RSC Advances

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Cite this: RSC Adv., 2019, 9, 17975

Facile synthesis of 2-substituted benzo[b]furans and indoles by copper-catalyzed intramolecular cyclization of 2-alkynyl phenols and tosylanilines†

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Received 19th February 2019
Accepted 19th April 2019

DOI: 10.1039/c9ra01260e

rsc.li/rsc-advances

A catalytic amount of CuCl and Cs_2CO_3 was employed to synthesize a variety of 2-substituted benzo[b]furans and indoles by an intramolecular cyclization of 2-alkynyl phenols and tosylanilines. This protocol features mild conditions, high yields and broad substrate scope, which makes it a practical method for the synthesis of 2-substituted benzo[b]furans and indoles.

Introduction

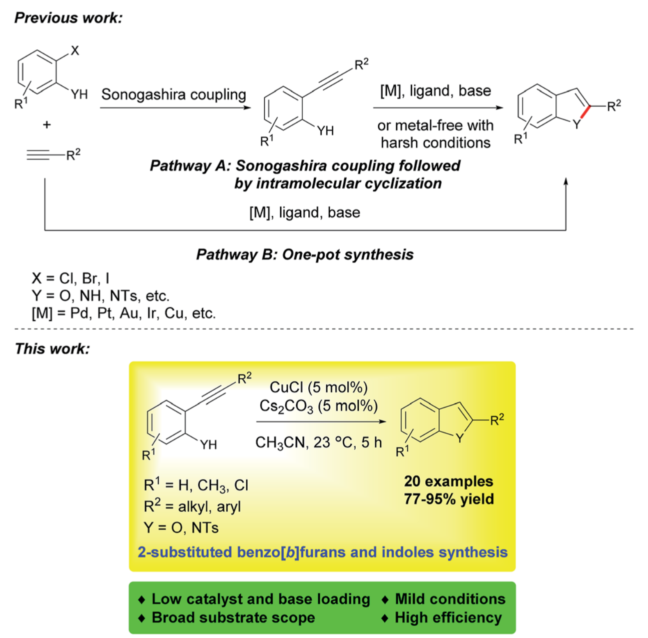
The skeletons of benzo[b]furans and indoles are widely spread in many naturally occurring compounds[1,2] and pharmaceutical molecules.[3,4] Many methods towards the synthesis of benzo[b]furan and indole derivatives have been developed over the last two decades.[5,6]

To synthesize 2-substituted benzo[b]furans or indoles, the most universal method seems to be the Sonogashira coupling of 2-halophenols or 2-haloanilines with alkynes, followed by heterocyclization of the hydroxyl or amino group with the triple bond (Scheme 1, Pathway A).[7] Some one-pot cascades have also been developed according to this strategy (Scheme 1, Pathway B).[8] However, these transformations usually require the participation of noble metals, ligands or harsh conditions to complete the cyclizations.

Copper, in the merit of cost, is a superior choice in organic catalysis.[9] It has also been used in the construction of benzo[b]furan and indole rings.[10] For example, Venkataraman and coworkers accomplished the synthesis of 2-arylbenzo[b]furans by exposing aryl acetylenes and 2-iodophenols to 10 mol% $[Cu(phen)(PPh_3)_2]NO_3$ and 2 equivalents of Cs_2CO_3 in toluene at 100 °C for 24 h. Similar transformations were realized with copper pincer complexes by Domínguez[11] and with $Cu(OTf)_2$-BINAM by Sekar.[12] 2-Substituted indoles can also be obtained after the reaction of 2-ethynylaniline derivatives under reflux in $Cu(OCOCF_3)_2$ aqueous solution for 24 h.[13] However, high reaction temperature and the use of stoichiometric amount of base are usually unavoidable to achieve high yields in these reactions. Herein, we report a facile and inexpensive method for the synthesis of 2-substituted benzo[b]furans and indoles by copper-catalyzed intramolecular cyclization of 2-alkynyl phenols and tosylanilines under mild conditions.

