Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201800863

Link to VoR: http://dx.doi.org/10.1002/adsc.201800863

10.1002/adsc.201800863

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Direct C-H Trifluoromethylation of Quinoxalin-2(1*H*)-ones under Transition-Metal-Free Conditions

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Received: ((will be filled in by the editorial staff))

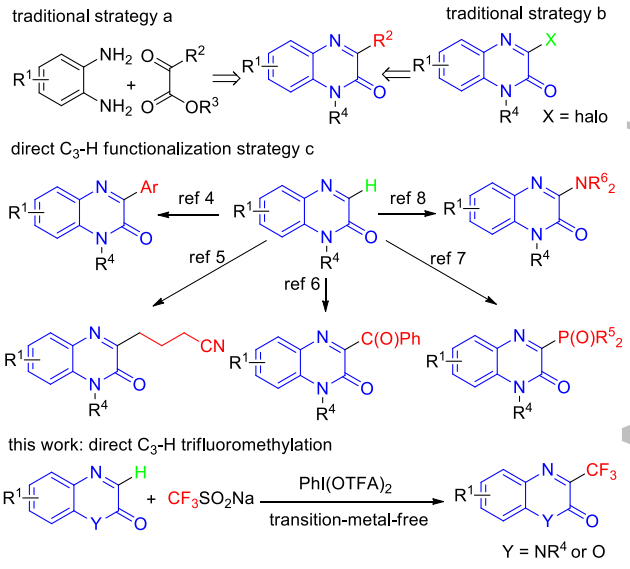
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. Disclosed herein is a direct C-H trifluoromethylation of quinoxalin-2(1*H*)-ones with sodium trifluoromethanesulfinate. This protocol affords a series of 3-trifluoromethylquinoxalin-2(1*H*)-one derivatives in moderate to excellent yields under transition-metal-free conditions. The present methodology features utilization of the inexpensive trifluoromethyl source without transition-metal-catalysts, mild reaction conditions and high functional group tolerance, which promises a convenient and efficient access to pharmaceutically interesting quinoxalinones.

Keywords: C-H Trifluoromethylation; Transition-Metal-Free; Sodium trifluoromethanesulfinate; Quinoxalin-2(1*H*)-ones

Introduction

The quinoxalin-2(1*H*)-one skeleton is a crucially structural motif widely distributed in natural products as well as pharmaceutical molecules.[1] Owing to their remarkable properties, extensive efforts have been devoted to the preparation of diverse 3-substituted quinoxalin-2(*1H*)-ones. For instance, one of the conventional strategy involves construction of the heterocycle from 1,2-diaminobenzenes (Scheme 1, strategy a).[2] The other classical strategy is functionalization of 3-haloquinoxalin-2(*1H*)-ones *via* transition-metal-catalyzed cross-coupling reactions (Scheme 1, strategy b).[3] However, several limitations still remain in the aforementioned strategies, including the requirement of pre-functionalized starting materials, poor atom economy and harsh reaction conditions. In contrast, the direct strategy for modification of available quinoxalin-2(1*H*)-ones has recently emerged as an efficient and ideal approach to 3-substituted quinoxalin-2(1*H*)-ones. But, only a handful of types of direct functionalization of quinoxalin-2(1*H*)-ones have been achieved, including C_3-H arylation[4], alkylation[5], acylation[6], phosphonation[7] and amination[8] of quinoxalin-2(1*H*)-ones (Scheme 1, strategy c). Despite the significance of the achievements, the direct C_3-H trifluoromethylation of quinoxalin-2(1*H*)-ones remains scarce. Due to importance of 3-trifluoromethyl-quinoxalin-2(1*H*)-one derivatives[1a-b], it is urgent in demand to conveniently embed the trifluoromethyl in the 3-position of quinoxalin-2(1*H*)-ones with various functional groups, which would promise its applications in new drug discovery and synthesis.



Scheme 1. Different strategies for synthesis of 3-substituted quinoxalin-2(1*H*)-ones.

