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C–N bond forming reaction under copper catalysis: a new synthesis of 2-substituted 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines

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ABSTRACT

We report copper-catalyzed intramolecular cyclization of 8-alkynyl-1,2,3,4-tetrahydroquinolines, obtained via a Pd/C-mediated Sonogashira coupling in water, to afford 2-substituted 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines. Further functionalization of the compounds synthesized was carried out under Heck, Sonogashira, and Suzuki reaction conditions.

Because of their interesting pharmacological properties,[1] 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline framework (**A**, Fig. 1), has attracted particular attention in the area of new drug discovery. For example, derivatives of compound **A** have shown potent histamine and platelet activating factor antagonism and 5-lipoxygenase inhibitory properties.[2] A promising compound KC 11404 that belongs to this class was identified as a lead candidate for the potential treatment of asthma. Another series of pyrrolo[3,2,1-*ij*]quinolines have been reported to be agonists at 5-HT_{2c} (5-hydroxytryptamine) with selectivity over 5-HT_{2a} for the potential treatment of epilepsy and obesity.[3] They were also found to be key intermediates for the synthesis of bioactive compounds.[4,5]

While a number of methods have been reported[6] for the synthesis of compounds containing the moiety **A**, all these strategies can be classified into two major categories, for example, construction of (i) six-membered saturated ring using an indole template **B** or (ii) five-membered ring using a suitably substituted 1,2,3,4-tetrahydroquinoline **C**. Recently, using the second approach, a Pd(II)-mediated intramolecular cyclization of 8-arylethynyl-1,2,3,4-tetrahydroquinolines leading to 2-aryl derivatives of **A** has been reported[6] (path 1, Scheme 1). Perhaps due to the requirement of expensive Pd(II) catalysts, this methodology was not established as a general procedure for the synthesis of **2** or similar class of compounds. No detailed study was conducted on the effect of other substituents present on the alkynyl moiety. Due to our continuing interest in the Cu-mediated cyclization processes[7] herein, we report a new synthesis of 2-substituted 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]-quinolines (**2**) under Cu-catalysis (path 2, Scheme 1) and their use in the preparation of diversity-based compounds under Pd-catalysis.

The starting alkynes (**1**) were prepared following a Pd/C-mediated coupling reaction in water.[8] Thus, 8-iodo-6-bromo-1,2,3,4-tetrahydroquinoline (**3**), prepared according to a known procedure,[6] was reacted with a number of terminal alkynes in the presence of 10%Pd/C–CuI–PPh_3 in water using 2-aminoethanol as a base to afford the desired coupled products (**1**) in good yields. The results are summarized in Table 1.

The intramolecular cyclization of alkyne **1a** was examined using a number of catalysts under various reaction conditions, for example, (a) ICl or I_2 in CH_2Cl_2 at 30 °C for 12 h or (b) I_2/K_2CO_3 in acetonitrile at 30 °C for 12 h or (c) $AgSbF_6/Et_3N$ in ethanol at 30 °C for 36 h. However the best results were obtained by using CuI in DMF at 100 °C for 12 h when the cyclized product **2a** was isolated in 85% yield (Table 2, entry 1). The use of other copper catalyst, for example, $Cu(OAc)_2$ was also examined but afforded lower yield of product. To assess the generality of Cu-mediated intramolecular C–N bond forming reaction[7,9] we then treated other alkynes,

