Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Copper-Catalyzed Annulation of α-Substituted Diazoacetates with 2-Ethynylanilines: The Direct Synthesis of C2-Functionalized Indoles

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

Copper-catalyzed direct annulation of α-substituted diazoacetates with 2-ethynylanilines leading to C2-functionalized indoles was achieved under mild reaction conditions. The C2-(carboxylate methyl) substituted indoles were obtained in moderate to high yields. In additon, this procedure tolerates a series of *N*-substituted and free substituted 2-ethynylanilines.

The indole nucleus is one of the most common motifs found in bioactive natural products and numerous pharmaceuticals.[1,2] Among the functionalized indoles, the C2-substituted indoles attracted much attention since they are good candidates for various transformations.[3] Moreover, the C2-(carboxylate methyl) substituted indole motifs have been found in many biologically active natural products (Figure 1).[4] And thus many efforts have been made toward simple and selective methods to access this type of indoles. In another part, the utilization of α-diazo compounds as precursor to access the heterocyclics[5] including indole has been reported recently.[6] In 2010, Yu *et al* reported a ruthenium-catalyzed C2-selective carbenoid functionalization of indoles by α-aryldiazoesters (Scheme 1, route **a**).[7] Nearly the same time, Kerr *et al* reported copper-catalyzed malonyl carbenoid insertion toward the synthesis of C2 functionalized indoles (Scheme 1, route **b**).[8] However, those approaches need two steps of synthesis toward the C2-(carboxylate methyl) substituted indole scaffold, namely the pre-synthesis of indole substrates and the following metal-catalyzed C2-functionalization. Clearly, it is of significance to develop a straightforward pathway to access this C2-(carboxylate methyl) functionalized nucleus.

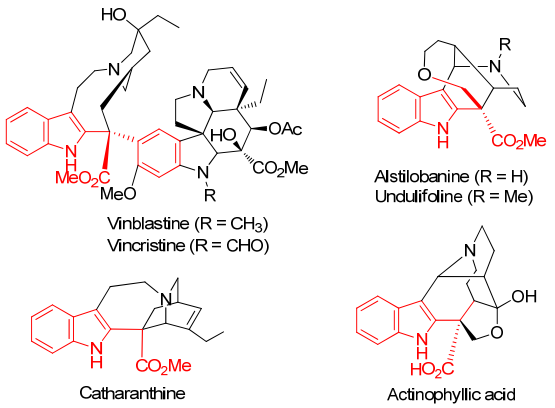
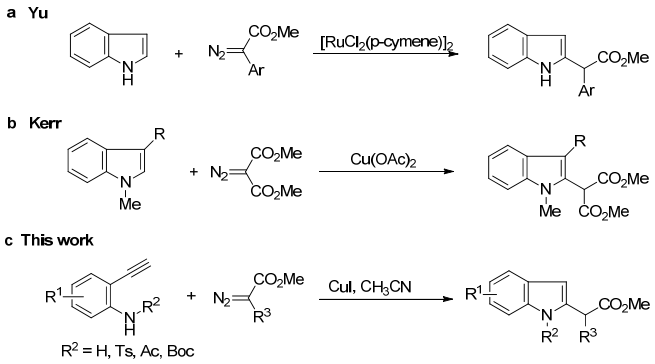


Fig. 1 Natural products containing 2-(carboxylate methyl)-indole moiety

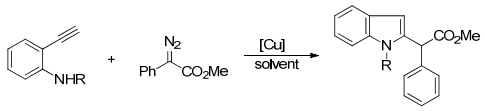
In 2004, Fu *et al* described the CuI-catalyzed coupling reaction of terminal alkynes with diazoacetates, which delivered the alkynoates under mild reaction conditions.[9] Later, Fox *et al* reported the Cu(II) (trifluoroacetylacetonate)2/3,6-di(2-pyridyl)-s-tetrazine-catalyzed method for coupling of diazo compounds with terminal alkynes to give substituted allenoates in the presence of potassium carbonate.[10] Based on the former reports and our own investigations,[11] we imagined that the combination of copper-catalyzed coupling of terminal alkynes with α-aryl-diazo compounds followed by the intramolecular cyclization would probably give the C2-(carboxylate methyl) substituted indoles in one-step. Herein, we report the utilization of this strategy to access this type of compounds under mild reaction conditions.



