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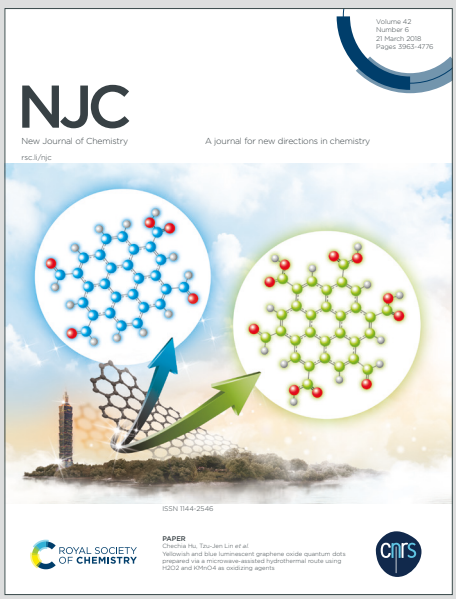


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COMMUNICATION

# Cu-catalyzed Cyclization to Construct Indoles from *N*-(ortho-chloromethyl)aryl Carbamates and Terminal Alkynes in a One-Pot Reaction

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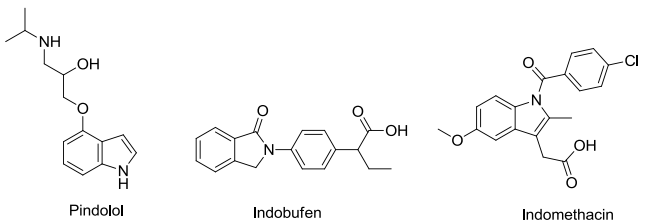
**In this reaction, a new strategy for the synthesis of indoles from *N*-(ortho-chloromethyl)aryl carbamates and terminal alkynes via Cu- catalyzed coupling-cyclization has been developed. The reactions proceeded smoothly under mild conditions with wide functional group tolerance.**

## Introduction

The indole is one of the most common heterocycles found in nature.[1] Many indole-containing compounds possess potent biological activity, which has earned this structural core the description of "privileged" in therapeutic discovery. As important heterocyclic alkaloids, indole and its derivatives have significant physiological activities. For instance, indole-structured drug Pindolol is responsible for the treatment of arrhythmias, angina pain and hypertension. Indobufen is an anticoagulant with significant anticoagulant properties. In addition, Indomethacin is a non-steroidal anti-inflammatory drug for rheumatic diseases and multiple arthritis.[1c,2] (Figure 1) As an advantageous structural motif, the excellent performance of indole compounds in medicine makes it very meaningful to explore new synthetic methods.

**Figure1**: Examples of biologically important molecules containing indole motifs.




Pindolol Indobufen Indomethacin

An impressive number of well-established classical methods are now available for the synthesis of indoles since Fischer indole synthesis.[3] Among all the existing synthetic methods for indoles, those using alkynes as substrates are particularly attractive because of the wide variability in alkyne reactivity, substituent tolerance, chemoselectivity, and ability to react with both nucleophiles and electrophiles. The excellent reactivity between alkynes and nitrogen containing compounds under transition metal-catalyzed cyclization conditions is a useful alternative to the synthesis of indoles. For example, Larock indole synthesis[4] is a method for synthesizing indole (Scheme 1.1) by coupling reaction between o-haloaniline and alkynes under Pd catalysis. Inspired by this work, many transition-metal-catalyzed reactions, including copper, molybdenum, iridium, mercury, gold, platinum, and rhodium have been explored extensively.[5] Because of their economic advantages and potential applications in largescale reactions, copper catalysts have attracted particular attention for this purpose. In the past ten years, people have become more and more enthusiastic about the use of transition metals to catalyse the synthesis of indole from o-aminophenylacetylene.[6] However, expensive transition metals, ligands and tedious experiments were needed. [6l] (Scheme 1.2**)** In the meanwhile，the using of the copper-catalyzed domino Sonogashira coupling/cyclization reaction of *N*-substituted ortho-haloanilines with terminal alkynes for the synthesis of indoles became a new strategy.[7]Our research group has been interested in the development of novel reactions for the synthesis of heterocycles.[8] Herein, we report a more convenient synthetic method for the synthesis of 2-substituted indole.

