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# CuI catalyzed *N*-arylation of amide as a key step for the preparation of 3-aryl β-carbolin-1-ones †

**Shaozhong Wang,[a] Jianwei Sun,[a] Gang Yu,[a] Xiaoyi Hu,[b] Jun O Liu[b] and Yuefei Hu*‡[a]**

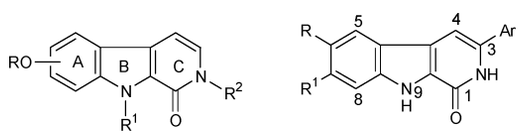
[a] *Department of Chemistry, Nanjing University, Nanjing 210093, P. R. China. E-mail: yfh@mail.tsinghua.edu.cn; Fax: +86 10 6277 1149; Tel: +86 10 6279 5380*

[b] *Department of Pharmacology and Molecular Sciences, John Hopkins University School of Medicine, 725 N. Wolfe Street, Baltimore, MD 21205, USA. E-mail: joliu@jhu.edu; Fax: +01 410 955 4520; Tel: +01 410 955 4619*

***Received 15th January 2004, Accepted 28th April 2004***
***First published as an Advance Article on the web 10th May 2004***

**An expedient synthetic route for 3-aryl β-carbolin-1-ones was developed starting from ethyl acetamidocyanoacetate and chalcone derivatives. The five- and six-membered nitrogen-containing rings in the β-carbolin-1-ones were elaborated efficiently by an intramolecular ketone-nitrile annulation and an intramolecular *N*-arylation of amide respectively.**

β-Carbolin-1-ones have served as important intermediates for the preparation of complex alkaloids[1] and are found to possess potent bioactivities on the central nervous system.[2] The first report that derivatives of β-carbolin-1-one (**1**) with alkoxy subsitituents on the A-ring could inhibit colon and lung tumors appeared in patent literature in 2001.[3] Subsequently, we found that 3-aryl-β-carbolin-1-one (**2**) and analogues inhibit the proliferation of HeLa cells with $IC_{50}$ values in the low micromolar range. Moreover, aromatic substitution on C3 in **2** proved to be essential for their biological activity.[4] The facile synthetic route to various derivatives of **2** disclosed here thus makes it possible to probe the structure and activity relationship for the carbolin-1-one family of alkaloids (Fig. 1).



**1** **2**

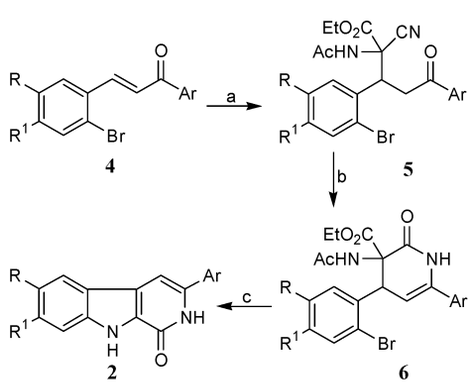
**Fig. 1** β-Carbolin-1-ones with antitumor activities.

To date, two practical strategies have been adopted to construct the skeleton of β-carbolin-1-one. One is to build pyridone rings by using acid- or palladium-catalyzed intramolecular cyclization of indole-2-carboxylic acid amides,[3,5] or intramolecular Heck reaction of 3-iodoindole-2-carboxylic acid amides.[6] The other is to modify the corresponding tricyclic precursors, such as dehydrogenation of polyhydro-β-carbolin-1-ones,[1a–b] or oxidation of β-carbolins to yield the corresponding *N*-oxides followed by a thermal rearrangement.[1c–d] Since the most suitable tricyclic precursors were obtained mainly from indole derivatives,[7] both strategies rely upon, to a great extent, the use of a few indole derivatives directly or indirectly as common starting materials, including indole-3-ethanamine, indole-2-carboxylic acid, 3-iodoindole-2-carboxylic acid or 3-iodoindole-2-carboxylaldehyde. For our purpose to synthesize 3-aryl β-carbolin-1-one (**2**), those methods suffered from either inaccessible starting materials or elaborate multi-step syntheses.

A number of lactams are readily prepared by the ketone–nitrile annulation[8] and the intramolecular *N*-arylation of amide can be achieved using palladium[9] and/or copper(I) as catalysts.[10] Herein, we report an expedient three-step synthetic route for 3-aryl β-carbolin-1-one (**2**). As shown in Scheme 1, the route starts from Michael addition of ethyl acetamidocyanoacetate (**3**) to chalcone (**4**) to afford a key precursor **5** with an efficient introduction of two nitrogen atoms. Then an intramolecular ketone–nitrile annulation of **5** yields dihydropyridone **6**. Finally, Cu(I) catalyzed intramolecular *N*-arylation of amide **6** affords the target compound **2**.

**Table 1** The preparation of compounds **5**, **6**, and **2**

| 4,5,6,2 | R | | $R^1$ | Ar | 5 | 6 | 2 |
|---|---|---|---|---|---|---|---|
| **a** | H | | H | $C_6H_5$ | 75 | 80 | 68 |
| **b** | H | | H | 4-$ClC_6H_4$ | 73 | 77 | 67 |
| **c** | H | | H | 4-$MeC_6H_4$ | 65 | 67 | 70 |
| **d** | | $OCH_2O$ | | $C_6H_5$ | 67 | 84 | 60 |
| **e** | | $OCH_2O$ | | 4-$ClC_6H_4$ | 75 | 81 | 64 |
| **f** | | $OCH_2O$ | | 4-$MeC_6H_4$ | 74 | 76 | 62 |
| **g** | MeO | | MeO | $C_6H_5$ | 65 | 88 | 65 |
| **h** | MeO | | MeO | 4-$ClC_6H_4$ | 72 | 80 | 72 |
| **i** | MeO | | MeO | 4-$MeC_6H_4$ | 60 | 80 | 60 |



**Scheme 1** The preparation of 3-aryl β-carbolin-1-ones (**2**). *Reagents and conditions*: a. ethyl acetamidocyanoacetate (**3**), cat. *t*-BuONa, THF, rt, 2 h; b. aq. HCl–HOAc, rt, 7 h; c. (1) CuI, NaH, DME, reflux, 7–10 h; (2) 10% $NH_4OH$, 2 h.

