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

Doohyun Lee, Young Ho Seo, 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. Because of their good biological activities quinoxalines, which contain 2,3-di-substituents, are of particular interest in medicinal chemistry and drug discovery programs. We screened diverse heterocyclic chemical compounds of in-house chemical libraries and identified biologically active 2,3,6-trisubstituted quinoxaline derivatives, 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. 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) (route a) or 2,3-dichloro-6-aminoquinoxaline (3) (route b) with reduction of a nitro moiety, addition of alcohol, and the 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 coupling 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 (96%), respectively.11

With large quantities of 2-chloroquinoline 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 coupling with 3-alkoxy-2-chloro-6-aminoquinoxaline 5 and acetylenes was performed in the presence of Pd(OAc)2, Cul, 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.
Recently, microwave (MW) irradiation has been shown to be a powerful tool for various organic chemical reactions.\textsuperscript{12} Interestingly, reaction of 5a with 4-ethynylanisole under MW irradiation condition (\textit{Pd(OAc)}\textsubscript{2}, CuI, PPh\textsubscript{3}, Et\textsubscript{3}N, DMSO, 100 °C, 20 min), led to the desired 3-alkoxy-2-substituted 6-aminoquinoxaline 1a (R = 4-OMe) in a 79% yield.\textsuperscript{13}

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

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Entry & Products & R\textsuperscript{1} & R\textsuperscript{2} & Yield (%)\textsuperscript{b} \\
\hline
1 & 1a & 4-OMe-Ph & 72  \\
2 & 1b & 4-OMe-2-Me-Ph & 85  \\
3 & 1c & 4-NMe\textsubscript{2}-Ph & 77  \\
4 & 1d & 4-OMe-Ph & 58  \\
5 & 1e & 4-Me-Ph & 62  \\
6 & 1f & 4-NMe\textsubscript{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\textsubscript{2}-Ph & 69  \\
11 & 1k & 4-OMe-Ph & 74  \\
12 & 1l & 4-Me-Ph & 71  \\
13 & 1m & 4-OMe-2-Me-Ph & 79  \\
\hline
\end{tabular}
\caption{2,3-Disubstituted 6-aminoquinoxalines 1 using the regioselective subsequent reactions\textsuperscript{a}}
\end{table}

\textsuperscript{a}1) alkoxylation: R\textsuperscript{1}OH, NaH, THF, rt or NaOMe, MeOH, 60 °C; 2) Sonogashira coupling: R\textsuperscript{2}-C≡CH, Pd(OAc)\textsubscript{2}, CuI, PPh\textsubscript{3}, Et\textsubscript{3}N, DMSO, 100 °C, 20 min. \textsuperscript{b}Two-step overall isolated yields from 2,3-dichloro-6-aminoquinoxaline (3).

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

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

\textbf{Acknowledgments.} This research was supported by
Kyungpook National University Research Fund, 2011.

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

**References**


6. The Chemistry of Heterocyclic Compounds


8. A typical procedure for preparing 2,3-disubstituted 6-aminoquinoline derivatives 1. To a solution of 2-chloro-3-(2-dimethylaminoethoxy)-quinoxalin-6-ylamine (1a), as exemplified for 3-(2-dimethylaminoethoxy)-2-(4-methoxy-phenethyl)-quinolin-6-ylamine (1a).

9. 2-Chloro-3-(2-dimethylaminoethoxy)-quinolin-6-ylamine (5a): 3-(2-Dimethylamoethoxy)-quinoxalin-6-ylamine (5b): 

10. Sonogashira coupling of 2,3-dichloro-6-nitroquinoline (2) and phenylacetylene gave mixtures of 2- or 3-phenylacetylene-substituted quinoxaline with 4:1 to 10:1 ratio in 1H NMR spectra analysis.

11. Spectroscopic data of compounds 5. For 2-chloro-3-(2-dimethylaminoethoxy)-quinoxalin-6-ylamine (5a): 


13. Spectroscopic data of compound 1a: 3-(2-Dimethylaminoethoxy)-quinoxalin-6-ylamine (5a) and 2-dimethylaminoethanol (0.53 mL, 5.25 mmol) in CDCl3 (20 mL) was added NaH (210 mg, 5.25 mmol, 60% dispersion in mineral oil) at 0 °C for 20 min, cooled and then diluted with CH2Cl2 (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 (1.21 g, 91%) as a light yellow solid.

14. General procedure for preparation of 2,3-disubstituted 6-aminoquinoline derivatives 1. A typical procedure for preparing 2,3-disubstituted 6-aminoquinoline derivatives 1, as exemplified for 3-(2-dimethylaminoethoxy)-2-(4-methoxy-phenethyl)-quinolin-6-ylamine (1a).

15. 2-Chloro-3-(2-dimethylaminoethoxy)-quinolin-6-ylamine (5a). To a solution of 2,3-dichloro-6-aminoquinoline (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.

16. 3-(2-dimethylaminoethoxy)-2-(4-methoxy-phenethyl)-quinolin-6-ylamine (1a). To a solution of 2-chloro-3-(2-dimethylaminoethoxy)-quinolin-6-ylamine (5a) (141 mg, 1.54 mmol) and 2-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.