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Tetrahedron Letters 45 (2004) 35–38

Tetrahedron Letters

# Copper-catalyzed tandem reaction between imines and alcohols leading to indoles

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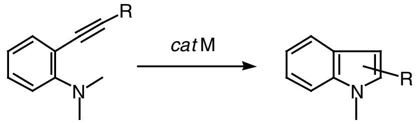
Received 11 September 2003; revised 11 October 2003; accepted 23 October 2003

**Abstract**—A copper-catalyzed tandem reaction between 2-alkynyl-*N*-arylideneanilines and alcohols is found to produce *N*-(alkoxybenzyl)indoles in good to high yields. A wide variety of substituted *N*-(alkoxybenzyl)indole derivatives can be synthesized by utilizing this protocol, since the derived indoles are essentially formed by the four-component assemblies of aldehydes, 2-iodoanilines, terminal alkynes, and alcohols.

Indoles are important chemicals, which exhibit a wide spectrum of biological activities.[1] It is well known that many naturally occurring compounds contain the indole skeleton as a backbone of their structural frameworks. Because of their many applications in pharmaceutical fields, investigations on indole derivatives from aspects both of their reactivity and the development of efficient preparative methods have continuously attracted many chemists. Among various strategies, catalytic transformations by means of transition metal catalysts is one of the modern approaches for the formation of indoles.[1,2] Most of the previously known procedures utilize *ortho*-alkynylaniline derivatives as a starting substrate, and direct or indirect cyclization catalyzed by transition metals gives indoles (Eq. 1).[3–6] We reported that in the presence of certain nucleophiles, Nu, tandem cyclization takes place smoothly to give the nucleophile incorporated indoles in good to high yields (Eq. 2).[7–9] For instance, 3-allyl-*N*-cyanoindoles are prepared by the three-component coupling reaction of 2-(alkynyl)phenylisocyanides, allyl methyl carbonate, and trimethylsilyl azide through the palladium mimic of the Curtius rearrangement (Eq. 3),[7] 3-allyl-*N*-(alkoxycarbonyl)indoles are formed by the Pd–Cu bimetallic catalyzed reaction between 2-(alkynyl)phenylisocyanates and allyl carbonate (Eq. 4),[8] and *N*-(alkoxycarbonyl)indoles are similarly synthesized by the reaction between 2-(alkynyl)phenylisocyanates and alcohols under dual role catalyst (Eq. 5).[9] The characteristic feature of these transformations using *ortho*-functionalized alkynylbenzenes as a substrate is that new bond formation takes place between C≡C and C=N unsaturated bonds by initiation by the addition of external nucleophilic reagents. In other words, these processes are a tandem reaction in which more than three bonds are formed concomitantly. We now report a novel tandem reaction between imines **1** and alcohols **2** in the presence of a catalytic amount of CuCl that affords imines **3** in good to high yields (Eq. 6).



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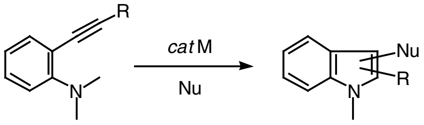

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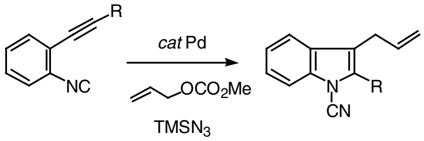

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*Keywords*: indole; copper catalyst; imine; alkyne; alcohol.

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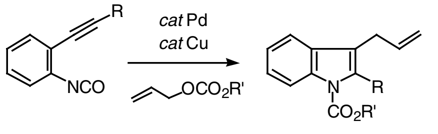
doi:10.1016/j.tetlet.2003.10.141



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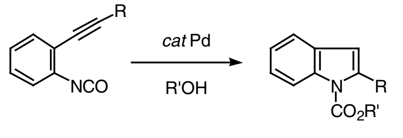

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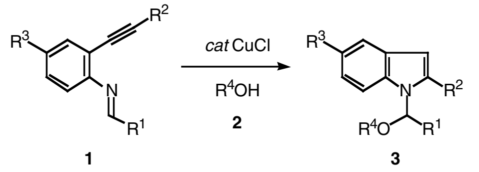

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We first examined the reaction of 2-(1-pentynyl)-*N*-(*p*-methylbenzylidene)aniline **1a**[10] and methanol **2a** with various metal salts to check their catalytic activity for the formation of *N*-(1-methoxy-(*p*-tolyl)methyl)-2-propylindole **3a**. Intensive screening revealed that late transition metals such as Pd, Cu, Ir, and Ru promoted the tandem reaction to give the desired indole **3a**.[11] Among them, Cu catalysts were the most convenient to use and maintained their activity under various conditions. CuCl gave the best results, whereas CuBr was less effective. Other copper salts, such as CuI, $CuCl(PPh_3)_3$, CuOAc, and $CuCl_2$, did not catalyze the reaction and the starting material **1a** was recovered. As for the solvents, toluene afforded **3a** in the highest yield. The use of methanol as a solvent did not improve the yield of **3a**. We carried out the indole forming reaction using a variety of imines **1** and MeOH **2a** under the optimized conditions. The results are summarized in Table 1.