Scheme 1 Previous pathways and our design plan leading to C2-(carboxylate methyl) substituted indole .

Initially, we tested the reaction of α-phenyl diazoacetate **5a** with amines (Table 1, **1a** to **4a**) in the presence of CuI (5 mol%) in acetonitrile at 60 °C. Treatment of ethynylaniline **1a** with **5a** gave the indole in moderate yield (Table 1, entry 1), while *N*-protected ethynylanilines (**2a** to **4a**) afforded the corresponding indoles in higher yields (Table 1, entries 2-4). CuBr displayed similar catalytic reactivity compared with CuI but with lower yield (Table 1, entry 5). Other copper catalysts gave very lower yields (Table 1, entries 7 to 9). High reaction temperature resulted in low isolated yield (Table 1, entry 10). The reaction was sluggish when had been conducted at room temperature (Table 1, entry 11, 23% yield). Higher catalyst loading (10 mol% CuI) gave slightly high yield and shorter reaction time (Table 1, entry 12). For the solvents examined, DMF and dichloromethane gave the product in much lower yield (Table 1, entries 13 and 14). So we chosen CuI (5 mol%) in acetonitrile at 60 °C as the optimized reaction condition for further investigation.

Table 1 Optimization of reaction conditions[a]



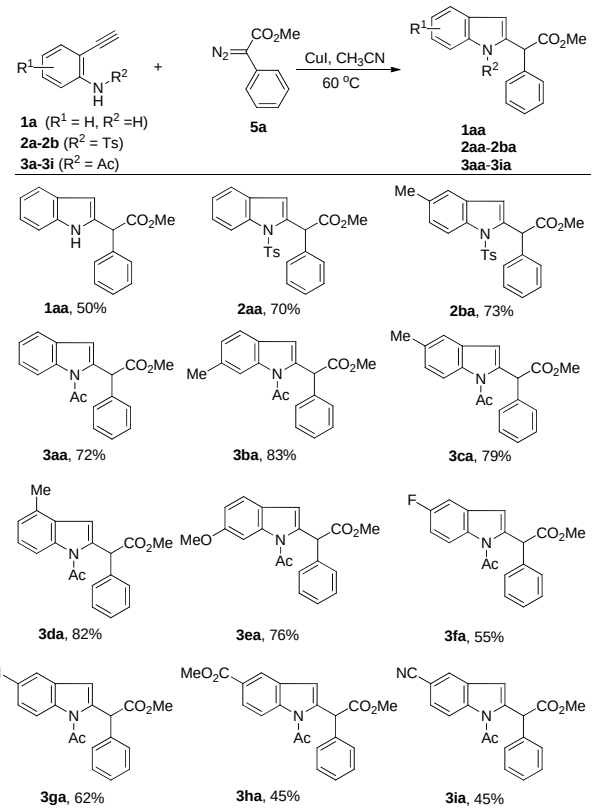
1a-4a **5a** **1aa-4aa**

Entry	[Cu] (mol%)	R (alkyne)	Solvent	Yield (%)[b]
1	CuI (5)	H (**1a**)	CH_3CN	50 (**1aa**)
2	CuI (5)	Ts (**2a**)	CH_3CN	70 (**2aa**)
3	CuI (5)	Ac (**3a**)	CH_3CN	72 (**3aa**)
4	CuI (5)	Boc (**4a**)	CH_3CN	54 (**4aa**)
5	CuBr (5)	Ac (**3a**)	CH_3CN	63 (**3aa**)
6	CuCl (5)	Ac (**3a**)	CH_3CN	62 (**3aa**)
7	$Cu(OAc)_2$	Ac (**3a**)	CH_3CN	<5 (**3aa**)
8	$Cu(OTf)_2$	Ac (**3a**)	CH_3CN	<5 (**3aa**)
9	$Cu(acac)_2$	Ac (**3a**)	CH_3CN	<5 (**3aa**)
10[c]	CuI (5)	Ac (**3a**)	CH_3CN	52 (**3aa**)
11[d]	CuI (5)	Ac (**3a**)	CH_3CN	23 (**3aa**)
12[e]	CuI (10)	Ac (**3a**)	CH_3CN	74 (**3aa**)
13	CuI (5)	Ac (**3a**)	CH_2Cl_2	30 (**3aa**)
14	CuI (5)	Ac (**3a**)	DMF	25 (**3aa**)

