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Brønsted Acid Mediated Alkenylation and Copper-Catalyzed Aerobic Oxidative Ring Expansion/Intramolecular Electrophilic Substitution of Indoles with Propargyl Alcohols: A Novel One-Pot Approach to Cyclopenta[*c*]quinolines

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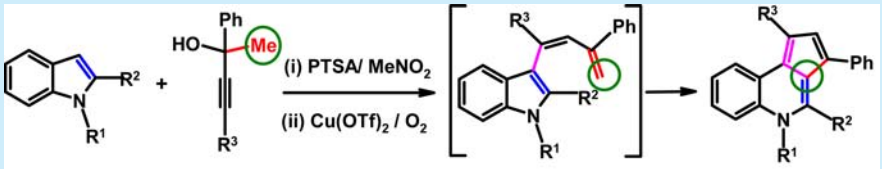
Supporting Information



One pot reaction involving alkenylation/ cycloisomerization and oxidative ring expansion

ABSTRACT: Copper-catalyzed oxidative ring-expansion/intramolecular electrophilic substitution of 3-dienylindoles leading to cyclopenta[*c*]quinolines and 3-indenylindoles under aerobic conditions is described. The precursors, 3-dienylindoles, are formed via Friedel−Crafts alkenylation followed by isomerization reactions of 2-substituted indoles with tertiary propargyl alcohols under Brønsted acid mediation. The methyl (sp^3-C) group present in the propargyl alcohol becomes a part of a six-membered ring in the final ring-expansion products, the cyclopenta[*c*]quinolines which are fluorescence active. Based on these observations, a novel one-pot strategy for ring expansion from indole to cyclopenta[*c*]quinoline is discovered.

Highly aromatic nitrogen-containing polycycles have attracted considerable attention because of their remarkable biological and pharmacological activity and also wide applications in photochemical, electrochemical, and materials science.[1,2] One such class of compounds is indoles which are important core structures present in numerous natural products and pharmaceuticals. For this reason, the synthesis and reactivity of indoles is currently a prime area of research activity.[1b,3] An important feature of this system is that the C−H bonds at C-2 and C-3 can be readily functionalized.[4] Utilizing this feature, there are only a handful of reports regarding the ring-expansion reactions of indoles.[5] The first example of cyclopentadienyl fused tetrahydroquinoline derivatives through a palladium-catalyzed ring-expansion reaction of indoles with alkynes has been reported recently by Jiao and co-workers.[6] The reaction of indoles with propargyl alcohols does lead to diverse carbo- or heterocycles, but in all the cases the indole core is intact.[7] Herein we report an unprecedented sequential Brønsted acid mediated and Cu(II)-catalyzed oxidative ring-expansion reaction of indoles with propargyl alcohols under aerobic conditions, which leads to substituted cyclopenta[*c*]quinolines. Although numerous reports of C−C/C−X bond formation via [Cu]-catalyzed oxidative dehydrogenation using molecular oxygen are known,[8] the reaction reported here adds a new facet to this chemistry. Quinolines and their derivatives are also important core structures in many natural products and functional materials.[9]

Initially, our aim was to synthesize indole based allenes as part of our studies on allene chemistry by using propargyl alcohols.[10] The reaction of indoles with tertiary propargyl alcohols is expected to lead to either allenes or alkynes in the presence of *p*-toluenesulfonic acid (PTSA),[7d] but only to alkynes in the presence of $Cu(OTf)_2$.[7i] Such products have been utilized elegantly for further derivatization to 1,3-butadienes or fused heterocycles.[7a,d,i,11] Surprisingly, when we attempted a similar reaction using 1-methyl-2-phenylindole in the presence of $Cu(OTf)_2$ (Scheme 1a), we isolated a pure compound (**I**) which exhibited only *two methyl signals* in the ^{1}H NMR spectrum. It can be noted that, for a compound similar to allene or alkyne, three methyl signals [O*Me*, N*Me*, C*Me*(Ph)] are expected. Thus, product **I** is different from any type of product reported by earlier workers,[7] and hence, we proceeded to probe this reaction further. However, when the same reaction was conducted in the presence of PTSA with the exclusion of $Cu(OTf)_2$, we isolated two products: 3-dienylindole (**II**) and 3-propargylindole (**III**; Scheme 1b, discussed later for details). It should be noted that Sanz and co-workers reported the formation of diene of type **II** (ca. 16%) from indoles and propargylic alcohols under Brønsted acid catalysis.[7d,l] Species **II** also shows only *two methyl* signals similar to **I**. For this reason, we surmised that **I** must have formed via diene **II** and therefore proceeded to optimize the conditions to obtain better yields of the dienes of type **II**.

