JOC The Journal of Organic Chemistry

Article

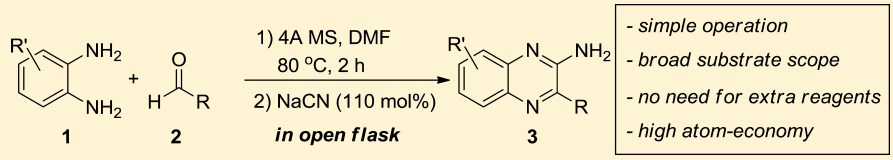
pubs.acs.org/joc

Synthesis of 2-Aminoquinoxalines via One-Pot Cyanide-Based Sequential Reaction under Aerobic Oxidation Conditions

Yeon-Ho Cho, Kyung-Hee Kim, and Cheol-Hong Cheon*

Department of Chemistry, Korea University, Anam-ro, Seongbuk-gu, Seoul 136701, Republic of Korea

Supporting Information



ABSTRACT: A highly efficient synthesis of 2-aminoquinoxalines has been developed via the one-pot two-step cyanide-mediated sequential reactions of *ortho*-phenylenediamines with aldehydes under aerobic oxidation conditions. A variety of substrates, including aliphatic aldehydes bearing acidic α-protons, are applicable to this protocol and afford the desired 2-aminoquinoxalines in high yields.

INTRODUCTION

Quinoxalines are common building blocks[1] found in a variety of biologically and pharmaceutically important compounds,[2] antibiotics,[3] and materials.[4] Consequently, significant efforts have been made to develop efficient methods for the synthesis of quinoxalines and their derivatives.[5] Among the various quinoxaline derivatives developed, 2-aminoquinoxalines have been considered one of the most important quinoxaline derivatives presumably due to their unique biological activities[6] and potential applications in the construction of complex druglike scaffolds in multicomponent reactions,[7] such as in the Groebke−Blackburn reaction.[8]

The conventional method for the synthesis of 2-aminoquinoxalines **3** involves the condensation of *ortho*-phenylenediamines **1** and α-carbonyl ester compounds to yield 2-quinoxalinones **5**. The reaction of **5** with $POCl_3$ affords 2-chloroquinoxalines **6**, which, in turn, are converted into 2-aminoquinoxalines **3** through subsequent substitution with amine nucleophiles (Scheme 1a).[9] These important compounds were synthesized through isocyanide-based multicomponent reactions of **1** and aldehydes using convertible isocyanides. Subsequent oxidation of 1,4-dihydroquinoxalines **7** with DDQ, followed by the removal of the convertible group, afforded 2-aminoquinoxalines **3** (Scheme 1b).[10] However, both methods require multiple steps to generate the quinoxaline scaffold and/or a free amino group at the 2-position of quinoxalines. Recently, Kurth and co-workers demonstrated an elegant synthesis of 2-aminoquinoxalines by the simple condensation of 2-nitrosoaniline **9** with 2-nitrobenzylcyanide **10** in the presence of base (Scheme 1c).[11] Although this protocol provided the corresponding 2-aminoquinoxalines in excellent yields, the substrate scope for this protocol has been limited to *ortho*-nitrobenzylcyanide derivatives and no other benzylcyanide derivatives without a nitro group at the *ortho* position have been tested.

Herein, we would like to report a highly efficient two-step one-pot synthesis of 2-aminoquinoxalines **3** via a cyanide-based sequential reaction of *ortho*-phenylenediamines **1** and aldehydes **2** under aerobic oxidative conditions (Scheme 1d). This reaction features operational simplicity, no need for extra steps and reagents for oxidation and deprotection, and a broad substrate scope, thus allowing for the expedient and atom-economical assembly of 2-aminoquinoxalines **3** from *ortho*-phenylenediamines **1**, aldehydes **2**, and NaCN in an open flask. These results are based on our recent findings of the unexpected formation of 2-aminoquinoxalines from *ortho*-phenylenediamine and aldehydes under the oxidative cyclization conditions previously used for the synthesis of other benzofused azole compounds in the presence of NaCN.

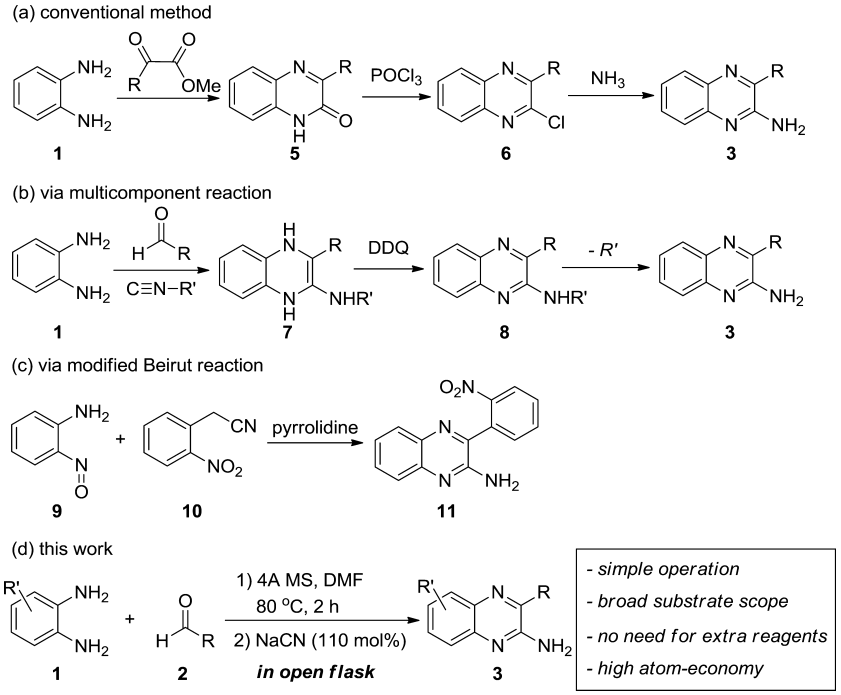
RESULTS AND DISCUSSION

Recently, our group reported that a nucleophile could act as an efficient catalyst for the synthesis of benzofused heteroaromatic compounds through aerobic oxidation. For example, we developed a highly efficient method for the synthesis of benzoxazoles and benzothiazoles from *ortho*-aminophenol, and *ortho*-aminothiophenol, respectively, via aerobic oxidative cyclization in the presence of cyanide as a nucleophilic catalyst (eq 1, Scheme 2).[12] As part of our continuing studies on the synthesis of biologically important heteroaromatic compounds via aerobic oxidation, we envisioned that this protocol could be extended to the synthesis of benzimidazoles **4** from *ortho*-phenylenediamines **1** and aldehydes **2** (eq 2, Scheme 2).[13]