The trifluoromethyl group has raised widespread concerns in pharmaceutical and agrochemical fields because of its outstanding performance in altering the

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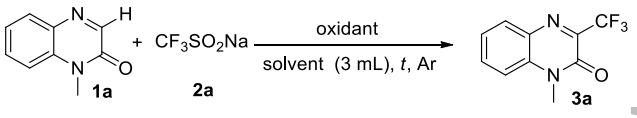
lipophilicity, metabolic activity, and bioavailability of potential drug candidates.[9] Therefore, several versatile trifluoromethyl reagents, such as Togni's reagent[10], Umemoto's reagent[11], Ruppert-Prakash reagent[12] and Langlois reagent[13], have been invented for the incorporation of trifluoromethyl into nominated pharmaceutical molecules, especially heteroarenes[14] and *N*,*N*-dialkylhydrazones[15]. Among these trifluoromethyl reagents, Langlois reagent takes the advantage of the low cost, good stability, easily handing and high efficiency. Consequently, a series of significant methodologies using Langlois reagent as the trifluoromethyl source have been accomplished.[16] However, most of the reaction systems involve transition-metal-catalysts which are costly, toxic and recognized as undesirable residual impurities in pharmaceutical products. Recently, hypervalent iodine oxidants have drawn extensive attention due to their low toxicity and high reactivity.[17] Hence, with the purpose of establishing an economical and transition-metal-free method for the synthesis of 3-trifluoromethylquinoxalinones, we envision that sodium trifluoromethanesulfinate is the ideal trifluoromethyl source with [bis(trifluoroacetoxy)iodo]benzene ($PhI(OTFA)_2$) as the oxidant. To the best of our knowledge, there is no precedent for a direct C-H trifluoromethylation of quinoxalin-2(1*H*)-ones.

Results and Discussion

We started our research with 1-methylquinoxalin-2(1*H*)-one (**1a**) as the model substrate and CF_3SO_2Na (**2a**) as the trifluoromethyl source. Referring to our recent works on difunctionalization of alkenes involving CF_3SO_2Na[18], our initial experiments were performed with *tert*-butyl hydroperoxide (TBHP, 70% solution in H_2O), $K_2S_2O_8$ or $PhI(OTFA)_2$ as the oxidant in the present of $Mn(OAc)_2{\cdot}4H_2O$ (20 mol %). As expected, the target molecule was obtained in 59% yield when $PhI(OTFA)_2$ was used as the oxidant (Table 1, entry 3). $K_2S_2O_8$ and TBHP also promoted the transformation but were not as efficient as $PhI(OTFA)_2$ (Table 1, entries 1-2). Considering our purpose of transition-metal-free conditions, we demonstrated the parallel experiments in the absence of $Mn(OAc)_2{\cdot}4H_2O$. To our delight, TBHP or $PhI(OTFA)_2$ itself was found to be sufficient to prompt the transformation without an apparent decrease in yield (Table 1, entries 4, 6). Inspired by this result, we screened other oxidants and found that $PhI(OTFA)_2$ was still the best. As results showed, cumyl hydroperoxide (CHP) was less effective than $PhI(OTFA)_2$, and the other oxidants including $PhI(OAc)_2$, *tert*-butyl peroxybenzoate (TBPB) and di-*tert*-butyl peroxide (DTBP) were invalid for this reaction (Table 1, entries 7-10). Then the loading of $PhI(OTFA)_2$ was further evaluated. 3 equiv of $PhI(OTFA)_2$ was appropriate for the reaction and the yield of **3a** increased to 75% (Table 1, entries 11-13). Subsequently, the yield of desired product was improved to 80% by using of 3 equiv of CF_3SO_2Na (Table 1, entry 14). The screening of reaction temperature showed room temperature was optimal. Finally, a survey of different solvents indicated that CH_3CN was more suitable than EtOAc and DMF (Table 1, entries 14-16). Overall, the reaction proceeded efficiently in the presence of **1a** (0.3 mmol), CF_3SO_2Na (3.0 equiv.) and $PhI(OTFA)_2$ (3.0 equiv.) in CH_3CN (3.0 mL) at room temperature.

Table 1. Selected reaction conditions optimization.[a)]



