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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 /Aromatization†

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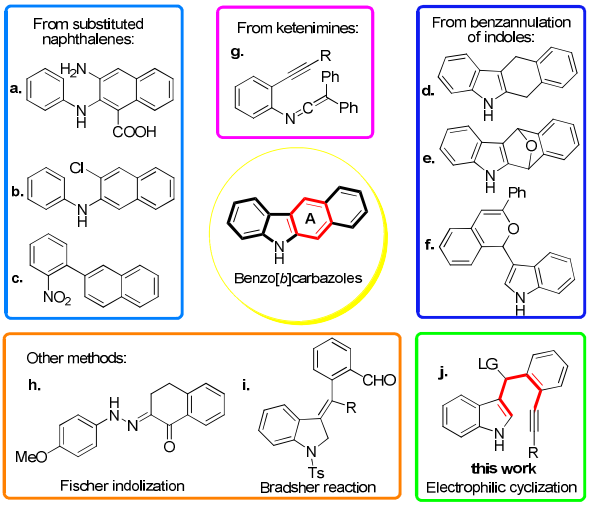
A convenient method to access 5*H*-benzo[*b*]carbazol-6-yl ketones *via* sequential Cu-catalyzed Friedel-Crafts alkylation reaction of indoles with 2-(2-(alkynyl)benzylidene) malonates and iodine-promoted electrophilic cyclization followed by nucleophilic substitution and aromatization was developed.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

Condensed heterocyclic aromatic compounds were particularly appealing in view of their unique biological activities and outstanding optoelectronic properties.[1-2] Carbazole and its fused aromatic analogues, as one class of heterocyclic aromatic compounds as well as indole alkaloids[3], have recently been the subject of intense investigation.[4] Some of carbazole alkaloids showed a range of promissing biological activities[5-9], such as antitumor[6-7], anti-inflammatory[8], antipsychotic properties[9] etc. Among carbazole analogues, the framework of benzo[*b*]carbazoles[10-13] was most extensively explored because they were isosteric species of antitumor drugs pyrido[4,3-*b*]carbazole alkaloid, ellipticine[7]. Approaches to the synthesis of benzo[*b*]carbazoles mainly started from different substituted naphthalenes[10] (Scheme 1, a-c) or indoles[11] (Scheme 1, d-f). Another kind of commonly used methods involved a biradical cyclization of ketenimine intermediates[12] (Scheme 1, g). Other methods[13] using Fischer indolization and Bradsher reaction as key step were also reported (Scheme 1, h, i). In addition, phase tag-assisted synthesis of benzo[*b*]carbazoles motif *via* SmI_2-mediated radical nucleophilic ring closure offered another novel apporach[13d-e]. However, for most of the procedures derived from substituted indole substrates[10], the key step to construct phenyl ring **A** (benzo[*b*]carbazoles in Scheme 1) involved a Diels-Alder reaction[10c-d] or a metal-catalyzed benzannulation of indoles[10j-k]. To the best of our knowledge, no examples were reported to form benzo[*b*]carbazoles *via* electrophilic cyclization in the annulation step. Given the great utilities 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 our continued interest in the reactions of indoles, we envision that when diethyl 2-(2-(phenylethynyl)benzylidene)malonate **2a** was employed as substrate, the corresponding product **3a**[16] with an alkynyl group would be a good precursor for 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* Cu-catalyzed Friedel-Crafts reaction of indoles with 2-(2-(alkynyl)benzylidene) malonates, followed by an iodine-

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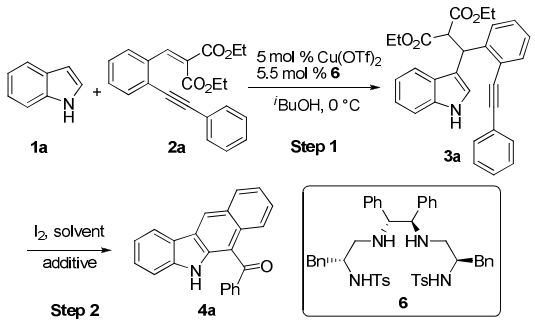
promoted electrophilic cyclization/nucleophilic substitution and further aromatization.

