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# Mild and efficient cyclization reaction of 2-ethynylaniline derivatives to indoles in aqueous medium

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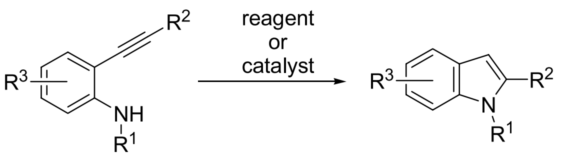
**Abstract**—Results of the optimized cyclization reaction of 2-ethynylaniline derivatives to indoles catalyzed by copper(II) salts are described. The reactions can be carried out in a mixture of $H_2O$ and MeOH in the presence of 1-ethylpiperidine at room temperature. These conditions can be applied to a bulky substrate, which is difficult to be cyclized efficiently by existing reaction conditions. Furthermore, this reaction condition was applied to a catalyst recycling reaction system.

## 1. Introduction

Heterocyclic compounds, particularly indoles, occur widely in nature as partial structures of alkaloids and have unique biological activities.[1] Among the many methods for indole ring synthesis, the ring closing reactions of 2-ethynylaniline derivatives are some of the most efficient because methods for synthesizing a variety of functionalized starting materials have already been established (Scheme 1).[2] Thus far, many kinds of reagents and reaction conditions have been reported for indole syntheses from 2-ethynylaniline derivatives, including basic conditions,[2c,3] early transition metal-catalyzed reactions,[4] gold(III),[5] copper(I),[2b,6,10a] copper(II) salt-catalyzed reactions,[7] and ammonium fluoride-mediated reactions.[8] The most frequently used reagents or catalysts for these ring-closing reactions are the palladium complexes,[2d,3a,5b,9,10,11] and many applications together with polymer-supported reactions[12] have also been established.



**Scheme 1.** Cyclization reaction of 2-ethynylaniline derivatives to indole derivatives.

Recent interest in indole synthesis from 2-ethynylaniline derivatives has focused on versatile applicability, convenient reagents and conditions, and tandem or sequential reactions. For such purposes, iodine-promoted cyclization to yield 3-iodoindoles[13], sequential cyclization-C3 functionalization reactions catalyzed by palladium complexes[5b,11] or gold(III) salt,[14] and carbazoles synthesis[15] were established. We have previously developed both copper(II) salt-catalyzed synthesis of indoles from 2-ethynylaniline derivatives[7a,c] and palladium-complex-catalyzed sequential coupling-cyclization reactions between methyl propiolate and 2-iodoaniline derivatives, with the latter's application to duocarmycin SA synthesis.[10d]

Copper(II) salt-catalyzed reactions can be applied to a variety of 2-ethynylaniline derivatives, including ones with the following features: (1) electron-donating or electron-withdrawing groups on the aromatic ring, (2) an alkyl, aryl, hydroxymethyl, or even methoxycarbonyl group on the acetylene terminal, and (3) sulfonamide, non-substituted aniline derivatives and carbamates (depending on the structure of the substrate). However, problems with efficiency (low solubility of the catalysts in organic media) and high temperature requirements (>70 °C) must be solved for copper(II) salt-catalyzed reactions to be useful. Herein, we describe solutions to these problems and improved procedures for copper(II) salt-catalyzed cyclization reactions of 2-ethynylaniline derivatives.

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*Keywords*: Indole; Copper(II) salt; 2-Ethynylaniline; Cyclization reaction.

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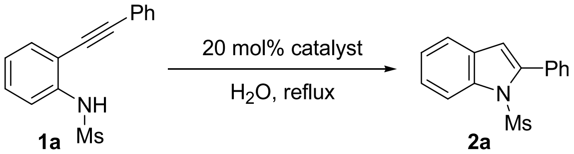
## 2. Results and discussion

### 2.1. Improvement of the reaction conditions

Copper(II) salt-catalyzed indole formation reactions appear as suspensions due to low solubility of the salts in organic solvents such as 1,2-dichloroethane. We have previously described how the ionic character of the copper–oxygen bond in copper(II) sulfonate is required for effective catalyst of the cyclization, which makes suspension in an organic solvent unavoidable.[7a] However, the bulky counter-anion in copper(II) carbonate (e.g., stearic acid) does not improve solubility or catalytic activity.[16] Therefore, we changed the solvent to $H_2O$. The results are summarized in Table 1. It was known that sulfonamides possess the highest reactivity among 2-ethynylaniline derivatives, so the mesylamide **1a** was selected as the substrate for establishing the new reaction conditions. Most of the copper(II) salts tested dissolved into $H_2O$ except for $Cu(OBz)_2$, but the reaction medium was again a suspension because of the low solubility of **1a** in $H_2O$. The copper(II) salts that catalyze the reactions in organic solvent [$Cu(OAc)_2$, $Cu(OTf)_2$, $Cu(OBz)_2$, and $Cu(OCHO)_2 \cdot xH_2O$] did not provide satisfactory results (Table 1, entries 1–4). Surprisingly, only $Cu(OCOCF_3)_2 \cdot xH_2O$ catalyzed the reaction, even though it forms a suspension in the reaction mixture (Table 1, entry 5). Why only this copper(II) salt works is not yet clear. However, it is apparent that $CF_3COOH$ is not a catalyst for this reaction (Table 1, entry 6). We selected $Cu(OCOCF_3)_2 \cdot xH_2O$ as the catalyst for further improvement of the reaction conditions.