Entry	Oxidant	**1a**/**2a**/ Oxidant	Solvent	Yield (%)[b)]
1[c)]	TBHP	1/2/2	CH_3CN	51
2[c)]	$K_2S_2O_8$	1/2/2	CH_3CN	15
3[c)]	$PhI(OTFA)_2$	1/2/2	CH_3CN	59
4	TBHP	1/2/2	CH_3CN	49
5	$K_2S_2O_8$	1/2/2	CH_3CN	trace
6	$PhI(OTFA)_2$	1/2/2	CH_3CN	58
7	$PhI(OAc)_2$	1/2/2	CH_3CN	N. D.[d)]
8	CHP[e)]	1/2/2	CH_3CN	37
9	TBPB	1/2/2	CH_3CN	N. D.
10	DTBP	1/2/2	CH_3CN	N. D.
11	$PhI(OTFA)_2$	1/2/2.5	CH_3CN	68
12	$PhI(OTFA)_2$	1/2/3	CH_3CN	75
13	$PhI(OTFA)_2$	1/2/3.5	CH_3CN	66
14	$PhI(OTFA)_2$	1/3/3	CH_3CN	80
15	$PhI(OTFA)_2$	1/3/3	EtOAc	69
16	$PhI(OTFA)_2$	1/3/3	DMF[f]	41

[a)] Unless specifically noted otherwise, reaction conditions: **1a** (0.3 mmol), **2a**, oxidant and solvent (3 mL), stirred at room temperature under an argon atmosphere. [b)] Yield of isolated product. [c)] In the present of $Mn(OAc)_2{\cdot}4H_2O$ (20 mol %). [d)] N. D. = No detected. [e)] Cumyl hydroperoxide (contains ca. 20% aromatic hydrocarbon). [f)] *N*, *N*-dimethylformamide.

After the optimal conditions were established, we examined the substrate scope of this reaction by using different quinoxalin-2(1*H*)-one derivatives (**1a-1w**) and 2*H*-benzo[*b*][1,4]oxazin-2-one (**1x**) (Table 2). Initial studies were focused on a series of quinoxalin-2(1*H*)-ones with different *N*-protecting groups and they were all suitable substrates, affording the anticipated products in good to excellent yields (**3a-3e)**. When quinoxalin-2(1*H*)-one (**1f**) was chosen as the substrate, due to its poor solubility, the result was disappointing. But the yield of **3f** was improved from 20% to 64% by replacing CH_3CN with DMF. Subsequently, various quinoxalin-2(1*H*)-ones with electron-donating or electron-withdrawing groups on the 7-position of quinoxalin-2(1*H*)-ones were tested. The substrates bearing electron-donating or moderately electron-withdrawing groups engaged in this reaction efficiently, affording the corresponding products in good yields (**3g**, **3h** and **3k**).

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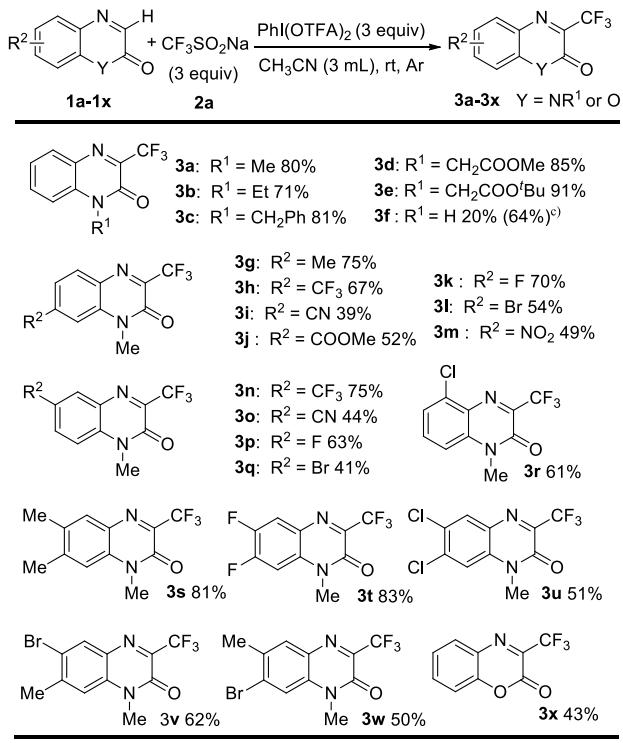
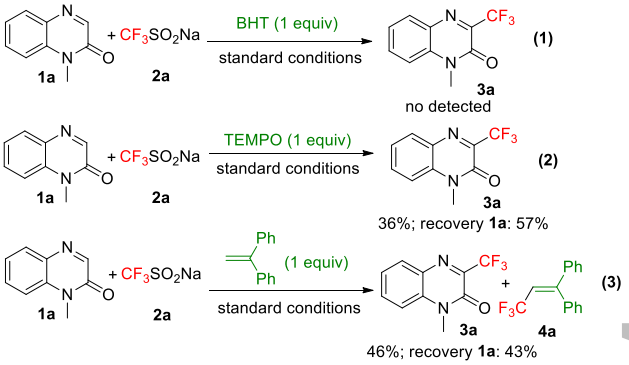
Unfortunately, for the strongly electron-deficient substrates, the corresponding products were provided in moderate yields (**3i** and **3m**). When investigating the quinoxalin-2(1*H*)-ones with different groups on the 6-position, we observed similar results that the substrates bearing CF_3 or F substituent furnished the desired products in higher yields compared with the substrates bearing CN or Br substituent (**3n-3q**). Moreover, reaction could also proceed smoothly in the case of 5-chloro-1-methylquinoxalin-2(1*H*)-one (**1r**) as the substrate and the corresponding 3-trifluoromethylated product was obtained in 61% yield (**3r**). In addition, disubstituted quinoxalin-2(1*H*)-ones were also used as substrates and the expected products were received in moderate to good yields (**3s-3w**). In general , our protocols have several advantages. Firstly, halogen moieties for further functionalization, including F, Cl and Br, were tolerated well with moderate to good yields (**3k**, **3l**, **3p-3r** and **3t-3w**). Additionally, characteristic functional groups such as CF_3, CN and NO_2 were compatible in this transformation (**3h**, **3i** and **3m-3o**). Encouraged by these results on quinoxalin-2(1*H*)-ones, we further tested 2*H*-benzo[*b*][1,4]oxazin-2-one (**1x**) under the standard conditions, and found that the corresponding 3-(trifluoromethyl)-2*H*-benzo[*b*][1,4]oxazin-2-one (**3x**) was obtained in an acceptable yield.