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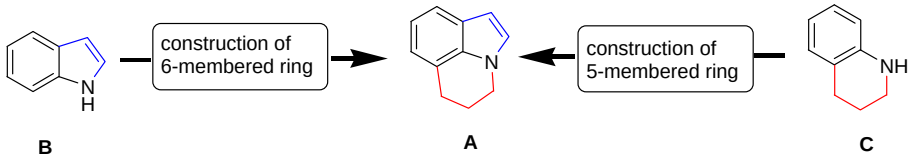
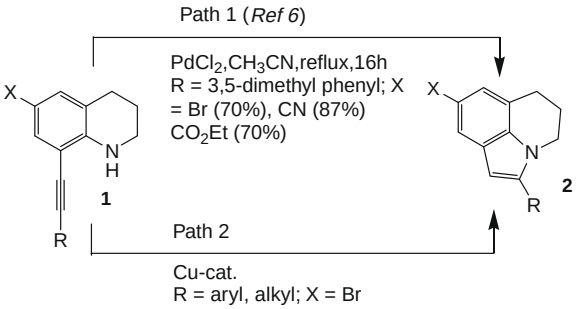
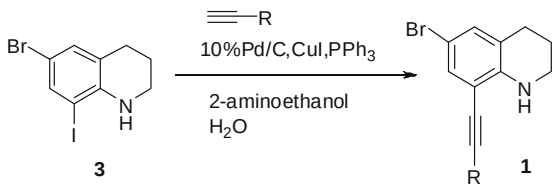


Figure 1. Pyrroloquinoline (**A**) and strategies for its synthesis.



Scheme 1. Transition metal-mediated synthesis of 2-substituted 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines.

Table 1
Pd/C-mediated synthesis of 8-alkynyl-1,2,3,4-tetrahydroquinolines (**1**) in water[a]



Entry	Alkynes; R =	Time (h)	Products (**1**)	Yields (%)
1	C_6H_5	4.0	**1a**	85
2	$C_6H_4CH_3$-*p*	3.0	**1b**	95
3	$C_6H_4NO_2$-*o*	30.0	**1c**	40
4	CH_2CH_2OH	16.0	**1d**	57
5	$(CH_2)_3OH$	18.0	**1e**	51

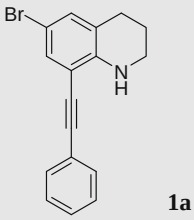
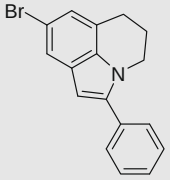
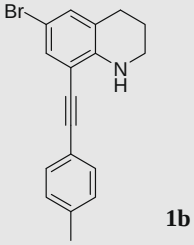
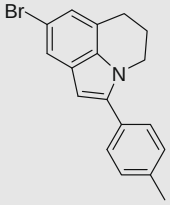
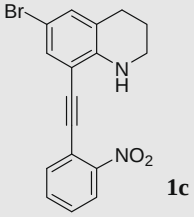
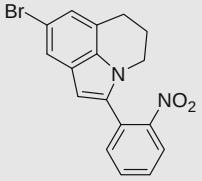
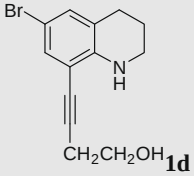
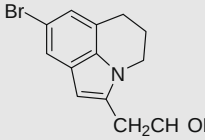
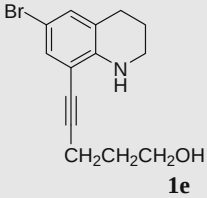
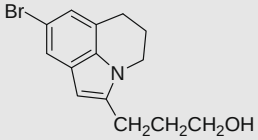
[a] All reactions were carried out by using **3** (1.0 equiv), terminal alkyne (3.0 equiv), 1:4:2 ratio of Pd/C–PPh_3–CuI and 2-aminoethanol (3 equiv) in water at 80 °C.

that is, **1b–e** with CuI in DMF and the results are presented in Table 2. All the 8-arylethynyl-1,2,3,4-tetrahydroquinolines (**1a–c**) provided the desired products (**2a–c**) in good yields (Table 2, entries 1–3) whereas the 8-alkylethynyl derivatives (**1d–e**) afforded the corresponding products (**2d–e**) in moderate yields (Table 2, entries 4 and 5).[10]

