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Facile synthesis of 5*H*-benzo[*b*]carbazol-6-yl ketones *via* sequential reaction of Cu-catalyzed Friedel–Crafts alkylation, iodine-promoted cyclization, nucleophilic substitution and aromatization†

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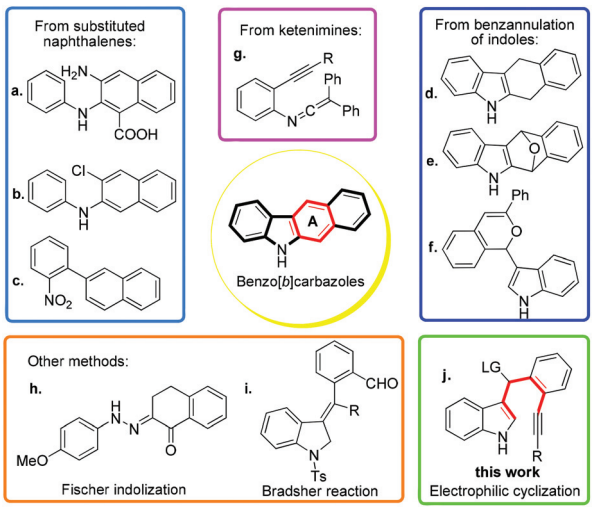
A convenient method to access 5*H*-benzo[*b*]carbazol-6-yl ketones *via* a sequential Cu-catalyzed Friedel–Crafts alkylation reaction of indoles with 2-(2-(alkynyl)benzylidene)malonates and iodine-promoted electrophilic cyclization followed by nucleophilic substitution and aromatization was developed. The products of the functional 5*H*-benzo[*b*]carbazol-6-yl ketones were obtained with up to 98% yield.

Condensed heterocyclic aromatic compounds are particularly appealing due to their unique biological activities and outstanding optoelectronic properties.[1,2] Carbazole and its fused aromatic analogues, which are a class of heterocyclic aromatic compounds as well as indole alkaloids,[3] have recently been the subject of intense investigation.[4] Some of the carbazole alkaloids showed a range of promising biological activities,[5–9] such as antitumor,[6,7] anti-inflammatory,[8] and antipsychotic properties.[9] Among all carbazole analogues, the framework of benzo[*b*]carbazoles[10–13] was most extensively explored because they are isosteric species of antitumor drugs based on pyrido[4,3-*b*]carbazole alkaloids, such as ellipticine.[7] Approaches to the synthesis of benzo[*b*]carbazoles mainly start from different substituted naphthalenes[10] (Scheme 1, a–c) or indoles[11] (Scheme 1, d–f). Another kind of commonly used method involves a biradical cyclization of ketenimine intermediates[12] (Scheme 1, g). Other methods,[13] using the Fischer indolization and the Bradsher reaction as key steps, have also been reported (Scheme 1, h and i). In addition, a phase tag-assisted synthesis of the benzo[*b*]carbazole motif *via* SmI_2-mediated radical nucleophilic ring closure offered another novel approach.[13d,e] However, for most of the procedures derived from substituted indole substrates,[11] the key step to construct phenyl ring **A** (benzo[*b*]carbazoles in Scheme 1) involved the Diels–Alder reaction[11c,d] or metal-catalyzed benzannulation of indoles.[11j,k] To the best of our knowledge, no examples have been reported yet, which show the formation of benzo[*b*]carbazoles *via* electrophilic cyclization in the annulation step. Given the great utility of benzo[*b*]carbazoles, exploring efficient alternatives to construct these structures is still highly desirable.



Scheme 1 Synthetic routes to benzo[*b*]carbazoles.