Table 2. Substrate scope.[a), b)]



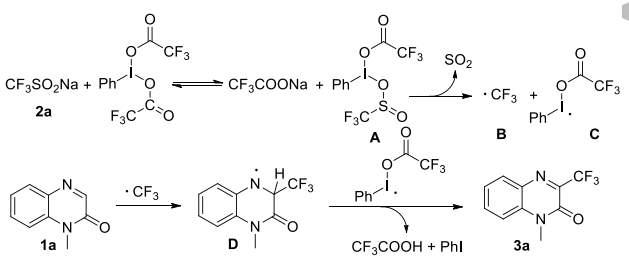
[a)] Unless specifically noted otherwise, reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), $PhI(OTFA)_2$ (0.9 mmol) and solvent (3 mL), stirred at room temperature under argon atmosphere. [b)] Isolated yield. [c)] In *N*, *N*-dimethylformamide.

After the test of substrate scope, several control experiments were carried out to elucidate the preliminary mechanism of this transformation (Scheme 2). The transform was completely suppressed in the presence of 1.0 equivalent of 2,6-di-*tert*-butyl-*p*-cresol (BHT) as a radical inhibitor (Equation 1). Besides, when 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as anther radical inhibitor was added under standard conditions, the reaction was partially suppressed. Only 36% yield of the desired products were obtained and 57% of model substrate **1a** were recovered (Equation 2). Moreover, in the presence of 1.0 equivalent of 1,1-diphenylethylene, another radical scavenger, the CF_3-trapped compound **4a** was observed[16p], and the target product was isolated in 46% yield with the starting material being recovered in 43% (Equation 3). These results indicated that the trifluoromethyl radical might be involved in the transformation.



Scheme 2. Control experiments.

Based on our controlled experiments and previous reports[15, 17a-c, 19], a tentative mechanism is proposed in Scheme 3. Initially, CF_3SO_2Na reacts with $PhI(OTFA)_2$ to afford iodine(III) sulfinate intermediate **A**. Decomposition of **A** gives two free radicals which are the CF_3 radical (**B**) and I-radical **C**[19], meanwhile, releasing SO_2. Subsequently, the CF_3 radical attacks quinoxalin-2(1*H*)-one **1a** to generate the aminyl radical intermediate **D**. Finally, oxidation of this intermediate followed by deprotonation in the presence of I-radical **C** furnishes the target product, leaving CF_3COOH and PhI.



Scheme 3. Tentative mechanism.