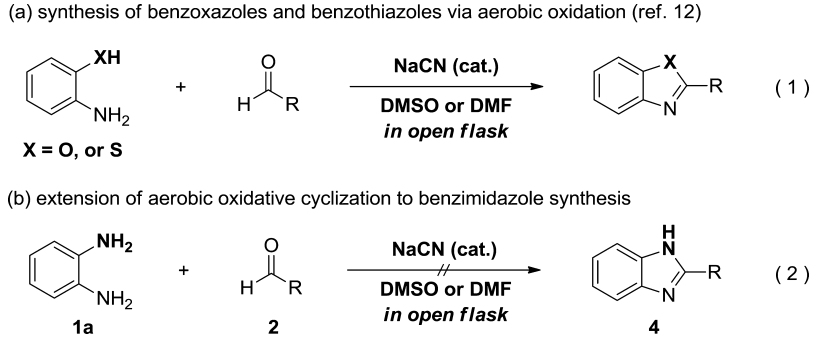
When *ortho*-phenylenediamine **1a** and benzaldehyde **2a** were subjected to the oxidative cyclization conditions[12] used for benzoxazole and benzothiazole synthesis in the presence of a catalytic amount of NaCN, however, the expected benzimida-

Received: October 1, 2013
Published: January 7, 2014

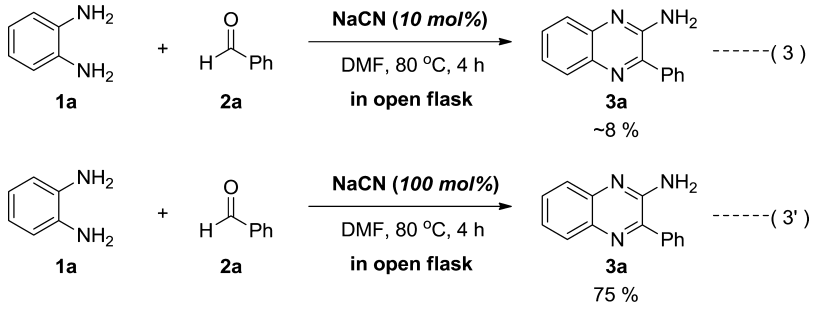
Scheme 1. Methods for the Synthesis of 2-Aminoquinoxalines 3



Scheme 2. Cyanide-Catalyzed Aerobic Oxidative Synthesis of Benzofused Azoles



Scheme 3. Formation of 2-Aminoquinoxaline 3a



zole **4** was not formed; instead, the corresponding imine was obtained as the major product along with an unexpected product in slightly lower yield than the amount of NaCN used (eq 3, Scheme 3). When a stoichiometric amount of NaCN was used under the same conditions, the unexpected product was obtained as the major product (eq 3′, Scheme 3). After careful structural analysis, the unexpected product was assigned to 3-phenyl 2-aminoquinoxaline **3a**.

With this unexpected result in hand, we conducted a literature survey and found that a similar transformation was already reported in the literature.[14] However, considering the importance of the 2-aminoquinoxaline scaffold and the convenience of this transformation, we were rather surprised to find that there have been only a few reports for this transformation ever since its first report. In addition, in the previous reports, only one or two examples were reported and the yields for the resulting 2-aminoquinoxalines were quite low (around 10−20%). Although the similar transformation was already reported in the literature, we felt that there would be room for improvement for this transformation and decided to

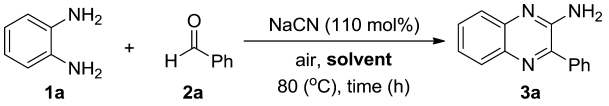
dx.doi.org/10.1021/jo4021908 | J. Org. Chem. 2014, 79, 901−907

investigate this cyanide-based multicomponent reaction[15] affording 2-aminoquinoxalines.

To explore the synthesis of 2-aminoquinoxalines via the cyanide-based reaction under aerobic oxidation conditions, we first optimized the reaction conditions for this transformation using *ortho*-phenylenediamine **1a** and benzaldehyde **2a** as model compounds in the presence of NaCN (Table 1). The choice of solvent turned out to be crucial for the success of the reaction (entries 1−6); the desired product **3a** was obtained in high yield in DMF and DMSO, whereas this reaction did not proceed in any other solvent and instead the corresponding imine was obtained as the major product. Molecular sieves had a slightly beneficial effect on the synthesis of 2-aminoquinoxaline, and **3a** was obtained in a similar yield, but with higher selectivity (entry 7). When the reaction was performed under an argon atmosphere, the desired product was obtained in low yield even after a long reaction time (entry 8). Under an argon atmosphere, **3a** was initially formed, but no further conversion was observed thereafter. The formation of **3a** at the beginning of the reaction might be due to the oxidation with the oxygen dissolved in solvent, and the oxidation reaction proceeded until the dissolved oxygen was completely consumed. After the complete consumption of the dissolved oxygen, no further formation of **3a** was observed. These results suggested that aerobic oxidation would play an important role in this transformation. Under these one-pot reaction conditions, we found that cyanide-catalyzed benzoin reaction of **2a**[16] competed with the formation of **3a**, which would lead to lower yield for this transformation. To overcome this problem, we developed a more efficient protocol through the subsequent addition of a stoichiometric amount of NaCN to the imine generated in situ from **1a** and **2a** in the same pot. Delightfully, the yield for this transformation could be further improved using this sequential one-pot protocol (entry 9).