Very recently, we have developed an efficient Cu-catalyzed asymmetric Friedel–Crafts alkylation reaction[14] of indoles with arylidene malonates, using bis(sulfonamide) diamine ligands.[15a–d] As part of our continued interest in the reactions of indoles, we envision that when diethyl 2-(2-(phenylethynyl)-benzylidene)malonate, **2a**, is employed as a substrate, the corresponding product **3a**,[16] including an alkynyl group, would be a good precursor for the subsequent cyclization, where the diethyl malonate moiety may act as a leaving group (LG) (Scheme 1, j). Herein, we describe a convenient way to synthesize 5*H*-benzo[*b*]carbazol-6-yl ketones *via* the Cu-cata-

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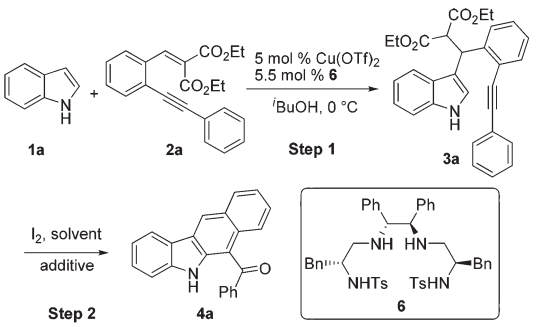
lyzed Friedel–Crafts reaction of indoles with 2-(2-(alkynyl)-benzylidene)malonates, followed by an iodine-promoted electrophilic cyclization, nucleophilic substitution and further aromatization.

Indole, **1a**, and diethyl 2-(2-(phenylethynyl)benzylidene)-malonate, **2a**, were selected as the substrates to optimize the reaction conditions in step 1 (Table 1). The screening of solvents and catalysts revealed that the catalytic system, which showed the best performance in our previously described Friedel–Crafts reaction of indole with arylidene malonates, remained the best choice for substrate **2a**.[15d,e] Subsequently, we set out to investigate the cyclization step of intermediate **3a**. An initial examination of the effect of electrophiles, such as iodine, NIS (*N*-iodosuccinimide), IPy_2BF_4 and DIH (1,3-diiodo-5,5-dimethylhydantoin), showed that only iodine could promote cyclization. However, the product was not the traditional product derived from electrophilic cyclization. 5*H*-Benzo[*b*]carbazol-6-yl ketone was unexpectedly obtained with 40% yield in CH_2Cl_2 at room temperature (Table 1, entry 1). It is noteworthy that Li and coworkers have reported $PdCl_2$-catalyzed domino reactions of 2-alkynylbenzaldehydes with indoles,[11j] in which 5*H*-benzo[*b*]carbazol-6-yl ketones were obtained in 39–73% yield at an elevated temperature (120 °C). The Diels–Alder reaction or thermal electrocyclization was proposed to be the key step in the process of constructing ring **A**.

Gratifyingly, our findings suggested that 5*H*-benzo[*b*]carbazol-6-yl ketones could be obtained at ambient temperature and this promising result encouraged us to investigate the reaction systematically. The continuous evaluation of the solvents in step 2 revealed that the solvents played a crucial role in the transformation and that CH_3CN was the optimal choice (Table 1, entries 1–7). When the reaction was performed in the open air or under oxygen atmosphere, a slight improvement of the yield was achieved (Table 1, entries 8 and 9). The sequential examination of the function of different additives revealed that a base, such as $NaHCO_3$, had a deleterious effect on the reaction, as hardly any product was found (Table 1, entry 10). Interestingly, a slight increase in the yield was observed when adding 1 equivalent of H_2O (Table 1, entry 11). The careful regulation of the I_2 amount showed that 2 equivalents of I_2 provided the best result, with 88% yield (Table 1, entry 12). Raising the temperature to 50 °C greatly accelerated the reaction with an increase in the yield (within 2 hours, 90% yield, Table 1, entry 13). Notably, when the reactions were conducted in one pot without separation of the intermediate **3a**, the reaction proceeded smoothly with a comparable yield (Table 1, entry 14). However, changing the solvent from ^{i}BuOH (in step 1) to CH_3CN (in step 2) was necessary. It is worth mentioning that the compatibility of the catalytic system with step 1 and step 2 is crucial for a one-pot reaction.[16] To our delight, our catalytic system wasn't affected by this problem. Given the simple operation, we decided to take advantage of the one-pot reaction in the following exploration of the substrate scope. The optimal conditions are: (step 1) 5 mol% $Cu(OTf)_2$, 5.5 mol% **6**, ^{i}BuOH, 0 °C, and (step 2) 2.0 equiv. I_2, 1.0 equiv. H_2O, CH_3CN, 50 °C.

