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

Subramanian Venkataraman, Deepak Kumar Barange and Manojit Pal*

Chemistry-Discovery Research, Dr. Reddy's Laboratories Ltd, Bollaram Road, Miyapur, Hyderabad 500 049, India

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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.
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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.

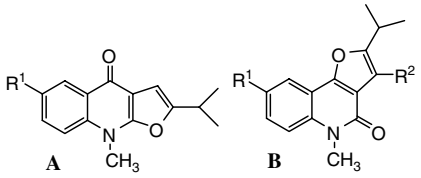

Figure 1.

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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* Corresponding author. Tel.: +91 40 23045439; fax: +91 40 23045438/23045007; e-mail: manojitpal@drreddys.com

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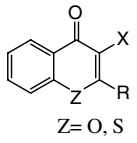
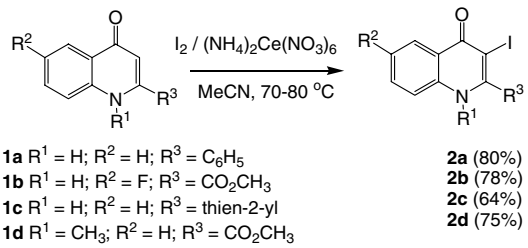


Figure 2.

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.

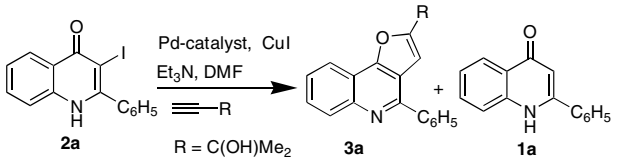
To initiate our studies, we first prepared a series of 3-iodoquinolin-4-ones **2a**–**d** in good yields through iodination of the corresponding quinolin-4-ones[29] using iodine and ceric ammonium nitrate (CAN) in acetonitrile at 70–80 °C (Scheme 1).[30a]

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.

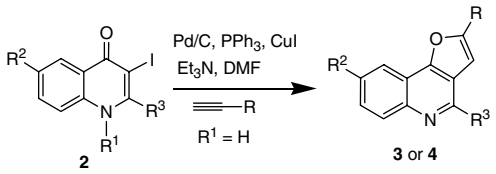
[f] CuI was not used.

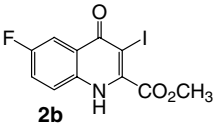
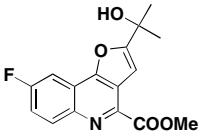
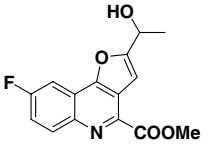
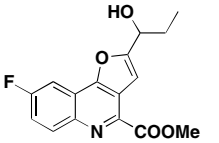
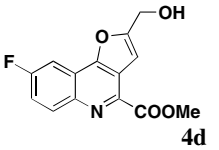
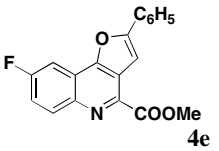
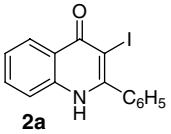
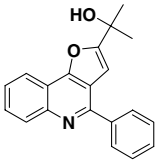
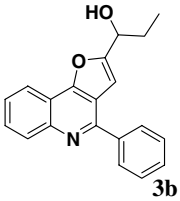
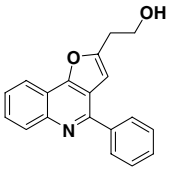
a cheaper source of palladium catalyst, we continued our studies using only this catalyst system. The results of our studies are summarized in Table 1. DMF was used as a solvent, other solvents such as THF (Table 1, entry 4) and acetonitrile were found to be less effective, perhaps due to the poor solubility 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-

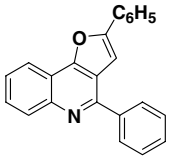
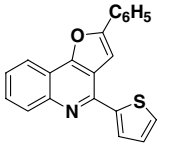
Table 2. Pd/C mediated synthesis of 2-substituted furo[3,2-*c*]quinolines[a]