Under these optimized reaction conditions, the substrate scope for this transformation was investigated (Table 2). Various aromatic aldehydes could be employed in this protocol.

Table 1. Optimization of Reaction Conditions

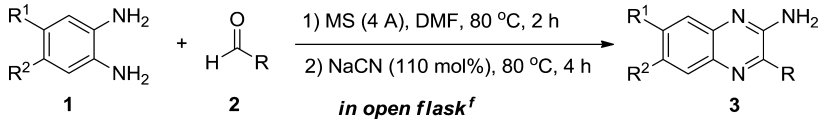


1a + **2a** → **3a**

entry	solvent	time (h)	yield (%)[a]
1	DMF	4	75
2	dioxane	24	[b]
3	toluene	24	[b]
4	EtCN	24	[b]
5	EtOH	24	[b]
6	DMSO	4	72
7[c]	DMF	4	77
8[c,d]	DMF	24	<10[e]
9[f]	DMF	4	87

[a]Isolated yield. [b]The corresponding imine was obtained as the major product. [c]With 4 Å molecular sieves. [d]Under an argon atmosphere. [e]Yield was determined by ^{1}H NMR analysis. [f]NaCN was added to the imine generated in situ from **1a** and **2a**.

Table 2. Substrate Scope[f]



1 + **2** → **3**

	2-aminoquinoxalines (**3**)				
entry	**3**	R^1	R^2	R	yield (%)[a]
1	**3a**	H	H	Ph	86
2	**3b**	H	H	4-$MeOC_6H_4$	80
3	**3c**	H	H	4-MeC_6H_4	77
4	**3d**	H	H	4-ClC_6H_4	93
5	**3e**	H	H	4-$MeO_2CC_6H_4$	92
6	**3f**	H	H	2-$MeOC_6H_4$	92
7	**3g**	H	H	2-ClC_6H_4	82
8	**3h**	H	H	2-HOC_6H_4	67
9[b]	**3i**	H	H	1-naphthyl	73
10[b]	**3j**	H	H	2-naphthyl	90
11	**3k**	H	H	2-furyl	90
12	**3l**	H	H	2-thienyl	64
13[c]	**3m**	H	H	2-pyridyl	64
14[c]	**3n**	H	H	*n*-hexyl	65
15[c]	**3o**	H	H	*c*-hexyl	60
16[c]	**3p**	H	H	*t*-butyl	70
17	**3q**	Me	Me	Ph	85
18	**3r**	Cl	Cl	Ph	60
19	**3s**	Me	H	Ph	88 (2:1)[d]
20	**3t**	Cl	H	Ph	72 (2:1)[e]

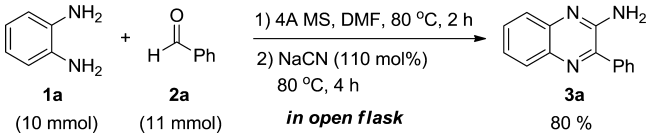
[a]Isolated yield. [b]NaCN was added to imine prepared from **1** and an aldehyde in ethanol. [c]Reaction was carried out through a simple one-pot protocol. [d]Two regioisomers were obtained as an inseparable mixture in a 2:1 ratio. [e]Two separable regioisomers were obtained in 48% and 24% yield, respectively. [f]No drying tube was used to exclude water vapor from air.

dx.doi.org/10.1021/jo4021908 | J. Org. Chem. 2014, 79, 901−907

The electronic properties of the aromatic aldehydes had little effect on the synthesis of **3**; the desired products were obtained in high yields regardless of the electronic nature of the aromatic rings (entries 1−5). Benzaldehyde derivatives bearing a substituent at the *ortho* position also provided the quinoxaline products in good to excellent yields (entries 6−8). In addition to benzaldehyde derivatives, fused aromatic aldehydes were also applied to this protocol, and the desired products were obtained in high yields (entries 9 and 10). This transformation could be extended to heteroaromatic aldehydes, and the corresponding quinoxalines were obtained in good to high yields depending on the nature of the heteroaromatic ring system (entries 11−13). We then attempted to extend the method to more challenging aliphatic substrates. Subsequent addition of NaCN to imines generated from aliphatic aldehydes provided the desired 2-aminoquinoxalines in moderate yields, along with several side-products.[17] However, when **1a**, an aliphatic aldehyde, and NaCN were added at once and stirred at 80 °C, the desired products **3** were obtained in good yields (entries 14−16). Next, the effect of substituents in *ortho*-phenylenediamines was evaluated on this transformation (entries 17−20). The electronic effect of substituents in *ortho*-phenylenediamines had some influence on the formation of **3**. Electron-rich *ortho*-phenylenediamines afforded the desired products in high yield (entries 17 and 19), whereas *ortho*-phenylenediamines bearing electron-withdrawing substituents showed much lower reactivities than the electron-rich *ortho*-phenylenediamines and yielded the desired products in good yields (entries 18 and 20).

To demonstrate the practicality of this method, we performed this transformation on a gram scale (Scheme 4). To our delight, **3a** could be prepared on a gram scale without loss of its efficiency.