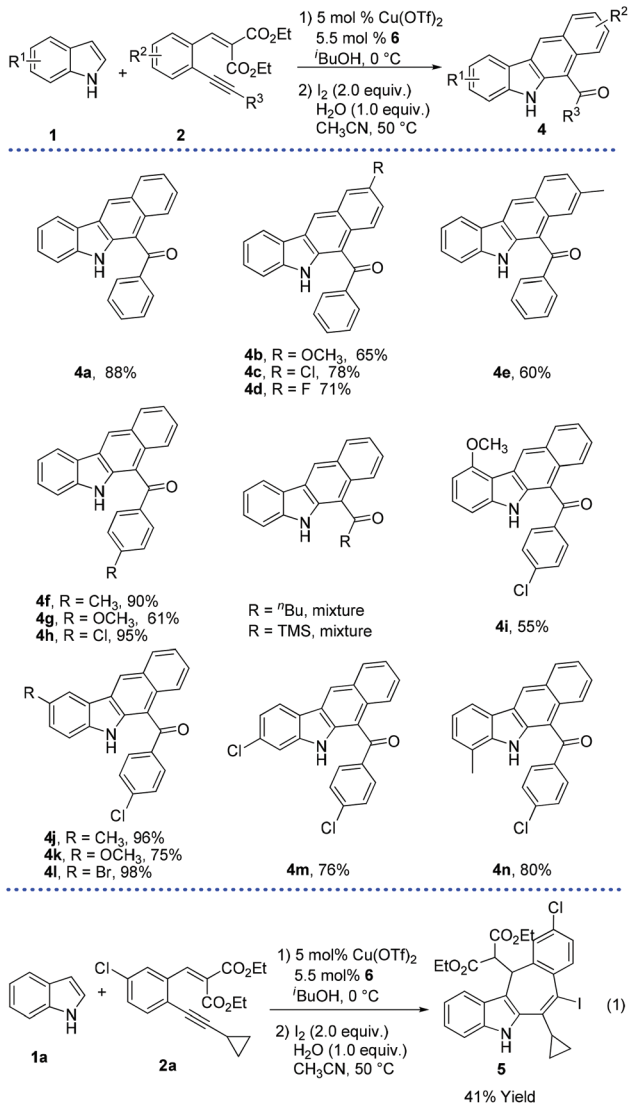
With the suitable reaction conditions in hand, the generality of the transformation was explored. Firstly, different R^2 groups of 2-(2-(alkynyl)benzylidene)malonate were investigated. Generally, the reaction proceeded smoothly to afford the products with moderate yields. However, for the R^2 groups, substrates with electron-withdrawing substituents provided slightly higher yields than those with electron-donating substituents (Scheme 2, entries 4b–4e). Subsequently, the substituent effect of the internal alkynyl moiety was evaluated. When the R^3 groups on the alkynyl moiety were aryl substituents, moderate to high yields were achieved (Scheme 2, entries 4f–4h). In contrast, when an aliphatic substituent R^3 group (*e.g.* ^{n}Bu and TMS) was involved on the alkynyl moiety, complex mixtures were observed. It is probable that when the alkynyl moiety was linked to the aliphatic substituent groups, the iodonium ion intermediate is not very stable, which may result in side reactions. Surprisingly, when substituent R^3 was a cyclopropyl group, electrophilic cyclization took place in a 7-*endo-dig* fashion and afforded a tetracyclic indoloazulene derivative, **5**, with 41% yield (eqn (1)). Product **5**, containing tetracyclic indole with a seven-membered ring, is a useful structural motif for a variety of pharmaceuticals, although

