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One-pot synthesis of 2-substituted furo[3,2-*c*]quinolines via tandem coupling–cyclization under Pd/C-copper catalysis☆

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Abstract—Pd/C–Cu catalyzed coupling reactions of 3-iodo-1*H*-quinolin-4-ones with a variety of terminal alkynes afforded furo[3,2-*c*]quinolines regioselectively in good to excellent yields. 3-Alkynyl quinolones were isolated under the same reaction conditions when the nitrogen of 3-iodo-1*H*-quinolin-4-one was substituted with an alkyl group.

Furoquinoline derivatives are of particular interest because they are isomers of the known family of furo[2,3-*b*]quinoline alkaloids, which possess a broad range of biological properties such as antiviral, antimicrobial, and antiplatelet aggregation activity.[1] Recently, linear and angular furoquinolinones (A and B, Fig. 1) have shown promising blocking activities of the voltage-gated potassium channel Kv1.3.[2] This channel is considered to be a novel pharmacological target for immunosuppressive therapy[3] and therefore potent, specific Kv1.3 inhibitors have the potential to be of utility in transplantation, autoimmune disease, and inflammation therapy.[3a]

Among the many methods reported[2,4–14] for the synthesis of furoquinoline derivatives, a common strategy involves the construction of a quinoline ring possessing an appropriate carbon chain at the C-3 position, which is then modified into the furan ring depending on the presence of an oxygen substituent at the C-2 or C-4 positions. A major drawback of this protocol is that once the quinoline ring has been constructed, incorporation of a carbon chain at C-3 through electrophilic aromatic substitution is difficult. While improved[12c] and alternative methodologies[15–17] have been reported to overcome this problem, a general methodology for the synthesis of angular furoquinolines has not been reported so far.

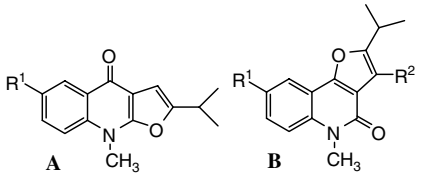

Figure 1.

Recently, the construction of furan rings[18] fused with benzene or other six-membered heterocycles via palladium-catalyzed annulation of alkynes[19] has attracted considerable interest. For example, furopyrimidine derivatives have been synthesized via palladium- or copper-catalyzed *5-endo-dig* cyclization of 5-alkynyluridines involving the C-4 pyrimidine oxygen and the acetylenic bond.[20,21] The use of a similar strategy has been revealed in the synthesis of linear furoquinolines.[22] However, most of these processes require isolation of the Sonogashira product followed by cyclization in the next step. While the use of copper acetylide under Castro reaction conditions afforded linear and angular quinolines in low yields (26–35%),[23] this methodology also suffered from a cumbersome, preparative procedure as well as the stoichiometric use of an organometallic reagent, the use of pyridine as a base and harsh reaction conditions. In connection with our studies on the use of halogenated enones of type –C=C(X)CO– (where X = I or Br, Fig. 2) under modified Sonogashira conditions, we have recently reported a new and one-pot synthesis of 3-enynyl(thio)flavones along with their 3-alkynyl

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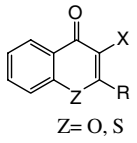
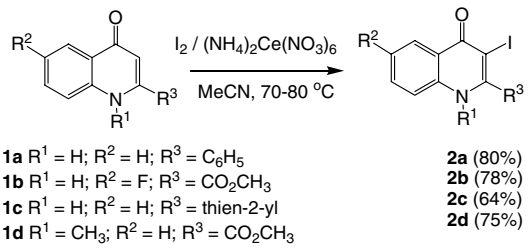


Figure 2.

analogues.[24] In continuation of this work, we now report the use of 2-substituted 3-iodo-1*H*-quinolin-4-one (Fig. 2, Z = NR′, R′ = H or CH_3) as a starting point to synthesize a variety of angular furoquinolines. Palladium-catalyzed alkynylation of aryl or heteroaryl rings (the Sonogashira coupling)[25a] has proved to be a powerful tool for the C–C bond formation;[25b] however, an one-pot process involving Sonogashira type coupling followed by the electrophilic or transition-metal-mediated cyclization of the resulting alkynes possessing a suitable nucleophilic group in proximity to the triple bond has now emerged as a versatile and efficient route to various substituted heterocyclic systems.[26] Typically these coupling–cyclization reactions are carried out using a palladium catalyst [e.g., $Pd(PPh_3)_4$, $(PPh_3)_2PdCl_2$, etc.] and a copper salt as co-catalyst in the presence of an amine base. While the use of Pd/C–CuI–PPh_3 as a less expensive catalytic system has been studied extensively[27] its application in coupling–cyclization is not common.[28] Due to our interest in Pd/C-based methodologies,[27a,28] we now report the first palladium (on charcoal)-copper mediated synthesis of diverse 2-substituted furo[3,2-*c*]quinolines.