In the literature, ethyl acetamidocyanoacetate (**3**) has rarely been employed as a nucleophilic donor in Michael addition reactions and one of its nitrogen-containing groups has often been "wasted" in other uses.[11] When we treated the mixture of **3** and **4a** with a catalytic amount of *t*-BuONa (10 mol%) at room temperature for 2 h, the desired adduct **5a** was obtained in 75% yield. Under similar conditions, the addition of **3** to other chalcones **4b–i** yielded the corresponding adducts **5b–i** in 60–75% yields (Table 1).

The intermediate **5** can be further elaborated by two possible pathways. One is to build the indole ring first by an intra-

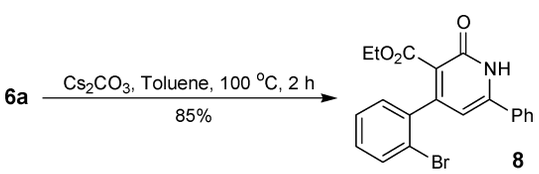
† Electronic supplementary information (ESI) available: NMR and experimental details. See http://www.rsc.org/suppdata/ob/b4/b406046f/

DOI: 10.1039/b406046f

molecular *N*-arylation of amide, and the other is to construct the pyridone ring by an intramolcular ketone–nitrile annulation. Unfortunately, **5a** did not offer any indole product in an intramolecular *N*-arylation of amide catalyzed by $Pd(OAc)_2$/P(*o*-tolyl)$_3$/$Cs_2CO_3$[9b] or $Pd(OAc)_2$/DPEphos/$Cs_2CO_3$[9d] at 100 °C in toluene for 10 h, while the chalcone **4a** was recovered almost in quantitative yield. A control experiment revealed that this result arose from the retro-Michael addition of **5a** catalyzed by $Cs_2CO_3$.

Although the acid-catalyzed ketone–nitrile annulation of **5a** with $H_3PO_4$–$P_2O_5$[8b–c] or EtOH–$H_2SO_4$[8a,d] did give **6a** as white crystals, the low yields (24–46%) were obtained due largely to the poor solubility of both starting material and product in the solvent used. However, we found that a good yield (80%) of **6a** can be obtained easily by standing the mixture of **5a** in aqueous HCl–HOAc at room temperature for 7 h. Using the same procedure, compounds **5b**–**i** were converted to the corresponding products **6b**–**i** in 67–88% yields (Table 1).

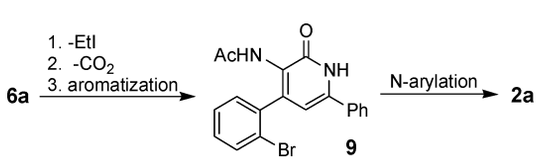
To our disappointment, an intramolecular *N*-arylation of amide **6a** catalyzed by $Pd(OAc)_2$/P(*o*-tolyl)$_3$/$Cs_2CO_3$[9b] failed. Instead of the target product **2a**, it gave ethyl 4-(2-bromophenyl)-2-pyridone-3-carboxylate (**8**) in 85% yield (Scheme 2). Since the same result was also obtained without $Pd(OAc)_2$ and P(*o*-tolyl)$_3$, the formation of **8** must result from a $Cs_2CO_3$ promoted elimination of acetamido group, which has been shown to be a good leaving group under basic conditions.[12]




**Scheme 2** $Cs_2CO_3$ promoted elimination of acetamido group.

Fortunately, when compound **6a** was treated under improved Goldberg reaction conditions (CuI/NaH/DMF at 90 °C for 2h), the desired product **2a** was obtained in 20% yield. By varying the reaction conditions, the best result (68%) was obtained by refluxing the mixture of **6a**/CuI/NaH (1 : 2 : 4 by mole) in DME (ethylene glycol dimethyl ether) followed by work-up with 10% aq. $NH_4OH$. Under similar conditions, **6b**–**i** were converted into the corresponding **2b**–**i** smoothly in moderate yields (60–72%, Table 1).

Since 3-acetamido-4-(2-bromophenyl)-6-phenyl-2-pyridone (**9**) was captured and it can be converted into **2a** with CuI/NaH, therefore, this novel one-step conversion of **6** to **2** actually was a tandem reaction sequenced by the cleavage of the ester, a decarboxylation–aromatization and an *N*-arylation of amide. CuI played a critical role both in the initiation step to cleave the ester and in the end step to promote the intramolecular *N*-arylation of intermediate **9** to give target compound **2** (Scheme 3).




**Scheme 3** CuI initialized tandem reaction.

In summary, a novel preparation of 3-aryl β-carbolin-1-one was developed. Ethyl acetamidocyanoacetate (**3**) was employed as a nucleophilic donor in a Michael addition reaction for efficient introduction of two nitrogen-containing functional groups to the adduct **5**. Then a very mild intramolecular ketone–nitrile annulation of **5** gave the desired pyridone intermediate **6** conveniently. Finally, the indole ring was assembled efficiently by an intramolecular *N*-arylation of amide **6** catalyzed by CuI to yield target compound **2**.


## Acknowledgements

We are grateful to the National Natural Science Foundation of China for financial support.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‡ *Current address*: Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China.



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