[a] Reaction conditions: To a 10 mL Schlenk tube was added ethynylphenylamine (1.0 mmol), copper catalyst (0.05 mmol) and CH_3CN (2 mL) under a nitrogen atmosphere. Then the diazo substrate (1.1 mmol) in CH_3CN (1 mL) was added into the reaction mixture and was stirred at 60 °C for 3 hours. [b] Isolated yield. [c] Reaction temperature is 80 °C. [d] Reaction temperature is 25 °C. [e] Reaction time is 1 hour.

With the optimized reaction conditions in hand, the different substituted ethynylanilines for this cyclization were studied. As expected, both electron-donating and electron-withdrawing substituted ethynylanilines tolerated well under this procedure (Scheme 2). The *N*-Ac-protected ethynylanilines gave higher yields than the *N*-Ts-protected ethynylanilines (Scheme 2, **3ca** vs **2ba**). For the *N*-Ac-protected ethynylanilines, the electron-donating substitutes gave positive effect on the reaction reactivity and the corresponding indoles were obtained in high yields (Schem 2, **3ba** to **3ea**). On the contrary, the electron-withdrawing substitutes gave negtive effect and the indoles were obtained in moderate yields (Scheme 2, **3fa** to **3ia**).

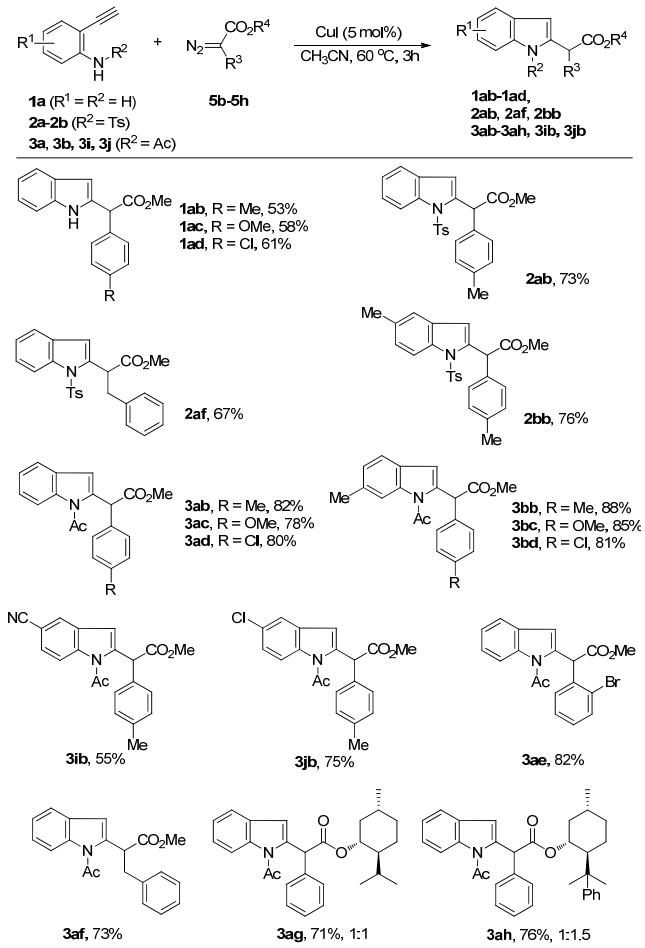
Scheme 2 Substrate scope[a, b, c]



[a] To a 10 mL Schlenk tube was added ethynylphenylamine (1.0 mmol), CuI (0.05 mmol) and CH_3CN (2 mL) under a nitrogen atmosphere. Then **5a** (1.1 mmol) in CH_3CN (1 mL) was added and the whole mixture was stirred at 60 °C for 3 hours. [b] Isolated yield.