Table 1 Optimization of the reaction conditions[a]



Entry	Solvent	Additives	T (°C)	Yield[b] (%)
1	CH_2Cl_2	—	RT	40
2	DCE	—	RT	37
3	Et_2O	—	RT	21
4	THF	—	RT	17
5	CH_3CN	—	RT	76
6	Toluene	—	RT	41
7	^{i}BuOH	—	RT	N.R.
8[c]	CH_3CN	—	RT	79
9[d]	CH_3CN	—	RT	80
10[c]	CH_3CN	$NaHCO_3$	RT	N.R.
11[c,e]	CH_3CN	H_2O	RT	81
12[c,e,f]	CH_3CN	H_2O	RT	88
13[c,e,f]	CH_3CN	H_2O	50	90
14[c,e,f,g]	CH_3CN	H_2O	50	88

[a] Unless otherwise noted, all reactions were performed with **3a** (0.3 mmol) and electrophile I_2 (0.5 mmol) in 2 mL solvent under argon for 6–24 h. [b] Isolated yields. [c] The reaction was performed in the open air. [d] The reaction was performed under oxygen. [e] 1.0 equiv. H_2O was added. [f] 2.0 equiv. I_2 (0.6 mmol) was used. [g] The reaction was carried out in one pot: when step 1 was finished after 6 h, the solvent ^{i}BuOH was removed under reduced pressure. Intermediate **3a** was transformed in step 2 without further purification and the reaction was finished in 2 h.



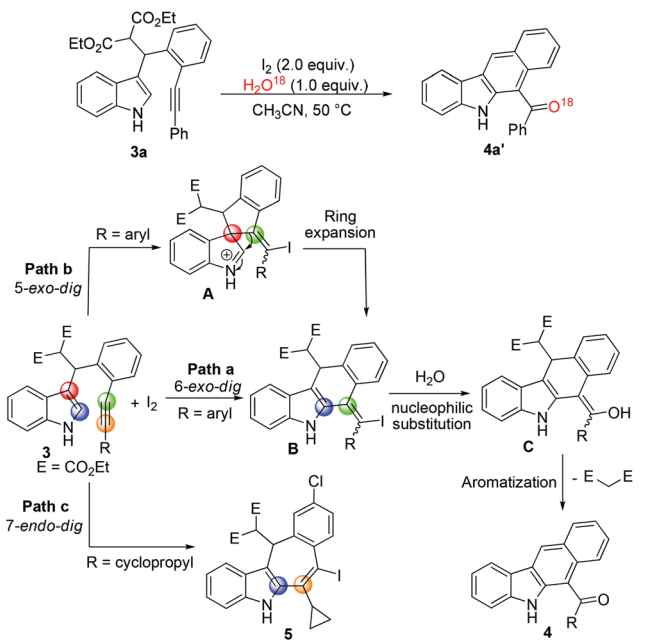
Scheme 2 Cu-catalyzed Friedel–Crafts alkylation and I_2-promoted electrophilic cyclization of indoles, **1**, with various 2-(2-(alkynyl)benzylidene)malonates, **2**.

there are only few ways to synthesise it.[17] The molecular structure of **5** was unambiguously determined by X-ray crystallography of its *N*-Ts derivative (see the ESI†).

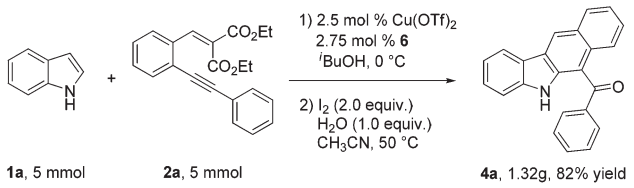
Likewise, the electronic properties and steric hindrance effect on the indole scaffold were examined. Good yields were acquired regardless of the electron-donating or -withdrawing groups at position 5, 6 or 7 of the indole ring (Scheme 2, entries 4j–4n). However, methoxyl-substituted indole at position 4 afforded the corresponding product with lower yield because of the steric hindrance (Scheme 2, entry 4i).

