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Multifold Bond Cleavage and Formation between MeOH and Quinoxalines (or Benzothiazoles): Synthesis of Carbaldehyde Dimethyl Acetals

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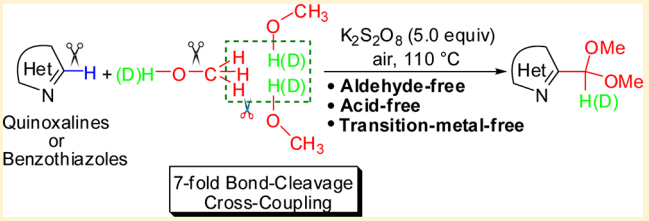
Supporting Information

ABSTRACT: A $K_2S_2O_8$-mediated direct cross-coupling of quinoxalines (or benzothiazoles) with methanol leading to 2-quinoxalinyl (or 2-benzothiazolyl) carbaldehyde dimethyl acetals has been achieved. 2-Quinoxalinyl carbaldehyde dimethyl acetals were readily converted into 2-quinoxalinyl carbaldehydes in good to excellent yields under acidic conditions. Preliminary mechanistic studies suggest that the reaction proceeds via multifold bond cleavage and formation between methanol and *N*-heterocycles involving a dioxygen-participated radical process. This method allows for the synthesis of a variety of 2-quinoxalinyl (or 2-benzothiazolyl) carbaldehyde dimethyl acetals directly via cross-coupling of simple *N*-heterocyclic C−H bond and methanol under aldehyde-, acid-, and transition-metal-free conditions.



INTRODUCTION

Methanol is a fundamental raw material in chemical industries that is annually prepared in large scale from the fossil-fuel-based syn-gas.[1] Preparation of methanol from the biomass-based syn-gas[2] or via the direct hydrogenation of carbon dioxide[3] is currently in progress, which will further add its feature of sustainability. Hence, there is a significant interest in the utilization of this readily available, inexpensive, and sustainable feedstock for the production of useful commodity chemicals as well as other complex organic molecules.[1,4−6] As far as the functionalization of methanol (C−H, C−O, and O−H) is concerned,[1,4−6] it is still a hard task to achieve direct C(sp^3)−H functionalization, much less to accomplish multifold C(sp^3)−H functionalization of this smallest alcohol with high selectivity,[6,7a] although much progress in the α-C(sp^3)−H activation/functionalization of alcohols has been made in recent years.[7,8] Therefore, it is highly desirable to develop effective ways for the (multifold) C(sp^3)−H functionalization of methanol.

On the other hand, acetals, known as masked aldehydes or ketones, are fundamental industrial products as well as useful precursors for the conversion to other functional groups.[9] The preparation of aldehyde acetals basically relies on aldehydes as the reactants catalyzed by a Lewis- or Brønsted acid (Scheme 1A).[9,10] This strategy is usually associated with several persistent disadvantages including the need for aldehydes as substrates, limited functionality and/or substrate (especially for heterocycles) compatibility under acidic conditions, and the use of environmentally harmful acid catalysts.[9,10e,h] Direct oxidation of terminal alkenes to aldehyde acetals in the presence of alcohols represents an aldehyde-free strategy for the synthesis of acetals, but transition-metal catalysts and/or expensive hypervalent iodine reagents have to be used in these reactions (Scheme 1B).[11] Direct cross-coupling between a heterocyclic C−H bond and 1,3-dioxolane could realize aldehyde-free synthesis of acetals, but the method suffered from low selectivity (Scheme 1C).[20e] In light of the recent success in the C−H bond functionalization[7,8] and the great advantages of the methanol economy,[1] we envisioned that the direct cross-coupling of a C−H bond with methanol via multifold bond cleavage and formation would be an ideal alternative strategy for the aldehyde-free synthesis of aldehyde acetals (Scheme 1D). In 2004, Minisci et al.[6d] reported a silver-catalyzed direct cross-coupling of protonated lepidine with methanol to access formylated lepidine. Herein, we report on the one-pot synthesis of a variety of 2-quinoxalinyl (or 2-benzothiazolyl) carbaldehyde dimethyl acetals directly via cross-coupling between quinoxaline (or benzothiazole) C−H bond and methanol under aldehyde-, acid-, and transition-metal-free conditions.[12]

RESULTS AND DISCUSSION

The motivation of this research originated in our recent study on the regiospecific preparation of nitroarenes via palladium-catalyzed direct *ortho*-nitration of aromatic C−H bonds assisted by a nitrogen donor.[13] In solvent screening investigations, a reaction of 2-phenylquinoxaline **1a** with $AgNO_2$ (2 equiv based

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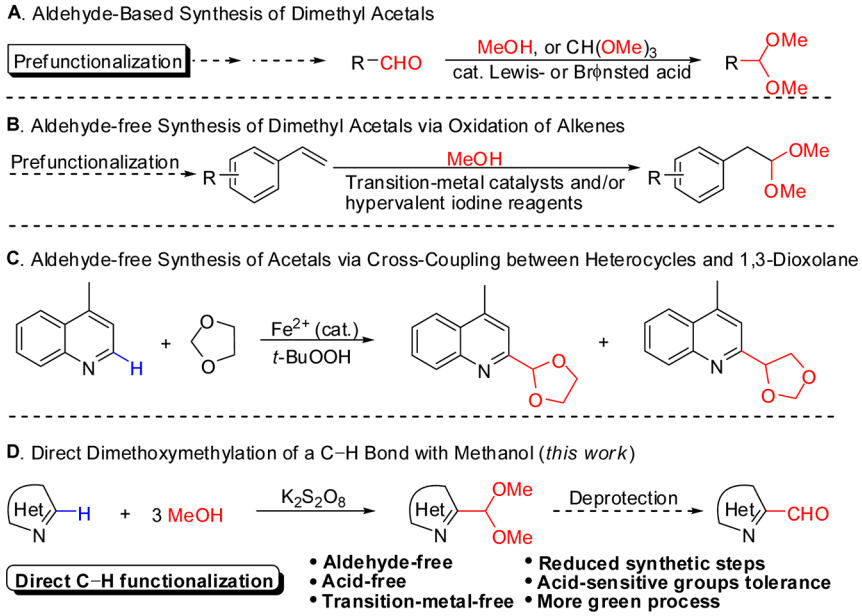
Scheme 1. Strategies for the Synthesis of Aldehyde (Dimethyl) Acetals



on **1a**) and $K_2S_2O_8$ (2 equiv) catalyzed by $Pd(OAc)_2$ (10 mol %) was conducted in anhydrous methanol at 130 °C for 48 h. No desired nitration product was formed, but 3-phenylquinoxaline-2-carbaldehyde dimethyl acetal **2a** was unexpectedly isolated in 12% yield instead (entry 1, Table 1). It was found that in the absence of $AgNO_2$ and $Pd(OAc)_2$ **2a** could also be produced in 26% yield at 130 °C for 24 h (entry 2, Table 1), indicating that $AgNO_2$ and $Pd(OAc)_2$ did not participate in the reaction. Our interest in the conciseness of the reaction to furnish 2-quinoxalinyl carbaldehyde dimethyl acetals from simple starting materials prompted us to optimize the reaction conditions so as to make the reaction synthetically valuable (Table 1). We were pleased to find that the yield of **2a** could be significantly improved to 56% when 5 equiv of $K_2S_2O_8$ was used at 130 °C for 12 h (entry 3, Table 1). A higher yield (72%) of **2a** could be obtained by lowering the temperature to 110 °C and shortening the reaction time to 6 h (entry 5, Table 1). Further increasing the amount of $K_2S_2O_8$ resulted in a decrease in the yield of **2a** (entry 8, Table 1). When hydrated methanol (containing 0.2 wt % of water) was used, the reaction produced **2a** in 42% yield along with a formylated product **3a** in 24% yield (entry 10, Table 1). A range of other oxidants were surveyed, all showed lower efficiency than $K_2S_2O_8$ for the reaction (entries 11−18, Table 1). The reaction did not occur in the absence of $K_2S_2O_8$ (entry 22, Table 1). When ethanol was used as the substrate and solvent under otherwise identical conditions as the entry 5, the reaction failed to give the desired product (entry 23, Table 1).

Under the established reaction conditions, the scope of the $K_2S_2O_8$-mediated direct cross-coupling of quinoxalines **1** with methanol was investigated (Table 2). A variety of quinoxaline derivatives **1**, equipped with halo, aryl, alkyl, cyano, methoxy, and heterocyclic groups, could be smoothly dimethoxymethylated with methanol to furnish various 2-quinoxalinyl carbaldehyde dimethyl acetals **2** in moderate to excellent yields (63−97%, entries 1−20, Table 2). It was found that **1** substituted with aryl groups at the 3-position generally gave higher yields of desired products than those substituted with alkyl groups (entries 1−16 vs 17−20, Table 2). Note that acid-sensitive groups such as cyano and thiophene could be well-tolerated under the reaction conditions, as demonstrated in the dimethoxymethylation of **1j** and **1p** with methanol, respectively (entries 10 and 16, Table 2). The reaction time should be controlled within 0.75 h for a monodimethoxymethylation of **1q**, otherwise a 2-fold dimethoxymethylation of **1q** at the 2- and 3-position would happen (entry 17, Table 2). When substrate **1s** bearing a cyclopropyl group was subjected to the oxidative reaction conditions, the cyclopropyl group remained intact in the dimethoxymethylation process and the desired product was obtained in 65% yield (entry 19, Table 2). The subsequent conversion of **2** to **3** was readily accomplished in 1,4-dioxane in the presence of an aqueous solution of HCl (1 N) at 70 °C for 6 h,[14] thus a broad range of 2-quinoxalinyl carbaldehydes[15] could be conveniently prepared from quinoxalines and methanol via a two-step process in synthetically useful yields (81−95%, entries 1−20 except 9, Table 2). A one-pot procedure for the synthesis of **3a** without the purification of **2a** was also tried, and **3a** was obtained in 65% yield based on **1a** (entry 1, Table 2). The reaction showed highly regiospecific fashion, in all cases the dimethoxymethylation took place at the α-position of a nitrogen atom of the quinoxaline ring. The regioselectivity of the dimethoxymethylation was unambiguously established on the basis of the spectral analyses, which was further confirmed by X-ray diffraction analysis of a related derivative **2i** (Figure S1, Supporting Information).