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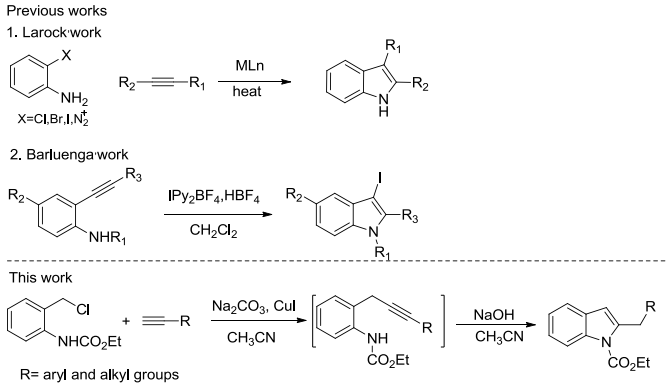
[d] *Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x*

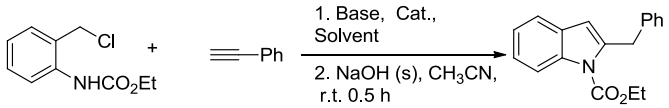
**Scheme 1**. Synthesis of indole




## Results

First, the reaction was investigated using ethyl (2(chloromethyl)phenyl)carbamate **1a** and ethynylbenzene **2a**. Initially, the reaction was carried out at room temperature using $Na_2CO_3$ as the base in acetonitrile (Table 1, entry 1). Gratifyingly, the desired intramolecular cyclization product was isolated in 46% yield. To our delight, when the reaction temperature increases, the reaction time is shortened, and the product yield increased from 46% to 85% (Table 1, entries 1 and 2, respectively). To further improve the chemical yields, several bases were screened (Table 1, entries 3–10). However, the reaction yield has not been significantly improved. Overall, the use of an organic base is less effective than inorganic base for the reaction. Once an efficient base was identified, the effect of the solvent was also investigated. Other commonly used solvents such as DMF, $CH_3CN$, $CH_3OH$, 1,4-dioxane, and toluene failed to further improve the yield (Table 1, entries 11–19, respectively). Finally, we screened the catalysts such as $Ag_2O$, $Pd(AcO)_2$, $CuCO_3$, $Cu(AcO)_2$, $Cu(CF_3SO_3)_2$, $Cu_2O$ (entries 20–25) and found that the reaction was still optimal under CuI conditions. Thus, we established the optimal reaction conditions as shown in entry 2a