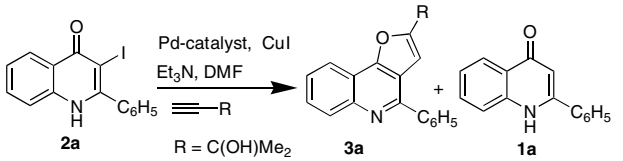
To initiate our studies, we first prepared a series of 3-iodoquinolin-4-ones **2a**–**d** in good yields through iodination of the corresponding quinolin-4-ones[29] using iodine and ceric ammonium nitrate (CAN) in acetonitrile at 70–80 °C (Scheme 1).[30a]

Firstly, 3-iodo-2-phenyl-1*H*-quinolin-4-one **2a** was treated with 2.0 equiv of 2-methyl-3-butyn-2-ol in dimethylformamide (DMF) in the presence of 10% Pd/C (0.03 equiv), PPh_3 (0.12 equiv), CuI (0.06 equiv), and triethylamine (5 equiv) under a nitrogen atmosphere to give 2-(4-phenylfuro[3,2-*c*]quinolin-2-yl)-2-ol **3a** in 70% yield along with a minor quantity of de-iodinated product (Table 1, entry 1). The use of $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ in the place of Pd/C–PPh_3 improved the yield of **3a** to 80–85% and no de-iodinated product was detected (Table 1, entries 2 and 3). Notably, the use of **2b** in the presence of 10%Pd/C–PPh_3–CuI as a catalyst afforded the desired product in 83% yield (Table 2, entry 1).[30b] Encouraged by this result and Pd/C being



Scheme 1. Preparation of 3-iodoquinolin-4-one derivatives.

Table 1. The effect of palladium catalysts on the coupling reaction of 3-iodo-2-phenyl quinolin-4-one with 2-methyl-3-butyn-2-ol in DMF[a]



Entry	Pd-catalyst	Temp (°C); time (h)	Yield (%)[c]	
			3a[b]	**1a**[b]
1[d]	10% Pd/C–PPh_3	75–80; 3	70	11
2	$Pd(PPh_3)_4$	75–80; 2	85	n.d.
3	$Pd(PPh_3)_2Cl_2$	75–80; 2	80	n.d.
4[e]	10% Pd/C–PPh_3	75–80; 3	34	n.d.
5[f]	10% Pd/C–PPh_3	75–80; 3	n.d.	17
6	10% Pd/C	80; 3	22	n.d.

n.d. = not detected.

[a] Reaction conditions: **2a** (1.0 equiv), terminal alkyne (2.0 equiv), Pd-catalyst (0.03 equiv), CuI (0.06 equiv), Et_3N (5 equiv) in DMF under N_2 atmosphere.

[b] Identified by ^1H NMR, ^{13}C NMR, IR, and mass spectroscopy.

[c] Isolated yields.

[d] The reaction was carried out using a 1:4:2 ratio of Pd/C–PPh_3–CuI.

[e] THF was used in the place of DMF.

[f] CuI was not used.

a cheaper source of palladium catalyst, we continued our studies using only this catalyst system. The results of our studies are summarized in Table 1. DMF was used as a solvent, other solvents such as THF (Table 1, entry 4) and acetonitrile were found to be less effective, perhaps due to the poor solubility of **2a** in these solvents. The formation of only de-iodinated product (Table 1, entry 5) in the absence of copper salt highlighted the crucial role of CuI in this coupling–cyclization process. The absence of PPh_3 resulted in a poor yield of **3a** (Table 1, entry 6).

In view of the encouraging results obtained using **2b**, we decided to explore the generality and scope of this coupling–cyclization process. Thus **2b** was treated with a variety of terminal alkynes under the conditions described earlier (Table 1, entry 1) and the results are summarized in Table 2. Good yields of the desired furo[3,2-*c*]quinolines **4** were obtained irrespective of the nature of terminal alkynes used (Table 2, entries 1–5). Aryl, alkyl, and hydroxy groups present in the terminal alkynes were well tolerated. Similarly, **2a** was treated with a number of terminal alkynes to afford the corresponding furo[3,2-*c*]quinolines **3** in 67–72% yields (Table 2, entries 6–9). The use of 3-iodo-2-thien-2-yl-1*H*-quinolin-4-one **2c** also afforded the desired product albeit in moderate yield (Table 2, entry 10). Notably, in contrast to the earlier observations[22a,b] no 3-alkynyl quinolone was isolated in our examples. However, de-iodinated product (**1a** or **1c**) was isolated, at least in 10–12% yields, when **2a** or **2c** was used. This was not observed when $Pd(PPh_3)_4$ was employed in place of Pd/C–PPh_3 and better yields (>80%) of **3** were obtained.

The key features of the present tandem coupling–cyclization process are the transition-metal-mediated activa-