When imine **1a** was treated with **2a** in the presence of 5 mol % CuCl, the corresponding indole **3a** was obtained in 70% yield (entry 1).[12] The regioisomers **1b** and **1c** also afforded the desired products **3b** and **3c** in 73% and 53% yields, respectively (entries 2 and 3). With increase of steric congestion around the imine moiety, prolonged reaction times were required. In the case of **1c**, bearing a methyl group at the *ortho* position, a decrease in the yield was observed. Imines having an electron-donating methoxy group **1d** and a methylthio group **1e** at the *para* position in the $R^1$ group produced the corresponding indoles **3d** and **3e** in good yields within 2.5 h (entries 4 and 5). The reaction of **1f** proceeded smoothly to give **3f** in 69% yield (entry 6). The introduction of halogens, such as Br **1g** and Cl **1h**, did not exert a significant influence on the reaction progress and the desired indoles **3g** and **3h** were formed in good yields, respectively (entries 7 and 8). The substrate **1i** containing a nitro group gave **3i** in good yield, although a long time was needed to complete the reaction (entry 9). It seemed that introduction of a strong electron-withdrawing group retards the reaction progress. The imine **1j** derived from cinnamaldehyde gave the expected indole **3j** in 58% yield, whereas the imine **1k** prepared from pivalaldehyde produced only a trace amount of the corresponding product **3k** after 24 h, probably due to steric reasons (entries 10 and 11). We next changed the $R^2$ group at the end of the alkyne moiety. The reaction of imine **1l** attached to a cyclohexyl group gave the indole **3l** in 77% yield (entry 12). On the contrary, the imine **1m** bearing a bulky *t*-Bu group did not produce the desired indole **3m** even after 24 h and a significant amount of the starting material **1m** was recovered (entry 13). It was observed that an increase in the steric congestion around the alkyne moiety hampers the reaction progress. The imine

**Table 1.** Copper-catalyzed synthesis of indoles **3** from various imines **1** and methanol **2a**[a]

| Entry | $R^1$ | $R^2$ | $R^3$ | **1** | Time (h) | **3** | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | $p$-Me–$C_6H_4$ | Pr | H | **1a** | 2.5 | **3a** | 70 |
| 2 | $m$-Me–$C_6H_4$ | Pr | H | **1b** | 4 | **3b** | 73 |
| 3 | $o$-Me–$C_6H_4$ | Pr | H | **1c** | 10.5 | **3c** | 53 |
| 4 | $p$-MeO–$C_6H_4$ | Pr | H | **1d** | 2.5 | **3d** | 64 |
| 5 | $p$-MeS–$C_6H_4$ | Pr | H | **1e** | 2.5 | **3e** | 72 |
| 6 | Ph | Pr | H | **1f** | 3 | **3f** | 69 |
| 7 | $p$-Br–$C_6H_4$ | Pr | H | **1g** | 4 | **3g** | 58 |
| 8 | $p$-Cl–$C_6H_4$ | Pr | H | **1h** | 6 | **3h** | 67 |
| 9 | $p$-$O_2N$–$C_6H_4$ | Pr | H | **1i** | 66 | **3i** | 74 |
| 10 | *trans*-CH=CH–Ph | Pr | H | **1j** | 3.5 | **3j** | 58 |
| 11 | *t*-Bu | Pr | H | **1k** | 24 | **3k** | Trace[c] |
| 12 | $p$-Me–$C_6H_4$ | Cyclohexyl | H | **1l** | 6 | **3l** | 77 |
| 13 | $p$-Me–$C_6H_4$ | *t*-Bu | H | **1m** | 24 | **3m** | No reaction[d] |
| 14 | $p$-Me–$C_6H_4$ | H | H | **1n** | 1.5 | **3n** | 42 |
| 15 | $p$-Me–$C_6H_4$ | Ph | H | **1o** | 12 | **3o** | 83 |
| 16 | $p$-Me–$C_6H_4$ | $p$-MeO–$C_6H_4$ | H | **1p** | 3.5 | **3p** | 67 |
| 17 | $p$-Me–$C_6H_4$ | $p$-MeOCO–$C_6H_4$ | H | **1q** | 25 | **3q** | 33 |
| 18 | $p$-Me–$C_6H_4$ | $Me_3SiC{\equiv}C$ | H | **1r** | 4 | **3r** | 58 |
| 19 | $p$-Me–$C_6H_4$ | Ph | MeO | **1s** | 3 | **3s** | 73 |
| 20 | $p$-Me–$C_6H_4$ | Ph | CN | **1t** | 12.5 | **3t** | 73 |

[a] The reaction of imines **1** and MeOH **2a** (2 equiv) was conducted in toluene (0.5 M) in the presence of a catalytic amount of CuCl (5 mol %) at 100 °C for the time shown in Table 1.