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Scheme 1. Reaction of *N*-Methyl-2-phenylindole with Propargyl Alcohol Leading to Compounds I–III

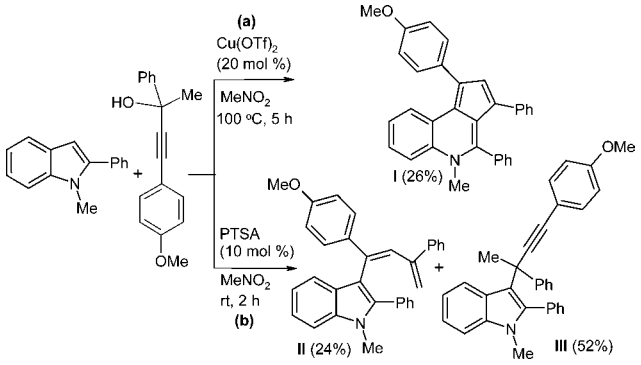
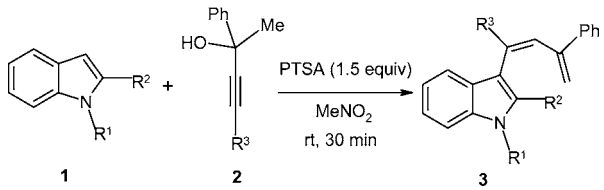


Table 1. Brønsted Acid Mediated Synthesis of 3-Dienylindoles 3 from Indoles and Propargyl Alcohols[a]



1 2 3

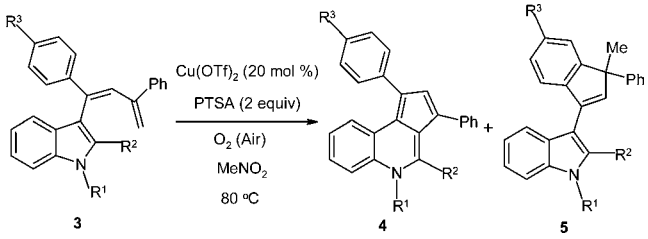
entry	1, R^1/R^2	2, R^3	product (3)	yield (%)[b]
1	**1a**, Me/Ph	**2a**, Ph	**3aa**	83
2	**1a**	**2b**, *p*-MeC_6H_4	**3ab**	81
3	**1a**	**2c**, *p*-$MeOC_6H_4$	**3ac** (X-ray)	75
4	**1a**	**2d**, *p*-ClC_6H_4	**3ad**	87
5	**1a**	**2e**, *p*-$NO_2C_6H_4$	**3ae**	86
6	**1b**, Me/*p*-MeC_6H_4	**2a**	**3ba**	82
7	**1c**, Me/*p*-FC_6H_4	**2a**	**3ca**	79
8	**1d**, Me/Me	**2e**	**3de**	66
9	**1e**, H/Ph	**2a**	**3ea**	91

[a]Reaction conditions: **1** (1 equiv), **2** (1.1 equiv), PTSA (1.5 equiv), and $MeNO_2$ (4.0 mL) at rt (25 °C) for 30 min in air. [b]Isolated yields.

