Regioselective alkynylation followed by Suzuki coupling of 2,4-dichloroquinoline: Synthesis of 2-alkynyl-4-arylquinolines

Ellanki A. Reddy, Aminul Islam, K. Mukkanti, Venkanna Bandameedi, Dipal R. Bhowmik and Manojit Pal*

Abstract
A two step synthesis of 2-alkynyl-4-arylquinolines has been accomplished via Pd/C-mediated regioselective C-2 alkynylation of 2,4-dichloroquinoline in water followed by Suzuki coupling at C-4 of the resulting 4-chloro derivative.

Introduction
2-Alkynyl pyridine and its benzo (i.e. quinoline) derivative possessing an aryl group at the C-4 position (A, Figure 1) have attracted considerable interest due to their utility in the development of compounds of potential pharmacological interest [1-3]. 2-Alkenyl/alkynylquinolines, have been reported to possess anti-retroviral properties [4]. Only few methods are known for the synthesis of A. Considering the possible C–C bond forming reactions on a pyridine/quinoline ring (Figure 1), the synthesis of A can be carried out following two main strategies e.g. (a) arylation at C-4 followed by alkynylation at C-2 or (b) alkynylation at C-2 followed by arylation at C-4. Methodologies based on strategy ‘a’ have been reported earlier. For example, Sonogashira coupling of a terminal alkyne with 2-chloro-4-aryl substituted quinoline [3] in the presence of (PPh$_3$)$_2$PdCl$_2$-CuI or treatment of 4-aryl pyridine-N-oxide with alkynyl Grignard [5] provided the required quinoline or...
Scheme 1: Sequential synthesis of 2-alkynyl-4-arylquinolines from 2,4-dichloroquinoline under palladium catalysis.

**Scheme 2: The reaction mechanism of stepwise C–C bond forming reactions.**
Table 1: Pd/C-mediated [Pd/C (10 mol%)–CuI (5 mol%)–PPh₃ (20 mol%)] synthesis of 2-alkynyl-4-chloroquinolines (3).a

| Entry | Terminal alkynes (2) | Time (h) | Products (3)b | Yield (%)^c |
|-------|---------------------|----------|---------------|-------------|
| 1.    | 2a                  | 10       | 3a            | 88          |
| 2.    | 2b                  | 8        | 3b            | 85          |
| 3.    | 2c                  | 10       | 3c            | 90          |
| 4.    | 2d                  | 12       | 3d            | 92          |
| 5.    | 2e                  | 12       | 3e            | 90          |
| 6.    | 2f                  | 8        | 3f            | 87          |

aAll the reactions were carried out by using compound 1 (1.0 equiv), terminal alkyne 2 (1.5 equiv), 10% Pd/C (0.026 equiv), PPh₃ (0.20 equiv), CuI (0.05 equiv), and Et₃N (3.0 equiv) at 80 °C.
bIdentified by ¹H NMR, IR, and MS.
cIsolated yields.

2,4 dichloroquinoline (1) with terminal alkynes (2) in water proceeds via normal Sonogashira pathway [6]. Due to the presence of electronegative nitrogen atom the chloro group at the azomethine carbon is more susceptible to undergo oxidative addition with Pd(0) than chloro group at C-4. Moreover, the coordination of quinoline nitrogen to the palladium [18,19] controls the regioselectivity in alkynylation of 2,4-dichloroquinoline at C-2 position. The 2-alkynyl-4-chloroquinolines 3 thus formed then undergo Suzuki reaction in the next step. Oxidative addition of Pd⁰ generated in situ to compound 3 followed by trans-organometallation of the resultant aryl-palladium complex formed with arylboronic acids provides the desired compound 5.

Conclusions
In conclusion, a two-step method consisting of alkynylation followed by arylation has been developed for the synthesis of 2-alkynyl-4-arylquinolines. The alkynylation step involved Pd/C–Cu mediated regioselective C-2 alkynylation of 2,4-dichloroquinoline in water to afford 2-alkynyl-4-
Table 2: Synthesis of 2-alkynyl-4-arylquinolines (5).

