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# CuSO<sub>4</sub>-Catalyzed Dual Annulation to Synthesize O, S or N-Containing Tetracyclic Heteroacenes

Xiang-Huan Shan,<sup>†a,</sup> Bo Yang,<sup>†a</sup> Jian-Ping Qu,<sup>b</sup> and Yan-Biao Kang <sup>\*a</sup>

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In this work, CuSO<sub>4</sub> is utilized as a practical redox catalyst for a tandem dual annulation in the synthesis of indole-fused tetracyclic heteroacenes, important skeletons in both medicinal chemistry and materials chemistry. Preparation of such skeletons in a convenient and efficient manner is in high demand. This method realizes modular synthesis of benzofuro-, benzothieno-, and indoloindoles from abundant feedstocks such as 2-halobenzyl halides and nitrile derivatives in up to 99% yields, providing a rapid access to diverse indole-fused heteroacenes with biological or optoelectronic properties.

benzofuro-.<sup>1,2</sup> Indole-fused heteroacenes, such as benzothieno-,<sup>3,4</sup> and indolo[3,2-b]indoles,<sup>5,6</sup> are important skeletons in both medicinal chemistry and materials chemistry. They are usually utilized to develop pharmaceutical agents exhibiting promising biological activities as well as in the engineering organic materials possessing attractive optical or electronic properties. However, the reported indole-fused heteroacenes are often prepared by multiple step procedures and are usually involved with noble metal reagents.<sup>1-11</sup> Several reports have been known for the synthesis of indole-fused heteroacenes, such as benzofuro-,12 benzothieno-,13-15 or indolo[3,2-b]indoles,<sup>16,17</sup> respectively, but divergent access to a variety of indole-fused heteroacenes directly from simple starting materials is scarce.<sup>18-24</sup> Given the importance of functionalized indole-fused heteroacenes, the development of a concise, efficient and environmentally benign method towards their synthesis is in high demand.

Potassium *tert*-butoxide plays a key role in a variety of organic reactions as a powerful base or a reagent for electron transfer reactions.<sup>25-36</sup> It was found that <sup>t</sup>BuOK could promote the

cleavage of benzylic C-H bond, and the resulting carbanion can pass through a radical addition to unsaturated bonds like C-O double bonds which is followed by an intramolecular alkoxy radical addition to haloarenes.<sup>37</sup> Recently, a catalytic approach has been reported for the generation of substituted indoles with naturally abundant cupric sulfate.<sup>38</sup> As part of our ongoing research interest in potassium *tert*-butoxide promoted heterocycles synthesis, we envisaged that a strategy through benzylic C-H addition and iminyl radical relay can enable the cyclization of 2-halobenzyl halides and nitriles to indole-fused heteroacenes. Herein, we report our recent results in details.

Reaction conditions were first investigated using 2-((2iodobenzyl)oxy)benzonitrile 3a, generated from 2-halobenzyl halides 1a and nitrile 2a, as a model substrate and potassium tert-butoxide as a base. The cyclization of 3a in the absence of any catalyst affords the corresponding product benzofuro[3,2b]indole 4a in 18% of yield (Table 1, entry 1). However, the addition of 5 mol% of cupric sulfate improves the yields of 4a dramatically, and decreasing the concentration results in the increase of yield up to 98% (entries 2-4). The reaction in the presence of toluene or DMF could also progress smoothly albeit with slightly decreased yields (entries 5-6), while the reaction in dioxane affored the desired product in only 44% yield (entry 7). In addition, other copper salts such as CuCl<sub>2</sub>, CuO, Cu<sub>2</sub>O could also catalyze the cyclization reaction of 3a giving 4a in moderate to good yields (entries 8-10). Moreover, the study of the effects of base indicates that the involvement of <sup>t</sup>BuOK is necessary for the the cyclization of **3a** as no reaction occured when <sup>t</sup>BuONa, <sup>t</sup>BuOLi, or NaH was utilized as the base (entry 11). The reaction conditions in entry 4 were chosen as the standard conditions with 5 mol % CuSO<sub>4</sub>.

Various substituted halides **3**, including iodides, bromides as well as chlorides, were subjected to the standard reaction conditions to prepare benzofuro[3,2-b]indole **4** and the desired products could be obtained in moderate to high yields (Schemes 1 and 2). Halogen such as bromides (**4b-d**, **4j**, and **4n-p**), chlorides (**4e**, **4k**, **4t**, and **4u**), and fluoride (**4f**) can survive under this basic conditions. Starting materials with either electron

<sup>&</sup>lt;sup>a.</sup> Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China

E-mail: ybkang@ustc.edu.cn

<sup>&</sup>lt;sup>b.</sup> Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, China

<sup>&</sup>lt;sup>+</sup> X.H.S and B.Y. contributed equally to this work.

