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Copper-catalyzed tandem arylation-cyclization of 2-alkynylaryl isothiocyanates with diaryliodonium salts: an efficient synthesis of thiochromeno[2,3-*b*]indoles

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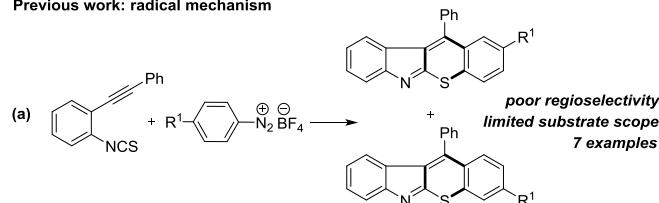
A catalytic tandem arylation–cyclization approach from 2-alkynylphenyl isothiocyanates with diaryliodonium salts is described. The reaction is performed under mild conditions and the thiochromeno[2,3-*b*]indoles are obtained in moderate to good yields. This tandem protocol involves chemoselective *S*-arylation, regioselective *5-endo-trig* cyclization and Friedel–Crafts-type cyclization process. Two C–C bonds, one C–S bond, and two heterocyclic rings are formed in a single step. Preliminary mechanistic studies indicate that a carbocation mechanism is involved.

Introduction

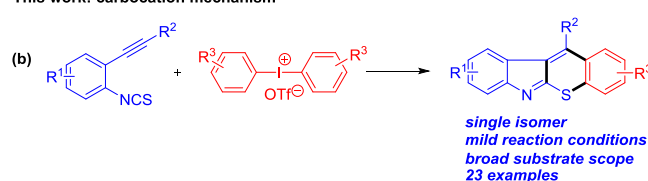
It is found that 2,3-fused polycyclic indole derivatives widely exist in bioactive natural products,¹ which are exemplified by aspidospermine,² yohimbine,³ and strychnine.⁴ Over the past decade, indoles containing heteroacenes have also received much attention because of their potential application in organic field-effect transistors (OFETs) and organic light emitting diodes (OLEDs).⁵ In addition, fused-thiopyran scaffolds have been found to exhibit a broad spectrum of bioactivities, such as anti-cancer,⁶ anti-bacterials,⁷ anti-hyperplasia activities.⁸ Certain thiopyrano[2,3-*b*]indoles have also shown to possess analgesic activity.⁹ Despite of various methodologies developed for the preparation of 2,3-fused indoles,¹⁰ including thiopyrano[2,3-*b*]indoles,¹¹ sometimes, they suffer from tedious multistep routes and high cost transition metals. Therefore, it would be desirable to develop a more concise method.

Due to its high reactivity and low toxicity, the diaryliodonium salt has merged as an efficient arylating reagent in organic synthesis.¹² In the last three years, significant progress has been made in the tandem arylation-cyclization reactions to construct various heterocyclic compounds initiated by diaryliodonium salts.¹³ Nitriles,¹⁴ alkenes,¹⁵ and alkynes¹⁶ were frequently employed as substrates in these transformations. However, cyclization based on isothiocyanates is still underdeveloped.

Previous work: radical mechanism



This work: carbocation mechanism



Scheme 1 Synthesis of thiochromeno[2,3-*b*]indoles

Recently, the construction of fused heterocycles through bicyclization¹⁷ has attracted significant attention due to their high efficiency, especially using 2-alkynylaryl isothiocyanates¹⁸ as starting materials. In 2003, Nanni and coworkers¹⁹ reported a radical cyclization of 2-alkynylphenyl isothiocyanates with aryl radicals, generated from diazonium tetrafluoroborates, to synthesize thiochromeno[2,3-*b*]indoles via imidoyl radicals (Scheme 1a). Only 7 examples were obtained as mixtures of isomers through competitive [4+2] and [4+1] radical cyclizations. We envisioned that the 2-alkynylphenyl isothiocyanates could be combined with a aryl carbocation generated from diaryliodonium salts, in which a single isomer of thiochromeno[2,3-*b*]indoles might be generated through [4+2] cyclization exclusively. However, control of the chemo- and regioselectivity is challenging, because alkynes are known to react with diaryliodonium salts.²⁰ In continuation of our previous study,²¹ we report herein a Cu-catalyzed chemo- and regioselective domino arylation-cyclization approach for the synthesis of thiochromeno[2,3-*b*]indoles as single isomer from

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2-alkynylaryl isothiocyanates and diaryliodonium salts (Scheme 1b).