**Table 1.** Optimization of reaction conditions




1a 2a 3a

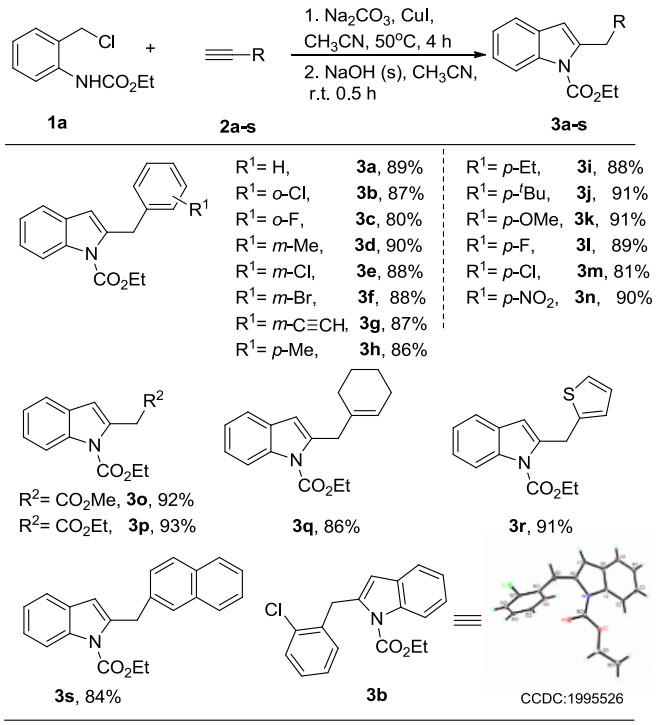
| Entry[a] | Cat. | Solvent | Base | T (℃) | T(h) | Yield ([b]/%) |
|---|---|---|---|---|---|---|
| 1 | CuI | $CH_3CN$ | $Na_2CO_3$ | r.t. | 12 | 46 |
| 2 | CuI | $CH_3CN$ | $Na_2CO_3$ | 50 | 2 | 85 |
| 3 | CuI | $CH_3CN$ | $K_2CO_3$ | 50 | 2 | 35 |
| 4 | CuI | $CH_3CN$ | $Cs_2CO_3$ | 50 | 2 | 30 |
| 5 | CuI | $CH_3CN$ | NaOH | 50 | 2 | 16 |
| 6 | CuI | $CH_3CN$ | $NaHCO_3$ | 50 | 2 | 84 |
| 7 | CuI | $CH_3CN$ | $NEt_3$ | 50 | 2 | < 10 |
| 8 | CuI | $CH_3CN$ | Py. | 50 | 2 | < 10 |
| 9 | CuI | $CH_3CN$ | Piperidine | 50 | 2 | < 10 |
| 10 | CuI | $CH_3CN$ | $CH_3CO_2Na$ | 50 | 2 | 60 |
| 11 | CuI | DMSO | $Na_2CO_3$ | 50 | 2 | trace |
| 12 | CuI | THF | $Na_2CO_3$ | 50 | 2 | 53 |
| 13 | CuI | $CHCl_3$ | $Na_2CO_3$ | 50 | 2 | 13 |
| 14 | CuI | Tol. | $Na_2CO_3$ | 50 | 2 | 32 |
| 15 | CuI | Dioxane | $Na_2CO_3$ | 50 | 2 | 34 |
| 16 | CuI | DMF | $Na_2CO_3$ | 50 | 2 | 60 |
| 17 | CuI | $CH_2Cl_2$ | $Na_2CO_3$ | 50 | 2 | 49 |
| 18 | CuI | EA | $Na_2CO_3$ | 50 | 2 | 56 |
| 19 | CuI | $CH_3OH$ | $Na_2CO_3$ | 50 | 2 | trace |
| 20 | $Ag_2O$ | $CH_3CN$ | $Na_2CO_3$ | 50 | 2 | 46 |
| 21 | $Pd(AcO)_2$ | $CH_3CN$ | $Na_2CO_3$ | 50 | 2 | trace |
| 22 | $CuCO_3$ | $CH_3CN$ | $Na_2CO_3$ | 50 | 2 | 51 |
| 23 | $Cu(AcO)_2$ | $CH_3CN$ | $Na_2CO_3$ | 50 | 2 | 76 |
| 24 | $Cu(CF_3SO_3)_2$ | $CH_3CN$ | $Na_2CO_3$ | 50 | 2 | 50 |
| 25 | $Cu_2O$ | $CH_3CN$ | $Na_2CO_3$ | 50 | 2 | 74 |

[a] Reaction conditions: a mixture of **1a** (1.0 mmol), **2a** (1.2 mmol), base (1.2 mmol) and Cat. (0.5mmol%) in solvent (2.0 mL) was stirred at 50℃ for a certain period of time.

[b] Isolated yield.

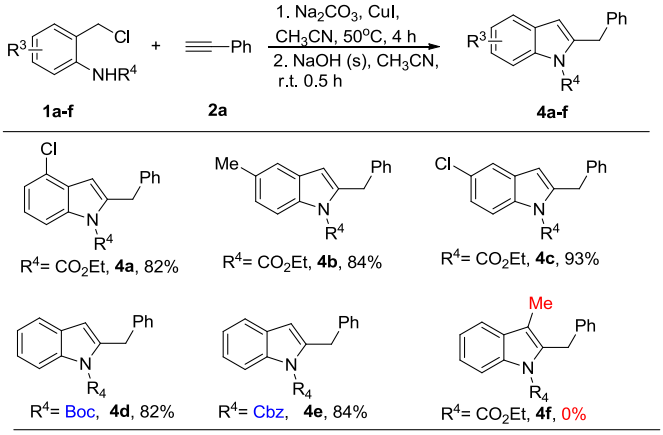
With the optimized reaction conditions, substrates scope was investigated for this transformation (Scheme 2). Various substituted terminal alkynes with electron-withdrawing and electron-donating groups were compatible under the optimized reaction conditions, affording the corresponding products in good yields (80–93%), and the structure of 3b was confirmed by X-ray analysis. When terminal alkynes were alkynyl esters, the reaction yields are higher (**3o**, **3p**), and the indole product can be directly obtained without adding NaOH in the second step. When the substrate was a heterocycloalkyne, the yield was also good (**3r**).