Next, exploration of the present protocol for the dimethoxymethylation of a range of benzothiazoles was carried out. In most cases, the reaction proceeded smoothly to furnish corresponding 2-benzothiazolyl carbaldehyde dimethyl acetals in synthetically acceptable yields (39−76%, **5a**−**5h**, Table 3). It generally required longer reaction times for the dimethoxymethylation of benzothiazoles to be completed than that of quinoxalines (Table 3 vs Table 2). It was found that substrate **4** bearing electron-deficient groups generally furnished the desired products in higher yields than those bearing electron-rich groups (**5c**−**5h** vs **5b**, Table 3). The position where a substituent placed on the phenyl ring of benzothiazoles had a significant effect on the reaction outcome. For example, while

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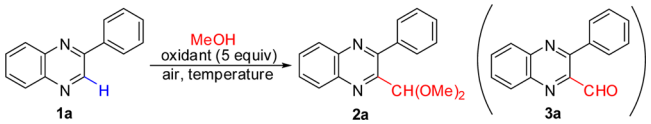
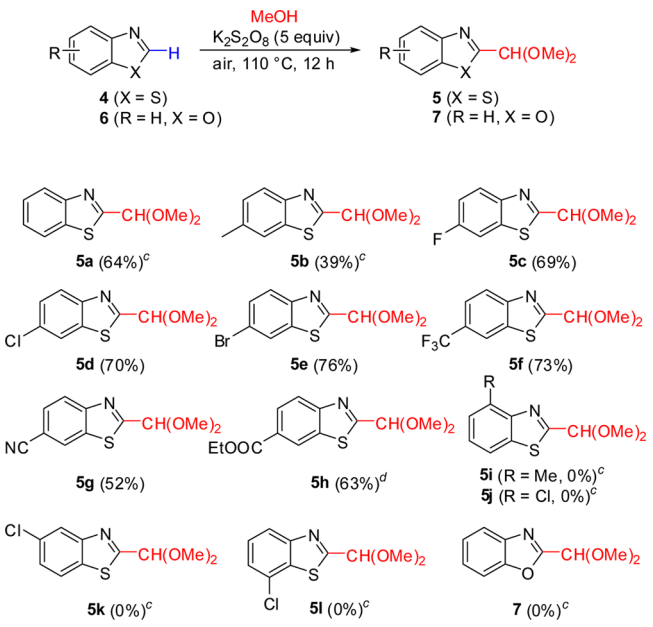
Table 1. Screening for Optimal Conditions[a]



entry	oxidant (equiv)	temp (°C)	time (h)	yield of **2a**[b] (%)
1	$K_2S_2O_8$ (2)	130	48	12[c]
2	$K_2S_2O_8$ (2)	130	24	26 (28[d])
3	$K_2S_2O_8$	130	12	56
4	$K_2S_2O_8$	110	12	62
5	**$K_2S_2O_8$**	**110**	**6**	**72**
6	$K_2S_2O_8$	110	3	68
7	$K_2S_2O_8$ (3)	110	6	49
8	$K_2S_2O_8$ (7)	110	6	61
9	$K_2S_2O_8$	90	12	0
10	$K_2S_2O_8$	110	6	42[e] (24[f])
11	$(PhCOO)_2$	110	12	trace
12	TBHP[g]	110	12	trace
13	CAN[h]	110	12	21
14	DDQ[i]	110	12	trace
15	$(NH_4)_2S_2O_8$	110	12	25
16	BQ[j]	110	12	0
17	$^tBuOO^tBu$	110	12	trace
18	$PhI(OAc)_2$	110	12	trace
19	$K_2S_2O_8$	110	6	30[k]
20	$K_2S_2O_8$	110	6	46[l]
21	$K_2S_2O_8$	110	6	17[m,n]
22	none	110	12	0
23	$K_2S_2O_8$	110	6	0[o]

[a]Reaction conditions: **1a** (0.2 mmol), oxidant (5 equiv) in anhydrous MeOH (6 mL) unless otherwise noted. [b]Isolated yields. [c]In the presence of $AgNO_2$ (2 equiv) and $Pd(OAc)_2$ (10 mol %). [d]Reaction temperature is 110 °C. [e]Hydrated methanol (containing 0.2 wt % of water) was used. [f]Yield of **3a**. [g]TBHP = *tert*-Butyl hydroperoxide. [h]CAN = cerium ammonium nitrate. [i]DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone. [j]BQ = Benzoquinone. [k]2 mL of methanol was used. [l]4 mL of methanol was used. [m]0.4 mL of MeOH (24 equiv) and 4 mL of 1,2-dichloroethane were used. [n]70% of **1a** was recovered. [o]Ethanol was used as the substrate and solvent.

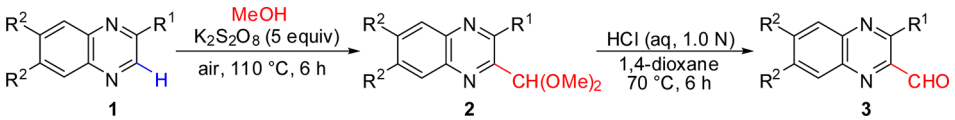
Table 3. $K_2S_2O_8$-mediated Direct Dimethoxymethylation of Benzothiazoles (or Benzoxazole) with Methanol[a,b]



[a]Reaction conditions: **4** or **6** (0.2 mmol), $K_2S_2O_8$ (5 equiv) in anhydrous MeOH (6 mL), 110 °C, 12 h unless otherwise noted. [b]Isolated yields. [c]Reaction time is 15 h. [d]Reaction time is 22 h.

the 6-position substituted benzothiazoles could be smoothly dimethoxymethylated (**5b**–**5h**, Table 3), those with the 4-, 5-, or 7-position substituted benzothiazoles were inert substrates for the reaction (**5i**–**5l**, Table 3). Benzoxazole **6** failed to give the desired acetal under the standard conditions (**7**, Table 3). In addition, more *N*-containing heterocycles including pyridine, quinoline, isoquinoline, acridine, 4-methyl quinoline, pteridine-2,4(1H,3H)-dione, 2,4(1H,3H)-pyrimidine-dione were investigated for the present reaction. Unfortunately, all these substrates failed to give desired products. At present stage, the substrate scope is still limited to only quinoxalines and benzothiazoles. The exact reason that why the present

Table 2. $K_2S_2O_8$-mediated Synthesis of 2-Quinaoxalinyl Carbaldehyde Dimethyl Acetals 2 and Their Subsequent Conversion to 3[a,b]



entry	R^1, R^2 (**1**)	product	yield (%)[c] (**2**/**3**)	entry	R^1, R^2 (**1**)	product	yield (%)[c] (**2**/**3**)
1	Ph, H (**1a**)	**2a**/**3a**	72/84(65[d])	11	Ph, Me (**1k**)	**2k**/**3k**	89/93
2	4-MeC_6H_4, H (**1b**)	**2b**/**3b**	63/85	12	4-$MeOC_6H_4$, Me (**1l**)	**2l**/**3l**	87/91
3	4-$MeOC_6H_4$, H (**1c**)	**2c**/**3c**	71/89	13	4-ClC_6H_4, Me (**1m**)	**2m**/**3m**	91/95
4	3-$MeOC_6H_4$, H (**1d**)	**2d**/**3d**	85/87	14	Ph, Cl (**1n**)	**2n**/**3n**	91/89
5	2-$MeOC_6H_4$, H (**1e**)	**2e**/**3e**	92/87	15	4-FC_6H_4, Cl (**1o**)	**2o**/**3o**	88/91
6	4-PhC_6H_4, H (**1f**)	**2f**/**3f**	91/87	16	2-thiophenyl, H (**1p**)	**2p**/**3p**	86/91
7	4-FC_6H_4, H (**1g**)	**2g**/**3g**	92/89	17	H, H (**1q**)	**2q**/**3q**	66[f]/87
8	4-ClC_6H_4, H (**1h**)	**2h**/**3h**	95/90	18	Et, H (**1r**)	**2r**/**3r**	69/84
9	4-BrC_6H_4, H (**1i**)	**2i**/**3i**	97/--[e]	19	cyclopropyl, H (**1s**)	**2s**/**3s**	65/81
10	4-CNC_6H_4, H (**1j**)	**2j**/**3j**	88/90	20	^iPr, Me (**1t**)	**2t**/**3t**	71/86

[a]Reaction conditions for the synthesis of **2**:**1** (0.2 mmol), $K_2S_2O_8$ (5.0 equiv) in anhydrous MeOH (6 mL) at 110 °C for 6 h unless otherwise noted. [b]Reaction conditions for the synthesis of **3**:**2** (0.2 mmol), 1 N HCl (3 mL) in 1,4-dioxane (5 mL) at 70 °C for 6 h. [c]Isolated yields. [d]Isolated yield based on **1a** via one-pot procedure without the purification of **2a**. [e]It is difficult to get pure **3i**. [f]Reaction time is 0.75 h.

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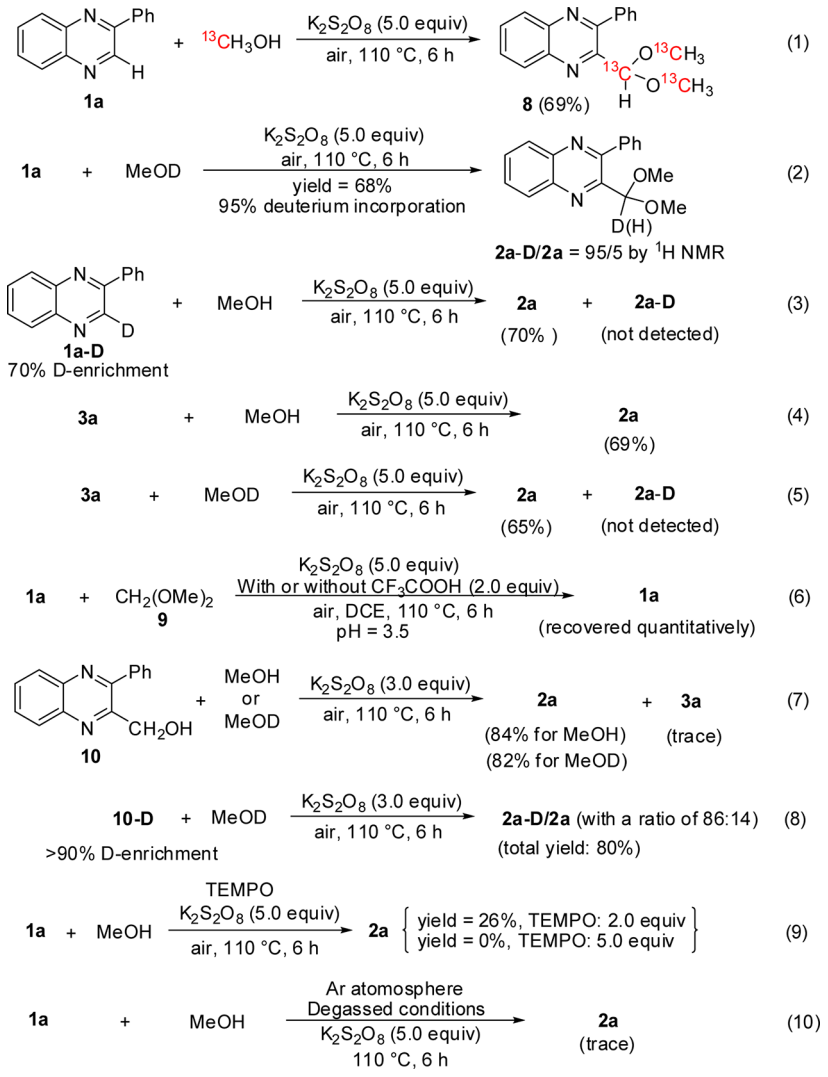
Scheme 2. Preliminary Mechanistic Studies



reaction is so sensitive to the substrate structure has not been fully understood, according to the proposed mechanism (*vide infra*, Scheme 3), we speculate that the occurrence of the present reaction may mainly depend on whether the corresponding reaction intermediates (e.g., heterocycle-substituted methanol species) could form or not.