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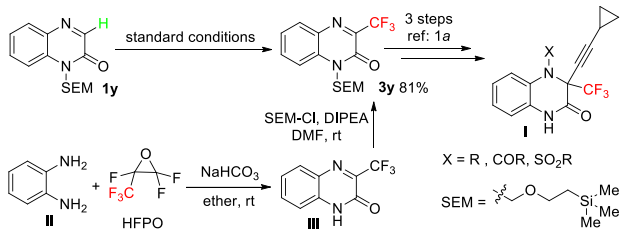
In order to demonstrate the application of our protocol in pharmaceutical synthesis, we chose the *N*-SEM protected quinoxalin-2(1*H*)-one (**1y**) as a special substrate. As expected, the reaction also proceeded well and afforded the desired products (**3y**) in 81% yield. According to the previous report[1a], the pivotal precursor **3y** undergoes a sequence of addition of lithium cyclopropylacetylide, alkylation (acylation or sulfonylation) and deprotection to furnish a series of 3-trifluoromethyl-quinoxalin-2(1*H*)-one derivatives (**I**) as HIV-1 reverse transcriptase inhibitors. The aforementioned synthetic method for **3y** involved a condensation of 1,2-diaminobenzene with hexafluoropropylene oxide (HFPO), followed by *N*-protection using 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl). It is cautionary that HFPO is an expensive, irritant and gaseous reagent, and not easy to operate in laboratories.[20] Obviously, our method provides a convenient and economical approach to 3-trifluoromethyl-quinoxalin-2(1*H*)-ones.



Scheme 4. The application in pharmaceutical synthesis.

Conclusion

In summary, we have developed an original direct C-H trifluoromethylation of quinoxalin-2(1*H*)-ones under transition-metal-free conditions. Both the trifluoromethyl source and oxidant are low-cost and readily available. A variety of 3-trifluoromethyl-quinoxalin-2(1*H*)-ones with different functional groups are obtained in moderate to excellent yields under mild conditions. Predictably, this protocol would offer a cheap, practical and efficient access to pharmaceutically active 3-trifluoromethyl-quinoxalin-2(1*H*)-one derivatives without transition-metal residues.

Experimental Section

General Experimental Details

All reactions involving air- and moisture-sensitive reagents were carried out under an argon atmosphere. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-P 400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C and 376 MHz for ^{19}F) in $CDCl_3$ (with TMS as internal standard) or DMSO-*d*6. Chemical shifts (δ) were measured in ppm relative to TMS δ = 0 for ^{1}H, or to chloroform δ = 77.0 for ^{13}C as internal standard. Coupling constants, *J*, are reported in hertz. Mass data were measured with Thermo Scientific DSQ II mass spectrometer. Melting points (uncorrected) were obtained on Shanghai Inesa WRS-3 melting point apparatus. The starting materials were purchased from Energy Chemical or J&K Chemicals and used without further purification. Solvents were dried and purified according to the procedure from "Purification of Laboratory Chemicals book". The reaction procedure was monitored through thin-layer chromatography (TLC), which was performed using 0.25 mm silica gel plates (60 F254) and was visualized with UV lamp (254 nm). The crude products were purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate as an eluent, and the reported yields are the actual isolated yields of pure products.

General procedures for the direct trifluoromethylation of quinoxalin-2(1*H*)-ones

To a Schlenk tube charged with a magnetic stirring bar, quinoxalin-2(1*H*)-ones (**1a-1w, 1y)** or its derivatives (**1x**) (0.3 mmol), CF_3SO_2Na (0.9 mmol), [Bis(trifluoroacetoxy)iodo]benzene ($PhI(OFA)_2$) (0.9 mmol) were added successively and the Schlenk tube was purged with argon for three times. Anhydrous CH_3CN (3 ml) was then added *via* syringe and the mixture was stirred at room temperature in water bath under argon atmosphere until the substrate was consumed (12 h~18 h, monitored by TLC). Then the solvent was removed under reduced pressure and the resulting residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the corresponding 3-trifluoromethylated products (**3a-3y)**.

Characterization of the Products

1-methyl-3-(trifluoromethyl)quinoxalin-2(1*H*)-one (3a): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3a** (80% yield, 54.8 mg) as light yellow solid, m. p. = 134-136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (dd, *J* = 1.2 Hz, *J* = 44 Hz, 1H), 7.76-7.72 (m, 1H), 7.48-7.40 (m, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.59, 142.81 (q, *J* = 33.7 Hz), 133.54, 132.56, 130.72, 129.85, 123.52, 118.87 (q, *J* = 274.8 Hz), 113.02, 28.15; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.12 (s, 3F); HRMS (ESI): m/z calcd for $C_{10}H_7F_3N_2KO^+$ $[M+K]^+$ 267.0142. Found 267.0148.

