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Pd/C–Cu in coupling-cyclization process: a general synthesis of 2-substituted 6-oxopyrrolo[3,2,1-*ij*]quinoline derivatives

Mohosin Layek [a,b], Vikas Gajare [a], Dipak Kalita [a], Aminul Islam [a], K. Mukkanti [b], Manojit Pal [c,*]

[a] Custom Pharmaceuticals Services, Dr. Reddy's Laboratories Ltd, Bollaram Road, Miyapur, Hyderabad 500 049, India
[b] Chemistry Division, Institute of Science and Technology, JNT University, Kukatpally, Hyderabad 500 072, India
[c] New Drug Discovery, R&D Center, Matrix Laboratories Ltd, Anrich Industrial Estate, Bollaram, Jinnaram Mandal, Medak District, Andra Pradesh 502 325, India

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ABSTRACT

A general and practical synthesis of 2-substituted 6-oxopyrrolo[3,2,1-*ij*]quinolines has been achieved following a single-step Pd/C-mediated coupling-cyclization strategy. The methodology involves the reaction of 8-iodo-4-oxo-1,4-dihydro quinoline-3-carboxylic acid ethyl ester with a variety of terminal alkynes in the presence of 10% Pd/C–PPh_3–CuI as a catalyst system in EtOH. The reaction mechanism and utility of the methodology have been discussed.

While pyrrolo[3,2,1-*ij*]quinoline ring **A** (Fig. 1) has been found to be integral part of several natural products,[1] natural occurrence of 6-oxopyrroloquinoline ring **B** (Fig. 1) is rather unusual. Synthetic 6-oxopyrroloquinolines have been reported in the literature preparation of which mainly involve two general approaches, for example, (i) the construction of a pyrrole ring onto a quinoline by a standard indole synthesis,[2–9] or (ii) the construction of a new six-membered ring between N1 and C7 of an indole.[1,10–18]

In 1997, a palladium-mediated synthesis of 6-oxopyrroloquinoline was reported via the coupling of 8-iodo-4-oxo quinoline with propargyl alcohol.[19] However, only one example was reported and no detailed study on the methodology including the use of other terminal alkynes has been carried out. Recently, synthesis and scale-up of a 6-oxopyrroloquinoline based promising antiviral agent, that is, PHA-529311 has been reported by using the same methodology as a key synthetic step.[20] Removal of residual palladium and copper from the penultimate and final products was a concern and therefore an appropriate scale-up sequence was designed to avoid the metal contamination in the final product. Nevertheless, the coupling reaction was carried out using $(PPh_3)_2PdCl_2$/CuI as a catalyst system in refluxing EtOH to afford the coupled product in 60% yield. In the recent past, the use of 10%Pd/C–PPh_3–CuI has been reported as an efficient catalyst system for coupling-cyclization process.[21–25] Because of easy recovery of palladium along with the reduced burden of metal contamination to the products, the use of Pd/C as a heterogeneous catalyst is known to be advantageous compared to other Pd-catalysts or salts. Herein, we report a highly efficient and practical method for the synthesis of 6-oxopyrroloquinolines (**3**) from 8-iodo-4-oxo-1,4-dihydro quinoline-3-carboxylic acid ethyl ester (**1**) and terminal alkynes (**2**) using 10% Pd/C-PPh_3–CuI as a catalyst system in EtOH (Scheme 1).

The key iodo compound (**1**) required for our study was prepared according to a similar process reported in the literature[20] (Scheme 2). Thus heating 2-iodoaniline (**4**) and diethylethoxymethylene malonate (DEEM) in refluxing toluene provided the enamine (**5**) in 80% yield which on treatment with phosphorus pentoxide in

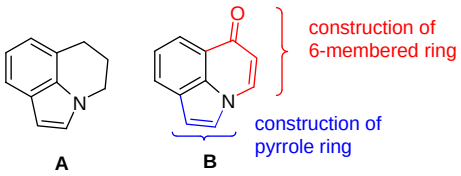
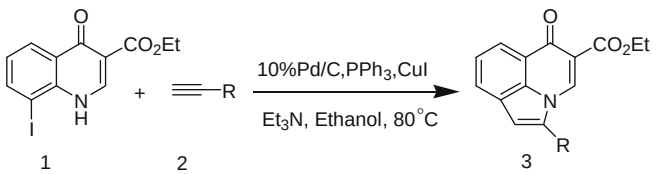


Figure 1. Pyrrolo[3,2,1-*ij*]quinoline (**A**) and 6-oxopyrroloquinoline (**B**).