Preliminary experiments were done to gain a mechanistic insight into the dimethoxymethylation reaction (Scheme 2). A ^{13}C-labeling experiment unambiguously established that all the three carbon atoms in the dimethoxymethyl group of the target acetals originated from methanol (eq 1, Scheme 2). When the dimethoxymethylation of **1a** was performed in methanol-d_1 (>99% D-enrichment of the hydroxyl proton), **2a-D** and **2a** were obtained in a total yield of 68% with a ratio of 95:5, suggesting 95% D-enriched at the methine proton of **2a** (eq 2, Scheme 2). A treatment of **1a-D** (70% D-enrichment) with MeOH furnished acetal **2a** in 70% yield without the formation of **2a-D** (eq 3, Scheme 2). These results suggest that the C−H and C−O bonds in one molecule of MeOH were all cleaved in the course of the dimethoxymethylation, and the methine proton of the resulting C*H*$(OMe)_2$ moiety finally derived from the hydroxy proton of methanol. A treatment of the preparative 3-phenylquinoxaline-2-carbaldehyde **3a** with MeOH under the standard conditions could afford **2a** in 69% yield (eq 4, Scheme 2). Further conducting a reaction of **3a** with MeOD under otherwise identical conditions still produced **2a** in a similar yield (65%) without the formation of **2a-D** (eq 5, Scheme 2). Direct reaction of **1a** with formaldehyde dimethyl acetal **9** in the presence of $K_2S_2O_8$ resulted in the recovery of **1a** quantitatively, thus the possibility of formaldehyde dimethyl acetal **9** as a reaction intermediate was unlikely (eq 6, Scheme 2). When the preparative 2-hydroxymethyl-3-phenylquinoxaline **10** was treated with methanol or methanol-d_1 (>99% D-enrichment of the hydroxyl proton) in the presence of 3 equivalent of $K_2S_2O_8$ at 110 °C for 6 h, **2a** was obtained as the major product along with trace amount of **3a** without the detection of **2a-D** (for the case of methanol-d_1) (eq 7, Scheme 2). Surprisingly, conducting a reaction of **10-D** (>90% D-enrichment of the hydroxyl proton) with MeOD under otherwise identical conditions could afford **2a-D** and **2a** in a total yield of 80% with a ratio of 86:14 (eq 8, Scheme 2), suggesting **10** being the possible intermediate. The reaction of **1a** and MeOH under the standard conditions gave a decreased yield of **2a** (26%) in the presence of 2 equiv of TEMPO and failed to give **2a** by using 5 equiv of TEMPO (eq 9, Scheme 2), demonstrating that the reaction may involve a radical process.[16] Note that the dimethoxymethylation of **1a** with MeOH hardly took place when degassed MeOH was used

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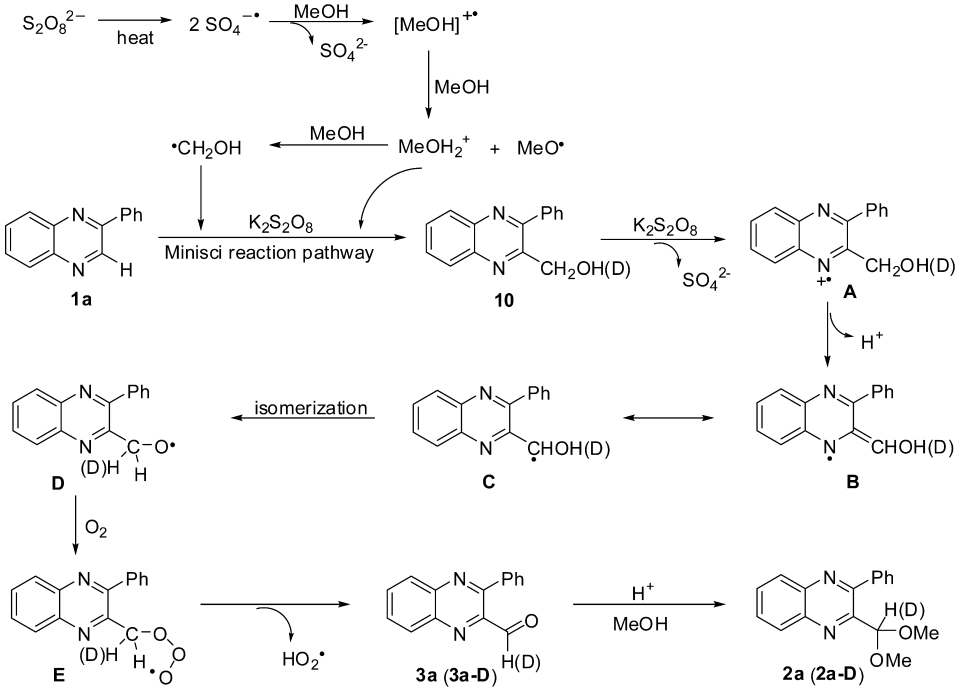
Scheme 3. Proposed Mechanism



under argon atmosphere (eq 10, Scheme 2), implying that dioxygen possibly participated in the reaction process.[17,18]

On the basis of the above-mentioned mechanistic experiments, a proposed mechanism was depicted in Scheme 3. First, potassium peroxydisulphate may be decomposed to sulfate radical anion upon heating.[19] Then methoxy radicals, hydroxymethyl radicals, and protons were produced via reactions of methanol with sulfate radical anions.[19] The Minisci hydroxymethylation reaction involving hydroxymethyl radicals and **1a** in the presence of $K_2S_2O_8$ and protons led to the formation of the intermediate **10**.[6d,19,20] Reaction of **10** with $K_2S_2O_8$ may produce a radical species **C** which subsequently isomerized to form a radical species **D**.[21] Oxidation of **D** to aldehyde **3a** occurred in the presence of dioxygen via a trioxy radical species **E**.[18] Acetalization of E by methanol finally gave dimethyl acetal **2a**.[9]

CONCLUSION

In summary, we have described a direct and green access to 2-quinoxalinyl (or 2-benzothiazolyl) carbaldehyde dimethyl acetals via dimethoxymethylation of *N*-heterocyclic C−H bond with methanol under aldehyde-, acid-, and transition-metal-free conditions.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, commercial reagents were used directly without further purifications. MeOH was distilled over magnesium prior to use. MeOD (>99% D-enrichment of the hydroxyl proton) was dried over molecular sieve before use. Other solvents for reactions were dried and distilled prior to use according to standard methods. Column Chromatography was performed on silica gel (100−200 mesh) or neutral alumina (200−300 mesh) with solvents specified below. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a spectrometer at 25 °C in $CDCl_3$ at 500 MHz, 125 MHz, respectively, with TMS as internal standard. ^{19}F NMR spectra were recorded on a spectrometer at 25 °C in $CDCl_3$ at 376 MHz, with CF_3COOH as external standard. Chemical shifts (δ) are expressed in ppm and coupling constants J are given in Hz. The IR spectra were recorded on an FT-IR spectrometer. GC-MS experiments were performed with EI source, and high resolution mass spectra (HRMS) were obtained on a TOF MS instrument with EI or ESI source.

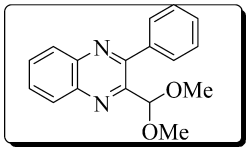
Starting Materials. The starting materials **1q**, **4a**, **6**, **9** and **13** are commercially available. **1a−1t** (except **1q**) were prepared according to the literature.[22−24] **4b−4l** were prepared according to the literature.[25,26]

Characterization of Unknown Starting Materials. *6,7-Dichloro-2-(4-fluorophenyl)quinoxaline (**1o**).* Yellow solid; mp 213−215 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.30 (s, 1H), 8.27−8.20 (m, 4H), 7.30−7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.6 (d, J = 250.6 Hz), 151.5, 143.8, 141.0, 140.2, 135.1, 134.1, 132.2 (d, J = 3.2 Hz), 130.1, 129.8, 129.6 (d, J = 8.4 Hz, 2C), 116.4 (d, J = 21.8 Hz, 2C); LRMS (EI): m/z (%) = 292 (100) $[M]^+$; HRMS (EI) for $C_{14}H_7Cl_2FN_2$ $[M]^+$: calcd 291.9970, found 291.9989.

*2-Isopropyl-6,7-dimethylquinoxaline (**1t**).* Orange oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.68 (s, 1H), 7.81 (s, 2H), 3.31−3.26 (m, 1H), 2.48 (s, 6H), 1.44 (s, 3H), 1.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.9, 143.7, 141.0, 140.3, 140.2, 139.2, 128.11, 128.08, 34.8, 22.1 (2C), 20.2, 20.1; LRMS (EI): m/z (%) = 200 (45) $[M]^+$; HRMS (EI) for $C_{13}H_{16}N_2$ $[M]^+$: calcd 200.1313, found 200.1325.

General Procedure for $K_2S_2O_8$-mediated Dimethoxymethylation of Quinoxalines. Quinoxalines **1** (0.2 mmol), $K_2S_2O_8$ (270 mg, 1.0 mmol), and anhydrous MeOH (6.0 mL) were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal (Figure 1). Then the flask was sealed and stirred at 110 °C for 6 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on neutral alumina (200−300 mesh) using petroleum ether-EtOAc (6:1, v/v) as the eluent to give pure **2**.

*2-(dimethoxymethyl)-3-phenylquinoxaline (**2a**).*



Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid

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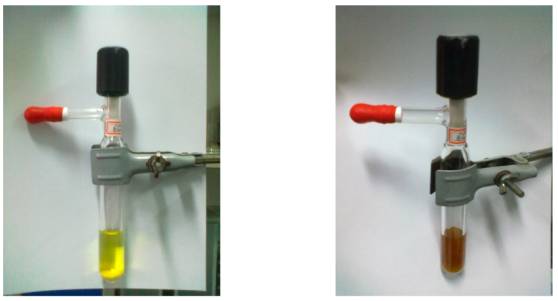
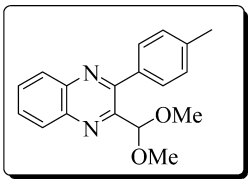


(a) (b)

Figure 1. Schlenk flask used in the reaction: (a) before reaction; (b) after reaction.

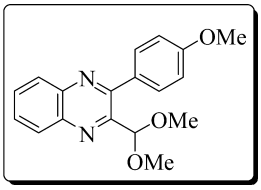
(40.4 mg, 72%); mp 91−92 °C; R_f = 0.36; IR (neat): ν = 3060, 2927, 2862, 1596, 1503, 1448, 1372 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.31 (dd, J_1 = 8.0 Hz, J_2 = 2.5 Hz, 1H), 8.15 (dd, J_1 = 8.0 Hz, J_2 = 2.5 Hz, 1H), 7.82−7.78 (m, 2H), 7.75−7.73 (m, 2H), 7.56−7.52 (m, 3H), 5.61 (s, 1H), 3.45 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 154.0, 149.4, 141.7, 140.7, 138.0, 130.6, 129.9, 129.6, 129.3 (2C), 129.14, 129.11, 128.4 (2C), 101.0, 54.3 (2C); LRMS (ESI): m/z (%) = 281.21 (100) $[M + H]^+$; HRMS (ESI) for $C_{17}H_{17}N_2O_2$ $[M + H]^+$: calcd 281.1290, found 281.1291.

*2-(Dimethoxymethyl)-3-p-tolylquinoxaline (**2b**).*



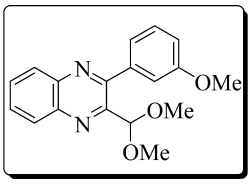
Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (37.1 mg, 63%); mp 72−73 °C; R_f = 0.35; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.30 (dd, J_1 = 7.0 Hz, J_2 = 1.5 Hz, 1H), 8.15 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 7.82−7.77 (m, 2H), 7.65 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 7.5 Hz, 2H), 5.64 (s, 1H), 3.46 (s, 6H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 154.1, 149.4, 141.8, 140.6, 139.2, 135.1, 130.5, 129.8, 129.7 (2C), 129.3 (3C), 129.2, 100.9, 54.3 (2C), 21.4; LRMS (ESI): m/z (%) = 295 (100) $[M + H]^+$; HRMS (ESI) for $C_{18}H_{19}N_2O_2$ $[M + H]^+$: calcd 295.1447, found 295.1433.

*2-(Dimethoxymethyl)-3-(4-methoxyphenyl)quinoxaline (**2c**).*



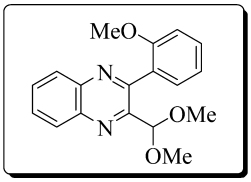
Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (44.1 mg, 71%); mp 76−78 °C; R_f = 0.33; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.30 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 8.14 (dd, J_1 = 7.0 Hz, J_2 = 2.5 Hz, 1H), 7.82−7.73 (m, 4H), 7.08 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 2H), 5.65 (s, 1H), 3.91 (s, 3H), 3.48 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.5, 153.7, 149.3, 141.8, 140.5, 130.9 (2C), 130.5, 130.3, 129.7, 129.6, 129.0, 113.9 (2C), 100.9, 55.4, 54.2 (2C); LRMS (ESI): m/z (%) = 311.18 (100) $[M + H]^+$; HRMS (ESI) for $C_{18}H_{19}N_2O_3$ $[M + H]^+$: calcd 311.1396, found 311.1389.