[b] Isolated yield.

[c] Significant amounts of the starting material **1k** were recovered.

[d] Significant amounts of the starting material **1m** were recovered.

**1n** having a terminal alkyne moiety produced a moderate yield of the corresponding indole **3n** (entry 14). The imines **1o–q** attached to aromatic substituents afforded the corresponding products **3o–q** in good to allowable yields, respectively (entries 15–17). The installation of an electron-donating group seemed to facilitate the formation of indoles. The imine **1r** containing a diyne moiety furnished the expected indole **3r** in 58% yield (entry 18). We examined further the effect of the substituent $R^3$ on the aniline ring. Both imines having a methoxy group **1s** and a cyano group **1t** afforded the corresponding indoles **3s** and **3t** in good yields (entries 19 and 20).

We next conducted the reaction of imine **1a** with various alcohols **2** in the presence of the copper catalyst and the results are summarized in Table 2. The reaction using *n*-PrOH **2b** afforded the corresponding indole **3u** in 64% yield (entry 1). The reaction of *i*-PrOH **2c** gave the corresponding product **3v**, whereas a complex mixture of unidentified products was obtained in the case of *t*-BuOH **2d** (entries 2 and 3). The sterically demanding alcohol did not afford indoles smoothly. Even acidic alcohols **2e–g** were applicable to the present indole forming reaction. For example, the reactions using phenols **2e** and **2f** were complete in shorter times and the corresponding products **3x** and **3y** were obtained in high yields, respectively (entries 4 and 5). 2,2,2-Trifluoroethanol **2g** also gave the expected indole **3z** in a high yield (entry 6). Allyl alcohol **2h** and benzyl alcohol **2i** also furnished the desired indoles **3A** and **3B** in high yields (entries 7 and 8). 2-(Trimethylsilyl)ethanol **2j** afforded the expected indoles **3C** in a good yield (entry 9).

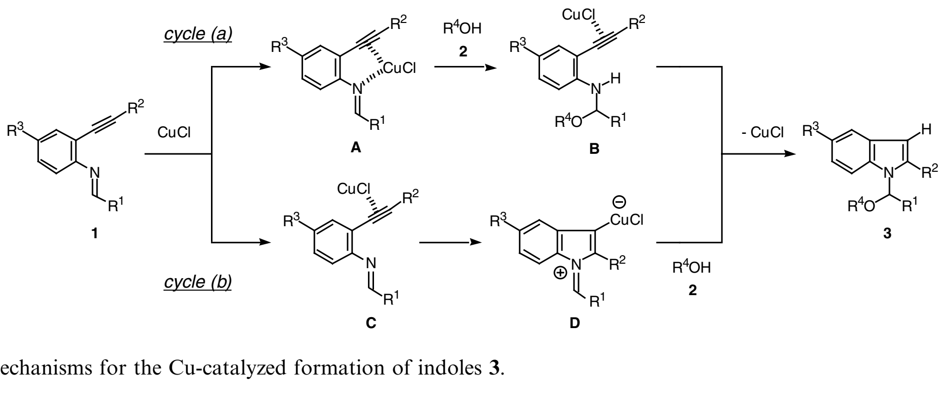
Possible reaction mechanisms are illustrated in Scheme 1. Two reaction pathways can be conceived for the present copper-catalyzed indole forming reaction. In cycle (a), the reaction starts with formation of the intermediate **A**, in which the CuCl behaves as a Lewis acid–transition metal dual role catalyst and coordinates to both the lone pair on nitrogen atom of the imine (σ-electrons) and the C≡C triple bond of the alkyne (π-electrons) in the starting material **1**.[9,13] The Lewis adicity of CuCl enhances the electrophilicity of the imine and facilitates the addition of the alcohol **2** to form the aniline derivative **B**. Then, CuCl activates the C≡C triple bond as a transition metal catalyst and promotes the intramolecular *trans*-hydroamination of the alkyne to furnish the indole **3** as the final product.[4] Alternatively, in cycle (b), the reaction begins with formation of the intermediate **C**, in which the CuCl acts as a transition metal catalyst and coordinates to the C≡C triple bond of the alkyne (π-electrons) in substrate **1**.[4] The copper salt decreases the electron density of the alkyne and promotes the intramolecular addition of the nitrogen atom of the imine to generate the cyclized zwitterion intermediate **D**.[14] It should be noted that the imine moiety can be activated by the Lewis acidic alkyne coordinated by CuCl (copper–alkyne π-complex). Addition of the alcohol **2** to the iminium cation part and protonation of the C–Cu bond of **D** afford the final product **3** with regeneration of the copper catalyst. At present, no conclusive evidence is