Scheme 1. Synthesis of 2-substituted 6-oxopyrrolo[3,2,1-*ij*]quinolines.

* Corresponding author. Tel.: +91 08458279301; fax: +91 08458279305.
E-mail addresses: manojitpal@rediffmail.com, palmanojit@yahoo.co.uk (M. Pal).

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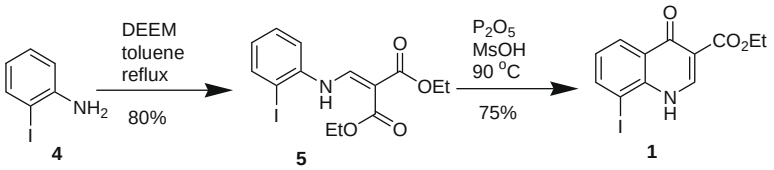
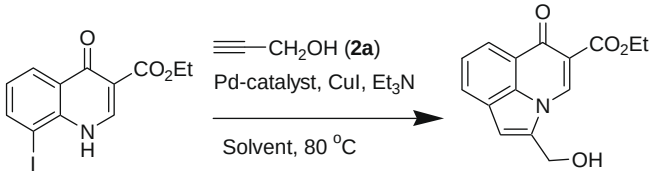


Scheme 2. Preparation of 8-iodo-4-oxo-1,4-dihydro quinoline-3-carboxylic acid ethyl ester (**1**).

Table 1
Effect of bases/solvents on the coupling reaction of 8-iodo-4-oxo-1,4-dihydro quinoline-3-carboxylic acid ethyl ester (**1**) with propargyl alcohol (**2a**)[a]



Entry	Solvent; catalysts	Time (h)	Yield[b] (%)
1	Toluene; $(PPh_3)_2PdCl_2$	48.0	55
2	Ethanol; $(PPh_3)_2PdCl_2$	4.0	68
3	Ethanol; 10% Pd/C–PPh_3	2.0	85[c]
4	H_2O; 10% Pd/C–PPh_3	5.0	55
5	Ethanol; 10% Pd/C–PPh_3	48.0	0[d]
6	Ethanol; 10% Pd/C–PPh_3	28.0	50[e]

[a] All reactions were carried out by using **1** (1.0 equiv), **2a** (1.5 equiv), catalysts and Et_3N (2.5 equiv) at 80 °C.
[b] Isolated yields.
[c] 1:4:10 ratio of 10% Pd/C: PPh_3: CuI was used.
[d] The reaction was carried out at 30 °C.
[e] The reaction was carried out at 50 °C.

methanesulfonic acid afforded the desired iodo compound (**1**) in 75% yield (Scheme 2).

We examined the reaction of **1** with a terminal alkyne, that is, propargyl alcohol (**2a**) using $(PPh_3)_2PdCl_2$–CuI as catalyst under the same reaction conditions as reported earlier.[20] The desired product **3a** was isolated in 55% yield (Table 1, entry 1). Incidentally, **3a** was isolated in 54% yield when $Ph(PPh_3)_2PdI$ was used as a Pd-catalyst earlier.[19] In order to improve the yield of **3a** the C–C bond forming reaction between **1** and **2a** was carried out in EtOH at a higher temperature (i.e., 80 °C). While the yield of **3a** was increased to 68% (Table 1, entry 2) the better yield however was noted when 10%Pd/C–PPh_3 was used (Table 1, entry 3) in place of $(PPh_3)_2PdCl_2$. Encouraged by this result and due to our continued interest in the Pd-catalyzed reaction in water we examined the use of water as a solvent in the present case. The reaction proceeded well in water to afford **3a** albeit in lower yield (Table 1, entry 4). Nevertheless, lowering of reaction temperature was found to be counter productive as **3a** was isolated in 0% and 50% yield when the reaction was carried out at 30 °C for 48 h (Table 1, entry 5) and 50 °C for 28 h (Table 1, entry 6), respectively. Thus, the use of 10%Pd/C–PPh_3–CuI as a catalyst system in EtOH at 80 °C was found to be optimum and we chose to use this reaction condition for our further studies. Accordingly, a variety of terminal alkynes (**2a–k**) were coupled with **1** and results of this study are summarized in Table 2.