*2-(Dimethoxymethyl)-3-(3-methoxyphenyl)quinoxaline (**2d**).*



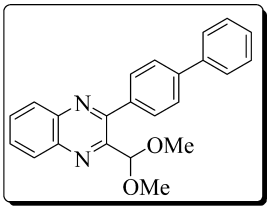
Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow oil (52.7 mg, 85%); R_f = 0.37; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.32−8.30 (m, 1H), 8.17−8.15 (m, 1H), 7.82−7.78 (m, 2H), 7.45 (t, J = 7.5 Hz, 1H), 7.32−7.28 (m, 2H), 7.08−7.06 (m, 1H), 5.63 (s, 1H), 3.89 (s, 3H), 3.46 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.6, 153.8, 149.4, 141.6, 140.8, 139.2, 130.6, 130.0, 129.7, 129.5, 129.2, 121.7, 115.1, 114.8, 100.9, 55.3, 54.4 (2C); LRMS (ESI): m/z (%) = 311.14 (100) $[M + H]^+$; HRMS (ESI) for $C_{18}H_{19}N_2O_3$ $[M + H]^+$: calcd 311.1396, found 311.1381.

*2-(Dimethoxymethyl)-3-(2-methoxyphenyl)quinoxaline (**2e**).*



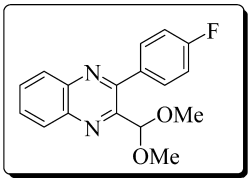
Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a white solid (57.1 mg, 92%); mp 76−79 °C; R_f = 0.35; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.33 (dd, J_1 = 7.0 Hz, J_2 = 3.5 Hz, 1H), 8.17 (dd, J_1 = 6.9 Hz, J_2 = 3.3 Hz, 1H), 7.80−7.78 (m, 2H), 7.51−7.48 (m, 1H), 7.42 (dd, J_1 = 7.4 Hz, J_2 = 1.7 Hz, 1H), 7.16 (t, J = 7.3 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 5.52 (s, 1H), 3.78 (s, 3H), 3.52 (s, 3H), 3.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.5, 152.4, 151.1, 141.8, 140.9, 130.7 (2C), 130.3, 129.9, 129.8, 129.1, 127.3, 121.1, 110.8, 101.1, 55.4, 54.9, 53.9; LRMS (ESI): m/z (%) = 310.97 (100) $[M + H]^+$; HRMS (ESI) for $C_{18}H_{19}N_2O_3$ $[M + H]^+$: calcd 311.1396, found 311.1387.

*2-(Biphenyl-4-yl)-3-(dimethoxymethyl)quinoxaline (**2f**).*



Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (64.8 mg, 91%); mp 116−119 °C; R_f = 0.38; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.31 (dd, J_1 = 8.0 Hz, J_2 = 2.5 Hz, 1H), 8.17 (dd, J_1 = 8.0 Hz, J_2 = 2.5 Hz, 1H), 7.86−7.77 (m, 6H), 7.69 (d, J = 8.5 Hz, 2H), 7.49 (dd, J_1 = 8.0 Hz, J_2 = 7.5 Hz, 2H), 7.40 (t, J = 7.5 Hz, 1H), 5.70 (s, 1H), 3.49 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.7, 149.4, 142.1, 141.8, 140.7, 140.5, 136.9, 130.7, 130.0, 129.9 (2C), 129.7, 129.2, 128.9 (2C), 127.7, 127.2 (2C), 127.18 (2C), 101.1, 54.3 (2C); LRMS (ESI): m/z (%) = 357.05 (100) $[M + H]^+$; HRMS (ESI) for $C_{23}H_{21}N_2O_2$ $[M + H]^+$: calcd 357.1603, found 357.1593.

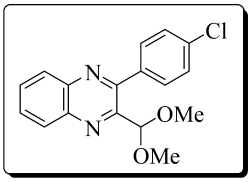
*2-(Dimethoxymethyl)-3-(4-fluorophenyl)quinoxaline(**2g**).*



dx.doi.org/10.1021/jo302450f | J. Org. Chem. XXXX, XXX, XXX−XXX

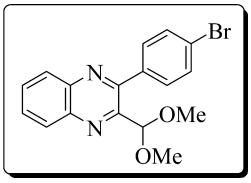
Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a white solid (54.9 mg, 92%); mp 78−80 °C; R_f = 0.38; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.30 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 8.14 (dd, J_1 = 7.5 Hz, J_2 = 2.5 Hz, 1H), 7.82−7.76 (m, 4H), 7.23 (dd, J_1 = 7.5 Hz, J_2 = 7.0 Hz, 2H), 5.58 (s, 1H), 3.46 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.5 (d, $^1J_{F-C}$ = 248.8 Hz), 153.0, 149.3, 141.7, 140.6, 134.1 (d, $^4J_{F-C}$ = 3.8 Hz), 131.4 (d, $^3J_{F-C}$ = 7.5 Hz, 2C), 130.7, 130.1, 129.6, 129.1, 115.4 (d, $^2J_{F-C}$ = 22.5 Hz, 2C), 101.5, 54.3 (2C); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −112.3 (s); LRMS (ESI): m/z (%) = 299.17 (100) $[M + H]^+$; HRMS (ESI) for $C_{17}H_{16}FN_2O_2$ $[M + H]^+$: calcd 299.1196, found 299.1188.

*2-(4-Chlorophenyl)-3-(dimethoxymethyl)quinoxaline (**2h**).*



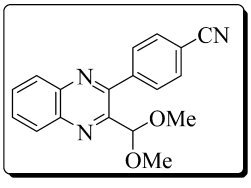
Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (59.8 mg, 95%); mp 91−92 °C; R_f = 0.32; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.30 (d, J = 9.5 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 7.84−7.80 (m, 2H), 7.74 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 2H), 7.53 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 2H), 5.58 (s, 1H), 3.47 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.8, 149.2, 141.6, 140.7, 136.5, 135.5, 130.84 (2C), 130.77, 130.2, 129.6, 129.2, 128.6 (2C), 101.5, 54.3 (2C); LRMS (ESI): m/z (%) = 315.17 (100) $[M + H]^+$; HRMS (ESI) for $C_{17}H_{16}ClN_2O_2$ $[M + H]^+$: calcd 315.0900, found 315.0891.

*2-(4-Bromophenyl)-3-(dimethoxymethyl)quinoxaline (**2i**).*



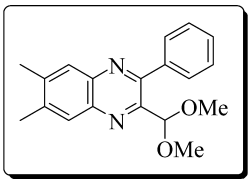
Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a light yellow solid (69.7 mg, 97%); mp 91−93 °C; R_f = 0.33; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.29 (dd, J_1 = 7.5 Hz, J_2 = 2.5 Hz, 1H), 8.14 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 7.84−7.80 (m, 2H), 7.69−7.66 (m, 4H), 5.58 (s, 1H), 3.46 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.9, 149.2, 141.7, 140.7, 137.0, 131.6 (2C), 131.1 (2C), 130.8, 130.3, 129.7, 129.2, 123.9, 101.5, 54.3 (2C); LRMS (ESI): m/z (%) = 359.15 (100) $[M + H]^+$; HRMS (ESI) for $C_{17}H_{16}BrN_2O_2$ $[M + H]^+$: calcd 359.0395, found 359.0389.

*4-(3-(Dimethoxymethyl)Quinoxalin-2-yl)benzonitrile (**2j**).*



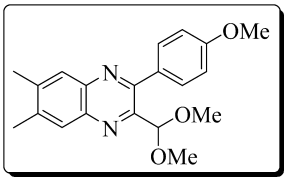
Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a white solid (53.7 mg, 88%); mp 112−113 °C; R_f = 0.32; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.30−8.28 (m, 1H), 8.17−8.15 (m, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.86−7.82 (m, 4H), 5.54 (s, 1H), 3.45 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.1, 149.2, 142.8, 141.5, 140.7, 131.9 (2C), 131.1 (2C), 130.7, 130.3, 129.6, 129.2, 118.6, 112.9, 102.7, 54.5 (2C); LRMS (ESI): m/z (%) = 306.19 (100) $[M + H]^+$; HRMS (ESI) for $C_{18}H_{16}N_3O_2$ $[M + H]^+$: calcd 306.1243, found 306.1233.

*2-(Dimethoxymethyl)-6,7-dimethyl-3-phenylquinoxaline (**2k**).*



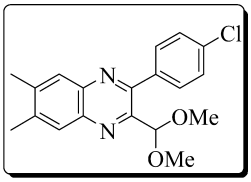
Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (54.9 mg, 89%); mp 77−80 °C; R_f = 0.36; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.05 (s, 1H), 7.89 (s, 1H), 7.73−7.71 (m, 2H), 7.54−7.50 (m, 3H), 5.58 (s, 1H), 3.43 (s, 6H), 2.512 (s, 3H), 2.508 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.1, 148.4, 141.3, 140.8, 140.6, 139.8, 138.3, 129.4 (2C), 128.9, 128.7, 128.4 (2C), 128.2, 101.0, 54.2 (2C), 20.43, 20.37; LRMS (ESI): m/z (%) = 309.03 (100) $[M + H]^+$; HRMS (ESI) for $C_{19}H_{21}N_2O_2$ $[M + H]^+$: calcd 309.1603, found 309.1596.

*2-(Dimethoxymethyl)-3-(4-methoxyphenyl)-6,7-dimethylquinoxaline (**2l**).*



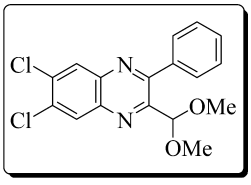
Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (58.9 mg, 87%); mp 97−98 °C; R_f = 0.34; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.04 (s, 1H), 7.88 (s, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 5.61 (s, 1H), 3.90 (s, 3H), 3.46 (s, 6H), 2.51 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.3, 152.7, 148.4, 141.2, 140.8, 140.3, 139.5, 130.9 (2C), 130.7, 128.6, 128.1, 113.9 (2C), 101.1, 55.4, 54.1 (2C), 20.4, 20.3; LRMS (ESI): m/z (%) = 339.30 (100) $[M + H]^+$; HRMS (ESI) for $C_{20}H_{23}N_2O_3$ $[M + H]^+$: calcd 339.1709, found 339.1703.

*2-(4-Chlorophenyl)-3-(dimethoxymethyl)-6,7-dimethylquinoxaline (**2m**).* Purification by column chromatography on neutral alumina



with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow oil (62.4 mg, 91%); R_f = 0.35; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.03 (s, 1H), 7.86 (s, 1H), 7.69 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 5.54 (s, 1H), 3.43 (s, 6H), 2.50 (s, 3H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 151.8, 148.2, 141.5, 140.9, 140.7, 139.7, 136.8, 135.2, 130.9 (2C), 128.6, 128.5 (2C), 128.1, 101.5, 54.2 (2C), 20.41, 20.38; LRMS (ESI): m/z (%) = 343.26 (100) $[M + H]^+$; HRMS (ESI) for $C_{19}H_{20}ClN_2O_2$ $[M + H]^+$: calcd 343.1213, found 343.1209.

*6,7-Dichloro-2-(dimethoxymethyl)-3-phenylquinoxaline (**2n**).*

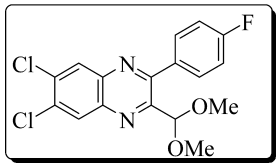


Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (63.6 mg, 91%); mp 90−91 °C; R_f = 0.31; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.43 (s, 1H), 8.28 (s, 1H), 7.75−7.73 (m, 2H), 7.57−7.55 (m, 3H),

dx.doi.org/10.1021/jo302450f | J. Org. Chem. XXXX, XXX, XXX−XXX

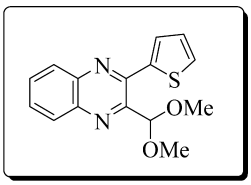
5.60 (s, 1H), 3.46 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.1, 150.6, 140.5, 139.4, 137.3, 135.4, 134.7, 130.2, 129.8, 129.6, 129.3 (2C), 128.5 (2C), 100.8, 54.4 (2C); LRMS (ESI): m/z (%) = 349.16 (100) $[M + H]^+$; HRMS (ESI) for $C_{17}H_{15}Cl_2N_2O_2$ $[M + H]^+$: calcd 349.0511, found 349.0499.

