

An Efficient and Regioselective Synthesis of 2,3-Disubstituted 6-Aminoquinoxaline Derivatives Using Alkoxylation and Microwave-assisted Sonogashira Coupling

Doohyun Lee,^a Young Ho Seo,^{†,a} Jong-Sup Bae, Sangkyu Lee, Tae Im Lee,[‡] Young-Dae Gong,^{§,*} and Taeho Lee^{*}

Research Institute of Pharmaceutical Sciences, College of Pharmacy, Kyungpook National University, Daegu 702-701, Korea
^{*}E-mail: tlee@knu.ac.kr

[†]College of Pharmacy, Keimyung University, Daegu 704-701, Korea

[‡]Osteogenic Core Technologies, Seongnam 463-400, Korea

[§]Center for Innovative Drug Library Research, Department of Chemistry, College of Natural Science, Dongguk University, Seoul 100-715, Korea. ^{*}E-mail: ydgong@dongguk.edu

Received April 10, 2013, Accepted May 22, 2013

Key Words : Quinoxaline, Parallel solution-phase synthesis, 2,3-Disubstituted 6-aminoquinoxaline, Regioselective synthesis, Microwave-assisted Sonogashira coupling

The quinoxalines are a common skeleton of nitrogen-containing heterocycles with biological properties.¹ Because of their good biological activities quinoxalines, which contain 2,3-di-substituents, are of particular interest in medicinal chemistry and drug discovery programs.² We screened diverse heterocyclic chemical compounds of in-house chemical libraries³ and identified biologically active 2,3,6-trisubstituted quinoxaline derivatives,⁴ containing 2,3-disubstituted 6-aminoquinoxalines **1** (see Figure 1) that inhibited the Wnt/ β -catenin signaling pathway and cell proliferation as anti-cancer agents.⁵ Herein, the synthetic routes of 2,3-disubstituted 6-aminoquinoxalines were developed with regioselective sequent substitutions for the further biological studies.

The synthesis of 2,3-disubstituted 6-aminoquinoxalines **1** was started from 2,3-dichloro-6-nitroquinoxaline (**2**)⁶ (route *a*) or 2,3-dichloro-6-aminoquinoxaline (**3**)⁷ (route *b*) with reduction of a nitro moiety, addition of alcohol, and the

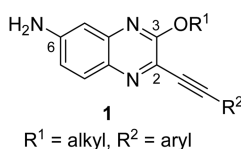
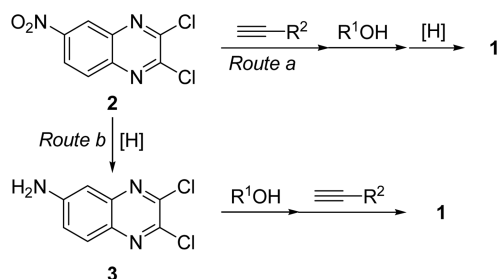


Figure 1. 2,3-Disubstituted 6-aminoquinoxalines **1**.

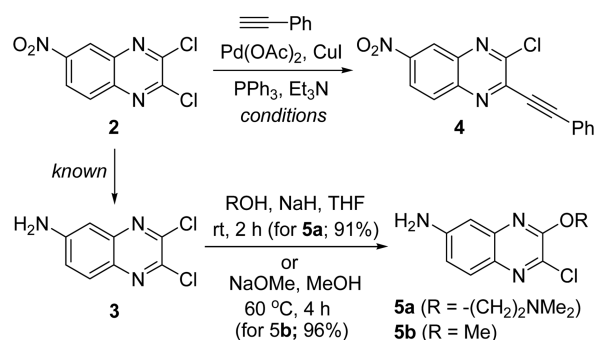


Scheme 1. Regioselective synthetic plans of **1**.