Having prepared a number of 8-bromo derivatives of 2-substituted 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline we decided to explore the reactivity of bromo group toward palladium-catalyzed reactions. Conversely, to demonstrate the scope of this Cu-mediated reaction we opted for further structural elaboration of the compounds synthesized. Accordingly, bromo derivative **2a** was exposed to Heck, Sonogashira, and Suzuki coupling reactions (Table 3). Heck reactions were carried out by using **2a** (1.0 equiv), an appropriate alkene (4.0 equiv), $Pd(OAc)_2$ (0.1 equiv), *n*-Bu_4NCl (1.0 equiv), and Na_2CO_3 (3 equiv) in DMF at 85 °C. After usual workup corresponding coupled products were isolated in good to moderate yields (Table 3, entries 1–3). Sonogashira reactions were carried out using **2a** (1.0 equiv), a terminal alkyne (3.0 equiv), $(PPh_3)_2PdCl_2$ (0.1 equiv), CuI (0.06), and Et_3N (5.0 equiv) in acetonitrile at refluxing temperature. The corresponding internal alkynes were isolated in 50–72% yields (Table 3, entries 4–6). Suzuki reactions were carried out by using **2a** (1.0 equiv), a boronic acid (1.5 equiv), $(PPh_3)_4Pd$ (0.1 equiv), and 2.0 M Na_2CO_3 (3 equiv) in 1,4-dioxane at 80 °C (Table 3, entries 7–9).

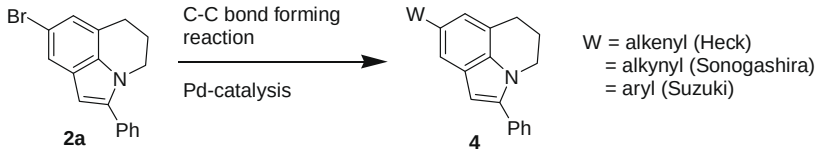
Overall, compound **2a** participated well in Pd-mediated C–C bond forming reactions providing an array of appropriately functionalized 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines (**4**). Thus an easy access to 8-alkenyl or alkynyl or aryl-substituted products

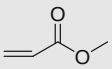
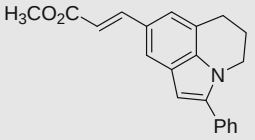
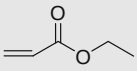
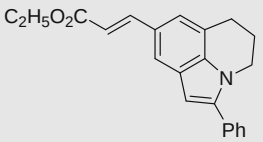
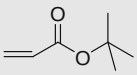
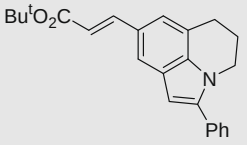
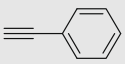
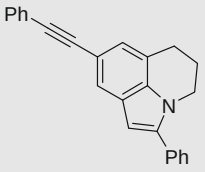
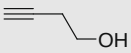
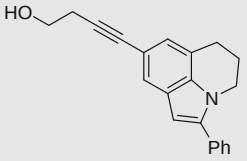
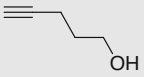
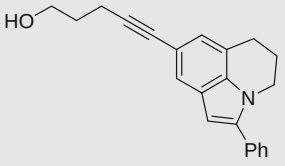
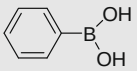
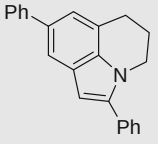
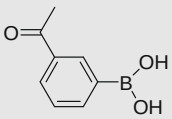
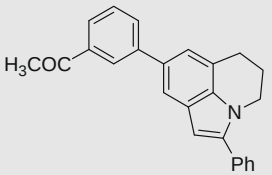
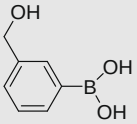
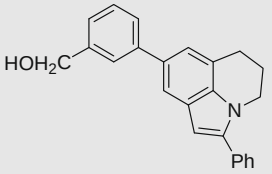
Table 2
Synthesis of 2-substituted 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines (**2**) under Cu-catalysis[a]

Entry	Alkynes (**1**)	Time (h)	Products (**2**)	Yields (%)
1	 **1a**	12.0	 **2a**	85
2	 **1b**	12.0	 **2b**	70
3	 **1c**	18.0	 **2c**	92
4	 **1d**	18.0	 **2d**	50
5	 **1e**	12.0	 **2e**	57