*6,7-Dichloro-2-(dimethoxymethyl)-3-(4-fluorophenyl)quinoxaline (**2o**).*



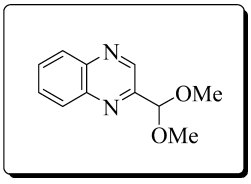
Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a white solid (64.6 mg, 88%); mp 77−80 °C; R_f = 0.33; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.42 (s, 1H), 8.26 (s, 1H), 7.80−7.77 (m, 2H), 7.28−7.23 (m, 2H), 5.56 (s, 1H), 3.47 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.7 (d, $^1J_{F-C}$ = 248.6 Hz), 154.0, 150.5, 140.4, 139.2, 135.5, 134.8, 133.4 (d, $^4J_{F-C}$ = 3.4 Hz), 131.5 (d, $^3J_{F-C}$ = 8.2 Hz, 2C), 130.2, 129.7, 115.6 (d, $^2J_{F-C}$ = 21.7 Hz, 2C), 101.3, 54.4 (2C); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −111.4 (s); LRMS (ESI): m/z (%) = 367.17 (100) $[M + H]^+$; HRMS (ESI) for $C_{17}H_{14}Cl_2FN_2O_2$ $[M + H]^+$: calcd 367.0416, found 367.0404.

*2-(Dimethoxymethyl)-3-(thiophen-2-yl)quinoxaline (**2p**).*



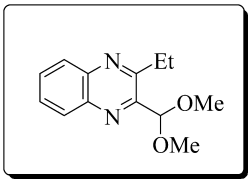
Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a taupe solid (49.2 mg, 86%); mp 63−65 °C; R_f = 0.36; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.25 (d, J = 9.5 Hz, 1H), 8.12 (d, J = 9.5 Hz, 1H), 7.95 (d, J = 3.5 Hz, 1H), 7.81−7.75 (m, 2H), 7.59 (d, J = 5.0 Hz, 1H), 7.22 (dd, J_1 = 5.0 Hz, J_2 = 4.0 Hz, 1H), 5.88 (s, 1H), 3.54 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.8, 147.2, 141.6, 141.3, 140.0, 130.8, 130.4, 129.89, 129.86, 129.5, 128.9, 128.2, 101.4, 54.1 (2C); LRMS (ESI): m/z (%) = 287.13 (100) $[M + H]^+$; HRMS (ESI) for $C_{15}H_{15}N_2O_2S$ $[M + H]^+$: calcd 287.0854, found 287.0847.

*2-(Dimethoxymethyl)quinoxaline[14] (**2q**).*



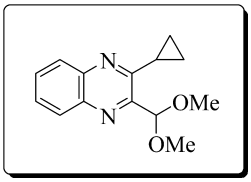
Reaction time: 0.75 h; purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a brown solid (26.9 mg, 66%); mp 83−85 °C (lit.[14] mp 85−86 °C); R_f = 0.40; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.11 (s, 1H), 8.18−8.14 (m, 2H), 7.82−7.79 (m, 2H), 5.58 (s, 1H), 3.51 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.1, 143.9, 142.5, 141.4, 130.3 (2C), 129.6, 129.3, 103.9, 54.2 (2C); LRMS (ESI): m/z (%) = 205.24 (100) $[M + H]^+$.

*2-(Dimethoxymethyl)-3-ethylquinoxaline (**2r**).*



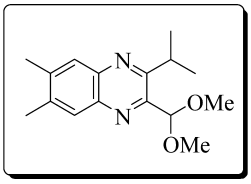
Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a brown oil (32.1 mg, 69%); R_f = 0.38; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.13 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 8.06 (dd, J_1 = 8.1 Hz, J_2 = 1.4 Hz, 1H), 7.76−7.69 (m, 2H), 5.59 (s, 1H), 3.51 (s, 6H), 3.23 (q, J = 7.5 Hz, 2H), 1.42 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.8, 150.3, 141.8, 139.6, 130.0, 129.2, 129.0, 128.4, 106.1, 55.1 (2C), 27.6, 12.9; LRMS (ESI): m/z (%) = 233.02 (100) $[M + H]^+$; HRMS (ESI) for $C_{13}H_{17}N_2O_2$ $[M + H]^+$: calcd 233.1290, found 233.1284.

*2-Cyclopropyl-3-(dimethoxymethyl)quinoxaline (**2s**).*



Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow oil (31.7 mg, 65%); R_f = 0.38; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.10 (dd, J_1 = 8.5 Hz, J_2 = 1.0 Hz, 1H), 7.93 (dd, J_1 = 8.3 Hz, J_2 = 1.3 Hz, 1H), 7.71−7.63 (m, 2H), 5.73 (s, 1H), 3.54 (s, 6H), 2.84−2.79 (m, 1H), 1.32−1.31 (m, 2H), 1.13−1.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.6, 150.0, 142.0, 139.2, 129.9, 129.2, 128.3 (2C), 106.0, 55.0 (2C), 13.4, 11.1 (2C); LRMS (ESI): m/z (%) = 245.05 (100) $[M + H]^+$; HRMS (ESI) for $C_{14}H_{17}N_2O_2$ $[M + H]^+$: calcd 245.1290, found 245.1281.

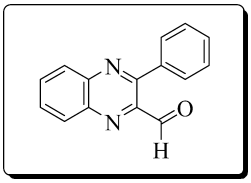
*2-(Dimethoxymethyl)-3-isopropyl-6,7-dimethylquinoxaline (**2t**).*



Purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a light yellow solid (38.9 mg, 71%); mp 81−83 °C; R_f = 0.40; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.86 (s, 1H), 7.81 (s, 1H), 5.59 (s, 1H), 3.79 (heptet, J = 6.8 Hz, 1H), 3.48 (s, 6H), 2.48 (s, 3H), 2.47 (s, 3H), 1.35 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.7, 148.6, 141.1, 140.3, 139.2, 138.5, 128.3, 127.7, 106.2, 54.9 (2C), 30.7, 22.3 (2C), 20.20, 20.18; LRMS (ESI): m/z (%) = 275.10 (100) $[M + H]^+$; HRMS (ESI) for $C_{16}H_{23}N_2O_2$ $[M + H]^+$: calcd 275.1760, found 275.1749.

*General Procedure for the Conversion of **2** to **3**.* The conversions of **2** to **3** were followed according to the literature procedure.[14] General Procedure: To a solution of **2** (0.2 mmol) in 1,4-dioxane (5 mL) was added an aqueous solution of HCl (1N, 3 mL), and the resulting mixture was heated slowly in an oil bath to an external temperature of 70 °C for 6 h. Upon cooling, the mixture was extracted with diethyl ether (2 × 20 mL). The diethyl ether layer was dried over $MgSO_4$ and concentrated under reduced pressure. Crude product was crystallization from ethanol or purified by column chromatography on silica gel (100−200 mesh) using petroleum ether-EtOAc (6:1, v/v) as the eluent.

*3-Phenylquinoxaline-2-carbaldehyde (**3a**).*

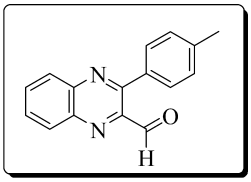


Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (39.3 mg, 84%); mp 130−132 °C; R_f = 0.40; IR (neat): ν = 3060, 2927, 2862, 1596, 1503, 1448, 1372 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.34

dx.doi.org/10.1021/jo302450f | J. Org. Chem. XXXX, XXX, XXX−XXX

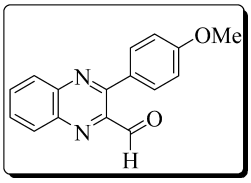
(s, 1H), 8.33 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 8.15 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 7.97−7.94 (m, 1H), 7.91−7.87 (m, 1H), 7.73−7.71 (m, 2H), 7.59−7.57 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.3, 154.5, 145.0, 142.8, 141.0, 136.6, 133.1, 130.9, 130.3, 129.9, 129.8 (2C), 129.4, 128.7 (2C); GC-MS (EI, 70 eV): m/z (%) = 234 (100) [M^+]; HRMS (EI) for $C_{15}H_{10}N_2O$ [M^+]: calcd 234.0793, found 234.0789.

*3-p-Tolylquinoxaline-2-carbaldehyde (**3b**).*



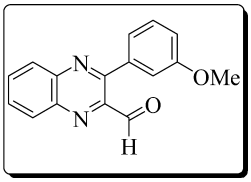
Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a white solid (42.2 mg, 85%); mp 123−126 °C; R_f = 0.42; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.33 (s, 1H), 8.31 (dd, J_1 = 8.5 Hz, J_2 = 1.0 Hz, 1H), 8.21 (dd, J_1 = 8.5 Hz, J_2 = 1.0 Hz, 1H), 7.94−7.85 (m, 2H), 7.63 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.3, 154.5, 145.1, 142.9, 140.9, 140.1, 133.7, 132.9, 130.7, 130.3, 129.9, 129.5(2C), 129.4 (2C), 21.4; GC-MS (EI, 70 eV): m/z (%) = 248 (100) [M^+]; HRMS (EI) for $C_{16}H_{12}N_2O$ [M^+]: calcd 248.0950, found 248.0944.

*3-(4-Methoxyphenyl)quinoxaline-2-carbaldehyde (**3c**).*



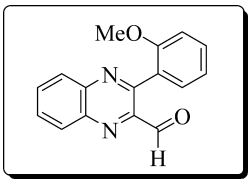
Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (47.0 mg, 89%); mp 146−150 °C; R_f = 0.42; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.34 (s, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.95−7.84 (m, 2H), 7.71 (dd, J_1 = 11.6 Hz, J_2 = 2.9 Hz, 2H), 7.10 (dd, J_1 = 11.6 Hz, J_2 = 2.9 Hz, 2H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.5, 161.2, 154.0, 145.0, 142.8, 140.8, 133.0, 131.5 (2C), 130.6, 130.3, 129.2, 128.7, 114.3 (2C), 55.5; GC- MS (EI, 70 eV): m/z (%) = 264 (100) [M^+]; HRMS (EI) for $C_{16}H_{12}N_2O_2$ [M^+]: calcd 264.0899, found 264.0885.

*3-(3-Methoxyphenyl)quinoxaline-2-carbaldehyde (**3d**).*



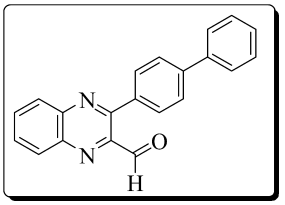
Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (46.0 mg, 87%); mp 115−116 °C; R_f = 0.41; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.33 (s, 1H), 8.33 (dd, J_1 = 8.4 Hz, J_2 = 1.0 Hz, 1H), 8.23 (dd, J_1 = 8.5 Hz, J_2 = 1.0 Hz, 1H), 7.97−7.93 (m, 1H), 7.91−7.87 (m, 1H), 7.48 (t, J = 7.9 Hz, 1H), 7.29−7.23 (m, 2H), 7.11 (dd, J_1 = 8.3 Hz, J_2 = 2.7 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.1, 159.9, 154.4, 145.1, 142.8, 141.1, 137.8, 133.1, 131.0, 130.4, 129.8, 129.4, 122.4, 115.8, 115.1, 55.5; GC-MS (EI, 70 eV): m/z (%) = 264 (56) [M^+]; HRMS (EI) for $C_{16}H_{12}N_2O_2$ [M^+]: calcd 264.0899, found 264.0890.