1-ethyl-3-(trifluoromethyl)quinoxalin-2(1*H*)-one (3b): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3b** (71% yield, 51.6 mg) as white solid, m. p. = 98-100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 8 Hz, 1H), 7.75-7.71 (m, 1H), 7.45-7.41 (m, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.18, 143.88 (q, *J* = 33.6 Hz), 133.64, 133.51, 132.02, 131.21, 124.33, 119.96 (q, *J* = 274.7 Hz), 37.68, 12.36; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.01 (s, 3F); HRMS (ESI): m/z calcd for $C_{11}H_9F_3N_2KO^+$ $[M+K]^+$ 281.0299. Found 281.0303.

1-benzyl-3-(trifluoromethyl)quinoxalin-2(1*H*)-one (3c): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3c** (81% yield, 73.8 mg) as light yellow solid, m. p. = 103-104°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (dd, *J* = 1.2 Hz, *J* = 8.0 Hz, 1H), 7.63-7.58 (m, 1H), 7.42-7.26 (m, 7H), 5.53 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.77, 144.10 (q, *J* = 34.6 Hz), 134.46, 134.02, 133.48, 131.90, 131.21, 129.11, 128.09, 127.06, 124.54, 119.93 (q, *J* = 274.8 Hz), 114.81, 46.06; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -69.91 (s, 3F); HRMS (ESI): m/z calcd for $C_{16}H_{11}F_3N_2NaO^+$ $[M+Na]^+$ 327.0716. Found 327.0713.

methyl 2-(2-oxo-3-(trifluoromethyl)quinoxalin-1(2*H*)-yl)acetate (3d): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3d** (85% yield, 73.2 mg) as pale yellow solid, m. p. = 139-141°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, *J* = 8 Hz, 1H), 7.73-7.69 (m, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 8 Hz, 1H), 5.09 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.90, 151.17, 143.85 (q, *J* = 34.6 Hz), 133.76, 132.14, 131.02, 124.86, 119.73 (q, *J* = 274.9 Hz), 53.12, 43.27; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -69.99 (s, 3F); HRMS (ESI): m/z calcd for $C_{12}H_9F_3N_2NaO_3^+$ $[M+Na]^+$ 309.0457. Found 309.0455.

***tert*-butyl 2-(2-oxo-3-(trifluoromethyl)quinoxalin-1(2*H*)-yl)acetate (3e)**: The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3e** (91% yield, 90 mg) as light yellow solid, m. p. = 87-89°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (dd, *J* = 0.8 Hz, *J* = 8.0 Hz, 1H), 7.72-7.68 (m, 1H), 7.46-7.42 (m, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 4.97 (s, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.33, 150.16, 142.78 (q, *J* = 34.0 Hz), 132.84, 132.60, 130.97, 129.93, 123.68, 118.75 (q, *J* = 274.8 Hz), 112.57, 43.04, 26.91; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.00 (s, 3F); HRMS (ESI): m/z calcd for $C_{15}H_{15}F_3N_2NaO_3^+$ $[M+Na]^+$ 351.0927. Found 351.0931.

3-(trifluoromethyl)quinoxalin-2(1*H*)-one (3f): After substrate **1f** was completed consumed (in *N*,*N*-dimethylformamide), water was added and the mixture was extracted with dichloromethane for three times, the combined organic solution was washed with saturated aqueous NaCl solution, dried over Na_2SO_4. The solvent was removed under reduced pressure, then the residue product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1:1 as an eluent) to afford the product **3f** (64% yield, 41.2 mg) as yellow solid, m. p. = 183-185°C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ: 13.06 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 2H), 3.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ: 151.63, 143.96 (q, *J* = 32.3 Hz), 133.66, 133.42, 129.84, 129.81, 124.10, 120.02 (q, *J* = 274.5 Hz), 115.80; ^{19}F NMR (376 MHz, DMSO-*d6*) δ: -68.55 (s, 3F); HRMS (ESI): m/z calcd for $C_9H_6F_3N_2O^+$ $[M+H]^+$ 215.0427. Found 215.0427.