Results and discussion

Our studies started with the intramolecular cyclization of 2-(phenylethynyl)phenol **1a** as the substrate and the results were summarized in Table 1. When exposing **1a** to different commercial available copper salts in dimethyl sulfoxide (DMSO), no reaction took place after 24 h at 23 °C (entries 1–5). Then 1 equivalent of triethylamine was added to each of these



Scheme 1 Previous synthetic strategies for 2-substituted benzo[b]furans or indoles and our optimal conditions.

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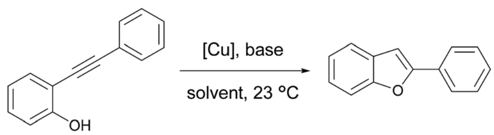
† Electronic supplementary information (ESI) available: General methods and experimental procedures, characterization and spectra of substrates and products. See DOI: 10.1039/c9ra01260e

Table 1 Optimization of reaction conditions[a]



1a 2a

Entry	[Cu]	Base	Solvent	Reaction time (h)	Yield[b] (%)
1	CuCl	—	DMSO	24	NR[c]
2	CuBr	—	DMSO	24	NR
3	$CuCl_2$	—	DMSO	24	NR
4	$CuBr_2$	—	DMSO	24	NR
5	$Cu(OTf)_2$	—	DMSO	24	NR
6	CuCl	Et_3N	DMSO	48	48
7	CuBr	Et_3N	DMSO	48	Trace
8	$CuCl_2$	Et_3N	DMSO	48	Trace
9	$CuBr_2$	Et_3N	DMSO	48	30
10	$Cu(OTf)_2$	Et_3N	DMSO	48	Trace
11	CuCl	Et_3N	DMSO	48	45
12	CuCl	DIPEA[d]	DMSO	48	40
13	CuCl	Pyridine	DMSO	48	Trace
14	CuCl	DBU[e]	DMSO	48	36
15	CuCl	K_2CO_3	DMSO	12	59
16	CuCl	KOH	DMSO	12	55
17	CuCl	Cs_2CO_3	DMSO	12	84
18	CuCl	Cs_2CO_3	CH_2Cl_2	12	61
19	CuCl	Cs_2CO_3	THF	12	Trace
20	CuCl	Cs_2CO_3	Toluene	9	69
21	CuCl	Cs_2CO_3	DMF	9	55
22	CuCl	Cs_2CO_3	CH_3CN	3	95
23[f]	CuCl	Cs_2CO_3	CH_3CN	5	95
24[f]	—	Cs_2CO_3	CH_3CN	24	NR

[a] Unless otherwise noted, all reactions were performed with **1a** (0.2 mmol), [Cu] (0.01 mmol), base (0.2 mmol) at 23 °C. [b] The yield of **2a** was determined by NMR with 1,3,5-trimethylbenzene as the internal standard. [c] NR = no reaction. [d] DIPEA = *N*,*N*-diisopropylethylamine. [e] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [f] 0.01 mmol of Cs_2CO_3 was used.

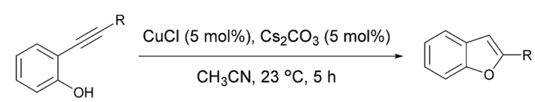
reactions and we observed the slow formation of our desired product **2a**, with CuCl giving the best yield (48%) after 48 h (entry 6). This result pushed us to examine different commercial available bases using CuCl as the catalyst and DMSO as the solvent. After careful screening, Cs_2CO_3 stood out from a variety of organic and inorganic bases to give the best yield (84%) after 12 h at 23 °C (entry 17). We then tested various commonly used solvents and found out that acetonitrile dramatically accelerated the reaction to produce 2-phenylbenzo[*b*]furan **2a** with 95% yield after 3 h at 23 °C (entry 22).

To our surprise, adjusting the loading of Cs_2CO_3 to 5 mol% did not cause any decrease in yield, although a slightly longer reaction time was needed (entry 23). When the experiment was carried out in the absence of CuCl, no reaction took place after 24 h (entry 24), which suggested that copper catalyst was essential for this conformation although recently Gao and co-workers reported that this reaction could be completed at a higher temperature without any transition metal catalyst.[14] Compared with other copper-catalyzed methods for benzo[*b*]furan synthesis,[11–13,15] our optimized conditions featured lower catalyst and base loading, ambient temperature and ligand free.

