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

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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 libraries[3] 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-aminoqunoxaline (**3**)[7] (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]

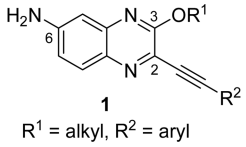
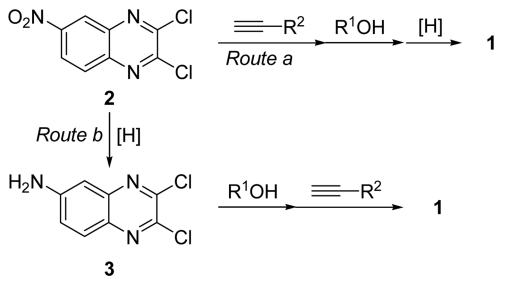


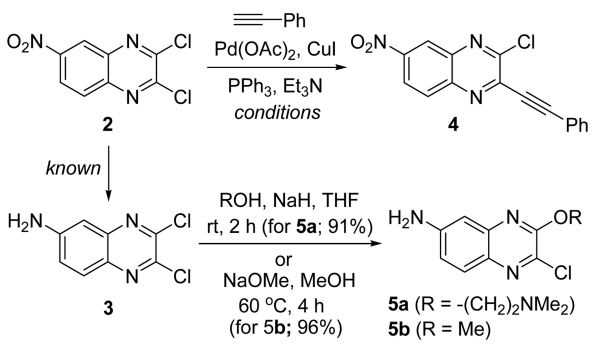
Figure 1. 2,3-Disubstituted 6-aminoquinoxalines **1**.



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

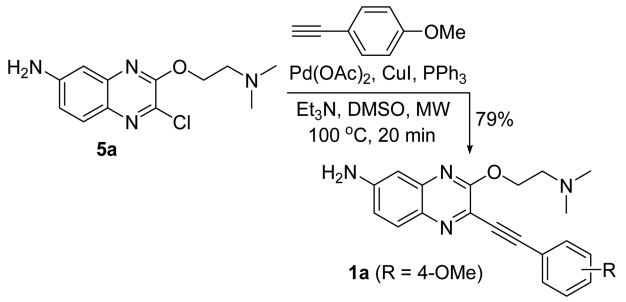
The initial attempt to prepare **4** *via* route *a* by the palladium-catalyzed Sonogashira coupling[9] of 2,3-dichloro-6-nitroquinoxaline (**2**) did not bring about complete conversion and gave low regioselectivities with hardship of isolations, even when high temperature conditions (60 °C to 120 °C) 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-aminoqunixaline (**3**), which was prepared from the reduction of 6-nitroqunoxaline **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-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[9] with 3-alkoxy-2-chloro-6-aminoquinoxaline **5** and acetylenes was performed in the presence of $Pd(OAc)_2$, CuI, PPh_3, and Et_3N. 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**.

[a]These authors contributed equally to this work.

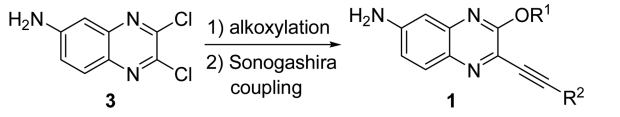


Scheme 3. Pd-catalyzed Sonogashira coupling of **5a**.

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, PPh_3, Et_3N, DMSO, 100 °C, 20 min), led to the desired 3-alkoxy-2-substituted 6-aminoquinoxaline **1a** (R = 4-OMe) in a 79% yield.[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-aminoqunixaline (**3**) by parallel solution-phase synthetic strategies.[14] The desired quinoxaline library was constructed with appropriate

Table 1. 2,3-Disubstituted 6-aminoquinoxalines **1** using the regioselective subsequent reactions[a]



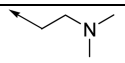
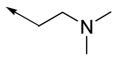
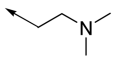
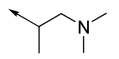
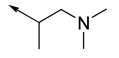
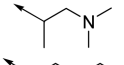
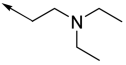
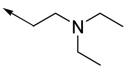
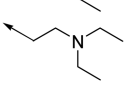
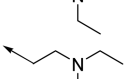
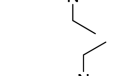
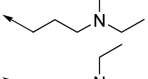
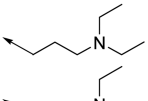
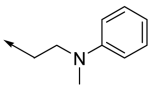
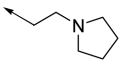
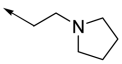
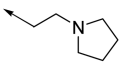
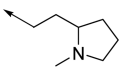
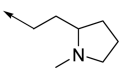
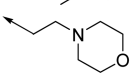
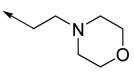
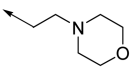
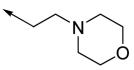
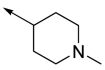
Entry	Products	R^1	R^2	Yield (%)[b]
1	**1a**		4-OMe-Ph	72
2	**1b**		4-OMe-2-Me-Ph	85
3	**1c**		4-NMe_2-Ph	77
4	**1d**		4-OMe-Ph	58
5	**1e**		4-Me-Ph	62
6	**1f**		4-NMe_2-Ph	53
7	**1g**		4-OMe-Ph	74
8	**1h**		4-OMe-2-Me-Ph	78
9	**1i**		4-Me-Ph	73
10	**1j**		4-NMe_2-Ph	69
11	**1k**		4-OMe-Ph	74
12	**1l**		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

[a]1) alkoxylation: R^1OH, NaH, THF, rt or NaOMe, MeOH, 60 °C; 2) Sonogashira coupling: R^2-C≡CH, $Pd(OAc)_2$, CuI, PPh_3, Et_3N, DMSO, 100 °C, 20 min. [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^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-aminoqunoxaline. In addition, the desired 6-aminoqunoxalines 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-aminoquinoxaline derivatives. Further studies in this area are underway, and the results of these studies will be reported in due course.

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

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10. 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 ^{1}H NMR spectra analysis.
11. Spectroscopic data of compounds **5**. For 2-chloro-3-(2-dimethylaminoethoxy)-quinoxalin-6-ylamine (**5a**): ^{1}H NMR (500 MHz, $CDCl_3$) 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-methoxy-quinoxalin-6-amine (**5b**): ^{1}H NMR (500 MHz, $CDCl_3$) 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 ($[M+1]^+$).
12. 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.
13. Spectroscopic data of compound **1a**: ^{1}H NMR (500 MHz, $CDCl_3$) 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 ($[M+1]^+$).
14. **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-aminoqunixaline (**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 CH_2Cl_2, washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by flash silica gel column chromatography (CH_2Cl_2/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), Ph_3P (26 mg, 0.10 mmol), CuI (39 mg, 0.20 mmol), and Et_3N (1.66 mL, 11.8 mmol). The mixture was stirred under microwave irradiation at 100 °C for 20 min, cooled and then diluted with CH_2Cl_2, washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by flash silica gel column chromatography (CH_2Cl_2/MeOH, 10:1) to give **1a** (439 mg, 79%) as a light yellow solid.