| Entry | 4-Chloro compd (3) | Arylboronic acid (4) | Product\(^a\) (5) | Time (h) | Yield (%)** |
|-------|--------------------|----------------------|---------------------|----------|-------------|
| 1.    | 3e                 | phenylboronic acid (4a) | ![5a](image.png) | 4        | 83          |
| 2.    | 3b                 | 4a                   | ![5b](image.png) | 3        | 88          |
| 3.    | 3c                 | 4a                   | ![5c](image.png) | 2        | 87          |
| 4.    | 3d                 | 4a                   | ![5d](image.png) | 4        | 82          |
| 5.    | 3a                 | 4a                   | ![5e](image.png) | 2        | 84          |
| 6.    | 3f                 | 4a                   | ![5f](image.png) | 3        | 79          |

chloroquinoline. The arylation step is a Pd-mediated (Suzuki) coupling of 2-alkynyl-4-chloro derivative with arylboronic acids in aqueous media to give the target compounds. The process is amenable to the diversity-oriented synthesis of quinoline derivatives of potential pharmacological significance and may therefore find wide usage in organic/medicinal chemistry.
Table 2: Synthesis of 2-alkynyl-4-aryquinolines (5). (continued)

|    | 3a | 3-methoxy-phenylboronic acid (4b) | 2 | 86 |
|----|----|----------------------------------|---|----|
| 7. |  | ![Structure](attachment:structure.png) |  |  |
| 8. |  | ![Structure](attachment:structure.png) |  |  |

*Identified by $^1$H NMR, IR, and MS.

**Isolated yields.**

**Experimental**

General Procedure for the preparation of compound 5: A mixture of alkyne 3 (1.0 mmol) and (PPh$_3$)$_2$PdCl$_2$ (0.05 mmol) in dioxane (5.0 mL) was stirred for 10 min under nitrogen at room temperature and then heated to 80 °C. To this mixture was added a solution of PCy$_3$ (0.05 mmol) and CsCO$_3$ (3.5 mmol) dissolved in water (3.0 mL) and arylboronic acid (1.5 mmol) dissolved in dioxane (3.0 mL) at the same temperature. The mixture was stirred at 80 °C according to the time indicated in Table 2. After completion of the reaction the mixture was cooled to room temperature, concentrated under vacuum and the residue was extracted with EtOAc (3 × 30 mL). The organic layers were collected, combined, washed with cold water (3 × 30 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, using light petroleum ether (60–80 °C)–ethyl acetate to afford the desired product. Spectral data for selected compounds; Compound 5a; light brown gum, Rf (20% ethyl acetate/n-hexane) 0.21; $^1$H NMR (CDCl$_3$, 400 MHz) δ 8.14 (d, $J$ = 8.0 Hz, 1H), 7.85 (d, $J$ = 8.0 Hz, 1H), 7.69 (t, $J$ = 7.8 Hz, 1H), 7.50–7.41 (m, 7H), 2.49 (t, $J$ = 7.0 Hz, 2H), 1.69–1.21 (m, 8H), 0.91–0.8 (m, 3H); IR (cm$^{-1}$, neat) 2927, 2225, 1587, 1543, 1357; m/z (ES Mass) 314 (M+1, 100%); $^{13}$C NMR (CDCl$_3$, 50 MHz) 148.5, 143.6, 137.5 (2C), 129.6 (3C), 128.4 (2C), 126.7 (2C), 125.5 (3C), 124.3, 92.2, 81.0, 76.3, 31.3, 29.6, 28.0, 24.6, 22.5; HRMS (ESI): calcd for C$_{23}$H$_{23}$N (M+H)$^+$ 314.1909, found 314.1896. Compound 5b, low melting solid, Rf (20% ethyl acetate/n-hexane) 0.28; $^1$H NMR (CDCl$_3$, 400 MHz) δ 8.20 (d, $J$ = 7.8 Hz, 1H), 7.87 (d, $J$ = 7.8 Hz, 1H), 7.56–7.47 (m, 9H), 7.25–7.17 (m, 2H), 2.38 (s, 3H); IR (cm$^{-1}$, neat) 2924, 2216, 1583, 1541; m/z (ES Mass) 320 (M+1, 100%); $^{13}$C NMR (CDCl$_3$, 50 MHz) 148.6, 148.5, 143.2 (2C), 139.3 (2C), 137.3 (2C), 134, 132, 129.5 (3C), 129.3 (2C), 126.9 (2C), 125.6 (2C), 124.4, 118.9, 90.2, 88.8, 29.0; HRMS (ESI): calcd for C$_{24}$H$_{17}$N (M+H)$^+$ 320.1439, found 320.1454.

