# Synthesis of Indolo[2,3-*b*]quinolines by Palladium-catalyzed Annulation of Unsaturated Isothioureas

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Treatment of 1-(2-alkynyl)phenyl-3-aryl-2-methylisothioureas with 5 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ in the presence of CuTC (copper thiophenecarboxylate) and $Cs_2CO_3$ at 130 °C provided a wide range of 6-N-alkylated indolo[2,3-*b*]quinolines in good yields.

Cyclic amidines are important structural motifs that are frequently involved in natural products and biologically active molecules.[1] Cryptotackieine and perophoramidine (Figure 1) are representative indoloquinoline alkaloids.[2] A series of indolo[2,3-*b*]quinolines would be promising candidates as cytotoxic DNA intercalators and topoisomerase II inhibitors.[2]

Various synthetic methods have been developed to construct these target molecules. Most of these methods rely on the nucleophilic addition of amines to nitriles, amides, or their equivalents such as imidoyl chlorides, imidates, and thioimidates,[3] as well as the thermal cyclization of enyne-carbodiimides.[4] Recently, cascade radical annulations of benzotriazoles,[2c,5] *O*-phenyl oxime ethers,[6] and alkynyl *N*-arylthioureas[7] have been described as alternative methods. In contrast, few transition metal catalyzed reactions have been reported for the synthesis of indoloquinolines. Therefore, we investigated efficient synthetic methods for these target molecules by using a $Pd^0$-catalyzed amidination reaction.

Liebeskind pioneered the use of such amidinyl metal complexes as **2A** in the synthesis of protected aryl amidines from isothiourea and arylboronic acids.[8,9] Furthermore, we have already reported the Pd-catalyzed cyanoamidation of unsaturated carbamoyl cyanide to afford various oxindoles.[10] Based on these results, we selected methyl sulfide as a leaving group (X) of isothiourea **1** and explored the Pd-catalyzed reaction of **1** in the presence of CuTC (Scheme 1). We report here that the Pd-catalyzed intramolecular amidination of readily available alkynylisothioureas **1** provides a direct route to 6-*N*-alkylindolo[2,3-*b*]quinolines **3**.[11]

We initially examined the Pd-catalyzed reaction of 1,2-dimethylisothiourea **1a**, which was readily prepared by the reaction of thiourea with MeI, under various conditions (Table 1). Although the reaction did not proceed without palladium catalyst, treatment of **1a** with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5 mol %) and (2-furyl)$_3$P (40 mol %) in the presence of CuTC (1 equiv) and $Cs_2CO_3$ (2 equiv) at 130 °C provided the desired tetracyclic adduct **3a** in 43% yield, with no contamination by alkenyl sulfide **4** (Entry 1). After several optimization studies, we found that the use of somewhat bulky bidentate phosphine ligands such as dppb and dppf improved the chemical yield up to 74% (Entries 2–6). In addition, the same reaction with a catalytic amount of CuTC or with 1.5 equiv of $CuBr\cdot SMe_2$ resulted in a lower yield (Entries 7 and 8). The use of benzylisothiourea **1b** had only marginal effects on the reaction rate and yield (Entries 9 and 10).

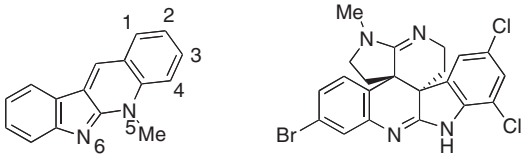
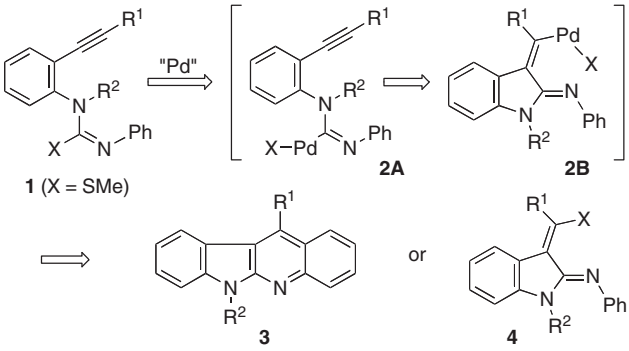
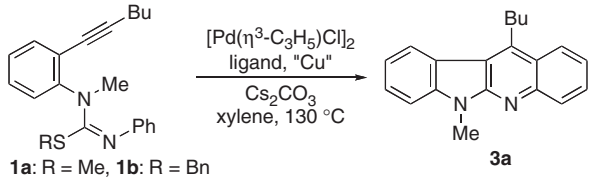