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donating groups (**4g-i**, and **4**I) and electron withdrawing groups (**4r** and **4s**) can undergo the cyclization in moderate yields. The selectivity sequence is I>Br>Cl. For example, **4t** is afforded without the formation of **4n** (X = Br).

### Table 1. Reaction Conditions

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entry <sup>a</sup>	cat.	base	solvent(mL)	<b>4a</b> (%)
1	none	<sup>t</sup> BuOK	PhCl(1)	18
2	CuSO <sub>4</sub>	<sup>t</sup> BuOK	PhCl(1)	62
3	CuSO <sub>4</sub>	<sup>t</sup> BuOK	PhCl(5)	70
4	$CuSO_4$	<sup>t</sup> BuOK	PhCl(10)	98
5	CuSO <sub>4</sub>	<sup>t</sup> BuOK	Toulene(10)	81
6	$CuSO_4$	<sup>t</sup> BuOK	DMF(10)	86
7	CuSO <sub>4</sub>	<sup>t</sup> BuOK	Dioxane(10)	44
8	CuCl <sub>2</sub>	<sup>t</sup> BuOK	PhCl(10)	90
9	CuO	<sup>t</sup> BuOK	PhCl(10)	77
10	Cu <sub>2</sub> O	<sup>t</sup> BuOK	PhCl(10)	73
11 <sup>b</sup>	CuSO <sub>4</sub>	other	PhCl(10)	n.r.

<sup>a</sup> Conditions: **3a** (0.5 mmol), catalyst (5 mol %), 90 °C, N<sub>2</sub>, 12 h, isolated yields.
<sup>b</sup> Other base refers to <sup>t</sup>BuONa, <sup>t</sup>BuOLi, or NaH, n.r. = no reactions.



Scheme 1. Synthesis of Benzofuro[3.2-b]indoles

This reaction was further explored in the construction of benzothienoindoles. Products **6a-i** were obtained in up to 98% yields (Scheme 3). Halogen are tolerated **(6c-g)**. These groups are leaving groups for cross coupling reactions, ensuring these products can be further converted to functionalized benzothienoindoles. Hydroxyl needs no protecting groups **(6h)**.



The N-containing analogues are indoloindole derivatives, which are also useful EL materials or natural products as well as pharmaceuticals. Indoloindoles **8** were obtained in 74-99% yields under the standard conditions (Scheme 4). Either *N*-aryl or *N*-alkyl indoloindoles ( $R^3$ ) are accessible (**8g** and **8a**, **8h-I**). Removable N-protecting groups can be tolerated (**8h** and **8i**).



**4k**, 16 h, 70% (10 mol % [Cu])



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The synthesis of tetracyclic heteroacenes **4**, **6** and **8** directly from **1** and 2-hydroxybenzonitriles **2** is also feasible. Halides **1** and nitriles **11** were treated under standard reaction conditions with 10 mol %  $CuSO_4$  and **4a-j** were obtained in moderate yields (Scheme 5). Benzothienoindoles **6a-6k** were also achieved. Potassium salts of **13** are not available with 'BuOK and KHMDS was used for in situ deprotonation. Indoloindoles **8** were obtained in moderate to good yields.



Scheme 5. Selected Examples for One-Pot Synthesis. <sup>*a*</sup> With 20 mol %  $CuSO_4$ . <sup>*b*</sup> 13 was in situ deprotonated with KHMDS (1.2 equiv) at 0 °C for 1 hr before the addition of  $CuSO_4$  and <sup>*i*</sup>BuOK.

Compound **8g** is a key intermediate for the synthesis of an EL material **10** (Scheme 6). By our method, **10** was obtained in two steps in over 20 gram scale. Dibromo indoloindole **8j** is a key intermediate for the synthesis of LED polymers. In previous work, such compounds are prepared in low overall yield

through 5 steps. By current method, **8j** was obtained in ሪዲሞ yield. This method is also applied in the ዋዕቶክትልን ያህዝቡ ይህታን ቆቶ **4H4TIDID** (Scheme 7).<sup>39</sup>





A proposed reaction mechanism is demonstrated in Scheme 8. This mechanism is based on the experimental study of our previous work. After deprotonation of benzylic proton, **3** passes through an anion-radical relay with  $CuSO_4$  to radical **A**, which transforms to **C** or **C'** via **B** or **B'**. Products **4** or **6** or **8** is afforded through a  $S_{RN}$ 1-type process via radical anion **E**. The radical process is supported by the radical inhibiting experiments (eq 1) as well as the previous report.<sup>38</sup>





Scheme 8. Proposed Mechanism

### Conclusions

In conclusion, we have developed a method for the synthesis of various O, S, or N-containing indole-fused heteroacenes via  $CuSO_4$ -catalyzed carbanion-radical redox relay, providing a rapid access to biological or optoelectronic heteroacenes.

### **Journal Name**

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## **Conflicts of interest**

The authors declare no competing financial interest.

### Notes and references

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