After several trials, gratifyingly, we found that *N*-methyl-2-phenylindole **1a** upon treating with propargyl alcohol **2a** in the presence of PTSA (1.5 equiv) at rt for 30 min in nitromethane led to the 3-dienylindole **3aa** in 83% yield (Table 1, entry 1). In an analogous manner, reaction of substituted indoles (**1**) with tertiary propargyl alcohols (**2**) afforded 3-dienylindoles **3** (cf. Table 1).[12] The presence of a phenyl group at the tertiary carbon of propargyl alcohol may be responsible for the formation of 3-dienylindole as the major product.[13]

We then treated *N*-methyl-3-dienylindole **3aa** with $Cu(OTf)_2$ (20 mol %) in nitromethane at 100 °C for 8 h in open air. This reaction resulted in the desired quinoline **4aa** (43%) together with product **5aa** (37%) [Supporting Information, Table S1, entry 1]. To our delight, though, when the reaction was performed at 80 °C for 5 h, **4aa** could be obtained in 55% yield along with **5aa** (33%; Table S1, entry 3). When pure O_2 was used as an oxidant instead of air, there was no significant change in the yield. A control reaction confirmed that the reaction did not proceed in the absence of a copper catalyst. $Cu(OAc)_2$ as a catalyst produced only traces of **4aa** and **5aa**. Surprisingly, the product **5aa** was obtained in 82% yield in the presence of TfOH (Table S1, entry 13). Thus, it appears that traces of triflic acid liberated from $Cu(OTf)_2$ is responsible for the formation of **5aa**. The yield of **4aa** was increased to 64% by using PTSA as an additive (Table S1, entry 20). Interestingly, use of a

Table 2. $Cu(OTf)_2$-Catalyzed Synthesis of Cyclopenta[*c*]quinolines 4 and Indenyl Indoles 5[a]



3 4 5

entry	3, $R^1/R^2/R^3$	yield (%) of 4[b]	yield (%) of 5[b]	combined yield (%)
1	**3aa**, Me/Ph/H	**4aa** (64)	**5aa** (22)	86
2	**3ab**, Me/Ph/Me	**4ab** (61)	**5ab** (26; X-ray)	87
3	**3ac**, Me/Ph/OMe	**4ac** (53)	**5ac** (30)	83
4	**3ad**, Me/Ph/Cl	**4ad** (63)	**5ad** (28)	91
5	**3ae**, Me/Ph/NO_2	**4ae** (74)	–	74
6	**3ba**, Me/*p*-MeC_6H_4/H	**4ba** (56)	–	56
7	**3ca**, Me/*p*-FC_6H_4/H	**4ca** (59)	**5ca** (32)	91
8	**3de**, Me/Me/NO_2	**4de** (70)	–	70
9[c]	**3ea**, H/Ph/Ph	**4ea** (trace)	**5ea** (71)	71

[a]Reaction conditions: **3** (1 equiv), $Cu(OTf)_2$ (20 mol %), PTSA (2 equiv), and $MeNO_2$ (4.0 mL) at 80 °C for 5 h, under air unless stated otherwise. [b]Isolated yields. [c]Traces of **4ea** were present in the reaction mixture but could not be isolated.

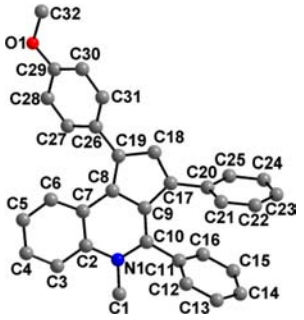


Figure 1. X-ray structure of compound **4ac** (H atoms omitted).

stoichiometric amount of $Cu(OTf)_2$ under a nitrogen atmosphere led to an increased yield (up to 75%, entry 22) of the ring expansion product, but synthetically, this procedure is not useful. Thus, the optimal reaction conditions are found to be as follows: $Cu(OTf)_2$ (20 mol %), PTSA (2 equiv), under an open atmosphere in $MeNO_2$ at 80 °C.