**Supporting Information**

**Supporting Information File 1**

Spectral data of 2-alkynyl-4-aryquinolines 5c–h.

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-32-S1.doc](http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-32-S1.doc)

**Acknowledgments**

The authors thank Dr. V. Dahanukar and Mr. A. Mukherjee for their encouragement and the analytical group for spectral data. Mr. E.A.R. thanks CPS-DRL, Hyderabad, India for allowing him to pursue this work as a part of his Ph.D. program.

**References**

1. Godel, T.; Hoffmann, T.; Schnider, P.; Stadler, H. Preparation of 4-phenylpyridines as neurokinin-1 receptor antagonists. World patent application WO 2002016324 A1, 2002. Chem. Abstr. 2002, 136, 216655.

2. Prostakov, N. S.; Mathew, K. J.; Kurichev, V. A. Khimiya Geterotsiklicheskikh Soedinenii 1967, 5, 876–879. Chem. Abstr. 1968, 69, 18882.
3. Angibaud, P. R.; Venet, M. G.; Pilatte, I. N. C. World Patent Application WO 2002024682 A1, 2002.

4. Fakhfakh, M. A.; Fournet, A.; Prina, E.; Mouscadet, J.-F.; Franck, X.; Hocquemiller, R.; Figadère, B. Bioorg. Med. Chem. 2003, 11, 5013–5023. doi:10.1016/j.bmc.2003.09.007

5. Andersson, H.; Almqvist, F.; Olsson, R. Org. Lett. 2007, 9, 1335–1337. doi:10.1021/ol070184n

6. Reddy, E. A.; Barange, D. K.; Islam, A.; Mukkanti, K.; Pal, M. Tetrahedron 2008, 64, 7143–7150. doi:10.1016/j.tet.2008.05.097

7. Nolan, J. M.; Comins, D. L. J. Org. Chem. 2003, 68, 3736–3738. doi:10.1021/jo3034122w

8. Elangovan, A.; Chen, T.-Y.; Chen, C.-Y.; Ho, T.-I. Chem. Commun. 2003, 2146–2147. doi:10.1039/b305943j

9. Seck, M.; Franck, X.; Hocquemiller, R.; Figadère, B.; Peyrat, J.-F.; Provot, O.; Brion, J.-D.; Alami, M. Tetrahedron Lett. 2004, 45, 1881–1884. doi:10.1016/j.tetlet.2004.01.019

10. Rodríguez, J. G.; de los Ríos, C.; Lafuente, A. Tetrahedron 2005, 61, 9042–9051. doi:10.1016/j.tet.2005.07.043

11. Toyota, M.; Komori, C.; Ihara, M. J. Org. Chem. 2000, 65, 7110–7113. doi:10.1021/jo000816i

12. Ciufolini, M. A.; Mitchell, J. W.; Roschangar, F. Tetrahedron Lett. 1996, 37, 8281–8284. doi:10.1016/0040-4020(96)01937-5

13. Yamanaka, H.; Shiraiwa, M.; Edo, K.; Sakamoto, T. Chem. Pharm. Bull. 1979, 27, 270–273.

14. Belmont, P.; Andreu, J.-C.; Allan, C. S. M. Tetrahedron Lett. 2004, 45, 2783–2786. doi:10.1016/j.tetlet.2004.02.022

15. Beletskaya, I. P.; Latyshev, G. V.; Tsvetkov, A. V.; Lukashev, N. V. Russ. Chem. Bull. 2004, 53, 189–193. doi:10.1023/B:RUCB.0000024849.57521.49

(See for the synthesis of 6-alkynylquinolines.)

16. Belmont, P.; Belhadj, T. Org. Lett. 2005, 7, 1793–1795. doi:10.1021/ol050380z

17. Tiano, M.; Belmont, P. J. Org. Chem. 2008, 73, 4101–4109. doi:10.1021/jo800249f

18. Shiota, T.; Yamamori, T. J. Org. Chem. 1999, 64, 453–457. doi:10.1021/jo981423a

19. Legros, J.-Y.; Primault, G.; Fiaud, J.-C. Tetrahedron 2001, 57, 2507–2514. doi:10.1016/S0040-4020(01)00076-X

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the Beilstein Journal of Organic Chemistry terms and conditions: (http://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at:

doi:10.3762/bjoc.5.32