Scheme 4. A Gram-Scale Reaction



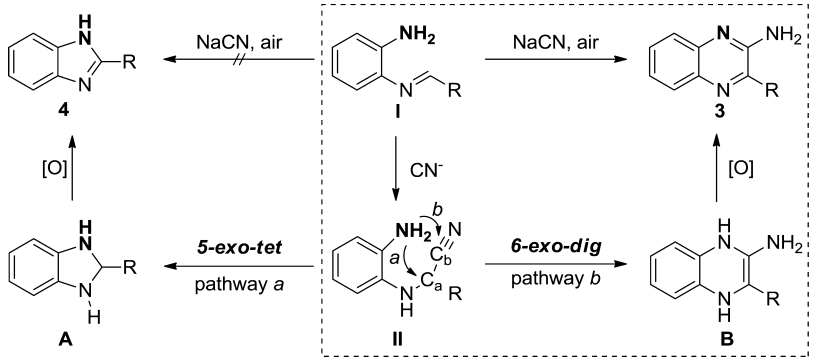
With these excellent results in hand, we attempted to rationalize the reaction mechanism for this transformation. In particular, we were curious why reactions of *ortho*-phenylenediamines**1** with aldehydes **2** in the presence of cyanide gave 2-aminoquinoxalines **3** rather than the expected benzimidazoles **4** under the conditions (eq 3′, Scheme 3) under which *ortho*-aminophenol and *ortho*-aminothiophenol provided benzoxazoles and benzothiazoles, respectively (eq 1, Scheme 2).

To explain the significant difference in the reaction pathway with *ortho*-phenylenediamine **1a** from those with *ortho*-aminophenol and *ortho*-aminothiophenol, we proposed possible reaction pathways with **1a** to afford either 2-aminoquinoxalines **3** or benzimidazoles **4** (Scheme 5). Cyanide undergoes nucleophilic addition to imine **I** to afford intermediate **II**. The resulting intermediate **II** can undergo two possible reaction pathways. The lone pair on the nitrogen atom can attack the sp^3-hybridized carbon atom (C_a in intermediate **II**) via *5-exo-tet* cyclization to yield benzimidazoline **A**. Subsequent aerobic oxidation of **A** would provide benzimidazole **4** (pathway *a*). On the other hand, the nitrogen atom can attack the sp-hybridized carbon (C_b in intermediate **II**) of the nitrile via *6-exo-dig* cyclization to furnish 2-amino dihydroquinoxaline **B**.[18] The desired 2-aminoquinoxaline **3** could be obtained after aerobic oxidation of **B** (pathway *b*). Under these conditions, *6-exo-dig* cyclization predominantly took place over *5-exo-tet* cyclization presumably due to better orbital orientation between HOMO and LUMO, which led to the exculsive formation of 2-aminoquinoxalines **3**. Although this transformation was previously reported in the literature, it should be noted that this transformation is operationally very simple and displayed a very broad substrate scope from aromatic aldehydes, heteroaromatic aldehydes, to more challenging aliphatic aldehydes. Furthermore, this method is much more expedient and atom-economical for the assembly of 2-aminoquinoxalines than the previously developed methods. For example, **3a** was previously prepared in 44% over three steps,[10b] whereas our new method provided the same compound in a single step in much better yield without any use of bases and oxidants.

CONCLUSIONS

In conclusion, we have developed a highly efficient method for the synthesis of 2-aminoquinoxalines **3** from *ortho*-phenylenediamines **1** and aldehydes **2** in the presence of a stoichiometric amount of cyanide in an open flask. Various aldehydes were readily applied to this new synthetic protocol, and the desired products were obtained in good to high yields. It is noted that this protocol is an expedient and atom-economical method for the assembly of 2-aminoquinoxalines from commercially available *o*-phenylenediamines, aldehydes, and NaCN. In addition, operational simplicity and no need for extra reagents are the attractive features of this protocol.

Scheme 5. Possible Reaction Pathways



dx.doi.org/10.1021/jo4021908 | J. Org. Chem. 2014, 79, 901−907

Further development of cyanide-based multicomponent reactions is currently underway in our laboratory.

EXPERIMENTAL SECTION

General. All reactions were carried out in oven- or flame-dried glassware under an air atmosphere unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin layer chromatography (TLC) using precoated silica gel glass plates (0.25 mm) with F254 indicator. Visualization was accomplished by UV light (254 nm), with the combination of phosphomolybdic acid solution as an indicator. Flash column chromatography was performed according to the method of Still using silica gel 60 (230−400 mesh). Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted. 1,2-Phenylenediamine and other commercial grade reagents and solvents were purchased from commercial suppliers and were used without further purification. Liquid aldehydes were freshly distilled under an atmosphere of dry argon, and solid aldehydes were purified by flash chromatography on silica gel. ^{1}H NMR spectra were recorded on 300 and 400 MHz spectrometers and ^{13}C NMR spectra were recorded on 75 and 100 MHz spectrometers, respectively. Tetramethylsilane and $CDCl_3$ were used as internal standards for ^{1}H NMR (δ: 0.0 ppm) and ^{13}C NMR (δ: 77.16 ppm), respectively. The proton spectra were reported as follows δ (position of proton, multiplicity, coupling constant J, number of protons) and the carbon spectra were reported as only δ (position of carbon). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (heptet), m (multiplet), and br (broad). High-resolution mass spectra (HRMS) were obtained using a quadrupole instrument using either electron ionization (EI) or electospary ionization (ESI) as the ionization method.

*General Procedure for the Synthesis of 3-Substituted 2-Aminoquinoxalines **3** (Table 2).* 1,2-Phenylenediamine **1** (0.20 mmol; 1.0 equiv) and aldehyde **2** (0.22 mmol; 1.1 equiv) and the molecular sieve (10 mg) were dissolved in DMF (1.0 mL). The reaction mixture was stirred at 80 °C in an open flask and monitored by TLC. On the complete consumption of compound **1**, NaCN (11 mg; 0.22 mmol; 1.1 equiv) was added to the above reaction mixture. On completion of the reaction, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by column chromatography on silica to give the corresponding 2-aminoquinoxaline product **3**.

*2-Amino-3-phenylquinoxaline (**3a**).* The spectroscopic data were in good agreement with the literature.[10b] A yellow solid. Yield: 38 mg (86%). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ.7.98 (d, J = 8.24 Hz, 1H), 7.79 (d, J = 6.32 Hz, 2H), 7.71 (d, J = 8.24 Hz, 1H), 7.44−7.65 (m, 5H), 5.24 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 150.9, 146.1, 141.4, 138.2, 137.2, 130.2, 129.9, 129.5, 129.3, 128.6, 125.7, 125.4.