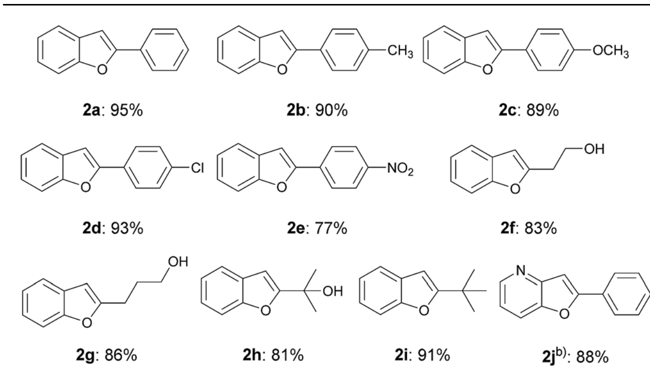
With the optimal conditions in hand, we started to explore the substrate scope of this transformation and a variety of 2-alkynyl phenols were employed. In general, this transformation showed good functional group tolerance and the results were listed in Table 2. 2-Arylethynyl phenols bearing either electron-donating or electron-withdrawing substitutes on the alkynyl-moiety proved to be suitable substrates to produce the corresponding 2-aryl benzo[*b*]furans (**2a–e**) in good to excellent yields. To our delight, the presence of hydroxyl group did not interrupt the reaction, which afforded the desired benzo[*b*]furans (**2f–h**) in excellent yields. 2-*tert*-Butylethynyl phenol and 2-phenylethynyl-3-hydroxyl pyridine also reacted smoothly to give the corresponding products in 91% and 88% yield, respectively.

Similar to 2-substituted benzo[*b*]furans, we proposed that 2-substituted indoles could also be synthesized under our standard conditions. When 2-(phenylethynyl)aniline was used, however, no reaction was observed, probably due to the low acidity of the protons on the amino group. Hence, 2-(phenylethynyl)tosylaniline **3a** was submitted to the standard conditions and the reaction proceeded smoothly to afford *N*-tosyl-2-phenyl indole **4a** in 95% yield. Then various 2-alkynyl tosylanilines were tested under the standard conditions and the results were shown in Table 3. We found that in all cases, 2-arylethynyl tosylanilines gave the desired products (**4a–c**) in excellent yields. Similar results were obtained when different 2-alkylethynyl tosylanilines (**3d–f**) were used as the substrates. Hydroxyl group was still tolerated in this transformation and tosylanilines with Me or Cl substitutes remained active to give the corresponding tosylindoles **4i** and **4j** in 86% and 82% yield, respectively.

Table 2 Substrate scope of benzo[*b*]furan synthesis[a]

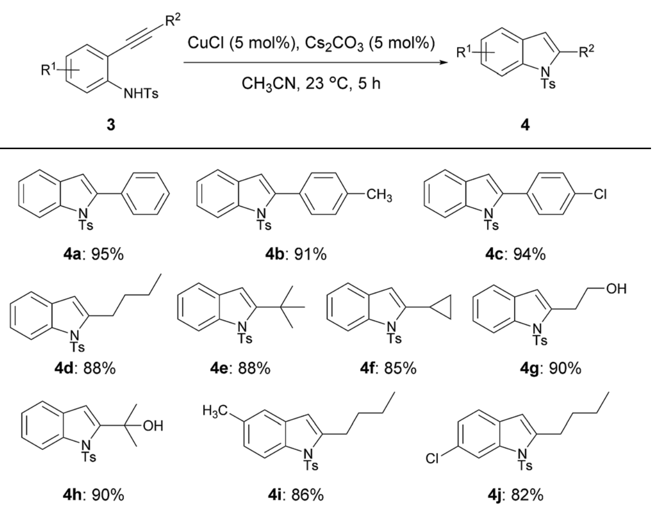


1 2

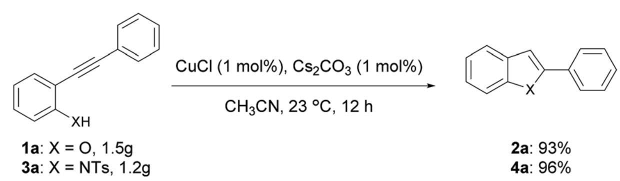


[a] All reactions were performed with 1 (0.5 mmol), CuCl (0.025 mmol), Cs_2CO_3 (0.025 mmol) in CH_3CN (2 mL) at 23 °C for 5 h. Isolated yields of **2** were listed. [b] 2-Phenylethynyl-3-hydroxyl pyridine was used as the substrate.