Sonogashira-type cross-coupling reaction in a regioselective manner (Scheme 1).^{7,8}

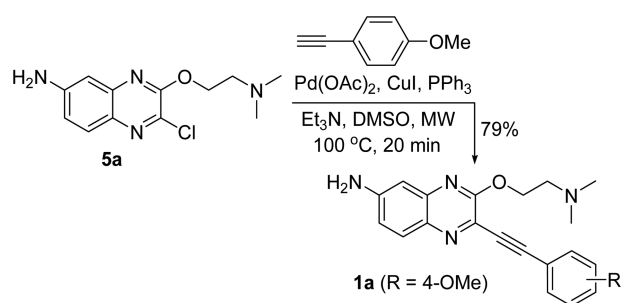
The initial attempt to prepare **4** via route *a* by the palladium-catalyzed Sonogashira coupling⁹ of 2,3-dichloro-6-nitroquinoxaline (**2**) did not bring about complete conversion and gave low regioselectivities with hardship of isolations, even when high temperature conditions (60 °C to 120 °C) and various solvents (acetonitrile, THF, DMF, or DMSO) were used (Scheme 2).¹⁰ In contrast, the regioselective alkoxylation via route *b* at C-2 position of 2,3-dichloro-6-aminoquinoxaline (**3**), which was prepared from the reduction of 6-nitroquinoxaline **2**,⁶⁻⁸ took place efficiently when 2-(dimethylamino)ethanol/NaH and NaOMe/MeOH were used conditions for **5a** (91%) and **5b**^{8b} (96%), respectively.¹¹

With large quantities of 2-chloroquinoxaline **5a** in hand, the next stage was set for exploration of procedures needed to transform 3-alkoxy-2-chloro-6-aminoquinoxaline **5** to the corresponding 2,3-disubstituted 6-aminoquinoxaline derivatives **1** (Scheme 3). The palladium-catalyzed Sonogashira coupling⁹ with 3-alkoxy-2-chloro-6-aminoquinoxaline **5** and acetylenes was performed in the presence of Pd(OAc)₂, CuI, PPh₃, and Et₃N. This process did not lead to high yielding formation of 2,3-disubstituted 6-aminoquinoxaline derivatives **1**, even in THF, acetonitrile, toluene, DMF, or DMSO.



Scheme 2. Regioselective synthesis of **4** and **5**.

^aThese authors contributed equally to this work.



Scheme 3. Pd-catalyzed Sonogashira coupling of **5a**.

Recently, microwave (MW) irradiation has been shown to be a powerful tool for various organic chemical reactions.¹² Interestingly, reaction of **5a** with 4-ethynylanisole under MW irradiation condition (Pd(OAc)₂, CuI, PPh₃, Et₃N, DMSO, 100 °C, 20 min), led to the desired 3-alkoxy-2-substituted 6-aminoquinoline **1a** (R = 4-OMe) in a 79% yield.¹³

On the basis of the regioselective two-step sequent reaction conditions, 2,3-disubstituted 6-aminoquinoline derivatives **1** can be formed from 2,3-dichloro-6-aminoquinoline (**3**) by parallel solution-phase synthetic strategies.¹⁴ The desired quinoline library was constructed with appropriate

Table 1. 2,3-Disubstituted 6-aminoquinolines **1** using the regioselective subsequent reactions^a

| Entry | Products | R ¹ | R ² | Yield (%) ^b |
|-------|-----------|----------------|------------------------|------------------------|
| 1 | 1a | | 4-OMe-Ph | 72 |
| 2 | 1b | | 4-OMe-2-Me-Ph | 85 |
| 3 | 1c | | 4-NMe ₂ -Ph | 77 |
| 4 | 1d | | 4-OMe-Ph | 58 |
| 5 | 1e | | 4-Me-Ph | 62 |
| 6 | 1f | | 4-NMe ₂ -Ph | 53 |
| 7 | 1g | | 4-OMe-Ph | 74 |
| 8 | 1h | | 4-OMe-2-Me-Ph | 78 |
| 9 | 1i | | 4-Me-Ph | 73 |
| 10 | 1j | | 4-NMe ₂ -Ph | 69 |
| 11 | 1k | | 4-OMe-Ph | 74 |
| 12 | 1l | | 4-Me-Ph | 71 |
| 13 | 1m | | 4-OMe-2-Me-Ph | 79 |

