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# Assembly of 3-Acyloxindoles via CuI/L-Proline-Catalyzed Intramolecular Arylation of β-Keto Amides

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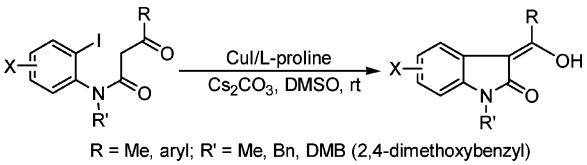
## ABSTRACT




R = Me, aryl; R' = Me, Bn, DMB (2,4-dimethoxybenzyl)

**Intramolecular coupling of β-keto 2-iodoanilides catalyzed by CuI/L-proline in DMSO occurs at room temperature, affording substituted 3-acyloxindoles in good yield. Electronic effects on the aromatic ring have little influence on this reaction. Variations at the 1, 3, 4, 5, and 6 positions of the oxindoles were achieved by employing the corresponding amides.**

3-Acyloxindoles constitute a common structural motif in a considerable number of pharmaceutically interesting compounds. Representative molecules include GSK3 kinase inhibitor **1**[1] (Figure 1), influenza endonuclease inhibitor **2**,[2] as well as Tendiap **3**, a potent inhibitor of cyclooxygenase (CO) with excellent activity in rheumatoid arthritis and osteoarthritis clinical trials.[3] Apart from their biological importance, 3-acyloxindoles have been reported as intermediates for assembling heterocyclic compounds.[4] The current approach toward 3-acyloxindoles mainly relies on acylation

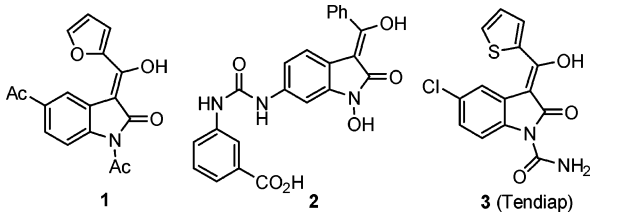



**Figure 1.** Biologically active 3-acyloxindoles.

of the oxindoles with acyl chlorides and condensation of the oxindoles with esters.[4b,5] One of the drawbacks of these methods is that preparation of some oxindoles was so tedious due to poor regioselectivity.[6] Another notable method is rhodium-catalyzed carbenoid insertion into aromatic C−H

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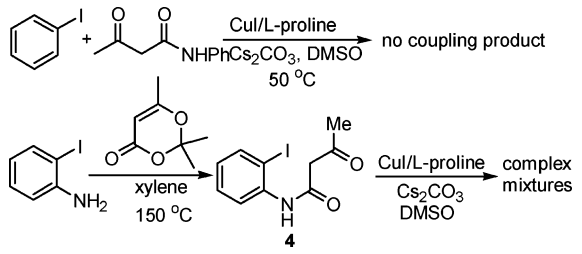
bonds,[7] which is obviously limited to small-scale synthesis because of the expensive catalytic system. Thus, a general and practical method to prepare 3-acyloxindole is still required.

Recently, we[8] and others[9−12] have reported that CuI-catalyzed coupling of activated methylene compounds with aryl halides can be conducted under relatively mild conditions by using some additives such as L-proline, 2-phenylphenol, chelating Schiff bases, and *N*,*N*′-dimethylethylenediamine. Further exploration of the scope and limits of this reaction revealed that *β*-keto amides were poor substrates under our standard conditions, as the starting materials were recovered (Scheme 1). Although the reason for this poor reactivity was

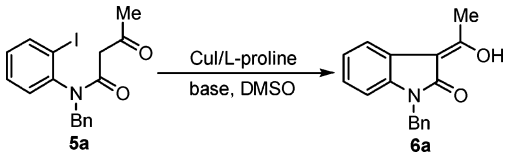
**Scheme 1**




not clear, we still envisioned that an intramolecular coupling reaction of *β*-keto 2-iodoanilides could take place, thereby giving 3-acyloxindoles directly. With this idea in mind, we prepared amide **4** by heating a mixture of 2-iodoaniline with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one.[13] However, the reaction of **4** catalyzed by CuI/L-proline gave a complex mixture under several conditions (temperatures, rt to 50 °C; solvent, DMSO; base, $Cs_2CO_3$, $K_3PO_4$, $K_2CO_3$).