We then examined a spectrum of substituted 3-dienylindoles to explore the generality of this novel reaction. A range of differently substituted 3-dienylindoles (**3**) with electron-donating or -withdrawing groups gave moderate to good yields of the ring expansion products, the cyclopenta[*c*]quinolines (**4**), along with indenylindoles (**5**) (Table 2, entries 1–8). The latter compounds were isolated only in five cases because of the closeness in R_f values with the quinolines. When the 3-dienylindole **3ea** with the NH group intact was used as a substrate, only the five-membered ring compound **5ea** was isolated as the major product (Table 2, entry 9). The combined yield of the isolated products in all the cases was good to excellent (>80%) with the 3-dienylindole being completely consumed. The structure of compound **4ac** was confirmed by X-ray crystallography (Figure 1).

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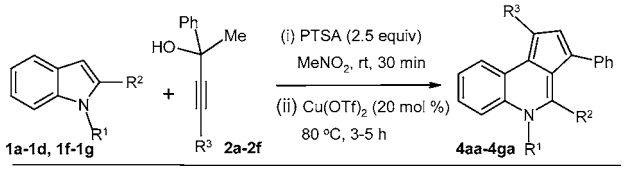
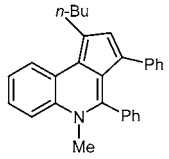
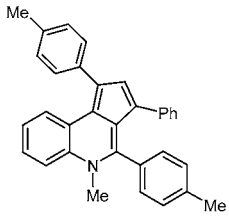
Scheme 2. One-Pot Synthesis of Cyclopenta[*c*]quinolines 4aa−4ga[a]



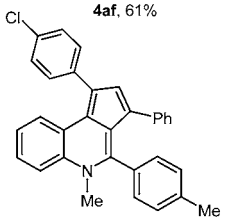
4aa, 65% **4ab**, 58% **4ac**, 52%



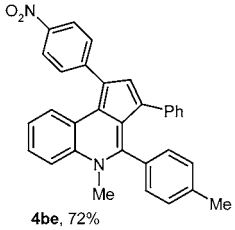
4ad, 67% **4ae**, 78% **4af**, 61%



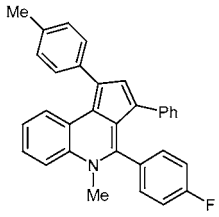
4ba, 60% **4bb**, 53%



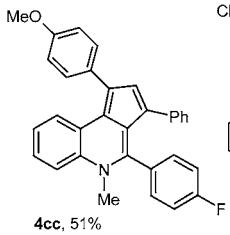
4bd, 64%



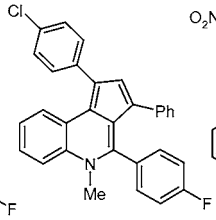
4be, 72% **4ca**, 66%



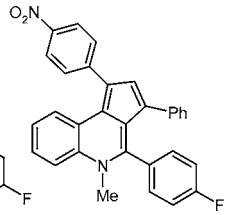
4cb, 56%



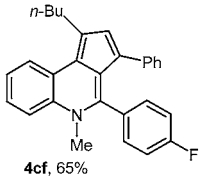
4cc, 51%



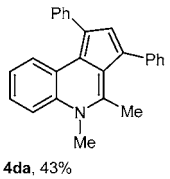
4cd, 70%



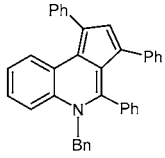
4ce, 75%



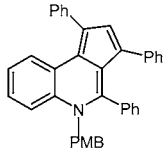
4cf, 65%



4da, 43% **4de**, 58%



4fa, 56%

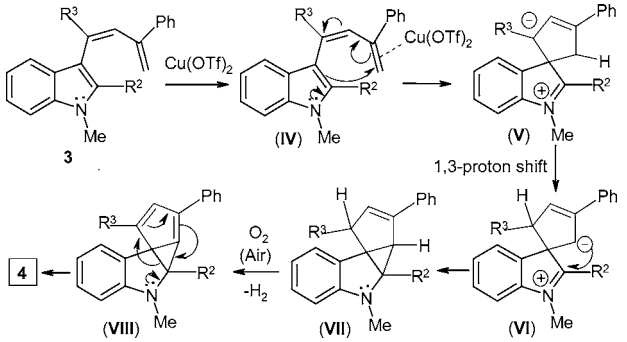


4ga, 49%

[a]Reaction conditions: **1** (1 equiv), **2** (1.1 equiv), PTSA (2.5 equiv), $Cu(OTf)_2$ (20 mol %), and $MeNO_2$ (4 mL) at 80 °C in air. Yields are after isolation.