Results and discussion

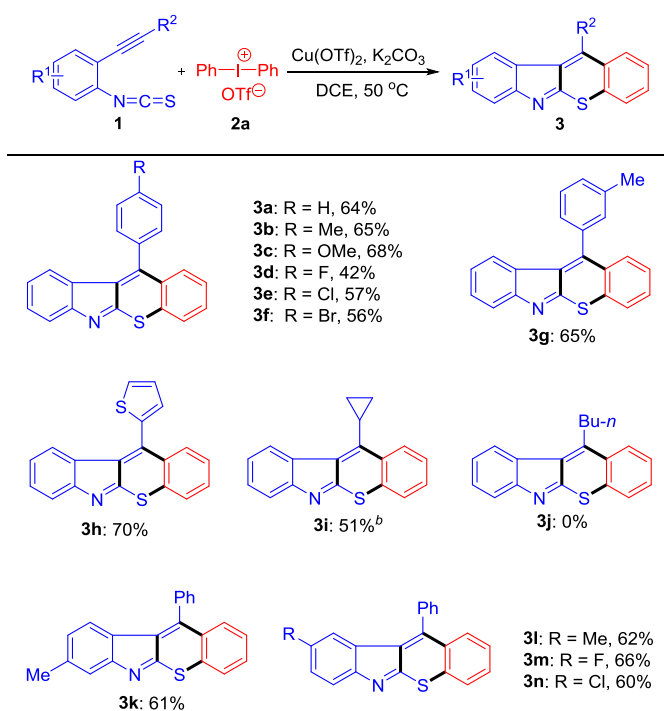
Initially, we examined several different copper catalysts using 2-(2-phenylethynyl)phenyl isothiocyanate **1a** with diphenyliodonium triflate **2a** (Table 1, entries 1–4), and found that Cu(OTf)₂ gave the best result. The 11-phenylthiochromeno[2,3-*b*]indole **3a** was obtained in 45% yield. In the absence of Cu catalyst, no desired product was observed (entry 5). Moreover, lower yields were obtained when anions of the diphenyliodonium salts were changed to hexafluorophosphate (PF₆⁻) or tetrafluoroborate (BF₄⁻) (entries 6 and 7). Diminished yields were obtained at decreased or elevated temperature (entries 8 and 9). In order to further improve the yield, a base was added to quench trifluoromethanesulfonic acid formed during the reaction (entries 10–13). Pleasingly, the yield of **3a** was up to 64% when 1 equiv K₂CO₃ was added (entry 10). The yield of **3a** was not improved with the catalyst loading increased to 20 mol% or reduced to 5 mol% (entries 14 and 15). After optimization, the best conditions were established as follows: Cu(OTf)₂ (0.1 equiv) as the catalyst and K₂CO₃ (1.0 equiv) as the base in DCE (1.0 mL) at 50 °C under N₂ for 6 h. The structure of **3a** was confirmed by the X-ray diffraction analysis (Fig. S1 in the ESI).

Table 1 Optimization of the reaction conditions^a

entry	catalyst (mol %)	X	base (eq)	T [°C]	yield (%) ^b
1	CuCl (10)	OTf		50	20
2	CuBr (10)	OTf		50	32
3	Cu(OTf) ₂ (10)	OTf		50	45
4	CuTc (10)	OTf		50	0
5	-	OTf		50	0
6	Cu(OTf) ₂ (10)	PF ₆		50	25
7	Cu(OTf) ₂ (10)	BF ₄		50	34
8	Cu(OTf) ₂ (10)	OTf		30	26
9	Cu(OTf) ₂ (10)	OTf		80	31
10	Cu(OTf)₂ (10)	OTf	K₂CO₃ (1.0)	50	64
11	Cu(OTf) ₂ (10)	OTf	Na ₂ CO ₃ (1.0)	50	37
12	Cu(OTf) ₂ (10)	OTf	Cs ₂ CO ₃ (1.0)	50	42
13	Cu(OTf) ₂ (10)	OTf	DABCO (1.0)	50	0
14	Cu(OTf) ₂ (20)	OTf	K ₂ CO ₃ (1.0)	50	37
15	Cu(OTf) ₂ (5)	OTf	K ₂ CO ₃ (1.0)	50	28

^a Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv), DCE (1.0 mL), 6 h, N₂. ^b Isolated yield.