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). Screening of solvents and catalysts revealed that the catalytic system which showed the best performance in our previous work of Friedel-Crafts reaction of indole with arylidene malonates remained the best choice for substrate **2a**[15d-e]. Subseqently, we set out to investigate the cyclization step of intermediate **3a**. 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 the cyclization. However, the product was not the traditional product derived from electrophilic cyclization. 5*H*-benzo[*b*]carbazol-6-yl ketones 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 the $PdCl_2$-catalyzed domino reactions of 2-alkynylbenzaldehydes with indoles[10j], 5*H*-benzo[*b*]carbazol-6-yl ketones were obtained in 39–73% yield at elevated temperature (120 °C). A Diels-Alder reaction or thermal electrocyclization was proposed to be the key step therein in the process of constructing ring **A**.

Table 1. Optimization of reaction conditions[a]



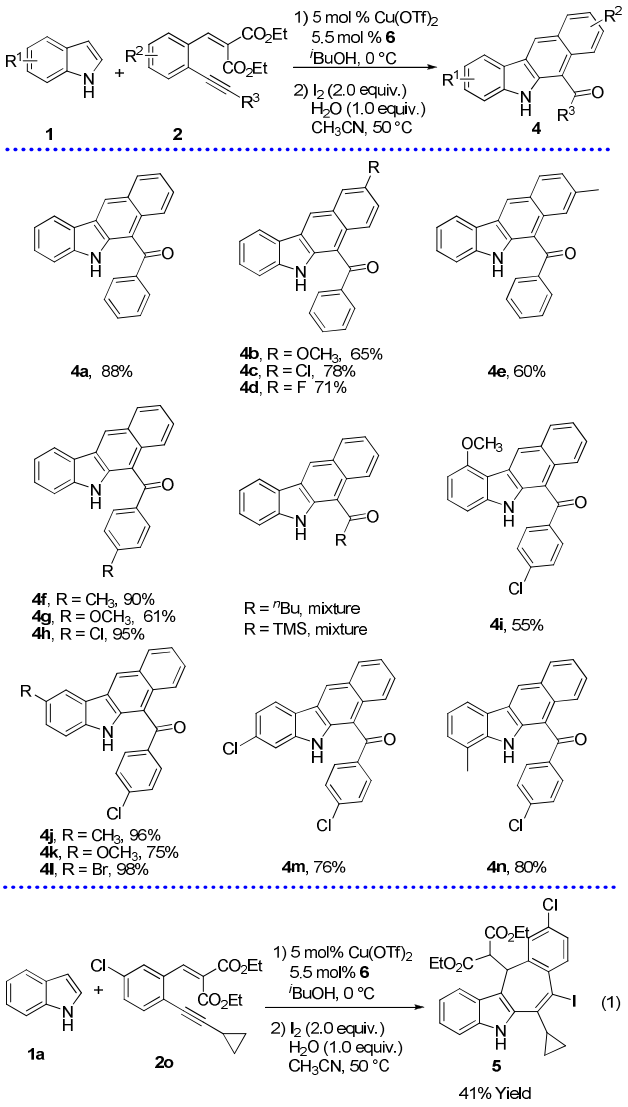
Entry	solvent	additives	T (°C)	yield(%)[b]
1	CH_2Cl_2	--	RT	40
2	DCE	--	RT	37
3	Et_2O	--	RT	21
4	THF	--	RT	17
5	CH_3CN	--	RT	76
6	Toluene	--	RT	41
7	*i*BuOH	--	RT	N.R.
8[c]	CH_3CN	--	RT	79
9[d]	CH_3CN	--	RT	80
10[c]	CH_3CN	$NaHCO_3$	RT	N.R.
11[c,e]	CH_3CN	H_2O	RT	81
12[c,e,f]	CH_3CN	H_2O	RT	88
13[c,e,f]	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 6–24h. [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 for 6 h, the solvent ^{t}BuOH was removed under reduced pressure. Intermediate **3a** was transformed in step 2 without further purification, the reaction was finished for 2 h.

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. Continuous evaluation of the solvents in step 2 revealed that the solvent played a crucial role in the transformation and 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). Sequential examination on the function of different additives revealed that base such as $NaHCO_3$ showed a deleterious effect on the reaction, and 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). Careful regulation on the amount of I_2 showed that 2 equivalent 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 intermediate **3a**, the reaction proceeded smoothly with comparable yield (Table 1, entry 14). However, changing the solvent from ^{t}BuOH (in step 1) to CH_3CN (in step 2) was necessary. It is worth mentioning that the compatibility of catalytic system between step 1 and step 2 was crucial for one-pot reaction[16]. To our delight, our catalytic system wasn't beset by this problem. Given the simple operation, we decided to take advantage of one-pot reaction in the following exploration of substrate scope. The optimal conditions are: step 1 (5 mol% $Cu(OTf)_2$, 5.5 mol% **6**, ^{t}BuOH, 0 °C), step 2 (2.0 equiv. I_2, 1.0 equiv. H_2O, CH_3CN, 50 °C).