1,7-dimethyl-3-(trifluoromethyl)quinoxalin-2(1*H*)-one (3g): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3g** (75% yield, 54.8 mg) as white solid, m. p. = 170-171°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* =7.2 Hz, 1H), 7.19 (s, 1H), 3.75 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.83, 145.14, 142.54 (q, *J* = 33.5 Hz), 134.57, 131.41, 129.20, 126.01, 120.09 (q, *J* = 274.5 Hz), 114.04, 29.07, 22.45; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -69.94 (s, 3F); HRMS (ESI): m/z calcd for $C_{10}H_6F_3N_2KO^+$ $[M+K]^+$ 281.0299. Found 281.0284.

1-methyl-3,7-bis(trifluoromethyl)quinoxalin-2(1*H*)-one (3h): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3h** (67% yield, 59.3 mg) as pale yellow solid, m. p. = 148-149°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (s, 1H), 7.95 (dd, *J* = 1.6 Hz, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.32, 145.53 (q, *J* = 34.3 Hz), 136.80, 130.17, 129.71 (d, *J* = 3.1 Hz), 129.23 (d, *J* = 3.8 Hz), 126.94 (q, *J* = 34.0 Hz), 123.26 (q, *J* = 270.5 Hz), 119.52 (q, *J* = 275.2 Hz), 114.92, 29.47; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.31 (s, 3F), -70.39 (s, 3F); HRMS (ESI): m/z calcd for $C_{11}H_6F_6N_2NaO^+$ $[M+Na]^+$ 319.0277. Found 319.0244.

4-methyl-3-oxo-2-(trifluoromethyl)-3,4-dihydroquinoxaline-6-carbonitrile (3i): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 to 1:1 as an eluent) to afford the product **3i** (39% yield, 29.7 mg) as white solid, m. p. = 223-224°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (d, *J* = 1.6 Hz, 1H), 7.95 (dd, *J* =1.6 Hz, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.04, 146.09 (q, *J* = 34.6 Hz), 137.58, 136.06, 135.56, 130.37, 119.35 (q, *J* = 275.3 Hz), 117.08, 115.35, 108.36, 29.54; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.39 (s, 3F); HRMS (ESI): m/z calcd for $C_{11}H_7F_3N_3O^+$ $[M+H]^+$ 254.0536. Found 254.0544.

methyl 4-methyl-3-oxo-2-(trifluoromethyl)-3,4-dihydroquinoxaline-6-carboxylate (3j): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3j** (52% yield, 44.6 mg) as white solid, m. p. = 166-167°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.65 (d, *J* = 1.6 Hz, 1H), 8.35 (dd, *J* = 1.6 Hz, *J* = 9.2 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 3.97 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.38, 151.44, 147.41 (q, *J* = 34.1 Hz), 137.62, 133.99, 133.54, 130.26, 126,54, 119.65 (q, *J* = 275.0 Hz), 114.21, 52.63, 29.49; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.28 (s, 3F); HRMS (ESI): m/z calcd for $C_{12}H_9F_3N_2NaO_3^+$ $[M+Na]^+$ 309.0457, found 309.0454.

7-fluoro-1-methyl-3-(trifluoromethyl)quinoxalin-2(1*H*)-one (3k): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3k** (70% yield, 51.7 mg) as pale yellow solid, m. p. = 155-156°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (dd, *J* = 6.0 Hz, *J* =

8.8 Hz, 1H), 7.19-7.14 (m, 1H), 7.08 (dd, *J* = 2.4 Hz, *J* = 10.0 Hz, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.40 (d, *J* = 254.7 Hz), 151.46, 142.79 (q, *J* = 33.8 Hz), 136.46 (d, *J* = 12.0 Hz), 134.14 (d, *J* = 10.9 Hz), 127.73, 119.86 (q, *J* = 274.7 Hz), 112.89 (d, *J* = 23.6 Hz), 101.05 (d, *J* = 27.9 Hz), 29.45; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.302 (s, 3F), -116.97 (s, 1F); HRMS (ESI): m/z calcd for $C_{10}H_6F_4N_2KO^+$ $[M+K]^+$ 285.0048. Found 285.0032.

7-bromo-1-methyl-3-(trifluoromethyl)quinoxalin-2(1*H*)-one (3l): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3l** (54% yield, 49.8 mg) as pale yellow solid, m. p. = 143-145°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, *J* = 2.0 Hz, 1H), 7.81 (dd, *J* = 2.0 Hz, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.20, 145.03 (q, *J* = 33.9 Hz), 136.28, 133.94, 133.71, 131.57, 119.62 (q, *J* = 275.1 Hz), 117.11, 115.49, 29.36; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.27 (s, 3F); HRMS (ESI): m/z calcd for $C_{10}H_6F_3BrN_2NaO^+$ $[M+Na]^+$ 328.9508. Found 328.9499.