**Scheme 2**. Substrate scope of terminal alkynes.




Next, various benzyl chlorides **1** underwent cyclization, affording **4** in 82–93% yields (Scheme 3, **4a**-**4c**). Both electron-withdrawing groups and electron-donating groups on aminobenzyl chloride were tolerated well and reacted smoothly with ethynylbenzene **2a**. Meanwhile, the yield of the reaction is not affected by using different protecting group as Boc and Cbz for the amino groups (**4d**, **4e**). In addition, substrates with substituents at the benzylic position as Me substituent did not undergo the transformation(**4f**). Although we had made many attempts, the addition product was not obtained. We believe it should be the effect of the chlorine atom which exhibits very low reactivity compared to other groups such as iodine or triflate in the Copper-mediated Sonogashira reaction.

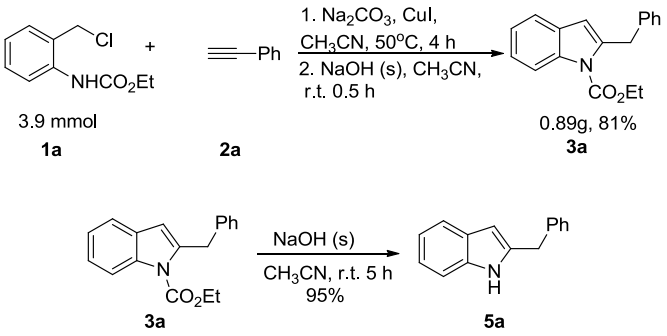
**Scheme 3**. Substrate scope of aminobenzyl chloride




To investigate the practical utility of this methodology, preparation of **3a** was carried out on a gram scale reaction (3.9 mmol of **1a** and 4.68 mmol of **2a**) under the optimized conditions.

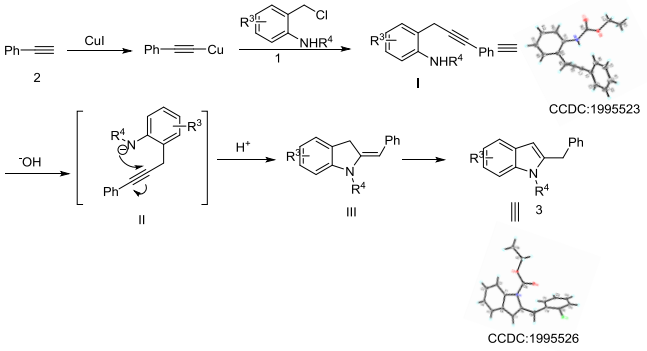
The preparative-scale reaction smoothly proceeded, affording the corresponding products in 81% yield (0.89g of **3a**). In the presence of NaOH, **3a** was successfully converted to **5a** in 95% yield (Scheme 4).

**Scheme 4.** Gram scale experiment and product derivation




On the basis of the experimental results and literature reports[9], a possible reaction mechanism is depicted in scheme 5. First, the Sonogashira cross coupling reaction between terminal alkyne **1** and aminobenzyl chloride **2** under the catalysis of cuprous ion generates compound **I** (CCDC: 1995523), then the intramolecular nucleophilic addition reaction diene intermediate generates intermediate **III** under the basic condition, and then aromatization into compound **3** (CCDC: 1995526).

**Scheme 5.** Proposed mechanism




## Conclusion

In conclusion, an efficient intramolecular cyclization between N-(ortho-chloromethyl)aryl carbamates and terminal alkynes to access indole structures in both good yields and mild conditions have developed. This new method demonstrates potentials for the synthesis of indole derivatives containing natural products and biologically active compounds.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgments

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[10] CCDC 1995523 and 1995526 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.