*3-(2-Methoxyphenyl)quinoxaline-2-carbaldehyde (**3e**).*



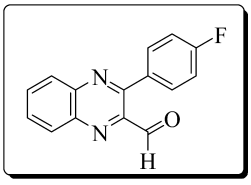
Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (46.0 mg, 87%); mp 114−118 °C; R_f = 0.38; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.13 (s, 1H), 8.31 (d, J = 8.2 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.91−7.85 (m, 2H), 7.73 (dd, J_1 = 8.1 Hz, J_2 = 1.7 Hz,1H), 7.53 (dt, J_1 = 1.7 Hz, J_2 = 8.3 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.4, 156.5, 151.5, 146.5, 143.3, 140.8, 132.4, 131.8, 131.0, 130.6, 130.3, 129.3, 125.9, 121.8, 110.8, 55.3; GC-MS (EI, 70 eV): m/z (%) = 264 (100) [M^+]; HRMS (EI) for $C_{16}H_{12}N_2O_2$ [M^+]: calcd 264.0899, found 264.0888.

*2-(Biphenyl-4-yl)quinoxaline-2-carbaldehyde (**3f**).*



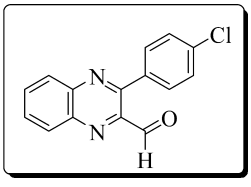
Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (54.0 mg, 87%); mp 163−165 °C; R_f = 0.41; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.40 (s, 1H), 8.33 (dd, J_1 = 8.5 Hz, J_2 = 1.0 Hz, 1H), 8.24 (dd, J_1 = 8.5 Hz, J_2 = 0.5 Hz, 1H), 7.97−7.87 (m, 2H), 7.83−7.79 (m, 4H), 7.70 (d, J = 8.5 Hz, 2H), 7.52−7.40 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.4, 154.1, 145.1, 142.9, 142.8, 141.0, 140.3, 135.5, 133.1, 130.9, 130.4, 130.3 (2C), 129.4, 128.9 (2C), 127.8, 127.4 (2C), 127.3 (2C); GC-MS (EI, 70 eV): m/z (%) = 310 (100) [M^+]; HRMS (EI) for $C_{21}H_{14}N_2O$ [M^+]: calcd 310.1106, found 310.1108.

*3-(4-Fluorophenyl)quinoxaline-2-carbaldehyde (**3g**).*



Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a light yellow solid (44.9 mg, 89%); mp 160−165 °C; R_f = 0.41; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.33 (s, 1H), 8.32 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 8.5 Hz, 1H), 7.98−7.95 (m, 1H), 7.92−7.90 (m, 1H), 7.73−7.71 (m, 2H), 7.28−7.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.4, 163.9 (d, $^1J_{F-C}$ = 248.8 Hz), 153.1, 144.9, 142.8, 141.0, 133.2, 132.8 (d, $^4J_{F-C}$ = 2.5 Hz), 131.8 (d, $^3J_{F-C}$ = 8.8 Hz, 2C), 131.0, 130.2, 129.4, 115.7 (d, $^2J_{F-C}$ = 21.3 Hz, 2C); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −111.2; GC-MS (EI, 70 eV): m/z (%) = 252 (100) [M^+]; HRMS (EI) for $C_{15}H_9FN_2O$ [M^+]: calcd 252.0699, found 252.0683.

*3-(4-Chlorophenyl)quinoxaline-2-carbaldehyde (**3h**).*

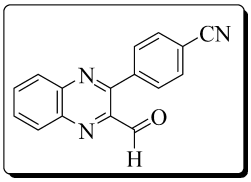


Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (48.4 mg,

dx.doi.org/10.1021/jo302450f | J. Org. Chem. XXXX, XXX, XXX−XXX

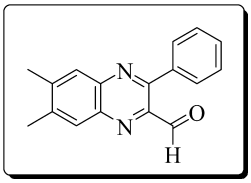
90%); mp 184−188 °C; R_f = 0.40; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 10.33(s, 1H), 8.32 (dd, J_1 = 8.4 Hz, J_2 = 1.0 Hz, 1H), 8.22 (dd, J_1 = 8.3 Hz, J_2 = 1.0 Hz, 1H), 7.98−7.95 (m, 1H), 7.92−7.89 (m, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.4, 153.0, 144.9, 142.8, 141.0, 136.3, 135.2, 133.3, 131.1 (3C), 130.2, 129.4, 128.8 (2C); GC-MS (EI, 70 eV): m/z (%) = 268 (100) [M^+]; HRMS (EI) for $C_{15}H_9ClN_2O$ [M^+]: calcd 268.0403, found 268.0394.

*4-(3-Formylquinoxalin-2-yl)benzonitrile (**3j**).*



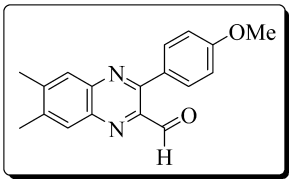
Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a light yellow solid (46.7 mg, 90%); mp 215−220 °C; R_f = 0.39; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 10.32 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.24 (d, J = 9.0 Hz, 1H), 8.01−7.96 (m, 2H), 7.81 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.6, 151.9, 144.7, 142.6, 141.5, 141.2, 133.7, 132.1 (2C), 131.6, 130.4 (2C), 130.2, 129.5, 118.5, 113.4; GC-MS (EI, 70 eV): m/z (%) = 259 (83) [M^+]; HRMS (EI) for $C_{16}H_9N_3O$ [M^+]: calcd 259.0746, found 259.0749.

*6,7-Dimethyl-3-phenylquinoxaline-2-carbaldehyde (**3k**).*



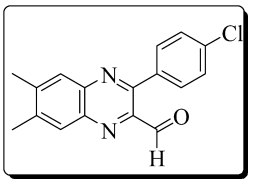
Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (48.8 mg, 93%); mp 140−143 °C; R_f = 0.41; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 10.30 (s, 1H), 8.06 (s, 1H), 7.97 (s, 1H), 7.71−7.69 (m, 2H), 7.57−7.55 (m, 3H), 2.57 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.4, 153.9, 144.6, 144.2, 141.9, 140.2, 136.9, 129.8 (2C), 129.6, 129.1, 128.6, 128.5 (2C), 128.3, 20.8, 20.5; GC-MS (EI, 70 eV): m/z (%) = 262 (100) [M^+]; HRMS (EI) for $C_{17}H_{14}N_2O$ [M^+]: calcd 262.1106, found 262.1120.

*3-(4-Methoxyphenyl)-6,7-dimethylquinoxaline-2-carbaldehyde (**3l**).*



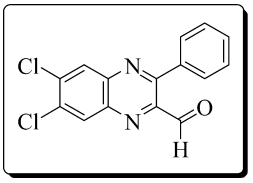
Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (53.2 mg, 91%); mp 212−214 °C; R_f = 0.41; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 10.30 (s, 1H), 8.03 (s, 1H), 7.94 (s, 1H), 7.67 (dd, J_1 = 8.7 Hz, J_2 = 2.7 Hz, 2H), 7.08 (dd, J_1 = 8.7 Hz, J_2 = 2.5 Hz, 2H), 3.91(s, 3H), 2.55 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.7, 161.0, 153.5, 144.4, 144.2, 142.0, 141.5, 140.0, 131.5 (2C), 129.2, 129.1, 128.2, 114.2 (2C), 55.4, 20.8, 20.4; GC-MS (EI, 70 eV): m/z (%) = 292 (100) [M^+]; HRMS (EI) for $C_{18}H_{16}N_2O_2$ [M^+]: calcd 292.1212, found 292.1226.

*3-(4-Chlorophenyl)-6,7-dimethylquinoxaline-2-carbaldehyde (**3m**).*



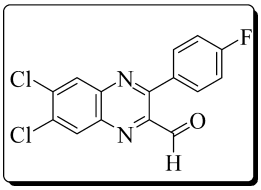
Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a light yellow solid (56.4 mg, 95%); mp 189−194 °C; R_f = 0.40; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 10.28 (s, 1H), 8.03 (s, 1H), 7.94 (s, 1H), 7.63 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 2.56 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.6, 152.3, 144.9, 144.0, 142.1, 141.8, 140.1, 135.9, 135.5, 131.1 (2C), 129.0, 128.7 (2C), 128.3, 20.8, 20.5; GC-MS (EI, 70 eV): m/z (%) = 296 (100) [M^+]; HRMS (EI) for $C_{17}H_{13}ClN_2O$ [M^+]: calcd 296.0716, found 296.0709.

*6,7-Dichloro-3-phenylquinoxaline-2-carbaldehyde (**3n**).*



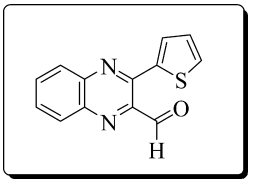
Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a light yellow solid (54.0 mg, 89%); mp 151−154 °C; R_f = 0.39; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 10.30 (s, 1H), 8.44 (s, 1H), 8.35 (s, 1H), 7.72−7.70 (m, 2H), 7.60−7.56 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.5, 155.2, 145.8, 141.4, 139.6, 138.1, 135.89, 135.84, 130.5, 130.3, 129.9, 129.8 (2C), 128.7 (2C); GC-MS (EI, 70 eV): m/z (%) = 302 (100) [M^+]; HRMS (EI) for $C_{15}H_8Cl_2N_2O$ [M^+]: calcd 302.0014, found 302.0018.

*6,7-Dichloro-3-(4-fluorophenyl)quinoxaline-2-carbaldehyde (**3o**).*



Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a light yellow solid (58.5 mg, 91%); mp 196−199 °C; R_f = 0.40; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 10.29 (s, 1H), 8.43 (s, 1H), 8.34 (s, 1H), 7.72−7.70 (m, 2H), 7.28−7.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.8, 164.1 (d, $^1J_{F-C}$ = 249.8 Hz), 153.9, 145.6, 141.4, 139.5, 138.3, 136.0, 132.1, 131.9 (d, $^3J_{F-C}$ = 8.5 Hz, 2C), 130.5, 129.9, 115.8 (d, $^2J_{F-C}$ = 21.9 Hz, 2C); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −110.2 (s); GC-MS (EI, 70 eV): m/z (%) = 320 (100) [M^+]; HRMS (EI) for $C_{15}H_7Cl_2FN_2O$ [M^+]: calcd 319.9919, found 319.9909.

*3-(Thiophen-2-yl)quinoxaline-2-carbaldehyde (**3p**).*

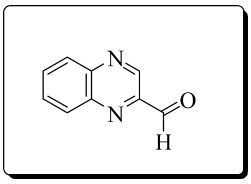


Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (43.7 mg, 91%); mp 102−106 °C; R_f = 0.40; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 10.44 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 8.5 Hz, 1H), 7.92−7.89

dx.doi.org/10.1021/jo302450f | J. Org. Chem. XXXX, XXX, XXX−XXX

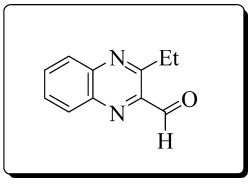
(m, 1H), 7.84−7.81 (m, 2H), 7.63 (d, J = 5.0 Hz, 1H), 7.27 (dd, J_1 = 5.0 Hz, J_2 = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.5, 147.3, 144.3, 142.7, 140.4, 140.2, 133.2, 131.3, 130.8, 130.6, 130.1, 129.0, 128.3; GC-MS (EI, 70 eV): m/z (%) = 240 (100) [M^+]; HRMS (EI) for $C_{13}H_8N_2OS$ [M^+]: calcd 240.0357, found 240.0351.

Quinoxaline-2-carbaldehyde[27] (***3q***).