**Figure 1.** Natural products bearing indolo[2,3-*b*]quinolines.




**Scheme 1.** Transition-metal-catalyzed amidination.

**Table 1.** Survey of annulation conditions[a]

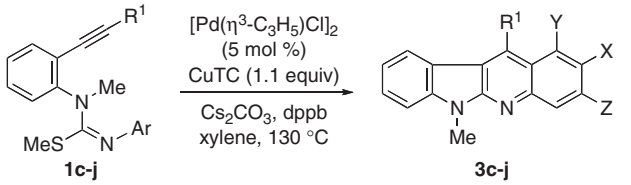



| Entry | R | Ligand (equiv) | "Cu" (equiv) | Yield/%[b] |
|---|---|---|---|---|
| 1 | Me | (2-furyl)$_3$P (0.4) | CuTC (1.0) | 43 |
| 2 | Me | (*p*-tolyl)$_3$P (0.4) | CuTC (1.1) | 54 |
| 3 | Me | (*o*-tolyl)$_3$P (0.4) | CuTC (1.1) | 17 |
| 4 | Me | BINAP (0.3) | CuTC (1.1) | 50 |
| 5 | Me | dppb (0.3) | CuTC (1.1) | 74 |
| 6 | Me | dppf (0.3) | CuTC (1.1) | 69 |
| 7 | Me | dppf (0.3) | CuTC (0.3) | 51 |
| 8 | Me | dppb (0.3) | $CuBr\cdot SMe_2$ (1.5) | 37 |
| 9 | Bn | dppb (0.3) | CuTC (1.1) | 64 |
| 10 | Bn | dppb (0.3) | — | 17 |

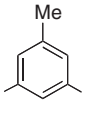
[a]All reactions were carried out with 5 mol % of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 2 equiv of $Cs_2CO_3$. [b]Isolated yield.

After having established optimal reaction conditions, we next explored the scope and limitation of the substrates. As shown in Table 2, a wide array of 1,2-dimethylisothioureas **1c**–**1j** can be cyclized to the corresponding indoloquinolines **3c**–**3j** in yields of 33 to 76%. Importantly, a variety of elec-

**Table 2.** Scope and limitation of substrates




1c-j 3c-j

| Entry | 1 ($R_1$) Ar | Time/h | Product | Yield/% |
|---|---|---|---|---|
| 1 | **1c** (Bu)  | 24 | **3c** (X = Me Y = Z = H) | 67 |
| 2 | **1d** (Bu)  | 19 | **3d** (X = OMe Y = Z = H) | 59 |
| 3 | **1e** (Bu)  | 3 | **3e** (X = $NMe_2$ Y = Z = H) | 50 |
| 4 | **1f** (Bu)  | 24 | **3f** (X = Cl Y = Z = H) | 76 |
| 5 | **1g** (Bu)  | 6.5 | **3g** (X = CN Y = Z = H) | 33 |
| 6 | **1h** (Bu)  | 5 | **3h** (X = H Y = Z = Me) | 45 |
| 7 | **1i** (Bu)  | 10 | **3ia** (Z = OMe, X = Y = H) **3ib** (Y = OMe, X = Z = H | 76[a] |
| 8 | **1j** (Ph) Ph | 24 | **3j** (X = Y = Z = H) | 76 |

[a]Total yield (**3ia**:**3ib** = 58:42).

tron-rich aryl groups on the aryl ring (Ar) promoted this process. Functional groups, such as ether, amine, chloride, and cyanide, were tolerated (Entries 1–5). However, substrates bearing an electron-withdrawing group tended to decrease the chemical yields (Entry 5). Indeed, the reaction of isothiourea bearing a 3,5-bis(trifluoromethyl)phenyl group gave no cyclized adduct. The *N*-arylisothioureas **1h** and **1i** with substituents in the meta position similarly underwent annulation, and gave the desired products in respective yields of 45 and 76% (Entries 6 and 7). In the latter case, two regioisomers **3ia** and **3ib** were obtained in a ratio of 58/42. With regard to the substituent ($R^1$) on the alkynyl group, both alkyl and phenyl groups were tolerated under these conditions (Entry 8).

The reaction proceeds through oxidative addition of the MeS–C bond to palladium(0),[8,9] followed by ligand exchange with CuTC, which promotes insertion to the internal alkyne, to give the alkenylpalladium complex **2B** (Scheme 1). Subsequently, nucleophilic attack of the aryl group[12] to the $Pd^{II}$ complex and reductive elimination of the resulting palladium complex afford the tetracyclic product **3**.

In conclusion, we demonstrated that the Pd-catalyzed annulation of 1,2-dialkylisothioureas proceeded efficently to give 6-*N*-alkylindoloquinolines in good yields. This method supplements the known pericyclic and electrocyclic routes to these compounds.

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