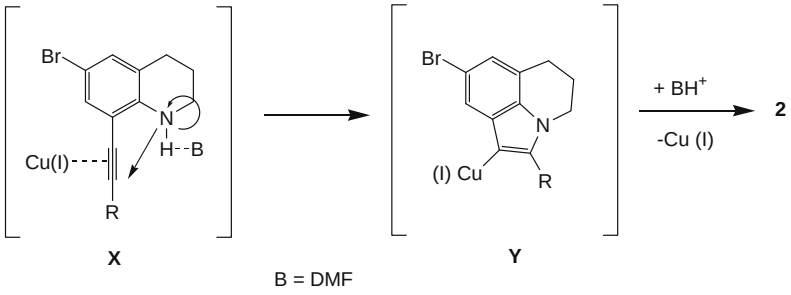
[a] All reactions were carried out by using **1** (1.0 equiv) and CuI (0.1 equiv) in DMF at 100 °C.

Table 3
Heck, Sonogashira, and Suzuki coupling reactions of **2a**



Entry no.	Reactants	Time (h)	Products	Yield[a] (%)
1		24.0	 **4a**	70
2		36.0	 **4b**	60
3		36.0	 **4c**	55
4		24.0	 **4d**	72
5		30.0	 **4e**	54
6		36.0	 **4f**	50
7		12.0	 **4g**	70
8		4.0	 **4h**	70
9		6.0	 **4i**	50

[a] Isolated yields.



Scheme 2. Probable mechanism for the Cu-mediated intramolecular cyclization of alkyne **1**.

has been demonstrated via Heck, Sonogashira, or Suzuki reaction, respectively.

A plausible mechanism for the Cu-mediated intramolecular cyclization of alkyne **1** is shown in Scheme 2. The reaction seemed to proceed via initial activation of the triple bond of **1** via coordination to the Cu-salt to form the σ-complex **X**. Regioselective nucleophilic attack of the tetrahydroquinoline moiety to the Cu-coordinated triple bond through its nitrogen in an *endo* dig fashion provides the Cu-vinyl species **Y**. This on subsequent protonation in situ regenerates the catalyst producing the pyrroloquinolines (**2**).

In conclusion, we have developed a new strategy for the intramolecular cyclization of 8-alkynyl 1,2,3,4-tetrahydroquinoline to afford 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines directly with high regioselectivity. The reaction proceeds via C–N bond forming reaction in the presence of Cu-catalyst. Further functionalization of the compounds synthesized was carried out under Sonogashira, Heck, and Suzuki reaction conditions. The methodology therefore should find applications in the short synthesis of pyrroloquinoline-based compounds of potential pharmacological interest.

Acknowledgments

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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.2009.06.041.