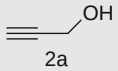
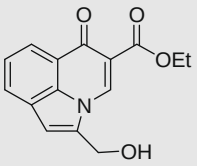
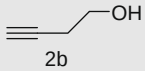
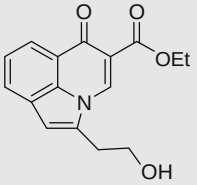
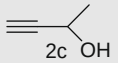
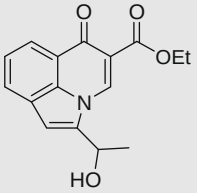
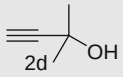
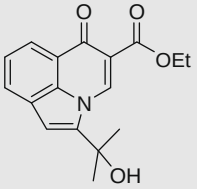
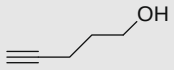
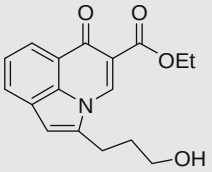
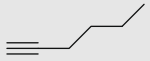
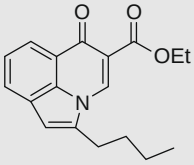
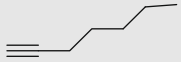
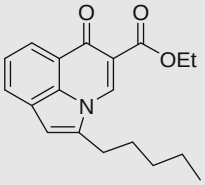
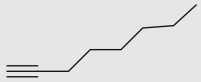
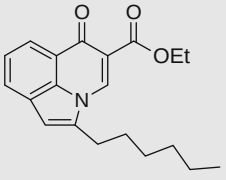
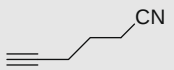
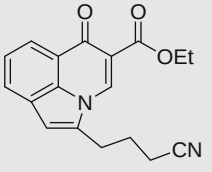
As presented in Table 2, the reaction proceeded well with both aliphatic (Table 2, entries 1–9) and aromatic alkynes (Table 2, entries 10–11).[26a] The alkyl side chain may contain a primary (Table 2, entries 1, 2 and 5) or secondary (Table 2, entry 3) or tertiary hydroxyl group (Table 2, entry 4). A cyano group on the alkyl side chain (Table 2, entry 9) was also well tolerated. All the reactions were generally completed within 2–6 h irrespective of the nature of substituents present in the terminal alkynes (**2a–k**). Yields of products were found to be moderate when terminal alkynes **2f**, **2g** and **2h** were used, possibly due to the quick evaporation of these reactant alkynes under the reaction conditions employed (Table 2, entries 6–8). Yields were found to be good in case of other alkynes and no lower degree of dimerization of reactant alkynes was observed under the present Pd/C–Cu catalysis. The aromatic alkynes **2j** and **2k** provided the corresponding products in 83% and 80% yields, respectively. All the new compounds synthesized were well characterized by spectral and analytical data.[26b]

Compounds containing appropriately substituted 6-oxopyrroloquinoline framework bearing an alkyl side chain (such as propyl group) at C-2 position containing a saturated cyclic amine (such as morpholine and piperidine) have been claimed as potential *anti*-atherosclerotic and *anti*-viral agents.[27,28] In order to demonstrate the scope and utility of our process we prepared compound **7**, using Pd/C-mediated coupling-cyclization as a key synthetic step (Scheme 3). Thus the chloro derivative **3l** was prepared by reacting the iodo compound **1** with an appropriate terminal alkyne, that is, 5-chloropent-1-yne (**2l**) using 10%Pd/C–PPh_3–CuI as catalyst system in EtOH. When reacted with morpholine, the chloro group of **3l** was conveniently replaced by a morpholine ring affording the desired compound **6**. The ester moiety of **6** could be then converted into the requisite carboxamide group to afford the compound **7**.