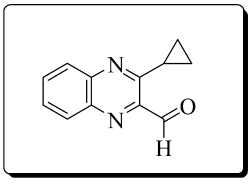
Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a brown solid (27.5 mg, 87%); mp 104−106 °C (lit.[27] mp 107 −108 °C); R_f = 0.42; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.30 (s, 1H), 9.44 (s, 1H), 8.27−8.21 (m, 2H), 7.97−7.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.7, 146.0, 144.5, 142.5, 141.9, 132.9, 131.1, 130.5, 129.6; GC- MS (EI, 70 eV): m/z (%) = 158 (100) [M^+].

3-Ethylquinoxaline-2-carbaldehyde (***3r***).



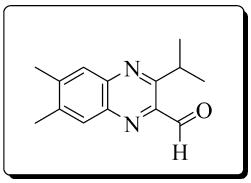
Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a brown solid (31.3 mg, 84%); mp 117−121 °C; R_f = 0.41; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.33 (s, 1H), 8.21 (dd, J_1 = 8.6 Hz, J_2 = 0.9 Hz, 1H), 8.12 (dd, J_1 = 8.2 Hz, J_2 = 0.8 Hz, 1H), 7.92−7.89 (m, 1H), 7.83−7.80 (m, 1H), 3.45 (q, J = 7.4 Hz, 2H), 1.41 (t, J = 7.4 Hz, 3H),; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.9, 158.3, 145.0, 143.0, 140.7, 132.8, 129.94, 129.91, 128.8, 28.7, 12.8; GC-MS (EI, 70 eV): m/z (%) = 186 (100) [M^+]; HRMS (EI) for $C_{11}H_{10}N_2O$ [M^+]: calcd 186.0793, found 186.0797.

3-Cyclopropylquinoxaline-2-carbaldehyde (***3s***).



Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a brown solid (32.1 mg, 81%); mp 107−109 °C; R_f = 0.41; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.37 (s, 1H), 8.16 (d, J = 9.0 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.86−7.83 (m, 1H), 7.76−7.73 (m, 1H), 3.49−3.44 (m, 1H), 1.39−1.38 (m, 2H), 1.23−1.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 194.4, 158.7, 144.7, 143.3, 140.2, 132.8, 130.0, 129.3, 128.6, 13.0, 12.3 (2C); GC-MS (EI, 70 eV): m/z (%) = 198 (100) [M^+]; HRMS (EI) for $C_{12}H_{10}N_2O$ [M^+]: calcd 198.0793, found 198.0799.

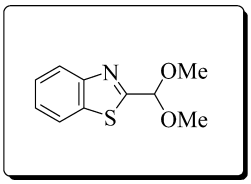
3-Isopropyl-6,7-dimethylquinoxaline-2-carbaldehyde (***3t***).



Purification by column chromatography on silica gel with 100−200 mesh (petroleum ether/EtOAc, 6/1, v/v) as a light yellow solid (39.3 mg, 86%); mp 124−127 °C; R_f = 0.42; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.30 (s, 1H), 7.93 (s, 1H), 7.90 (s, 1H), 4.25 (heptet, J = 6.8 Hz, 1H), 2.54 (s, 3H), 2.53 (s, 3H), 1.39 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 194.2, 161.2, 144.0, 143.7, 142.0, 140.5, 139.6, 128.7, 128.0, 30.8, 21.7 (2C), 20.6, 20.2; GC-MS (EI, 70 eV): m/z (%) = 228 (100) [M^+]; HRMS (EI) for $C_{14}H_{16}N_2O$ [M^+]: calcd 228.1263, found 228.1247.

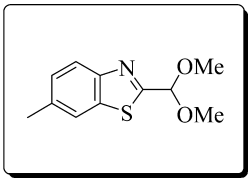
General Procedure for $K_2S_2O_8$-mediated Dimethoxymethylation of Benzothiazoles. Benzothiazoles **4** (0.2 mmol), $K_2S_2O_8$ (270 mg, 1.0 mmol), and anhydrous MeOH (6.0 mL) were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed and stirred at 110 °C for 12 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on neutral alumina (200−300 mesh) using petroleum ether-EtOAc (6:1, v/v) as the eluent to give pure **5**.

2-(Dimethoxymethyl)Benzo[D]Thiazole (***5a***).



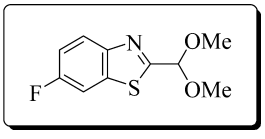
Reaction time: 15 h; purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow oil (26.8 mg, 64%); R_f = 0.40; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.10 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.52−7.49 (m, 1H), 7.44−7.40 (m, 1H), 5.71 (s, 1H), 3.51 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.7, 153.1, 135.2, 126.1, 125.5, 123.7, 121.8, 100.7, 53.7 (2C); GC-MS (EI, 70 eV): m/z (%) = 209 (14) [M^+]; HRMS (EI) for $C_{10}H_{11}NO_2S$ [M^+]: calcd 209.0511, found 209.0505.

2-(Dimethoxymethyl)-6-methylbenzo[d]thiazole (***5b***).



Reaction time: 15 h; purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow oil (17.4 mg, 39%); R_f = 0.41; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.96 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 7.31 (dd, J_1 = 8.3 Hz, J_2 = 1.2 Hz, 1H), 5.70 (s, 1H), 3.50 (s, 6H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.5, 151.2, 135.7, 135.3, 127.7, 123.2, 121.5, 100.7, 53.6 (2C), 21.5; GC-MS (EI, 70 eV): m/z (%) = 223 (23) [M^+]; HRMS (EI) for $C_{11}H_{13}NO_2S$ [M^+]: calcd 223.0667, found 223.0658.

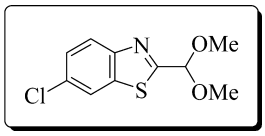
2-(Dimethoxymethyl)-6-fluorobenzo[d]thiazole (***5c***).



Reaction time: 12 h; purification by column chromatography on neutral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a white solid (31.3 mg, 69%); mp 62−65 °C; R_f = 0.41; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.03 (dd, J_1 = 9.0 Hz, J_2 = 4.8 Hz, 1H), 7.60 (dd, J_1 = 8.1 Hz, J_2 = 2.6 Hz, 1H), 7.26−7.22 (m, 1H), 5.68 (s, 1H), 3.51 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.5 (d, $^4J_{F-C}$ = 3.4 Hz), 160.7 (d, $^1J_{F-C}$ = 244.7 Hz), 149.7, 136.3 (d, $^3J_{F-C}$ = 11.4 Hz), 124.7 (d, $^3J_{F-C}$ = 9.3 Hz), 114.9 (d, $^2J_{F-C}$ = 25.0 Hz), 107.9 (d, $^2J_{F-C}$ = 26.5 Hz), 100.5, 53.7 (2C); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −115.7; GC-MS (EI, 70 eV): m/z (%) = 227 (12) [M^+]; HRMS (EI) for $C_{10}H_{10}FNO_2S$ [M^+]: calcd 227.0416, found 227.0408.

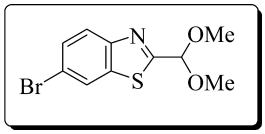
dx.doi.org/10.1021/jo302450f | J. Org. Chem. XXXX, XXX, XXX−XXX

*6-Chloro-2-(dimethoxymethyl)benzo[d]thiazole (**5d**).*



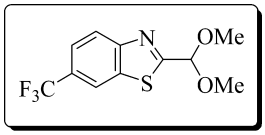
Reaction time: 12 h; purification by column chromatography on neatral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (34.1 mg, 70%); mp 60−61 °C; R_f = 0.39; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.0 (d, J = 8.8 Hz, 1H), 7.90 (d, J = 2.0 Hz, 1H), 7.46 (dd, J_1 = 8.7 Hz, J_2 = 2.2 Hz, 1H), 5.68 (s, 1H), 3.50 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.3, 151.7, 136.4, 131.6, 127.0, 124.5, 121.4, 100.5, 53.7 (2C); GC-MS (EI, 70 eV): m/z (%) = 243 (14) [M^+]; HRMS (EI) for $C_{10}H_{10}ClNO_2S$ [M^+]: calcd 243.0121, found 243.0112.

*6-Bromo-2-(dimethoxymethyl)benzo[d]thiazole (**5e**).*



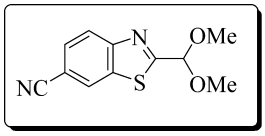
Reaction time: 12 h; purification by column chromatography on neatral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a white solid (43.8 mg, 76%); mp 100−103 °C; R_f = 0.39; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.05 (d, J = 1.9 Hz, 1H), 7.93 (d, J = 8.7 Hz, 1H), 7.59 (dd, J_1 = 8.7 Hz, J_2 = 1.9 Hz, 1H), 5.68 (s, 1H), 3.50 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.3, 151.9, 136.9, 129.7, 124.8, 124.4, 119.2, 100.4, 53.7 (2C); GC-MS (EI, 70 eV): m/z (%) = 287 (13) [M^+]; HRMS (EI) for $C_{10}H_{10}BrNO_2S$ [M^+]: calcd 286.9616, found 286.9607.

*2-(Dimethoxymethyl)-6-(trifluoromethyl)benzo[d]thiazole (**5f**).*



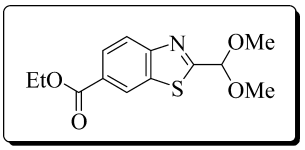
Reaction time: 12 h; purification by column chromatography on neatral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a white solid (40.5 mg, 73%); mp 113−116 °C; R_f = 0.38; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.24 (s, 1H), 8.20 (d, J = 8.6 Hz, 1H), 7.75 (dd, J_1 = 1.5 Hz, J_2 = 8.7 Hz, 1H), 5.73 (s, 1H), 3.53 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.1, 155.0, 135.3, 127.8 (q, J = 32.6 Hz), 125.2, 124.1, 123.1 (q, J = 7.7 Hz), 119.6 (q, J = 4.2 Hz), 100.4, 53.8 (2C); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −62.3 (s); GC-MS (EI, 70 eV): m/z (%) = 277 (1) [M^+]; HRMS (EI) for $C_{11}H_{10}F_3NO_2S$ [M^+]: calcd 277.0384, found 277.0388.

*2-(Dimethoxymethyl)benzo[d]thiazole-6-carbonitrile (**5g**).*



Reaction time: 12 h; purification by column chromatography on neatral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (24.3 mg, 52%); mp 124−126 °C; R_f = 0.37; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.29 (d, J = 1.0 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.76 (dd, J_1 = 8.5 Hz, J_2 = 1.4 Hz, 1H), 5.72 (s, 1H), 3.52 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.4, 155.4, 135.8, 129.2, 126.8, 124.6, 118.5, 109.2, 100.3, 53.9 (2C); GC-MS (EI, 70 eV): m/z (%) = 234 (1) [M^+]; HRMS (EI) for $C_{11}H_{10}N_2O_2S$ [M^+]: calcd 234.0463, found 234.0466.

*Ethyl 2-(Dimethoxymethyl)benzo[d]thiazole-6-carboxylate (**5h**).*



Reaction time: 22 h; purification by column chromatography on neatral alumina with 200−300 mesh (petroleum ether/EtOAc, 6/1, v/v) as a yellow solid (35.4 mg, 63%); mp 72−74 °C; R_f = 0.36; IR (neat): ν = 3032, 2926, 2866, 1598, 1509, 1448, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.68 (d, J = 0.5 Hz, 1H), 8.19 (dd, J_1 = 8.6 Hz, J_2 = 1.5 Hz, 1H), 8.13 (d, J = 8.6 Hz, 1H), 5.73 (s, 1H), 4.44 (q, J = 7.1 Hz, 2H), 3.53 (s, 6H), 1.44 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.4, 166.1, 155.8, 135.1, 127.8, 127.3, 124.1, 123.4, 100.5, 61.3, 53.8 (2C), 14.3; GC-MS (EI, 70 eV): m/z (%) = 281 (2) [M^+]; HRMS (EI) for $C_{13}H_{15}NO_4S$ [M^+]: calcd 281.0722, found 281.0728.