Next, the reaction of various amines and diazo compounds was examined under the optimized reaction conditions (Scheme 3). As observed, the free substituted anilines gave the corresponding indoles in lower yields compared with *N*-protected ones (Scheme 3, **1ab**-**1ad** vs others). For the α-aryl diazo substrates, the indoles were obtained in moderate to high yields for all of the cases. Generally, the ethynylanilines bearing strong electron-withdrawing substitutes gave the indoles in lower yields compared with electron-donating or weak electron-withdrawing substituted anilines (Scheme 3, **3ib** to others). In addition, the α-benzyl diazoacetate also gave the indoles in high yields (Scheme 3, **2af** and **3af**). Moreover, the chiral diazoesters also were examined in the reaction. **3ag** was obtained in 71% yield with two isomers in 1:1 ratio and **3ah** was obtained in 76% yield with 1.5:1 ratio.

Scheme 3 Substrate scope[a, b, c]



[a] To a 10 mL Schlenk tube was added ethynylphenylamine (1.0 mmol), CuI (0.05 mmol) and CH_3CN (2 mL) under a nitrogen atmosphere. Then **5** (1.1 mmol) in CH_3CN (1 mL) was added and the whole mixture was stirred at 60 °C for 3 hours. [b] Isolated yield. [c] The d.r. ratio was determined by NMR analysis of crude compounds for **3ag** and **3ah**. The absolute configuration was not assigned.

Although the mechanism remained unclear currently, based on the pioneering work of Fu, Fox and ourseleves, a proposed mechanism was outlined in Figure 2. As mentioned by Fu *et al*, the reaction of alkynes with diazoesters catalyzed by CuI in acetonitrile delivered the alkynoates as the major products (Figure 2, route **a**).[9] Fox *et al* examined the reaction of copper acetylide with phenyl diazoacetate, which did not give any allenoate product (Figure 2, route **b**).[10] So their observation provided support for the mechanism that did not involve initial formation of copper acetylide. Our recent study also disclosed that the presence of base played an important role on the selective formation of alkynoates and allenoates.[11]

For the plausible reaction mechanism, we postulated that the reaction of CuI with α-diazoacetate generates carbenoid **A** (Firgure 2, route **c**). Subsequent reaction with *ortho*-alkyne-aniline affords the formation of intermediate **B**, which undergoes the leaving of copper complex accompanied with hydrogen migration to give the intermediate **C**. Subsequent copper-catalyzed annulation delivers the indole product.

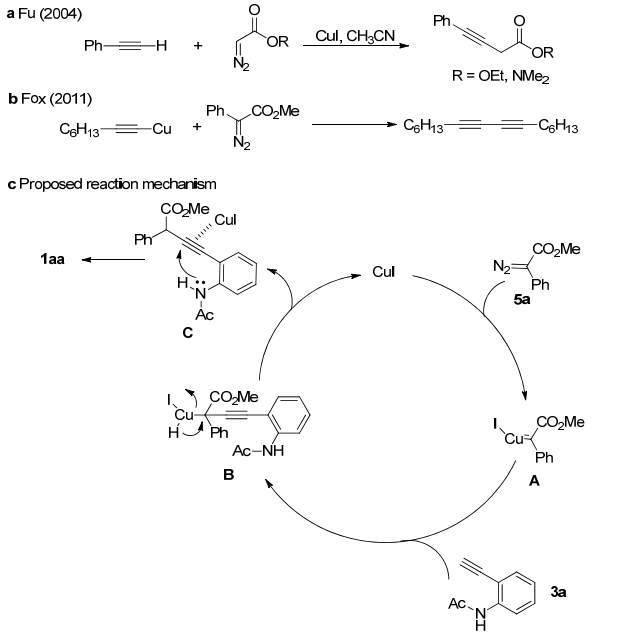


Fig. 2 Proposed reaction mechanism

In conclusion, we have developed a simple and efficient approach to access the C2-(carboxylate methyl) substituted indoles with good functional group tolerance under mild reaction conditions. The indoles were obtained in moderate to high isolated yields. Efforts to expand the strategy to new reactions and to elucidate the mechanism in detail are underway.

We gratefully acknowledge the National Natural Science Foundation of China (21172023), Jiangsu Yabang Pharmaceutical Group and A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD) for their financial support.

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† Electronic Supplementary Information (ESI) available: [details of experiment procedures, NMR and HRMS data for new compounds. See DOI: 10.1039/b000000x/

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