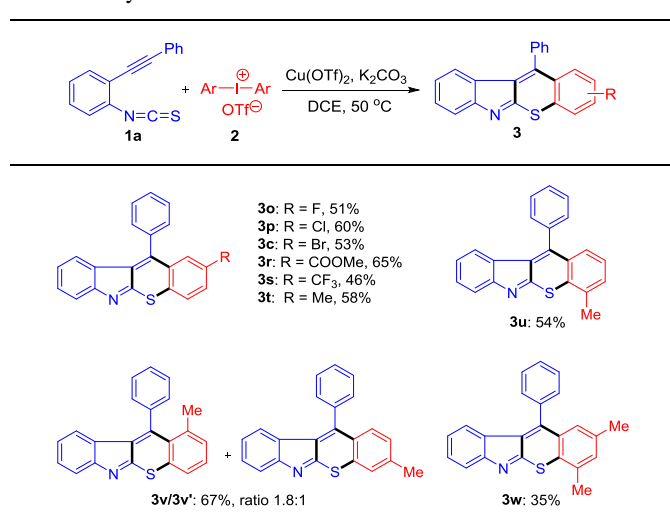
Table 2 Synthesis of thiochromeno[2,3-*b*]indoles **3a-3n** from various 2-alkynylaryl isothiocyanates **1^a**



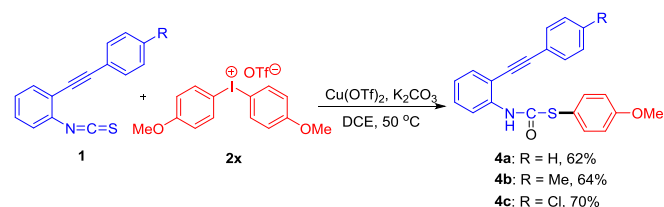
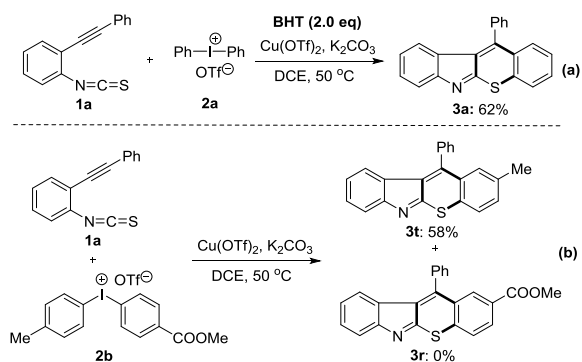
^a Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 equiv), Cu(OTf)₂ (0.1 equiv), K₂CO₃ (1.0 equiv), DCE (2.5 mL), 50 °C, 6 h, N₂. ^b Reaction time is 15 min.

With the optimal conditions in hand, a variety of alkynylaryl isothiocyanates were tested (Table 2). The R² group in substrates **1** exhibited obvious electronic effects. Products **3b**, **3c** and **3g** were afforded in good yields (65–68%) when R² was an electron-donating aryl group such as 4-MeC₆H₄, 4-MeOC₆H₄ and 3-MeC₆H₄. Whereas R² was an electron-withdrawing aryl group, such as 4-FC₆H₄, 4-ClC₆H₄, and 4-BrC₆H₄, the reaction proceeded to generate compounds **3d-3f** in moderate yields (42–57%). Substrate with a thiophene group was also tolerated and product **3h** was isolated in 70% yield. Moreover, product **3i** was obtained in 51% yield when R² was a cyclopropyl group (a group can stabilize the adjacent carbocation). Unfortunately, no desired product **3j** was formed when R² was an *n*-butyl group, probably due to this group could not stabilize the adjacent positive charge. In addition, products **3k-3n** were obtained in good yields (60–66%), regardless of the substitution positions and electronic properties of R¹ group.