Table 1. Continued

| Entry | Products | R ¹ | R ² | Yield (%) ^b |
|-------|-----------|----------------|------------------------|------------------------|
| 14 | 1n | | 4-OMe-Ph | 70 |
| 15 | 1o | | 3-OMe-Ph | 80 |
| 16 | 1p | | 4-Me-Ph | 74 |
| 17 | 1q | | 4-NMe ₂ -Ph | 73 |
| 18 | 1r | | 3-OMe-Ph | 78 |
| 19 | 1s | | 4-Me-Ph | 73 |
| 20 | 1t | | Ph | 77 |
| 21 | 1u | | 4-OMe-Ph | 81 |
| 22 | 1v | | 4-Me-Ph | 79 |
| 23 | 1w | | 4-NMe ₂ -Ph | 75 |
| 24 | 1x | | 4-Me-Ph | 49 |
| 25 | 1y | Me | 4-Me-Ph | 78 |

^a1) alkoxylation: R¹OH, NaH, THF, rt or NaOMe, MeOH, 60 °C; 2) Sonogashira coupling: R²-C≡CH, Pd(OAc)₂, CuI, PPh₃, Et₃N, DMSO, 100 °C, 20 min. ^bTwo-step overall isolated yields from 2,3-dichloro-6-aminoquinoline (**3**).

alcohols (or NaOMe) and substituted phenylacetylenes, and the synthetic 2,3-disubstituted 6-aminoquinoline derivatives **1** displayed with isolated yields in Table 1.

When the R¹ in 6-aminoquinoline **1** is a secondary alkyl group, the 2,3-disubstituted 6-aminoquinoline derivatives **1** were obtained in lower yields and high purities (Table 1, entries 4-6 and 24). In most cases (entries 1-3, 7-23, and 25), 2,3-disubstituted 6-aminoquinoline derivatives **1** were obtained with good yields and high purities, > 95% as judged from LC-MS traces (integration of diode array 200-400 nm traces).

In summary, the yields for 2,3-disubstituted 6-aminoquinoline derivatives produced through regioselective subsequent synthetic reactions (alkoxylation and microwave-assisted Sonogashira coupling) ranged from 49 to 85% from known 2,3-dichloro-6-aminoquinoline. In addition, the desired 6-aminoquinolines with two-diversity points were obtained in high purities (> 95%) as judged from LC-MS and ¹H NMR analyses. This strategy allows for a ready access to a large library and is potentially applicable to the preparation of other 6-aminoquinoline derivatives. Further studies in this area are underway, and the results of these studies will be reported in due course.

Acknowledgments. This research was supported by

Kyungpook National University Research Fund, 2011.

Supporting Information. General and analytical data of compounds **1a-1y**.