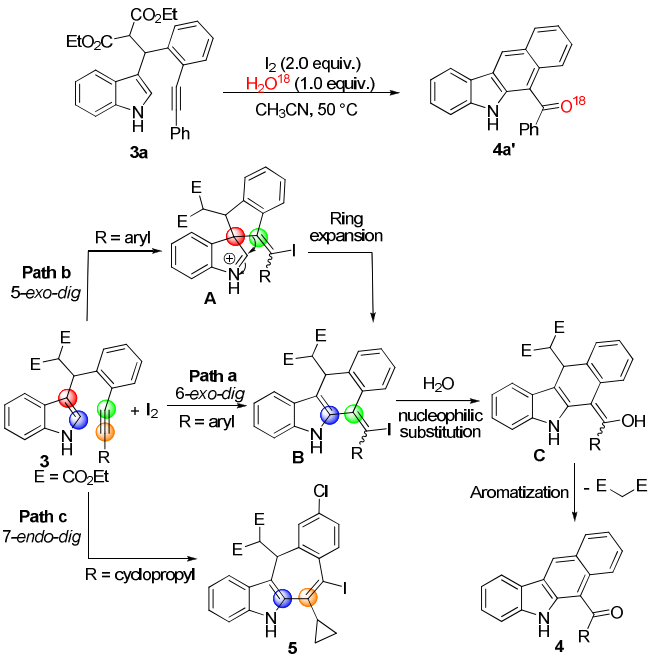
With the suitable reaction conditions in hand, the generality of the transformation was explored. First, different R^2 groups of 2-(2-(alkynyl)benzylidene)malonate were investigated. Generally, the reaction proceeded smoothly to afford the products with moderate yields. However, for the R^2 groups, substrates with electron-withdrawing substituents provided slightly higher yields than those with electron-donating substituents (Scheme 2, entries 4b–4e). Subsequently, the substituent effect of internal alkynyl moiety was evaluated. When R^3 groups on the alkynyl moiety were aryl substituents, moderate to high yields were achieved (Scheme 3, entries 4f–4h). In contrast, when aliphatic substituent of R^3 group (e.g. ^{n}Bu and TMS) on alkynyl moiety was involved, complex mixtures were observed. It is probable that when alkynyl moiety linked with aliphatic substituent groups, iodonium ion intermediate are not very stable which may result in side reactions. Surprisingly, when substituent R^3 was cyclopropyl group, electrophilic cyclization took place in a *7-endo-dig* fashion and afforded tetracyclic indoloazulene derivative **5** with 41% yield (eq. 1). Product **5** containing tetracyclic indole with a seven-membered ring was a useful structural motif in a variety of pharmaceuticals albeit with few accesses to its synthesis[17]. The molecule structure of **5** was unambiguously determined by X-ray crystallography of its *N*-Ts derivative (See Supporting Information).

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



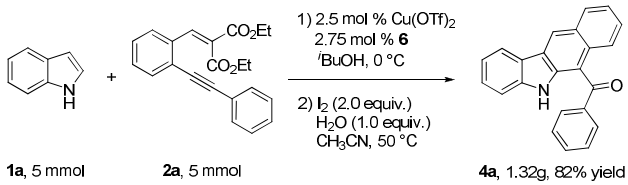
Scheme 2 Cu-catalyzed Friedel-Crafts alkylation and I_2-promoted electrophilic cyclization of indoles **1** with various 2-(2-(alkynyl)benzylidene)malonates **2**

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



Scheme 3 Proposed mechanism

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 lower catalyst loading (2.5 mol%) under standard reaction condition. The reaction proceeded smoothly and the corresponding product **4a** was obtained with 82% yield (Scheme 4).



Scheme 4 A large scale reaction

Conclusions

In summary, we have developed a facile method to access 5*H*-benzo[*b*]carbazol-6-yl ketones *via* sequential reaction of Cu-catalyzed Friedel-Crafts alkylation of indoles with 2-(2-(alkynyl)benzylidene) malonates and then iodine-promoted cyclization/nucleophilic substitution/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 substituent on alkynyl moiety was cyclopropyl group. Moreover, a gram-scale experiment was conducted to illustrate its simple operation and practicality.

Acknowledgements

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