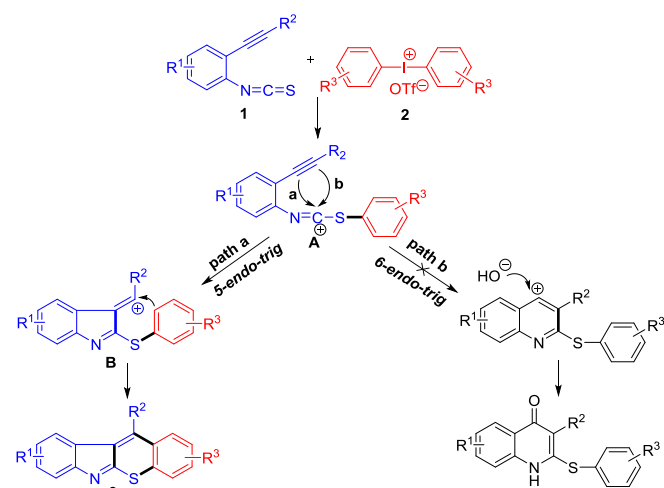
We next investigated the scope of diaryliodonium salts **2** under the optimal conditions (Table 3). Substrates bearing fluoro, chloro, bromo, ester, and trifluoromethyl groups at *para*-position of the aryl ring all worked well to produce the desired thiochromeno[2,3-*b*]indoles **3o-3s** in 46–65% yields. The expected products **3t-v** were afforded smoothly regardless of methyl position on the phenyl ring. While *meta* substituted substrate gave two inseparable isomers in 1.8:1 ratio and 67% overall yield (**3v/3v'**). Additionally, diaryliodonium salts with 2,4-dimethyl groups also afforded the desired products **3w**, albeit in lower yield.

Table 3 Synthesis of thiochromeno[2,3-*b*]indoles **3o-3w** from various diaryliodonium salts **2^a**

^a Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 equiv), Cu(OTf)₂ (0.1 equiv), K₂CO₃ (1.0 equiv), DCE (2.5 mL), 50 °C, 6 h, N₂.

**Scheme 2** The reaction of **1** with **2x**.**Scheme 3** Control experiments.

Notably, when diaryliodonium salt with strong electron-donating group (4-OMe) **2x** was used to react with **1**, the carbamothioates **4a-c** were separated in 62–70% yields rather than the desired cyclization products (Scheme 2). Moreover, when bis(2-methoxyphenyl)iodonium salt was used to react with **1**, no separable product was formed. The structures of **4** were confirmed by X-ray diffraction analysis of **4a** (Fig. S2 in the ESI). The reason that **2x** can not form the thiochromeno[2,3-*b*]indole remains unclear, however, the separation of carbamothioates **4** supports the formation of the proposed intermediate **A** (Scheme 4).

**Scheme 4** Proposed reaction mechanism.

Control experiments were carried out to investigate the reaction mechanism. Initially, a radical scavenger 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the reaction mixture under the optimal conditions. The reaction was not inhibited and **3a** was obtained in 62% yield (Scheme 3a). In addition, a competition reaction was performed using 2-alkynylphenyl isothiocyanate **1a** with unsymmetrical diaryliodonium salt **2b** under the standard conditions, product **3t** was afforded exclusively in 58% yield and no product **3w** was detected (Scheme 3b). These results indicate that a carbocation mechanism might be involved in the reaction.^{14c,22}

On the basis of our experiment results, a possible mechanism for the copper-catalyzed domino reaction was proposed (Scheme 4). According to literatures and our previous work,^{16,21} both the isothiocyanate group and alkyne group in substrate **1a** could be arylated by diaryliodonium salts. In this paper, a phenyl carbocation is chemoselectively transferred by a well-established Cu(III) species¹⁶ to the isothiocyanate group of **1a** to generate a cationic intermediate **A**. Then, intermediate **A** is captured by the vicinal alkyne group to give intermediate **B** through a regioselective 5-*endo-trig* cyclization (path a). The newly formed carbocation in intermediate **B** could be stabilized by the adjacent phenyl group. Finally, the thiochromeno[2,3-*b*]indole is obtained by intramolecular Friedel–Crafts-type cyclization of intermediate **B**. Another reaction path b through 6-*endo-trig* cyclization to form quinolin-4(1*H*)-ones was not observed.

Conclusions

In conclusion, an efficient copper-catalyzed tandem arylation-cyclization process is developed with readily available starting materials 2-alkynylaryl isothiocyanates and diaryliodonium salts. The tetracyclic thiochromeno[2,3-*b*]indoles are obtained in good yield through a sequence of chemoselective S-arylation, regioselective 5-*endo-trig* cyclization, and Friedel–Crafts-type cyclization process. Moreover, this method features broad substrates scope,

simple operation, and the formation of three chemical bonds and two heterocyclic rings in a single step. Further studies to expand the scope of isothiocyanate-based cyclization with diaryliodonium salts are ongoing in our laboratory.

Acknowledgements

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