*2-Amino-3-(4-methoxyphenyl)-quinoxaline (**3b**).* A light brown solid. Yield: 40 mg (80%). R_f = 0.3 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ.7.95 (d, J = 8.24 Hz, 1H), 7.76 (d, J = 8.52 Hz, 2H), 7.68 (d, J = 8.24 Hz, 1H), 7.59 (t, J = 7.97 Hz, 1H), 7.44 (t, J = 7.97 Hz, 1H)), 7.06 (d, J = 8.52 Hz, 2H), 5.11 (br, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 161.0, 150.9, 145.9, 141.2, 138.4, 130.1, 129.9, 129.5, 129.1, 125.8, 125.4, 114.8, 55.7. HRMS (EI) calcd for $C_{15}H_{13}N_3O$ (M^+) 251.1059, found 251.1054.

*2-Amino-3-(4-methylphenyl)-quinoxaline (**3c**).* A yellow solid. Yield: 6 mg (77%). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.96 (d, J = 8.24 Hz, 1H), 7.69 (d, J = 8.24 Hz, 3H), 7.60 (t, J = 8.24 Hz, 1H), 7.45 (t, J = 8.24 Hz, 1H), 7.36 (d, J = 7.97 Hz, 2H), 5.07 (br, 2H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 150.8, 146.2, 141.3, 140.1, 138.4, 134.3, 130.1, 130.1, 129.2, 128.5, 125.8, 125.4, 21.7. HRMS (EI) calcd for $C_{15}H_{13}N_3$ (M^+) 235.1109, found 235.1107.

*2-Amino-3-(4-chlorophenyl)-quinoxaline (**3d**).* The spectroscopic data were in good agreement with the literature.[19] A yellow solid. Yield: 48 mg (93%). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.95 (d, J = 8.24 Hz, 1H), 7.77 (d, J = 8.52 Hz, 2H), 7.70 (d, J = 8.24 Hz, 1H) 7.62 (t, J = 7.55 Hz, 1H), 7.54 (d, J = 8.52 Hz, 2H), 7.47 (t, J = 7.55 Hz, 1H), 5.01 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 150.6, 144.8, 141.4, 138.3, 136.1, 135.6, 130.5, 130.1, 129.7, 129.2, 125.9, 125.7.

*2-Amino-3-(4-acethylphenyl)-quinoxaline (**3e**).* A yellow solid. Yield: 51 mg (92%). R_f = 0.2 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.23 (d, J = 8.24 Hz, 2H), 7.97 (d, J = 8.24 Hz, 1H), 7.90 (d, J = 8.24 Hz, 2H), 7.71 (d, J = 7.97 Hz, 1H), 7.64 (t, J = 8.10 Hz, 1H), 7.48 (t, J = 8.24 Hz, 1H), 5.03 (br, 2H), 3.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.6, 150.5, 144.8 141.5, 138.3, 131.3, 130.7, 130.6, 129.3, 128.8, 125.9, 125.8, 52.6. HRMS (EI) calcd for $C_{16}H_{13}N_3O_2$ (M^+) 279.1008, found 279.1005.

*2-Amino-3-(2-methoxyphenyl)-quinoxaline (**3f**).* A light gray solid. Yield: 46 mg (92%). R_f = 0.3 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.97 (d, J = 8.24 Hz, 1H), 7.71 (d, J = 8.24 Hz, 1H), 7.61 (t, J = 7.69 Hz, 1H), 7.43−7.51 (m, 3H), 7.15 (t, J = 7.42 Hz, 1H), 7.05 (d, J = 8.24 Hz, 1H), 4.95 (br, 2H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 157.2, 151.6, 145.3, 141.6, 138.0, 131.5, 131.3, 130.1, 129.3, 126.2, 125.9, 125.3, 121.9, 111.7, 56.0. HRMS (EI) calcd for $C_{15}H_{13}N_3O$ (M^+) 251.1059, found 251.1054.

*2-Amino-3-(2-chlorophenyl)-quinoxaline (**3g**).* A light brown solid. Yield: 42 mg (82%). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.97 (d, J = 8.24 Hz, 1H), 7.73 (d, J = 7.97 Hz, 1H), 7.65 (t, J = 7.55 Hz, 1H), 7.46−7.58 (m, 5H), 4.84 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 150.8, 144.6, 141.9, 137.7, 135.7, 133.3, 131.2, 131.1, 130.7, 130.6, 129.3, 128.0, 126.1, 125.6. HRMS (EI) calcd for $C_{14}H_{10}ClN_3$ (M^+) 255.0563, found 255.0564.

*2-Amino-3-(2-hydroxyphenyl)-quinoxaline (**3h**).* A yellow solid. Yield: 32 mg (67%). R_f = 0.3 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.03 (d, J = 7.69 Hz, 1H), 7.87 (d, J = 8.24 Hz, 1H), 7.70−7.60 (m, 2H), 7.48 (t, J = 8.24 Hz, 1H), 7.40 (t, J = 8.52 Hz, 1H), 7.16 (d, J = 8.24 Hz, 1H), 7.01 (t, J = 8.24 Hz, 1H), 5.28 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 158.5, 150.7, 143.8, 140.6, 135.7, 132.3, 130.6, 127.7, 127.2, 126.2, 126.0, 119.8, 119.3, 119.0. HRMS (ESI) calcd for $C_{14}H_{12}N_3O$ ((M + H)$^+$) 238.0980, found 238.0981.