References

- (a) Balderas-Renteria, I.; Gonzalez-Barranco, P.; Garcia, A.; Banik, B. K.; Rivera, G. *Curr. Med. Chem.* **2012**, *19*, 4377-4398. (b) Noolvi, M. N.; Patel, H. M.; Bhardwaj, V.; Chauhan, A. *Eur. J. Med. Chem.* **2011**, *46*, 2327-2346. (c) Brown, D. J. Quinoxalines: Supplement II. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Wipf, P., Eds.; John Wiley & Sons: New Jersey, 2004.
- For recent selective examples, see: (a) Deng, J.; Feng, E.; Ma, S.; Zhang, Y.; Liu, X.; Li, H.; Huang, H.; Zhu, J.; Zhu, W.; Shen, X.; Miao, L.; Liu, H.; Jiang, H.; Li, J. *J. Med. Chem.* **2011**, *54*, 4508-4522. (b) Zhang, L.; Qiu, B.; Xiong, B.; Li, X.; Li, J.; Wang, X.; Li, J.; Shen, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2118-2122. (c) Li, J. J.; Carson, K. G.; Trivedi, B. K.; Yue, W. S.; Ye, Q.; Glynn, R. A.; Miller, S. R.; Connor, D. T.; Roth, B. D.; Low, J. E.; Heilig, D. J.; Yang, W.; Qin, S.; Hunt, S. *Bioorg. Med. Chem.* **2003**, *11*, 3777-3790.
- (a) Yang, S.-J.; Lee, S.-H.; Kwak, H.-J.; Gong, Y.-D. *J. Org. Chem.* **2013**, *78*, 438-444. (b) Kim, S.-G.; Jun, S.-L.; Lee, G.-H.; Gong, Y.-D. *ACS Comb. Sci.* **2013**, *15*, 29-40. (c) Lee, T.; Gong, Y.-D. *Molecules* **2012**, *17*, 5467-5496. (d) Gong, Y.-D.; Min, K. H.; Lee, T. *Bull. Korean Chem. Soc.* **2011**, *32*, 2453-2456. (e) Gong, Y.-D.; Lee, T. *J. Comb. Chem.* **2010**, *12*, 393-409. (f) Lee, T.; Lee, D.; Lee, I. Y.; Gong, Y.-D. *J. Comb. Chem.* **2010**, *12*, 95-99. (g) Lee, T.; Park, J.-H.; Lee, D.-H.; Gong, Y.-D. *J. Comb. Chem.* **2009**, *11*, 495-499. (h) Lee, T.; Park, J.-H.; Jeon, M.-K.; Gong, Y.-D. *J. Comb. Chem.* **2009**, *11*, 288-293. And references cited therein.
- (a) Lee, S. B.; Gong, Y.-D.; Park, Y. I.; Dong, M.-S. *Biochem. Biophys. Res. Commun.* **2013**, *431*, 746-752. (b) Lee, Y. B.; Gong, Y.-D.; Kim, D. J.; Ahn, C.-H.; Kong, J.-Y.; Kang, N.-S. *Bioorg. Med. Chem.* **2012**, *20*, 1303-1309. (c) Lee, Y. B.; Gong, Y.-D.; Yoon, H.; Ahn, C.-H.; Jeon, M.-K.; Kong, J.-Y. *Bioorg. Med. Chem.* **2010**, *18*, 7966-7974.
- Lee, S.-B.; Park, Y. I.; Dong, M.-S.; Gong, Y.-D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5900-5904.
- (a) Wang, Z.; Fraley, C.; Mezo, A. R. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1253-1256. (b) Ancizu, S.; Castrillo, N.; Perez-Silanes, S.; Aldana, I.; Monge, A.; Delagrange, P.; Caignard, D.-H.; Galiano, S. *Molecules* **2012**, *17*, 7737-7757. (c) Yang, Y.; Zhang, S.; Wu, B.; Ma, M.; Chen, X.; Qin, X.; He, M.; Hussain, S.; Jing, C.; Ma, Bing; Zhu, C. *ChemMedChem* **2012**, *7*, 823-835.
- (a) Jeon, M.-K.; Kim, D.-S.; La, H. J.; Gong, Y.-D. *Tetrahedron Lett.* **2005**, *46*, 4979-4983. (b) Ford, E.; Brewster, A.; Jones, G.; Bailey, J.; Sumner, N. *Tetrahedron Lett.* **2000**, *41*, 3197-3198.
- For recent examples of regioselective synthesis of 2,3-disubstituted quinoxaline from 2,3-dichloroquinoxaline. See: reference 7 and (a) Smits, R. A.; Lim, H. D.; Hanzer, A.; Zuiderveld, O. P.; Guaita, E.; Adami, M.; Coruzzi, G.; Leurs, R.; de Esch, I. J. P. *J. Med. Chem.* **2008**, *51*, 2457-2467. (b) Gong, Y.-D.; Jeon, M.-K.; Lee, T.; Hwang, S.-H.; Yoo, S.-e. *Korean Pat. No. KR2009090792*.