Mechanistically, the present coupling-cyclization process seems to proceed via Pd/C–Cu mediated coupling of **1** with terminal alkynes (**2**) to afford the internal alkyne **Z** in situ which undergoes Cu-mediated intramolecular cyclization to yield the product **3** (Scheme 4). The intermediacy of **Z** was supported by the fact that *N*-methyl derivative of compound **1** afforded the corresponding alkynyl substituted product when treated with terminal alkyne **2d** under the same reaction condition as presented in Table 2. Moreover, participation of copper salt in the intramolecular cyclization of the appropriately functionalized internal alkynes generated in situ has been documented well in the literature.[21–25]

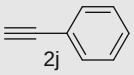
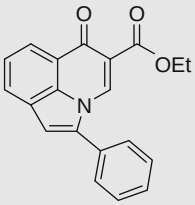
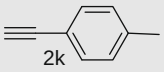
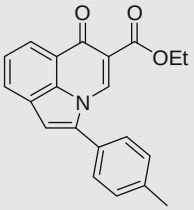
In conclusion, an easy and inexpensive method has been developed to access functionalized 2-substituted 6-oxopyrrolo[3,2,1-*ij*]quinoline derivatives following a single-pot coupling-cyclization strategy. The methodology involves the use of 10% Pd/C–PPh_3–CuI as a catalyst system and ethanol as a solvent. The process was found to be general as it worked with a variety of terminal alkynes and well tolerated with a range of functional groups. The methodology is amenable for the synthesis of compounds of potential pharmacological interest. Further applications of this method are under active investigation.

Table 2
Pd/C-mediated **s**ynthesis of 2-substituted 6-oxopyrroloquinolines (**3**)[a]

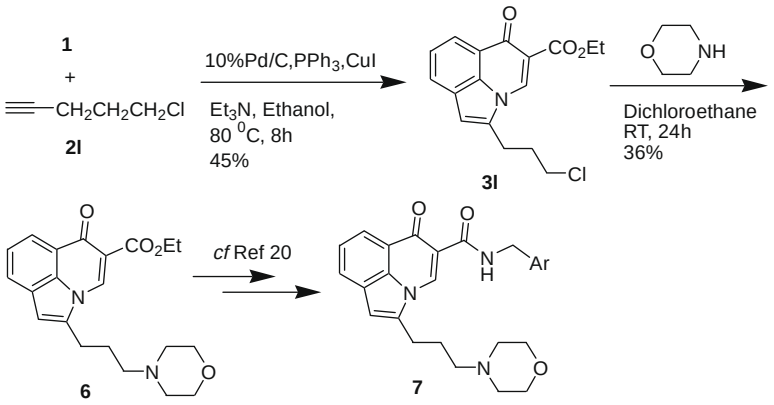
Entry	Alkynes (**2**)	Products (**3**)		Reaction time (h)	Yield (%)[b]
1	 2a		**3a**	2.0	85
2	 2b		**3b**	4.5	85
3	 2c		**3c**	4.0	95
4	 2d		**3d**	3.5	65
5	 2e		**3e**	6.0	81
6	 2f		**3f**	4.0	50
7	 2g		**3g**	5.0	55
8	 2h		**3h**	6.0	55
9	 2i		**3i**	4.0	75

(*continued on next page*)

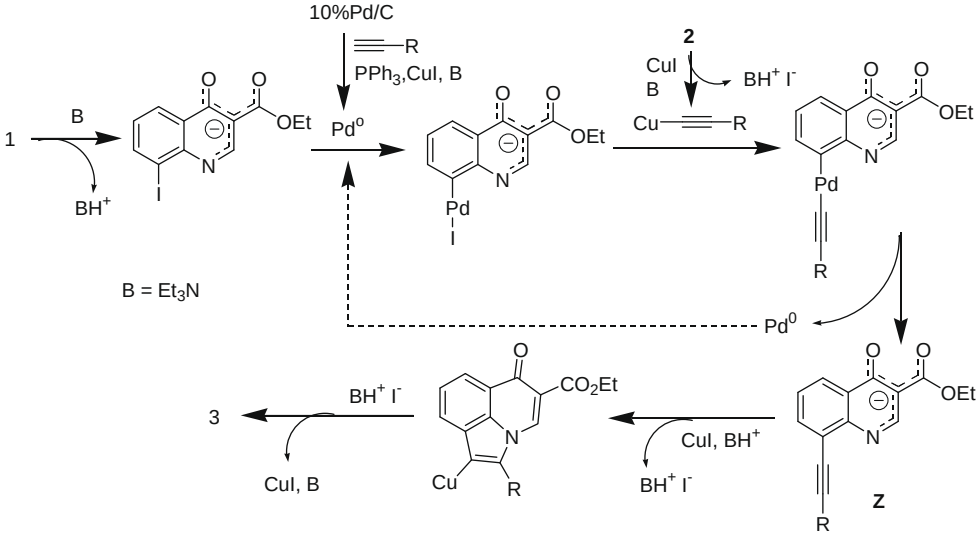
Table 2 (*continued*)