*2-Amino-3-(1-naphthyl)-quinoxaline (**3i**).* A light brown solid. Yield: 40 mg (73%). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.99 (t, J = 7.04 Hz, 2H), 7.94 (d, J = 8.22 Hz, 1H), 7.75 (d, J = 8.61 Hz, 1H), 7.65 (t, J = 7.04 Hz, 2H), 7.61 (d, J = 6.65 Hz, 2H), 7.54 (t, J = 7.04 Hz, 1H), 7.43−7.50 (m, 2H), 4.82 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 151.5, 145.9, 141.8, 138.0, 134.2, 133.9, 131.1, 130.5, 130.2, 129.4, 128.9, 127.4, 127.3, 126.8, 126.0, 125.9, 125.5, 125.2. HRMS (ESI) calcd for $C_{18}H_{14}N_3$ ((M + H)$^+$) 272.1188, found 272.1190.

*2-Amino-3-(2-naphthyl)-quinoxaline (**3j**).* A light yellow solid. Yield: 49 mg (90%). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.29 (s, 1H), 7.86−8.03 (m, 5H), 7.71 (d, J = 8.22 Hz, 1H), 7.61 (t, J = 7.44 Hz, 1H), 7.55−7.57 (m, 2H), 7.46 (t, J = 7.44 Hz, 1H), 5.14 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 150.9, 146.0, 141.4, 138.4, 134.5, 133.9, 133.5, 130.3, 129.4, 129.3, 128.7, 128.3, 128.1, 127.4, 127.0, 125.9, 125.8, 125.6. HRMS (ESI) calcd for $C_{18}H_{14}N_3$ ((M + H)$^+$) 272.1188, found 272.1186.

*2-Amino-3-(2-furyl)-quinoxaline (**3k**).* A brown solid. Yield: 38 mg (90%). R_f = 0.4 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.90 (d, J = 8.24 Hz, 1H), 7.62−7.66 (m, 2H), 7.56 (t, J = 7.55 Hz, 1H), 7.39−7.46 (m, 2H), 6.67 (dd, J = 3.30, 1.63 Hz, 1H), 6.89 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 152.6, 149.4, 143.9, 140.9, 137.6, 134.6, 130.1, 128.9, 125.6, 125.6, 113.0, 112.7. HRMS (EI) calcd for $C_{12}H_9N_3O$ (M^+) 211.0746, found 211.0739.

*2-Amino-3-(2-thienyl)-quinoxaline (**3l**).* A light yellow solid. Yield: 29 mg (64%). R_f = 0.3 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.94 (d, J = 8.24 Hz, 1H), 7.77 (d, J = 3.57 Hz, 1H), 7.67 (d, J = 8.24 Hz, 1H), 7.56−7.62 (m, 2H), 7.46 (t, J = 8.24 Hz, 1H), 7.21 (dd, J = 3.85, 1.10 Hz, 1H), 5.27 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 150.1, 141.2, 140.8, 139.6, 138.1, 130.2, 129.4, 129.0, 128.2, 127.3, 125.8, 125.7. HRMS (ESI) calcd for $C_{12}H_{10}N_3S$ ((M + H)$^+$) 227.0595, found 228.0596.

dx.doi.org/10.1021/jo4021908 | J. Org. Chem. 2014, 79, 901−907

*2-Amino-3-(2-pyridyl)-quinoxaline (**3m**).* A yellow solid. Yield: 28 mg (64%). R_f = 0.5 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.78 (d, J = 8.24 Hz, 1H), 8.66 (d, J = 4.94 Hz, 1H), 7.90−7.97 (m, 2H), 7.57−7.66 (m, 2H), 7.38−7.45 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 156.6, 152.6, 147.4, 142.4, 138.7, 137.3, 130.8, 129.5, 125.5, 124.8, 124.1, 123.9. HRMS (ESI) calcd for $C_{13}H_{11}N_4$ ($(M + H)^+$) 223.0984, found 223.0978.

*2-Amino-3-(n-hexyl)-quinoxaline (**3n**).* A yellow solid. Yield: 30 mg (65%). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.88 (d, J = 8.24 Hz, 1H), 7.64 (d, J = 8.24 Hz, 1H), 7.55 (t, J = 7.08 Hz, 1H), 7.45 (t, J = 7.08 Hz, 1H), 4.92 (br, 2H), 2.83 (t, J = 7.83 Hz, 2H), 1.86 (p, J = 7.59 Hz, 2H), 1.34−1.48(m, 6H), 0.90 (t, J = 6.87 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 151.0, 147.9, 140.9, 138.1, 129.3, 128.6, 125.8, 125.2, 34.7, 31.9, 29.5, 26.7, 22.8, 14.3. HRMS (EI) calcd for $C_{14}H_{19}N_3$ (M^+) 229.1579, found 229.1582.

*2-Amino-3-(cyclohexyl)-quinoxaline (**3o**).* A yellow solid. Yield: 27 mg (60%). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.88 (d, J = 8.24 Hz, 1H), 7.63 (d, J = 8.24 Hz, 1H), 7.56 (t, J = 7.69 Hz, 1H), 7.41 (t, J = 7.41 Hz, 1H), 4.96 (br, 2H), 2.70 (tt, J = 11.26, 2.75 Hz, 1H), 1.93 2.05 (m, 4H), 1.74−1.82 (m, 3H), 1.34−1.47 (m, 2H), 1.22−1.28 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 151.3, 150.4, 140.5, 138.3, 129.2, 128.8, 125.7, 125.1, 41.9, 30.9, 26.7, 26.2. HRMS (EI) calcd for $C_{14}H_{17}N_3$ (M^+) 227.1422, found 227.1418.

*2-Amino-3-(t-butyl)-quinoxaline (**3p**).* The spectroscopic data were in good agreement with the literature.[20] A brown oil. Yield: 28 mg (70%). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.88 (d, J = 8.24 Hz, 1H), 7.62 (d, J = 8.24 Hz, 1H), 7.54 (t, J = 7.55 Hz, 1H), 7.41 (t, J = 7.55 Hz, 1H), 5.09 (br, 2H), 1.53 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 152.8, 150.6, 140.5, 137.4, 129.4, 129.1, 125.2, 125.0, 38.0, 28.7.