**Table 2.** Copper-catalyzed synthesis of indoles **3** from **1a** and various alcohols **2**[a]

| Entry | $R^4OH$ | **2** | Time (h) | **3** | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | *n*-PrOH | **2b** | 2.5 | **3u** | 64 |
| 2 | *i*-PrOH | **2c** | 4 | **3v** | 55 |
| 3 | *t*-BuOH | **2d** | 5 | **3w** | Mixture |
| 4 | PhOH | **2e** | 1.5 | **3x** | 77 |
| 5 | *p*-MeO–$C_6H_4$–OH | **2f** | 1 | **3y** | 80 |
| 6 | $CF_3CH_2OH$ | **2g** | 1.5 | **3z** | 80 |
| 7 | $CH_2{=}CHCH_2OH$ | **2h** | 5 | **3A** | 83 |
| 8 | $PhCH_2OH$ | **2i** | 2.5 | **3B** | 77 |
| 9 | $Me_3Si(CH_2)_2OH$ | **2j** | 2 | **3C** | 63 |

[a] The reaction of the imine **1a** ($R^1 = p$-Me–$C_6H_4$, $R^2 = $Pr, $R^3 = $H) and $R^4OH$ **2** (2 equiv) was conducted in toluene (0.5 M) in the presence of a catalytic amount of CuCl (5 mol%) at 100 °C for the time shown in Table 2.

[b] Isolated yield.



**Scheme 1.** Possible mechanisms for the Cu-catalyzed formation of indoles **3**.

available to which pathway is operative. According to the observations that the reactions are completed in shorter times when electron-donating groups are introduced at either the $R^1$ or $R^3$ positions of the starting imines **1**, and that even acidic alcohols such as phenols **2e**, **2f**, and trifluoroethanol **2g** afford the corresponding indoles **3x**, **3y**, and **3z**, it might be that cycle (b) is the favorable pathway. However, more detailed investigations are needed to clarify the mechanism for the present indole forming reaction.

In conclusion, we have achieved the synthesis of *N*-(alkoxybenzyl)indoles **3** via the copper-catalyzed tandem reaction between 2-alkynyl-*N*-arylideneanilines **1** and alcohols **2**. A wide variety of *N*-(alkoxybenzyl)indole derivatives can be synthesized by utilizing this protocol, since the derived indoles are essentially formed by the four-component assemblies of aldehydes, 2-iodoanilines, terminal alkynes, and alcohols. Studies of the reaction mechanism and synthetic applications are now in progress.

## Acknowledgements

This work was supported by a Grant-in-Aid for Encouragement of Young Scientists (B) from the Japan Society for the Promotion of Science. We thank members in the Instrumental Analysis Center for Chemistry at Tohoku University for measurements of mass spectra and elemental analyses.

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10. The starting imines **1** were prepared in two steps. The Sonogashira coupling reaction between 2-iodoanilines and terminal alkynes under a catalytic amount of $Pd(PPh_3)_4$ and CuI in $Et_2NH$ furnished 2-(1-alkynyl)anilines in high yields. Dehydration between the 2-(1-alkynyl)anilines and aldehydes in the presence of MS 4 Å afforded the 2-(1-alkynyl)-*N*-arylideneanilines **1**.
11. The transition metal catalysts, such as $[(\eta^3\text{-}C_3H_5)PdCl]_2$, CuCl, CuBr, $[IrCl(cod)]_2$, and $[RuCl(cod)]_2$, showed a catalytic activity.
12. Typical procedure for the copper-catalyzed indole forming reaction. To a toluene solution (1 mL) of 2-(1-pentynyl)-*N*-(*p*-methylbenzylidene)aniline **1a** (130.7 mg, 0.5 mmol) and CuCl (2.5 mg, 0.025 mmol) was added MeOH **2a** (41 μL. 1 mmol) and the mixture was stirred at 100 °C for 2.5 h. After consumption of **1a**, the reaction mixture was filtered through a Florisil pad and the eluent was concentrated. Purification with silica gel chromatography (*n*-hexane/ether) gave *N*-(1-methoxy-(*p*-tolyl)methyl)-2-propylindole **3a** in 70% yield (102.3 mg).
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