To gain insight into the mechanism, we examined the reaction solution of **3a** with iodine under optimal reaction conditions using HPLC-MS, when the reaction was conducted for 30 min. According to the spectrum, five substances with a molecular weight of 591.1 were detected, which is in accordance with the molecular weight of the corresponding electrophilic cyclization products. In addition, electrophilic cyclization product **5** was obtained when the cyclopropyl group was used as the substituent on the alkynyl moiety. These results reveal that the reaction undergoes an electrophilic cyclization process but in a different cyclization mode. The reaction was also performed with **3a** and 1.0 equiv. H_2O^{18}, for which the corresponding product **4a′** with an ^{18}O label was obtained as a major product. On the basis of these experiments, a mechanism is outlined to explain the process of this transformation (Scheme 3). The alkynyl moiety of the Friedel–Crafts alkylation compound, **3**, is activated by iodine and then undergoes an electrophilic cyclization reaction of indole through two pathways when the R groups are aryl groups: (1) **path a** *via* a 6-*exo-dig* mode (**3**–**B**) or (2) **path b** *via* a 5-*exo-dig* mode followed by ring expansion (**3**–**A**–**B**). Intermediate **B** undergoes nucleophilic substitution by H_2O, which affords intermediate **C**, followed by aromatization with the elimination of one molecule of the diethyl malonate[11i,j] to provide product **4**. Recently, an iodine-promoted cascade reaction of 2-alkynylbenzaldehyde and indole was reported by Yao's group.[17d] In their system, tetracyclic indoloazulene derivatives were obtained *via* iodocyclization in a 7-*endo-dig* fashion, while our system showed a different iodocyclization mode. However, when the R group is a cyclopropyl group, the electrophilic cyclization reaction provides tetracyclic indoloazulene derivatives, **5**, in a 7-*endo-dig* fashion (**path c**). Without the driving force of aromatization, the reaction stops at the step of electrophilic cyclization to afford product **5**.

To further demonstrate the application potential of this synthetic strategy, a gram-scale reaction was conducted. The reaction of diethyl 2-(2-(phenylethynyl)benzylidene)malonate, **2a**, (5 mmol, 1.74 g) with indole, **1a**, (5 mmol, 0.59 g) was carried out with a lower catalyst loading (2.5 mol%) under



Scheme 3 Proposed mechanism.



Scheme 4 A large scale reaction.

standard reaction conditions. The reaction proceeded smoothly and the corresponding product, **4a**, was obtained with 82% yield (Scheme 4).

Conclusions

In summary, we have developed a facile method to access 5*H*-benzo[*b*]carbazol-6-yl ketones *via* a sequential reaction of Cu-catalyzed Friedel–Crafts alkylation of indoles with 2-(2-(alkynyl)benzylidene)malonates, followed by iodine-promoted cyclization, nucleophilic substitution and aromatization. Functionalized 5*H*-benzo[*b*]carbazol-6-yl ketones were prepared in moderate to high yields. A product with the structure of tetracyclic indole, including a seven-membered ring, was also obtained when the substituent on the alkynyl moiety was a cyclopropyl group. Moreover, a gram-scale experiment was conducted to illustrate its simple operation and practicality.

Acknowledgements

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16 (*a*) When the reaction conditions reported by Wu[16*b*] and coworker were applied for step 1 (10 mol% $Sc(OTf)_3$ as catalyst in CH_3CN at room temperature for 24 h) to form product **3a**, followed by the optimal reaction conditions of step 2 in one pot, only a trace amount of product **4a** was obtained. This result revealed that the compatibility of the catalytic system with step 1 and step 2 was crucial for the one-pot reaction (*b*) K. Gao and J. Wu, *Org. Lett.*, 2008, **10**, 2251.

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