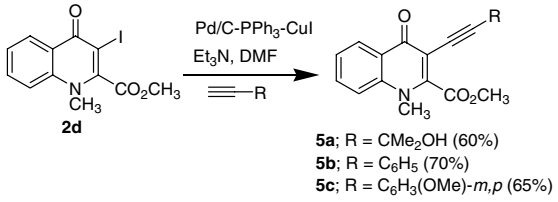
Entry	3-Iodoquinoline-4-one (**2**)	Alkyne	Time (h)	Product[b] (**3**/**4**)	Yield (%)[c]
1	 **2b**	≡—$C(OH)Me_2$	2	 **4a**	83
2	**2b**	≡—CH(OH)Me	2	 **4b**	85
3	**2b**	≡—$CH(OH)CH_2CH_3$	2	 **4c**	75
4	**2b**	≡—CH_2OH	2	 **4d**	75
5	**2b**	≡—Ph	1.5	 **4e**	76
6	 **2a**	≡—$C(OH)Me_2$	3	 **3a**	70
7	**2a**	≡—$CH(OH)CH_2CH_3$	3	 **3b**	68
8	**2a**	≡—CH_2CH_2OH	3	 **3c**	72

(*continued on next page*)

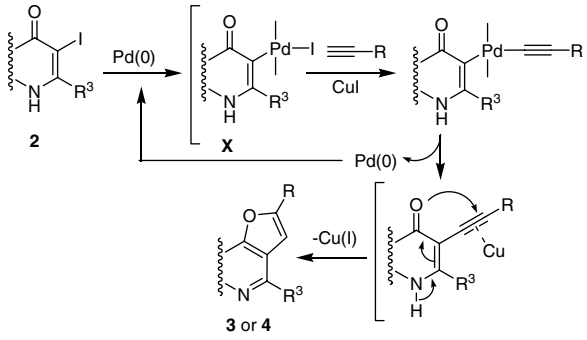
Table 2 (*continued*)

Entry	3-Iodoquinoline-4-one (**2**)	Alkyne	Time (h)	Product[b] (**3**/**4**)	Yield (%)[c]
9	**2a**	≡—Ph	3	 **3d**	67
10	**2c**	≡—Ph	3	 **3e**	60

[a] All reactions were carried out by using **2** (1.0 equiv), terminal alkyne (2.0 equiv), 10% Pd/C (0.03 equiv), PPh_3 (0.12 equiv), CuI (0.06 equiv), Et_3N (5 equiv) in DMF at 75–80 °C.
[b] Identified by ^1H NMR, ^{13}C NMR, IR, and mass spectroscopy.
[c] Isolated yields.



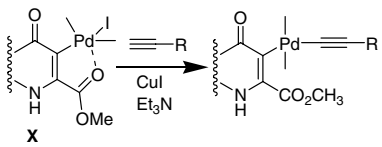
Scheme 2. Preparation of 2-substituted 9-methyl-9*H*-furo[2,3-*b*]-quinolin-4-ones **5**.



Scheme 3. Proposed mechanism for the tandem coupling–cyclization process.

tion of the triple bond of the 3-alkynyl quinoline generated in situ followed by an intramolecular attack of the oxygen on the activated triple bond with subsequent proton transfer and release of the metal ion to give the desired furoquinoline (see later for mechanistic discussion). The NH of the quinolone ring has a critical role in the cyclization step and perhaps facilitated the preferential participation of the C-4 quinoline oxygen over the ester when **2b** was used as the halide component. This is particularly interesting as a Lewis acid mediated cyclization of 2-ethynylbenzoic acid ester leading to a 3-substituted isocoumarin has been reported.[31] However, to assess the role of the N-hydrogen, we treated 3-iodo-1-methyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid methyl ester **2d** with terminal alkynes under the same conditions. Only 3-alkynyl quinolones **5** were isolated in these cases as a result of normal Sonogashira coupling and no formation of furoquinoline was observed, even in trace amounts (Scheme 2).

A plausible reaction mechanism is depicted in Scheme 3. The Pd(0) species generated in situ from Pd/C and PPh_3 catalyzes the coupling of 3-iodoquinolin-4-one **2** with copper(I) acetylide (generated in situ from the terminal alkyne) via intermediate **X** leading to the 3-alkynyl quinolin-4-one. This subsequently affords the corresponding furoquinoline (**3** or **4**) via activation of the triple bond through its complexation with the copper(I) salt followed by intramolecular cyclization[20,32] with regeneration of the Cu(I) catalyst.[33] The better yields observed in the case of **2b** perhaps resulted from an intramolecular coordination of the neighboring carbonyl oxygen to the palladium during the iodide displacement step (Scheme 4).



Scheme 4. Effect of neighboring group on the coupling of **X** with a terminal alkyne.