**Table 1**. Copper(II) salt-catalyzed cyclization reactions of **1a** in $H_2O$

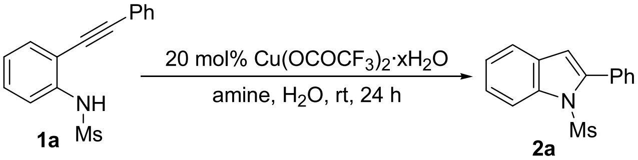


| Entry | Catalyst | Time (h) | Yield of **2a** (%) |
|---|---|---|---|
| 1 | $Cu(OAc)_2$ | 23 | Trace |
| 2 | $Cu(OTf)_2$ | 24 | 7 (76)[a] |
| 3 | $Cu(OBz)_2$ | 24 | 18 (66)[a] |
| 4 | $Cu(OCHO)_2 \cdot xH_2O$ | 24 | 22 (75)[a] |
| 5 | $Cu(OCOCF_3)_2 \cdot xH_2O$ | 24 | 96 |
| 6 | $CF_3COOH$ | 23 | No reaction |

[a] The numbers in parentheses are the yields of recovered **1a**.

High temperature is essential for the cyclization reactions of 2-ehtynylaniline derivatives catalyzed by copper(II) salts and the substrates can be recovered perfectly at room temperature. However, we have previously reported that the rate of copper(II) salt-catalyzed cyclization reactions is accelerated in the presence of 1-ethylpiperidine and realized the reaction at room temperature (room temperature for 72 h with 2.0 equiv of 1-ethylpiperidine, 76% yield).[7a] We now apply the $Cu(OCOCF_3)_2 \cdot xH_2O$-catalyzed cyclization reaction of **1a** with various amines in $H_2O$. The results are summarized in Table 2.

**Table 2**. $Cu(OCOCF_3)_2 \cdot xH_2O$-catalyzed cyclization reaction of **1a** in the presence of various amines



| Entry | Amine (2.0 equiv) | Yield of **2a** (%) |
|---|---|---|
| 1 | 1-Ethylpiperidine | 14 (85)[a] |
| 2 | Triethylamine | 10 (88)[a] |
| 3 | *N*,*N*-diisopropylethylamine | 17 (83)[a] |
| 4 | *N*,*N*-dimethylaniline | No reaction |
| 5 | Pyridine | No reaction |

[a] The numbers in parentheses are the yields of recovered **1a**.

The rate acceleration effect of the amine in $H_2O$ was less than in 1,2-dichloroethane. The addition of a tertiary aliphatic amine slightly accelerated the reaction, but the yield of **2a** was less than the amount of added catalyst and more than 80% of **1a** was recovered (Table 2, entries 1–3). Addition of a tertiary aromatic amine or pyridine did not accelerate the reaction (Table 2, entries 4 and 5). The addition of secondary amines (piperidine or *N*,*N*-diisopropylamine) or primary amines (butylamine, aniline, or ethylenediamine) also did not promote the reaction, and the starting material **1a** was completely recovered (data not shown). Since the reactions in $H_2O$ appear as a suspension, we speculated that the reason for the reactivity difference between $H_2O$ and 1,2-dichloroethane might be the low solubility of **1a** in $H_2O$. Therefore, we attempted the reaction in a mixed solvent system, with and without 1-ethylpiperidine (Table 3).

We wanted to dissolve both the catalyst and the substrate, so we chose an alcohol as the second solvent. Surprisingly, we discovered that the efficiency of the reaction is closely related to the carbon number of employed alcohol: as the carbon number of the alcohol solvent increased, the yield decreased (Table 3, entries 1–3). It is apparent from the above results that the reactivity is controlled by the balance of the solubility of the catalyst and the substrate. However, even with the second alcohol solvent, the reaction did not proceed at room temperature (Table 3, entry 4). The effect of 1-ethylpiperidine was remarkable, and the amount of catalyst could be reduced from 20 to 5 mol% (Table 3, entries 6 and 7). Note that less expensive $Cu(OAc)_2$, which did not show catalytic activities in $H_2O$ alone (Table 1, entry 1), can be used as the catalyst under optimized reaction conditions (Table 3, entry 8). While the reaction could be promoted with 1-ethylpiperidine in the absence of a copper(II) salt, the low yield can be disregarded (Table 3, entry 5).

### 2.2. Application to various kinds of substrates

Having established the cyclization reaction in aqueous solvent at room temperature, we applied it to other substrates. To avoid too long reaction time, we used same reaction condition shown in Table 3 entry 6 [20 mol% of $Cu(OCOCF_3)_2 \cdot H_2O$] and the results are summarized in Table 4.

For the substituents at the alkyne terminal, this condition