References and notes

1. Stanton, J. L.; Ackerman, M. H. *J. Med. Chem.* **1983**, *26*, 986–989.
2. Paris, D.; Cottin, M.; Demonchaux, P.; Augert, G.; Dupassieux, P.; Lenoir, P.; Peck, M. J.; Jasserand, D. *J. Med. Chem.* **1995**, *38*, 669–685.
3. Isaac, M.; Slassi, A.; O'Brien, A.; Edwards, L.; MacLean, N.; Bueschkens, D.; Lee, D. K. H.; McCallum, K.; Lannoy, I. D.; Demchyshyn, L.; Kamboj, R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 919–921.
4. Al-awar, R. S.; Ray, J. E.; Hecker, K. A.; Huang, J.; Waid, P. P.; Shih, C.; Brooks, H. B.; Spencer, C. D.; Watkins, S. A.; Patel, B. R.; Stamm, N. B.; Ogg, C. A.; Schultz, R. M.; Considine, E. L.; Faul, M. M.; Sullivan, K. A.; Kolis, S. P.; Grutsch, J. L.; Joseph, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3217–3220.
5. Zhu, G.; Conner, S. E.; Zhou, X.; Chan, H.-K.; Shih, C.; Engler, T. A.; Al-awar, R. S.; Brooks, H. B.; Watkins, S. A.; Spencer, C. D.; Schultz, R. M.; Dempsey, J. A.; Considine, E. L.; Patel, B. R.; Ogg, C. A.; Vasudevan, V.; Lytle, M. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3057–3061.
6. Marchand, P.; Puget, A.; Baut, G. L.; Emig, P.; Czech, M.; Günther, E. *Tetrahedron* **2005**, *61*, 4035–4041. and references cited therein.
7. Barange, D. K.; Nishad, T. C.; Swamy, N. K.; Bandameedi, V.; Kumar, D.; Sreekanth, B. R.; Vyas, K.; Pal, M. *J. Org. Chem.* **2007**, *72*, 8547.
8. Pal, M.; Batchu, V. R.; Subramanian, V.; Parasuraman, K.; Swamy, N. K.; Kumar, S. *Tetrahedron* **2005**, *61*, 9869.
9. Ezquerra, J.; Pedregal, C.; Lamas, C.; Barluenga, J.; Prez, M.; Garca-Martin, G. A.; Gonzlez, J. M. *J. Org. Chem.* **1996**, *61*, 5804.
10. *Spectra data for selected compounds*: compound **2a**: white solid; mp 103–105 °C; R_f (10% ethyl acetate/*n*-hexane) 0.35; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.62–7.41 (m, 6H, Ar-H), 7.03 (s, 1H, Ar-H), 6.54 (s, 1H, –CH=), 4.19 (t, J = 5.2 Hz, 2H, –CH_2), 2.93 (t, J = 5.6 Hz, 2H, –CH_2), 2.07–2.13 (m, 2H, –CH_2); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 22.4 (–CH_2), 23.9 (–CH_2), 43.3 (–CH_2), 99.5, 112.1, 119.5, 120.7, 124.5, 126.9, 127.9, 128.2 (2C), 128.4, 128.7, 131.4, 133.4, 140.5; IR (cm^{-1}, KBr) 2929, 1475, 763; Mass (ES) *m*/*z* 314.1 (M+3, 100%); HRMS (ESI): calcd for $C_{17}H_{15}BrN$ $(M+H)^+$ 312.039, found 312.038; compound **2b**: yellow solid; mp 92–95 °C; R_f (10% ethyl acetate/*n*-hexane) 0.35; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.5 (m, 3H, Ar-H), 7.30 (d, J = 7.8 Hz, 2H, Ar-H), 7.01 (s, 1H, Ar-H), 6.49 (s, 1H, –CH=), 4.17 (t, J = 5.2 Hz, 2H, –CH_2), 2.92 (t, J = 5.6 Hz, 2H, –CH_2), 2.37 (s, 3H, CH_3), 2.12–2.07 (m, 2H, –CH_2); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 20.7 (–CH_3), 22.4 (–CH_2), 23.9 (–CH_2), 43.2 (–CH_2), 99.0, 112.0, 119.3, 120.5, 124.4, 126.9, 128.1 (2C), 128.5, 129.3 (2C), 133.4, 137.4, 140.6; IR (cm^{-1}, KBr) 2924, 1720, 1477, 829; Mass (ES) *m*/*z* 326.0 (M+1, 100%); HRMS (ESI): calcd for $C_{18}H_{17}BrN$ $(M+H)^+$ 326.054, found 326.054; compound **2d**: colorless liquid; R_f (50% ethyl acetate/*n*-hexane) 0.3; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.39 (d, J = 1.9 Hz, 1H, Ar-H), 6.89 (d, J = 1.5 Hz, 1H, Ar-H), 6.14 (s, 1H, –CH=), 4.65 (br s, 1H, –CH_2*OH*), 4.04 (t, J = 5.6 Hz, 2H, –CH_2), 3.68 (t, J = 6.8 Hz, 2H, –CH_2), 2.90–2.87 (m, 4H, –CH_2), 2.13–2.06 (m, 2H, –CH_2); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 22.1 (–CH_2), 23.8 (–CH_2), 36.1 (–CH_2), 41.1 (–CH_2), 60.2 (–CH_2), 97.7, 111.4, 118.6, 119.4, 123.4, 126.9, 132.5, 139.1; IR (cm^{-1}, $CHCl_3$) 2928, 1717, 1480, 1216, 769; Mass (ES) *m*/*z* 282.0 (M+3, 100%); HRMS (ESI): calcd for $C_{13}H_{15}BrNO$ $(M+H)^+$ 280.033, found 280.033.