Mechanistic Studies. *^{13}C Labeling Experiment.* 2-Phenylquinoxaline **1a** (0.2 mmol), $K_2S_2O_8$ (270 mg, 1.0 mmol), and anhydrous $^{13}CH_3OH$ (99% ^{13}C-enrichment, 6.0 mL) were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed and stirred at 110 °C for 6 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on neutral alumina (200−300 mesh) using petroleum ether−EtOAc (6:1, v/v) as the eluent to give pure **8** as a yellow solid (39.1 mg, 69%).

Analytical Data of 8. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.32 (dd, J_1 = 9.8 Hz, J_2 = 2.6 Hz, 1H), 8.17 (dd, J_1 = 9.8 Hz, J_2 = 2.6 Hz, 1H), 7.83−7.74 (m, 4H), 7.56−7.54 (m, 3H), 5.62 (dt, $^1J_{^{13}C\text{-}^1H}$ = 162.6 Hz, $^3J_{^{13}C\text{-}^1H}$ = 4.7 Hz, 1H), 3.46 (dd, $^1J_{^{13}C\text{-}^1H}$ = 142.9 Hz, $^3J_{^{13}C\text{-}^1H}$ = 4.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): For spectrum being obtained from 3 times of scans: δ 100.9 ($^{13}CH(O^{13}CH_3)_2$), 54.3 ($^{13}CH(O^{13}CH_3)_2$); For spectrum being obtained from 500 times of scans: δ 154.0 (d, J = 9.0 Hz), 149.4 (d, J = 63.2 Hz), 141.7, 140.7 (d, J = 4.5 Hz), 137.9, 130.7, 130.0, 129.7, 129.3, 129.2, 129.1, 128.5, 101.0, 54.3; LRMS (ESI): m/z (%) = 284.12 (100) [M + H]$^+$.

Dimethoxymethylation of 1a in MeOD. 2-Phenylquinoxaline **1a** (41.2 mg, 0.2 mmol), $K_2S_2O_8$ (270 mg, 1.0 mmol), and anhydrous MeOD (>99% D-enrichment of the hydroxyl group, 6.0 mL) were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed and stirred at 110 °C for 6 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on neutral alumina (200−300 mesh) using petroleum ether−EtOAc (6:1, v/v) as the eluent to give a yellow solid (38.1 mg, 68%) which contains **2a-D** and **2a** with a ratio of 95:5.

Analytical Data of 2a-D/2a (95/5). ^1H NMR ($CDCl_3$, 500 MHz): δ 8.32 (dd, J_1 = 9.9 Hz, J_2 = 2.6 Hz, 1H), 8.16 (dd, J_1 = 9.9 Hz, J_2 = 2.6 Hz, 1H), 7.82−7.74 (m, 4H), 7.57−7.53 (m, 3H), 5.62 (s, 0.05H, **2a**), 3.46 (s, 6H); LRMS (ESI) for **2a-D**: m/z (%) = 282.19 (100) [M + H]$^+$.

Dimethoxymethylation of 1a in a Mixture of MeOH and MeOD (1:1, v/v). 2-Phenylquinoxaline **1a** (41.2 mg, 0.2 mmol), $K_2S_2O_8$ (270 mg, 1.0 mmol), and anhydrous MeOH (3.0 mL), MeOD (>99% D-enrichment of the hydroxyl group, 3.0 mL) were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed and stirred at 110 °C for 6 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on neutral alumina (200−300 mesh) using petroleum ether−EtOAc (6:1, v/v) as the eluent to give a yellow solid (39.2 mg, 70%) that was identified as compound **2a** without the detection of **2a-D** by ^1H NMR.

Dimethoxymethylation of 1a-D with MeOH. Preparation of Intermediate 12. **12** was synthesized according to the literature procedure.[23] Acetophenone-*methyl-d_3* **11**[28] (0.38 g, 3.0 mmol), CH_2Cl_2

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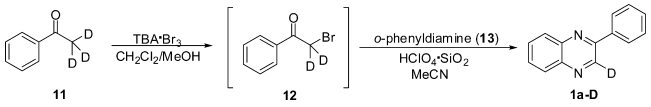
(15 mL), CH_3OH (6 mL), and TBA·Br_3 were added to a 50-mL flask. The mixture was stirred at 30 °C for 2 h until the light yellow took place. Then the solvent was removed under vacuum and the residue was diluted with water (10 mL) and extracted with ether (3 × 20 mL). The organic layer was then dried over Na_2SO_4, filtered and evaporated. The crude product was directly used for the next step.



Preparation of Intermediate 1a-D. **1a-D** was synthesized according to literature procedure.[22] To a suspension of **12** (0.41 g, 2.0 mmol) and $HClO_4$·SiO_2[24] (0.2 g) in CH_3CN (10 mL) was dropwise added a solution of *o*-phenyldiamine **13** (0.26 g, 2.4 mmol) in CH_3CN (2 mL) and the mixture was stirred at room temperature for 5 h. After completion (monitored by TLC), the reaction mixture was filtered and washed with CH_2Cl_2 (20 mL). The filtrate was concentrated and the residue was purified by column chromatography on silica gel (100−200 mesh) using petroleum ether−EtOAc (6:1, v/v) as the eluent to obtain **1a-D** (70% Deuterium enrichment) as a yellow solid (0.33 g, 78%).

Analytical Data of 1a-D (70% Deuterium Enrichment). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.35 (s, 0.30H, assigned to non-deuterated **1a**), 8.23−8.13 (m, 4H), 7.82−7.75 (m, 2H), 7.61−7.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 151.8 (d, J = 6.9 Hz), 143.4, 143.0 (t, J = 27.5 Hz), 142.3 (d, J = 3.7 Hz), 141.6 (d, J = 2.7 Hz), 136.8, 130.3, 130.2, 129.6, 129.5, 129.1, 127.6; GC-MS (EI, 70 eV): m/z (%) = 207 (100) [M^+]; HRMS (EI) for $C_{14}H_9DN_2$: calcd 207.0907, found 207.0912.

Dimethoxymethylation of 1a-D with MeOH. **1a-D** (41.2 mg, 0.2 mmol, 70% Deuterium-enrichment), $K_2S_2O_8$ (270 mg, 1.0 mmol), and anhydrous MeOH (6.0 mL), were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed and stirred at 110 °C for 6 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on neutral alumina (200−300 mesh) using petroleum ether−EtOAc (6:1, v/v) as the eluent to give a yellow solid (39.2 mg, 70%) which was identified as **2a** without the detection of **2a-D** by ^{1}H NMR.

Reaction of Intermediate 3a with MeOH. **3a** (46.8 mg, 0.2 mmol), $K_2S_2O_8$ (270 mg, 1.0 mmol), and anhydrous MeOH (6.0 mL), were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed and stirred at 110 °C for 6 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on neutral alumina (200−300 mesh) using petroleum ether−EtOAc (6:1, v/v) as the eluent to give a major product (38.6 mg, 69%) which was identified as **2a** by ^{1}H NMR and GC-MS. The reaction also gave a minor product **14** which was identified as methyl 3-phenylquinoxaline-2-carboxylate by GC-MS (m/z: 264 [$M]^+$).

Reaction of Intermediate 3a with MeOD. **3a** (46.8 mg, 0.2 mmol), $K_2S_2O_8$ (270 mg, 1.0 mmol), and anhydrous MeOD (>99% Deuterium-enrichment, 6.0 mL), were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed and stirred at 110 °C for 6 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on neutral alumina (200−300 mesh) using petroleum ether−EtOAc (6:1, v/v) as the eluent to give a major product (36.4 mg, 65%) which was identified as **2a** by ^{1}H NMR and GC-MS. The reaction also gave a minor product methyl 3-phenylquinoxaline-2-carboxylate **14** (GC-MS, m/z: 264 [$M]^+$).

Direct Reaction of 1a with Formaldehyde Dimethyl Acetal 9. **1a** (41.2 mg,, 0.2 mmol), $K_2S_2O_8$ (270 mg, 1.0 mmol), CF_3COOH (0 or 0.4 mmol), and anhydrous DCE (6.0 mL), were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed and stirred at 110 °C for 6 h. GC-MS analysis showed that none of **2a** was detected and **1a** was recovered quantitatively.

Reaction of Intermediate 10 (or 10-D) with MeOH and/or MeOD. *Preparation of Intermediate **10** and **10-D**.* The intermediate **10** was prepared via reduction of **3a** by $NaBH_4$ in wet THF according to a reported literature.[29] **10** was readily converted to **10-D** in the presence of NaH and D_2O in THF according to reported literature.[30]

*Analytical Data of **10**.* White solid; mp 142−143 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.25−8.23 (m, 2H), 7.86−7.84 (m, 2H), 7.67−7.65 (m, 2H), 7.58−7.57 (m, 3H), 5.00 (s, 2H), 2.89 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.3, 152.1, 141.8, 139.5, 137.0, 130.3, 130.1, 129.7, 129.5, 128.9 (2C), 128.6 (2C), 128.1, 62.5; HRMS (ESI) for $C_{15}H_{13}N_2O$ [M + H]$^+$: calcd 237.1028, found 237.1022.

*Reaction of **10** with MeOH or MeOD.* **10** (47.3 mg, 0.2 mmol), $K_2S_2O_8$ (162 mg, 0.6 mmol), and anhydrous MeOH (or MeOD (>99% Deuterium-enrichment), 6.0 mL), were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed and stirred at 110 °C for 6 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on neutral alumina (200−300 mesh) using petroleum ether−EtOAc (6:1, v/v) as the eluent to give **2a** (for reaction with MeOH, 84%; for reaction with MeOD, 82%).

*Reaction of **10-D** with MeOD.* **10-D** (>90% Deuterium-enrichment in hydroxyl proton, 47.3 mg, 0.2 mmol), $K_2S_2O_8$ (162 mg, 0.6 mmol), and anhydrous MeOD (>99% Deuterium-enrichment, 6.0 mL), were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed and stirred at 110 °C for 6 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on neutral alumina (200−300 mesh) using petroleum ether−EtOAc (6:1, v/v) as the eluent to give **2a-D** and **2a** in a total yield of 80% with a ratio of 86:14 determined by ^{1}H NMR.

Effect of Radical Scavenger TEMPO on the Reaction. **1a** (41.2 mg, 0.2 mmol), $K_2S_2O_8$ (270 mg, 1.0 mmol), TEMPO (62.5 mg, 0.4 mmol, 2 equiv; or 156.2 mg, 1.0 mmol, 5 equiv), and anhydrous MeOH (6.0 mL) were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed and stirred at 110 °C for 6 h. For entry 2, upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on neutral alumina (200−300 mesh) using petroleum ether−EtOAc (6:1, v/v) as the eluent to give **2a** (14.6 mg, 26%, TEMPO = 2 equiv; 0 mg, 0%, TEMPO = 5 equiv).

Reaction of 1a with MeOH under Degassed Reaction Conditions. **1a** (41.2 mg, 0.2 mmol), $K_2S_2O_8$ (270 mg, 1.0 mmol), and anhydrous MeOH (6.0 mL) were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the resultant mixture in the sealed tube was frozen by immersion of the flask in liquid N_2. When MeOH was completely frozen, the flask was opened to the vacuum (high vacuum) and pumped for 2−3 min, with the flask still immersed in liquid N_2. The flask was then closed and warmed until MeOH completely melted. This process was repeated three times and after the last cycle the flask was backfilled with an inert Ar gas. Then the sealed flask was stirred at 110 °C for 6 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was analyzed by GC-MS.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray structural data (CIF) of compound **2i**, charts for mechanistic studies as well as copies of ^{1}H NMR, ^{13}C NMR,

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and ^{19}F NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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