*2-Amino-6,7-dimethyl-3-phenyl-quinoxaline (**3q**).* A brown solid. Yield: 42 mg (85%). R_f = 0.3 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.77 (d, J = 7.97 Hz, 2H), 7.71 (s, 1H), 7.45−7.56 (m, 3H), 7.45 (s, 1H), 5.00 (br, 2H), 2.44 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 150.5, 144.9, 140.4, 139.9, 137.5, 137.1, 135.2, 129.6, 129.3, 128.6, 128.5, 125.3, 20.6, 20.1. HRMS (ESI) calcd for $C_{16}H_{16}N_3$ ($(M + H)^+$) 250.1344, found 250.1333.

*2-Amino-6,7-dichloro-3-phenyl-quinoxaline (**3r**).* A red brown solid. Yield: 35 mg (60%). R_f = 0.3 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.05 (s, 1H), 7.76−7.79 (m, 3H), 7.54−7.58 (m, 3H), 5.18 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 151.2, 147.1, 140.5, 137.1, 136.5, 134.3, 130.4, 129.8, 129.6, 129.1, 128.5, 126.7. HRMS (ESI) calcd for $C_{14}H_{10}Cl_2N_3$ ($(M + H)^+$) 290.0252, found 290.0234.

*2-Amino-6 (or 7)-methyl-3-phenyl-quinoxaline (**3s**).* The two regioisomers were obtained as an inseparable mixture in a 2:1 ratio. A brown solid. Yield: 42 mg (88%). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.84 (d, J = 8.24 Hz, 1H), 7.76−7.79 (m, 2H), 7.50−7.58 (m, 3H), 7.47 (s, 1H), 7.28 (d, J = 8.52 Hz, 1H), 5.04 (br, 2H), 2.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 151.0, 150.5, 145.9, 145.1, 141.4, 140.6, 139.5, 138.2, 137.4, 136.6, 135.3, 132.2, 129.8, 129.7, 129.4, 128.8, 128.6, 128.4, 127.5, 125.3, 124.9, 22.1, 21.6. HRMS (ESI) calcd for $C_{15}H_{14}N_3$ ($(M + H)^+$) 236.1188, found 236.1183.

*2-Amino-6 (or 7)-chloro-3-phenyl-quinoxaline (**3t**).* The two regioisomers were obtained in a 2:1 ratio. Major isomer: A yellow solid. Yield: 120 mg (48%). R_f = 0.3 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.86 (d, J = 9.00 Hz, 1H), 7.76 (d, J = 6.65 Hz, 2H), 7.66 (d, J = 1.96 Hz, 1H), 7.50−7.57 (m, 3H), 7.38 (dd, J = 9.00, 1.96 Hz, 1H), 5.13 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 151.3, 146.2, 142.0, 136.8, 136.7, 135.8, 130.3, 130.2, 129.5, 128.5, 126.2, 124.9. HRMS (ESI) calcd for $C_{14}H_{11}ClN_3$ ($(M + H)^+$) 256.0642, found 256.0612. Minor isomer: A yellow solid. Yield: 61 mg (24%). R_f = 0.2 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.95 (d, J = 1.92 Hz, 1H), 7.78 (dd, J = 7.55, 1.79 Hz, 2H), 7.53−7.64 (m, 5H), 5.10 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 150.8, 146.8, 140.0, 138.5, 136.8, 130.9, 130.6, 130.2, 129.5, 128.5, 128.2, 127.1. HRMS (ESI) calcd for $C_{14}H_{11}ClN_3$ ($(M + H)^+$) 256.0642, found 256.0629.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all 2-aminoquinoxalines **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +82-2-3290-3147. Fax: +82-2-3290-3121. E-mail: cheon@korea.ac.kr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and Future Planning (2013R1A1A1008434). C.-H.C. also thanks the Ministry of Education (NRF20100020209) for financial support from the NRF fund.

■ REFERENCES

(1) Sato, N. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Pergamon: Oxford, U.K., 2008; Vol. *8*, p 273.

(2) (a) Lindsley, C. W.; Zhao, Z. J.; Leister, W. H.; Robinson, R. G.; Barnett, S. F.; Defeo-Jones, D.; Jones, R. E.; Hartman, G. D.; Huff, J. R.; Huber, H. E.; Duggan, M. E. *Bioorg. Med. Chem. Lett.* **2005**, *13*, 761−764. (b) Seitz, L. E.; Wuling, W. J.; Reynolds, R. C. *J. Med. Chem.* **2002**, *45*, 5604−5606. (c) Zhou, D. H.; Zhou, P.; Evrard, D. A.; Meagher, K.; Webba, M.; Harrison, B. L.; Huryn, D. M.; Golembieski, J.; Hornby, G. A.; Schechter, L. E.; Smith, D. L.; Andree, T. H.; Mewshaw, R. E. *Bioorg. Med. Chem.* **2008**, *16*, 6707−6723. (d) Wagle, S.; Adhikari, A. V.; Kumari, N. S. *Eur. J. Med. Chem.* **2009**, *44*, 1135−1143. (e) Wilhelmsson, L. M.; Kingi, N.; Bergman, J. *J. Med. Chem.* **2008**, *51*, 7744−7750. (f) Menon, P.; Gopal, M.; Prasad, R. *J. Agric. Food Chem.* **2004**, *52*, 7370−7376. (g) Li, J. F.; Zhao, Y.; Cai, M. M.; Li, X. F.; Li, J. X. *Eur. J. Med. Chem.* **2009**, *44*, 2796−2806.

(3) (a) Dell, A.; William, D. H.; Morris, H. R.; Smith, G. A.; Feeney, J.; Roberts, G. C. K. *J. Am. Chem. Soc.* **1975**, *97*, 2497−2502. (b) Raw, S. A.; Wilfred, C. D.; Taylor, R. J. K. *Chem. Commun.* **2003**, 2286−2287.