Although the side products in the above reaction were not carefully analyzed, a possible side reaction was considered to be the formation of benzoxazoles because a similar transformation had been mentioned by several groups.[14] To prevent this side reaction, we decided to employ N-substituted amides as substrates. Accordingly, *N*-benzylamide **5a** was elaborated following the same procedure used for the preparation of **4**. We were pleased to find that the reaction of **5a**, catalyzed by CuI/L-proline at 40 °C, provided the desired 3-acyloxindole **6a** in 43% yield (entry 1, Table 1).

**Table 1.** CuI/L-Proline-Catalyzed Intramolecular Coupling of Amide **5a**[a]




| entry | base | *T* (°C) | yield[b] (%) |
|---|---|---|---|
| 1 | $Cs_2CO_3$ | 40 | 43 |
| 2 | $Cs_2CO_3$ | 25 | 75 |
| 3 | $Cs_2CO_3$ | 0 | 0 |
| 4 | $K_2CO_3$ | 25 | 30 |
| 5 | $K_3PO_4$ | 25 | 51 |
| 6 | $Cs_2CO_3$ | 25 | 0[c] |

[a] Reaction conditions: amide **5a** (0.5 mmol), CuI (0.05 mmol), L-proline (0.1 mmol), $Cs_2CO_3$ (2 mmol), DMSO (5 mL), 24 h. [b] Isolated yield. [c] L-Proline was not added.

Since a relatively quick conversion was observed, we next attempted to improve the yield by reducing the reaction temperature. As we expected, a satisfactory yield was obtained at room temperature (entry 2), although no conversion was determined at 0 °C (entry 3). Changing the base to $K_2CO_3$ and $K_3PO_4$ resulted in decreased yields (entries 4 and 5). Furthermore, no coupling reaction occurred in the absence of L-proline (entry 6), indicating that the ligand effect is essential for this coupling reaction. It is noteworthy that when a bromide analogue of **5a** was employed under these conditions, none of the desired **6a** was detected. Therefore, iodides were used exclusively in the subsequent scope studies.

With optimized conditions in hand, the scope of this catalytic reaction was explored with various amides. The results are summarized in Table 2. *N*-Methyl- and DMB (2,4-dimethoxybenzyl)-substituted amides also gave good yields (entries 1 and 2), indicating that variations at the 1-position of 3-acyloxindoles are possible. Electronic effects on the aromatic ring have little influence on this reaction as complete conversion was observed in amides with both electron-withdrawing groups and electron-donating groups (compare entries 3−5 with entries 6−8). By using suitable starting materials, 4-, 5-, or 6-substituted 3-acyl oxindoles were elaborated (entries 3−8).


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**Table 2.** CuI/L-Proline-Catalyzed Intramolecular Coupling Reaction of $\beta$-Keto 2-Iodoanilides[a]

