scheme 4. Initially, the triple bond of **1a** is activated by Bi(III) to form a π-complex **VII**, which allows for the nucleophilic attack of the

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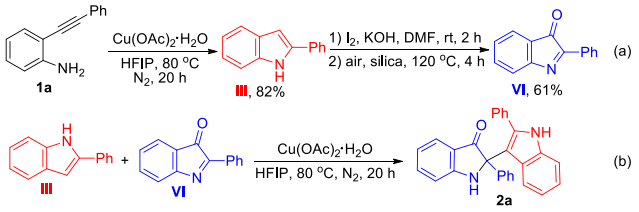
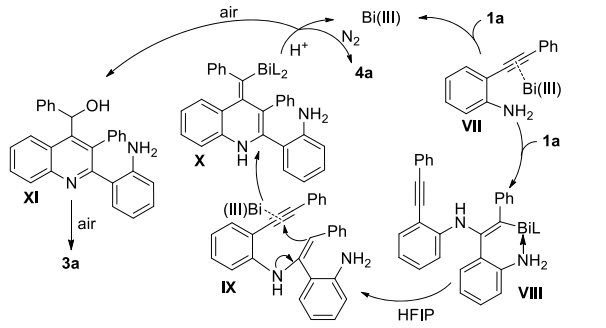
Scheme 3. Control Experiments



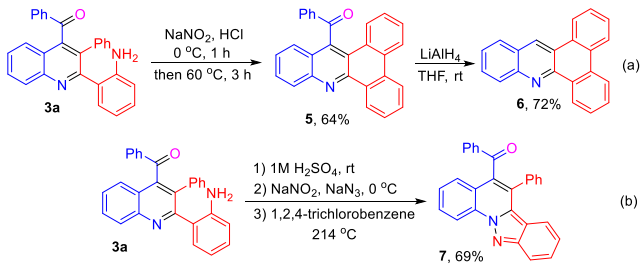
Scheme 4. Plausible Mechanism for the Formation of 3a/4a



NH_2 group of another molecule of **1a** to form intermediate **VIII**. Next, intermediate **IX** is formed through protonation of **VIII** with HFIP. **IX** undergoes an intramolecular C-nucleophilic addition of the enamine unit onto the activated triple bond to give **X**. Under N_2, **X** undergoes a demetalation/protonation/tautomerization cascade process to deliver **4a** and regenerate the Bi(III) catalyst. When the reaction is carried out under air, on the other hand, intermediate **X** is believed to undergo an oxidation and protonation/tautomerization to give intermediate **XI**. Finally, **XI** is oxidized in situ by air to give **3a**.

To demonstrate the usefulness of **3a** as an intermediate in organic synthesis, we performed the following transformations. First, **3a** was treated with $NaNO_2$/HCl at 0 °C for 1 h and then at 60 °C for 3 h to afford dibenzo[*a*,*c*]acridine **5** in a yield of 64%. Upon treatment with $LiAlH_4$, **5** could be transformed into its debenzoylation counterpart **6** in 72% yield (Scheme 5a). These transformations are valuable since dibenzo[*a*,*c*]-

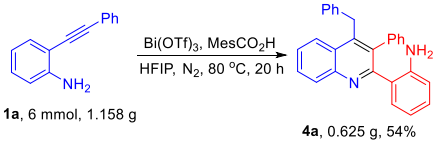
Scheme 5. Structural Elaborations of 3a



acridine derivatives possess remarkable biological activities and electronic properties.[10] Notwithstanding of their importance, reliable methods for their synthesis are rare.[11] As another aspect, **3a** was treated with diluted H_2SO_4, $NaNO_2$/NaN_3, and 1,2,4-trichlorobenzene sequentially to furnish a synthetically and pharmaceutically important indazolo[2,3-*a*]quinoline derivative **7** (Scheme 5b).[12,13]

Finally, a gram-scale reaction of **1a** (6 mmol) was also tried under the optimal conditions for the formation of **4a**. It turned out that under these conditions **4a** could be successfully furnished in 54% yield (Scheme 6).

Scheme 6. Gram-Scale Synthesis of 4a



To conclude, we have developed a selective and versatile synthesis of 2-indolyl-3-oxo-indoline and 2-(2-aminophenyl)-quinoline derivatives through controllable dimerization of 2-alkynylanilines. To our knowledge, this should be the first example in which 2-indolyl-3-oxo-indolines and 2-(2-aminophenyl)quinolines were formed selectively from the same acyclic substrates by finely turning the reaction conditions. This is also the first report that 2-(2-aminophenyl)-quinolines were formed via the dimerization of sterically hindered and less reactive internal alkynes. In addition, the usefulness of one of the 2-(2-aminophenyl)quinoline products was showcased by its ready transformation into important fused heterocycles such as dibenzo[*a*,*c*]acridine and indazolo-[2,3-*a*]quinoline derivatives. With advantages including accessible substrates, benign oxidant, inexpensive catalysts, controllable selectivity, and high versatility toward different kinds of valuable products, these novel synthetic protocols might be used in the preparation of related functional molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02323.

Experimental procedures, mechanism studies, data, and copies of ^{1}H and ^{13}C NMR spectra of all products (PDF)

Accession Codes

CCDC 2008500 and 2008507 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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