Entry	Alkynes (**2**)	Products (**3**)	Reaction time (h)	Yield (%)[b]
10		 **3j**	3.0	83
11		 **3k**	2.5	80

[a] All reactions were carried out by using **1** (1.0 equiv), **2** (1.5 equiv), 1:4:10 ratio of 10% Pd/C: PPh_3: CuI and Et_3N (2.5 equiv) in EtOH at 80 °C.
[b] Isolated yields.



Scheme 3. Application of the Pd/C-mediated coupling-cyclization methodology.



Scheme 4. Proposed mechanism for the formation of 6-oxopyrroloquinoline ring of **3** under the catalysis of Pd/C–CuI–PPh_3.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.048.

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26. (a) *General procedure for preparation of* **3**: A mixture of 8-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester **1** (300 mg, 0.869 mmol), 10% Pd/C (9.21 mg, 0.0087 mmol), PPh_3 (9.11 mg, 0.034 mmol), CuI (16.55 mg, 0.087 mmol) and Et_3N (2.17 mmol) in ethanol (3.0 mL) was stirred for 1 h under nitrogen. The acetylenic compound **2** (1.30 mmol) was added and the mixture was stirred at 80 °C for the time mentioned in Table 2. After completion, the reaction mixture was cooled to room temperature, filtered through Celite bed and the filtrate was concentrated under vacuum. The crude mass was diluted with chloroform (30 mL) and water (15 mL) and the mixture was extracted with chloroform (3 × 30 mL). The organic layers were collected, combined, washed with saturated aq NaCl (2 × 25 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude compound was purified by column chromatography on silica gel using 9:1 hexane/ethyl acetate to afford the desired product **3**. (b) *Spectral data of selected compounds; compound* **3a**: brown solid, mp 131 °C; R_f (90% ethyl acetate/*n*-hexane) 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.94 (s, 1H), 8.0 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.3 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 6.77 (s, 1H), 4.99 (d, J = 3.6 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 3.21 (br s, 1H), 1.39 (t, J = 7.2 Hz, 3H); IR (cm^{-1}, KBr) ν: 3354, 1707, 1618, 1557, 1217; Mass (ES): *m/z* 272.10 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 14.3, 56.0, 61.0, 110.9, 116.2, 122.8, 122.9, 125.7, 126.9, 128.7, 134.8, 139.5, 140.1, 164.6, 176.4; HRMS (ESI): calcd for $C_{15}H_{14}NO_4$ $(M+H)^+$ 272.092, found 272.091. Compound **3b**: light yellow solid; mp 139 °C; R_f (70% ethyl acetate/*n*-hexane) 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.86 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 6.72 (s, 1H), 4.34 (q, J = 7.2 Hz, 2H), 4.09 (t, J = 6.0 Hz, 2H), 3.17 (t, J = 6.0 Hz, 2H), 2.71 (br s, 1H), 1.40 (t, J = 7.2 Hz, 3H); IR (cm^{-1}, KBr) ν: 3398, 1724, 1621, 1559, 1220; Mass (ES): *m/z* 286.20 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 14.3, 29.0, 61.1 (2C), 110.4, 115.9, 122.0, 123.0, 125.6, 126.0, 129.4, 134.8, 139.2, 139.4, 164.9, 176.3; HRMS (ESI): calcd for $C_{16}H_{16}NO_4$ $(M+H)^+$ 286.107, found 286.107.
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