(4) (a) Radoslaw, P.; Agnieszka, M.; Szymczak, K. P. *Dyes Pigm.* **2009**, *82*, 365−371. (b) Son, H. J.; Han, W. S.; Yoo, D. H.; Min, K. T.; Kwon, S. N.; Ko, J.; Kang, S. O. *J. Org. Chem.* **2009**, *74*, 3175−3178. (c) Dailey, S.; Feast, J. W.; Peace, R. J.; Till, I. C.; Sage, S.; Wood, E. L. *J. Mater. Chem.* **2001**, *11*, 2238−2243. (d) Ott, S.; Faust, R. *Synlett* **2004**, 1509−1512.

(5) The most common method for the synthesis of quinoxalines is the condensation of *o*-aryldiamines with 1,2-dicarbonyl compounds. For a recent example, see: (a) Cho, S.; Ren, W. X.; Shim, S. C. *Tetrahedron Lett.* **2007**, *48*, 4665−4667. (b) Qi, C.; Jiang, H.; Huang, L.; Chen, Z.; Chen, H. *Synthesis* **2011**, 387−396 and references therein.

(6) For a recent review on 2-aminoquinoxaline derivatives for their biological application, see: González, M.; Cerecetto, H. *Expert Opin. Ther. Pat.* **2012**, *22*, 1289−1302.

(7) For a review, see: Dömling, A. *Chem. Rev.* **2006**, *106*, 17−89.

(8) (a) Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661−663. (b) Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. *Tetrahedron Lett.* **1998**, *39*, 3635−3638.

(9) (a) Hara, H.; van der Plas, H. C. *J. Heterocycl. Chem.* **1982**, *19*, 1285−1287. (b) Badr, M. Z. A.; El-Naggar, G. M.; El-Sherief, H. A. H.;

Adbel-Rahman, A. E.-S.; Aly, M. F. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 326−330. (c) Rauws, T. R. M.; Biancalani, C.; De Schutter, J. W.; Maes, B. U. W. *Tetrahedron* **2010**, *66*, 6958−6964.
(10) (a) Krasavin, M.; Parchinsky, V. *Synlett* **2008**, 645−648. (b) Krasavin, M.; Shkavrov, S.; Parchinsky, V.; Bukhryakov, K. *J. Org. Chem.* **2009**, *74*, 2627−2629. (c) Heravi, M. M.; Baghernejad, B.; Oskooie, H. A. *Tetrahedron Lett.* **2009**, *50*, 767.
(11) Haddadin, M. J.; El-Khatib, M.; Shoker, T. A.; Beavers, C. M.; Olmstead, M. M.; Fettigner, J. C.; Farber, K. M.; Kurth, M. J. *J. Org. Chem.* **2011**, *76*, 8421−8427.
(12) (a) Cho, Y.-H.; Lee, C.-Y.; Ha, D.-C.; Cheon, C.-H. *Adv. Synth. Catal.* **2012**, *354*, 2992−2996. (b) Cho, Y.-H.; Lee, C.-Y.; Cheon, C.-H. *Tetrahedron* **2013**, *69*, 6565−6573.
(13) For selected examples of the synthesis of benzimidazoles via aerobic oxidation, see: (a) Lei, M.; Ma, L.; Hu, L. *Synth. Commun.* **2012**, *42*, 2981−2993. (b) Behbahani, F. K.; Ziaei, P. *Chem. Heterocycl. Compd.* **2012**, *48*, 1011−1017. (c) Sharghi, H.; Beyzavi, M. H.; Doroodmand, M. M. *Eur. J. Org. Chem.* **2008**, 4126−4138. (d) Chen, Y.-X.; Qian, L.-F.; Zhang, W.; Han, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 9330−9333. (e) Lin, S.; Yang, L. *Tetrahedron Lett.* **2005**, *46*, 4315−4319. (f) Verner, E.; Katz, B. A.; Spencer, J. R.; Allen, D.; Hataye, J.; Hruzewicz, W.; Hui, H. C.; Kolennikov, A.; Li, Y.; Luong, C.; Matelli, A.; Radika, K.; Rai, R.; She, M.; Shrader, W.; Sprengler, P. A.; Trapp, S.; Wang, J.; Young, W. B.; Mackman, R. L. *J. Med. Chem.* **2001**, *44*, 2753−2771.
(14) (a) Ricciardi, F.; Joullie, M. M. *Synth. Commun.* **1986**, *16*, 35−42. (b) Hu, B.; Wrobel, J. E.; Jetter, W.; O'Neill, D. J.; Mann, C. W.; Unwalla, R. J. Patent WO2010054229A1.
(15) For selected examples of cyanide-based multicomponent reactions, see: (a) Guchhait, S. K.; Chaudhary, V.; Madaan, C. *Org. Biomol. Chem.* **2012**, *10*, 9271−9277. (b) Polyakov, A. I.; Eryomina, V. A.; Medvedeva, L. A.; Listratova, A. V.; Voskressensky, L. G. *Tetrahedron Lett.* **2009**, *50*, 4389−4393. (c) Montagne, C.; Shipman, M. *Synlett* **2006**, 2203−2206. (d) Schwerkoske, J.; Masquelin, T.; Perun, T.; Hulme, C. *Tetrahedron Lett.* **2005**, *46*, 8355−8357. (e) Shepherd, T.; Smith, D. M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 501−505.
(16) The cyanide anion is known to catalyze the benzoin reaction of aldehydes; see: March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structures*, 4th ed.; Wiley: New York, 1992; pp 969−970.
(17) Aliphatic aldehydes are known to undergo unwanted side reactions, such as intermolecular aldol reaction. See ref 13d.
(18) Similar *6-exo-dig* cyclization (reaction pathway *b*) has been already proposed in the literature without considering *5-endo-trig* cyclization (pathway *a*); see refs 11 and 15.
(19) Wu, M.; Hu, X.; Liu, J.; Liao, Y.; Deng, G.-J. *Org. Lett.* **2012**, *14*, 2722−2725.
(20) Iijima, C.; Morikawa, T.; Hayashi, E. *J. Pharm. Soc. Jpn.* **1975**, *95*, 784−792.