Instead of isolating the 3-dienylindole intermediates, it is more useful if one can produce the cyclopenta[*c*]quinolines in one pot by using the optimized conditions mentioned in Tables 1 and 2. Indeed we were able to obtain the desired product **4aa** in 65% yield (Scheme 2, entry 1) in one pot by starting with **1a** and **2a**. Inspired by this, the scope of the one-pot reaction was extended

Scheme 3. Plausible Mechanism for the Formation of Cyclopenta[*c*]quinolines



to various alkyl or aryl substituted indoles and propargyl alcohols to afford the cyclopenta[*c*]quinolines **4aa**−**4af**, **4ba**−**4bb**, **4bd**−**4be**, **4ca**−**4cf**, **4da**, **4de**, **4fa**, and **4ga** (Scheme 2). The products cyclopenta[*c*]quinolines are dark red in color and exhibit intense fluorescence in the solution state (Figure S1, Supporting Information).

Electron-withdrawing groups on propargyl alcohols furnished better yields when compared to those containing electron-donating groups. Alkyl chain containing propargyl alcohol **2f** also led to good yields of the products (e.g., **4af** and **4cf**). The use of an alkyl substituent on indole **1d** led to the ring-expansion products **4da** and **4de** in moderate yields. The products **4fa** and **4ga**, in which deprotection can be performed more readily, were also obtained in decent yields. In this one-pot method also, we did observe trace amounts of 3-indenylindoles but they did not affect the isolation of the desired cyclopenta[*c*]quinolines.

A possible pathway for the formation of cyclopenta[*c*]-quinolines (**4**) is shown in Scheme 3. Initially, the $Cu(OTf)_2$ coordination in the intermediate **IV** may activate the terminal alkene part of diene.[14] Then the lone pair on nitrogen may facilitate the formation of the ionic spiro intermediate **V**. Subsequent 1,3-proton migration produces intermediate **VI**. This ionic intermediate **VI** may form the fused cyclopropane ring containing intermediate **VII**. Finally, **VII** may undergo aerobic oxidation/aromatization[15] to produce intermediate **VIII**. Subsequent rearrangement will lead to the highly conjugated cyclopenta[*c*]quinoline **4**.

Formation of indenylindoles (**5**) may be rationalized by the initial attack of a proton on an isomeric allene intermediate of the 3-dienylindoles (**3**). This intermediate undergoes intramolecular electrophilic substitution[7i,16] to produce the desired products **5** (Scheme S1, Supporting Information). This assumption is based on the experimental observation that the yield of **5aa** from **3aa** can be maximized to 82% in the presence of triflic acid. While using $Cu(OTf)_2$, though, we assume that there are traces of triflic acid present in the medium.

In summary, we have developed a novel one-pot method for highly conjugated cyclopenta[*c*]quinolines and indenylindoles via copper-catalyzed ring-expansion/intramolecular electrophilic substitution of 3-dienylindoles using air as the oxidant. The reaction proceeds by Brønsted acid mediated Friedel−Crafts alkenylation and isomerization, followed by copper-catalyzed dehydrogenation/oxidative ring expansion. To our knowledge, the present work represents a new method of generating such ring-expansion products.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental details; characterization data; optimization Table S1; mechanism for the formation of indenylindoles **5** (Scheme S1); fluorescence spectra for **4ad**, **4cb**, and **4cc** (Figure S1); X-ray crystallographic data (cif file); structures of compounds **3ac**, **4ac**, and **5ab** (Figures S2−S4); and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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