| entry | substrate | product | yield (%)[b] | entry | substrate | product | yield (%)[b] |
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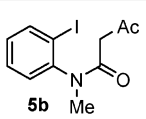
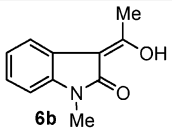
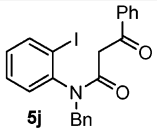
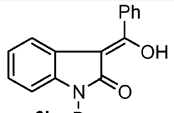
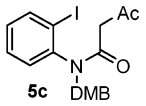
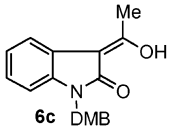
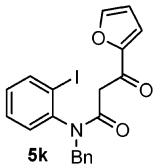
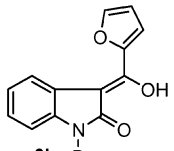
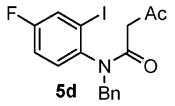
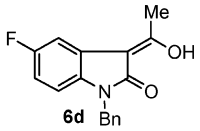
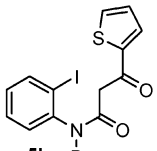
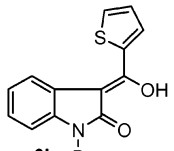
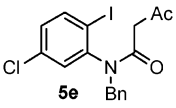
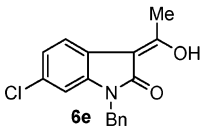
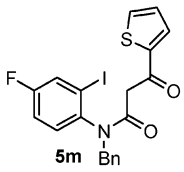
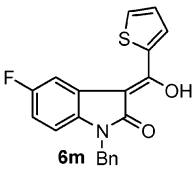
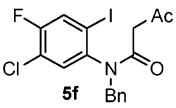
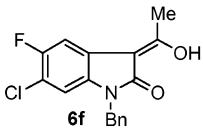
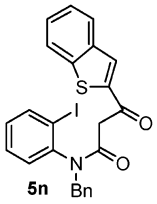
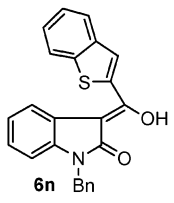
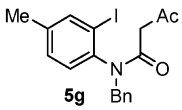
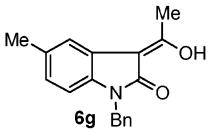
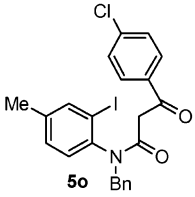
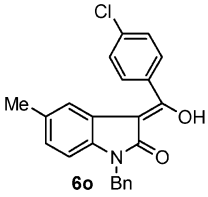
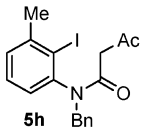
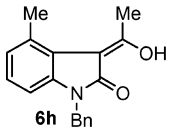
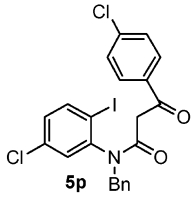
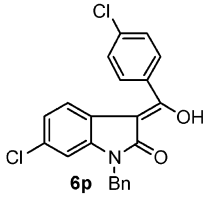
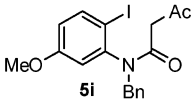
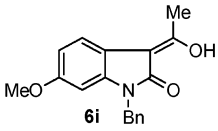
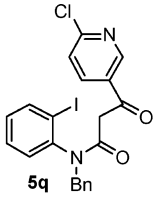
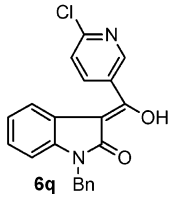
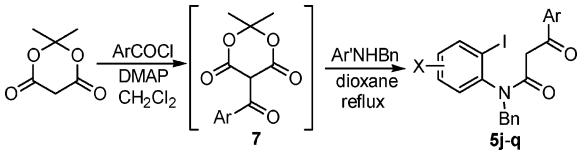
| 1 |  **5b** |  **6b** | 72 | 9 |  **5j** |  **6j** | 67 |
| 2 |  **5c** |  **6c** | 69 | 10 |  **5k** |  **6k** | 78 |
| 3 |  **5d** |  **6d** | 77 | 11 |  **5l** |  **6l** | 76 |
| 4 |  **5e** |  **6e** | 70 | 12 |  **5m** |  **6m** | 73 |
| 5 |  **5f** |  **6f** | 83 | 13 |  **5n** |  **6n** | 76 |
| 6 |  **5g** |  **6g** | 73 | 14 |  **5o** |  **6o** | 71 |
| 7 |  **5h** |  **6h** | 77 | 15 |  **5p** |  **6p** | 66 |
| 8 |  **5i** |  **6i** | 78 | 16 |  **5q** |  **6q** | 70 |

[a] Reaction conditions: amide **5** (0.5 mmol), CuI (0.05 mmol), L-proline (0.1 mmol), $Cs_2CO_3$ (2 mmol), DMSO (5 mL), rt, 22−24 h for entries 1−8; 3−6 h for entries 9−16. [b] Isolated yield.

To vary the substituents at the 3-position of the oxindoles, several amides with $\beta$-aromatic keto groups were prepared. Ketones **7**, condensation products of Meldrum's acid with acyl chlorides, were reacted with different anilines to give the corresponding amides **5** (Scheme 2). These substrates were found to cyclize faster under our standard conditions (3−6 h versus 22−24 h for amides **5a**−**i**). This acceleration effect was most likely due to the electron delocalization in the aryl moiety. Several 3-acyloxindoles containing different heterocycles were prepared using this same strategy (entries

**Scheme 2**




10−13 and 16). It is noteworthy that compounds **6l** and **6m** are similar to Tendiap in structure. These results illustrate the potential application of our method in medicinal chemistry and synthesis of natural products containing the oxindole structure.

In summary, we have developed a mild and efficient method for the preparation of 3-acyloxindoles involving a CuI/L-proline-catalyzed intramolecular arylation. In contrast to other metal-catalyzed reactions, our reaction conditions are less toxic and allow the cyclization to be carried out at room temperature. Both acetoacetylated substrates and aryl carbonyl acetylated substrates gave good yields. Thus, we believe this reaction will find considerable applications in the synthesis of Tendiap derivatives and natural products containing the 3-acyloxindole structure.

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**Supporting Information Available:** Experimental procedures and copies of $^{1}H$ NMR and $^{13}C$ NMR spectra for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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