In conclusion, we have shown that 2-substituted 3-iodoquinolones can react with a variety of terminal alkynes under the palladium/copper catalysis. These reactions proceed under mild conditions and afford furo[3,2-*c*]quinolines with remarkable regioselectivity irrespective of the nature of the substituent present at C-2 of the starting quinolone. The presence of an ester moiety at this position leads to the best yields of products. The present one-pot and regioselective synthesis of 2-substituted furo[3,2-*c*]quinolines via Pd/C based methodology does not involve the use of expensive

reagents or catalysts and therefore permits a new and practical access to angular furoquinolines. The ongoing work seeks to expand the scope of this process to the synthesis of compounds of pharmacological interest.

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29. 2-Phenyl-1*H*-quinolin-4-one **1a** was prepared according to a known procedure, see: (a) Kuo, S.-C.; Lee, H.-Z.; Juang, J.-P.; Lin, Y.-T.; Wu, T.-S.; Chang, J.-J.; Lednicer, D.; Paull, K. D.; Lin, C. M.; Hamel, E.; Lee, K.-H. *J. Med. Chem.* **1993**, *36*, 1146–1156; For the preparation of 6-fluoro-4-oxo-1,4-dihydroquinoline-2-carboxylic acid methyl ester **1b**, see: (b) Edmont, D.; Rocher, R.; Plisson, C.; Chenault, J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1831–1834; For the preparation of 1-methyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid methyl ester **1d**, see: (c) Cairns, H.; Payne, A. R. *J. Heterocycl. Chem.* **1978**, *15*, 551–553.
30. (a) To a solution of appropriately substituted quinolin-4-one (**1**, 4.52 mmol) in acetonitrile (25 mL) was added ceric ammonium nitrate (0.248 g, 0.45 mmol) followed by iodine (0.631 g, 4.97 mmol). The mixture was stirred at 70–80 °C under nitrogen for 3–8 h. After completion of the reaction, the mixture was cooled to room temperature and treated with an ice-cold aqueous solution of sodium thiosulfate with stirring. The resulting precipitated solid was filtered to afford the desired product.; (b) Typical procedure: preparation of 8-fluoro-2-(1-hydroxy-1-methylethyl)furo[3,2-*c*]quinoline-4-carboxylic acid methyl ester (**4a**, entry 1, Table 2): A mixture of **2b** (0.86 mmol), 10% Pd/C (0.026 mmol), PPh_3 (0.10 mmol), CuI (0.05 mmol), and triethylamine (4.3 mmol) in dry DMF (5 mL) was stirred for 1.5 h under a nitrogen atmosphere. To this was added 2-methylbut-3-yn-2-ol (1.72 mmol) slowly and the mixture was stirred at 75–80 °C for 2 h. The mixture was then cooled to room temperature and filtered through Celite. The filtrate was diluted with water (20 mL) and extracted with EtOAc (3×10 mL). The organic layers were collected, combined, washed with water (2×10 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue thus obtained was purified by column chromatography using EtOAc–petroleum ether (1:2) to afford the title compound as a pale brown solid; mp 194–196 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40–8.36 (m, 1H), 7.92–7.89 (m, 1H), 7.53–7.48 (m, 1H), 7.37 (s, 1H), 4.13 (s, 3H, $COOCH_3$), 2.22 (br s, D_2O exchangeable, –OH), 1.78 (s, 6H); *m*/*z* (CI) 304 (M+1, 100%); IR (cm^{-1}, neat) 3408, 2985, 1737, 1457, 1304, 1199, 819; UV (nm, MeOH) 254.50, 229.00; HPLC 98.5%, Column: INERTSIL ODS 3V (250×4.6) mm, mobile Phase: A: 0.01 M KH_2PO4, B: CH_3CN, gradient (T/%B) 0/40, 5/40, 20/80, 25/80, 30/40, 35/40, flow rate: 1.0 mL/min, UV 254 nm, retention time 12.4 min.
31. See for example: Sakamoto, T.; Annaka, M.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1986**, *34*, 2754–2759.
32. Cu(I) in DMF has been reported as an efficient catalytic system for a similar cyclization process; see for example: Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531–4534.
33. An alternative pathway involving activation of the carbonyl group through the coordination of Cu(I) to the carbonyl oxygen and the π-bond of the alkyne may also facilitate the intramolecular cyclization process, see Ref. 32.