Table 3 Substrate scope of copper-catalyzed indole synthesis[a]

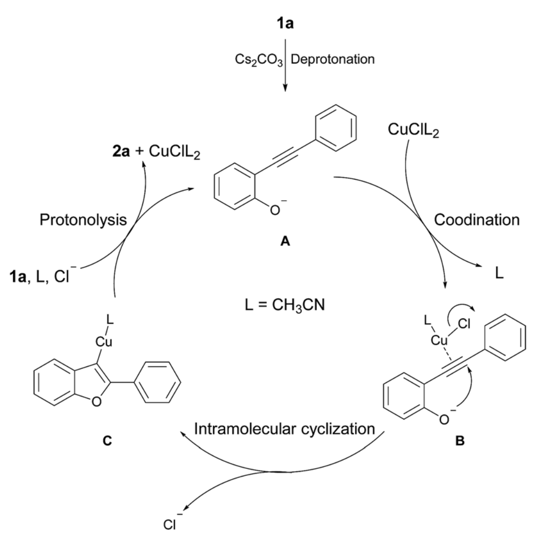


[a] All reactions were performed with **3** (0.5 mmol), CuCl (0.025 mmol), Cs_2CO_3 (0.025 mmol) in CH_3CN (2 mL) at 23 °C for 5 h. Isolated yields of **4** were listed.



Scheme 2 Gram scale preparation of **2a** and **4a**.

In order to demonstrate the utility and efficiency of this transformation, we performed the gram scale reactions of **1a** and **3a** in the presence of only 1 mol% of CuCl and Cs_2CO_3 (Scheme 2). Although the completion time was longer, both reactions afforded the desired products in high yields. Considering the low cost and high yield, this robust method offers a practical application for the facile synthesis of 2-substituted benzo[*b*]furans and indoles.



Scheme 3 Plausible reaction mechanism.

A plausible mechanism of this reaction is then proposed taking **1a** as an example (Scheme 3). At the outset, **1a** can be deprotonated by Cs_2CO_3 to form **A**, which can be activated by the solvated CuCl to afford intermediate **B**. Then **B** undergoes an intramolecular cyclization to give intermediate **C**. The subsequent protonolysis of **C** by **1a** could afford our final product **2a** accompanied with intermediate **A** for the next catalytic cycle.

Conclusions

In conclusion, a practical copper-catalyzed method has been developed for the facile synthesis of various 2-substituted benzo[*b*]furans and indoles. The transformation can be accomplished under mild conditions with low catalyst and base loading, featuring broad substrate scope and high efficiency, which shows great potential in the application for the large scale production.

Experimental

General procedure for copper-catalyzed synthesis of 2-substituted benzo[*b*]furans and indoles

CuCl (2.5 mg, 0.025 mmol) and Cs_2CO_3 (8.1 mg, 0.025 mmol) were added to a solution of 2-alkynyl phenol **1** (or 2-alkynyl tosylaniline **3**, 0.5 mmol) in CH_3CN (2 mL) and the mixture was stirred at 23 °C for 5 h. Then Et_2O (10 mL) was added and the resulting mixture was washed sequentially with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (hexane/EtOAc) to give 2-substituted benzo[*b*]furans **2** (or 2-substituted indoles **4**).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Zhejiang Provincial Top Key Discipline of Bioengineering (ZS2017014, ZS2018011 and ZS2015005), the Scientific Research Development Foundation of Zhejiang Wanli University and Zhejiang Provincial basic public welfare research project (LGN18H300001).

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