- For recent examples of Sonogashira cross-coupling of 2- or 3-haloquinoxaline. See: (a) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245-2267. (b) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Tetrahedron Lett.* **2004**, *45*, 2431-2434. (c) Armengol, M.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 978-984. (d) Armengol, M.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 154-158.
- The Sonogashira coupling of 2,3-dichloro-6-nitroquinoxaline (**2**) and phenylacetylene gave mixtures of 2- or 3-phenylacetylene-substituted quinoxaline with 4:1 to 10:1 ratio in ¹H NMR spectra analysis.
- Spectroscopic data of compounds **5**. For 2-chloro-3-(2-dimethylaminoethoxy)-quinoxalin-6-ylamine (**5a**): ¹H NMR (500 MHz, CDCl₃) δ 2.39 (s, 6H), 2.83 (t, *J* = 5.9 Hz, 2H), 4.11 (br s, 2H), 4.61 (t, *J* = 5.9 Hz, 2H), 6.92-6.96 (m, 2H), 7.69 (d, *J* = 8.7 Hz, 1H); LC-MS (ESI) *m/z* 267 ([M+1]⁺). For 2-chloro-3-methoxyquinoxalin-6-amine (**5b**): ¹H NMR (500 MHz, CDCl₃) δ 4.11-4.12 (m, 5H), 6.95-6.97 (m, 2H), 7.70 (dd, *J* = 1.5, 8.3 Hz, 1H); LC-MS (ESI) *m/z* 210 ([M+1]⁺).
- For recent reviews, see: (a) Tierney, J. P.; Lidström, P. *Microwave Assisted Organic Synthesis*; Blackwell: Oxford, U.K., 2005. (b) Molteni, V.; Ellis, D. A. *Curr. Org. Synth.* **2005**, *2*, 333-375. (c) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberin, R. *J. Comb. Chem.* **2002**, *4*, 95-105. And see references 3f-h.
- Spectroscopic data of compound **1a**: ¹H NMR (500 MHz, CDCl₃) δ 2.44 (s, 6H), 2.87 (t, *J* = 5.7 Hz, 2H), 3.84 (s, 3H), 4.18 (br s, 2H), 4.63 (t, *J* = 5.7 Hz, 2H), 6.89-6.91 (m, 3H), 6.95 (dd, *J* = 2.5, 8.8 Hz, 1H), 7.57 (d, *J* = 8.9 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 1H); LC-MS (ESI) *m/z* 363 ([M+1]⁺).
- General procedure for preparation of 2,3-disubstituted 6-aminoquinoxaline derivatives 1.** A typical procedure for preparing 2,3-disubstituted 6-aminoquinoxaline derivatives **1**, as exemplified for 3-(2-dimethylaminoethoxy)-2-(4-methoxy-phenylethynyl)-quinoxalin-6-ylamine (**1a**).
2-Chloro-3-(2-dimethylaminoethoxy)-quinoxalin-6-ylamine (5a). To a solution of 2,3-dichloro-6-aminoquinoxaline (**3**) (1.07 g, 5.00 mmol) and 2-dimethylaminoethanol (0.53 mL, 5.25 mmol) in THF (20 mL) was added NaH (210 mg, 5.25 mmol, 60% dispersion in mineral oil) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, and then diluted with CH₂Cl₂, washed with brine, and dried over MgSO₄. The solvent was removed, and the residue was purified by flash silica gel column chromatography (CH₂Cl₂/MeOH, 15:1) to give **5a** (1.21 g, 91%) as a light yellow solid.
3-(2-dimethylaminoethoxy)-2-(4-methoxy-phenylethynyl)-quinoxalin-6-ylamine (1a). To a solution of 2-chloro-3-(2-dimethylaminoethoxy)-quinoxalin-6-ylamine (**5a**) (411 mg, 1.54 mmol) and 4-ethynylanisole (0.30 mL, 2.31 mmol) in DMSO (10 mL) were added Pd(OAc)₂ (20 mg, 0.10 mmol), Ph₃P (26 mg, 0.10 mmol), CuI (39 mg, 0.20 mmol), and Et₃N (1.66 mL, 11.8 mmol). The mixture was stirred under microwave irradiation at 100 °C for 20 min, cooled and then diluted with CH₂Cl₂, washed with brine, and dried over MgSO₄. The solvent was removed, and the residue was purified by flash silica gel column chromatography (CH₂Cl₂/MeOH, 10:1) to give **1a** (439 mg, 79%) as a light yellow solid.