1-methyl-7-nitro-3-(trifluoromethyl)quinoxalin-2(1*H*)-one (3m): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3m** (49% yield, 40.2 mg) as yellow solid, m. p. = 186-187°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.30-8.25 (m, 2H), 8.19 (d, *J* = 8.4 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.94, 149.88, 147.36 (q, *J* = 34.5 Hz), 135.01, 133.82, 133.16, 119.32 (q, *J* = 277.5 Hz), 118.72, 109.94, 29.75; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.44 (s, 3F); HRMS (ESI): m/z calcd for $C_{10}H_6F_3N_3NaO_3^+$ $[M+Na]^+$ 296.0253. Found 296.0232.

1-methyl-3,6-bis(trifluoromethyl)quinoxalin-2(1*H*)-one (3n): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1 as an eluent) to afford the product **3n** (75% yield, 66.7 mg) as white solid, m. p. = 162-164°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.65 (s, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.19, 146.36 (q, *J* = 34.0 Hz), 134.79 (q, *J* = 33.1 Hz), 134.66, 132.68, 132.39, 123.15 (q, *J* = 271.9 Hz), 120.95, 119.53 (q, *J* = 277.1 Hz), 111.68, 111.54, 29.43; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.83 (s, 3F), -70.40 (s, 3F); HRMS (ESI): m/z calcd for $C_{11}H_7F_6N_2O^+$ $[M+H]^+$ 297.0457. Found 297.0433.

1-methyl-2-oxo-3-(trifluoromethyl)-1,2-dihydroquinoxaline-6-carbonitrile (3o): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3o** (44% yield, 33.5 mg) as pale yellow solid, m. p. = 176-177°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, *J* = 8.4 Hz, 1H), 7.71-7.67 (m, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.93, 146.90 (q, *J* = 34.3 Hz), 134.93, 132.77, 127.06, 119.36 (q, *J* = 275.5 Hz), 118.34, 117.37, 116.57, 29.48; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.40 (s, 3F); HRMS (ESI): m/z calcd for $C_{11}H_6F_3N_3NaO^+$ $[M+Na]^+$ 276.0355. Found 276.0350.

6-fluoro-1-methyl-3-(trifluoromethyl)quinoxalin-2(1*H*)-one (3p): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3p** (63% yield, 46.6 mg) as yellow solid, m. p. = 114-116°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (dd, *J* = 2.8 Hz, *J* = 8.0 Hz, 1H), 7.51-7.46 (m, 1H), 7.38 (d, *J* = 4.8 Hz, *J* = 9.2 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.10, 157.65, 151.22, 145.29 (q, *J* = 33.9 Hz), 131.33 (d, *J* = 11.1 Hz), 121.65 (d, *J* = 24.1 Hz), 119.69 (q, *J* = 275.0 Hz), 116.87 (d, *J* = 22.5 Hz), 115.35 (d, *J* = 8.7 Hz), 29.46; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.08 (s, 3F), -101.07 (s, 1F); HRMS (ESI): m/z calcd for $C_{10}H_7F_4N_2O^+$ $[M+H]^+$ 247.0489. Found 247.0492.

6-bromo-1-methyl-3-(trifluoromethyl)quinoxalin-2(1*H*)-one (3q): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3q** (41% yield, 37.9 mg) as light yellow solid, m. p. = 188-190°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 9.2 Hz, 1H), 7.55 (dd, *J* = 1.6 Hz, *J* = 7.2 Hz, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.27, 144.10 (q, *J* = 34.3 Hz), 135.50, 132.86, 129.70, 128.37, 128.00, 119.76 (q, *J* = 274.8 Hz), 117.19, 29.32; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.17 (s, 3F); HRMS (ESI): m/z calcd for $C_{10}H_7F_3BrN_2O^+$ $[M+H]^+$ 306.9688. Found 306.9677.

5-chloro-1-methyl-3-(trifluoromethyl)quinoxalin-2(1*H*)-one (3r): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1 as an eluent) to afford the product **3r** (61% yield, 48.1 mg) as light yellow solid, m. p. = 124-126°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91 (dd, *J* = 1.2 Hz, *J* = 8.0 Hz, 1H), 7.74 (dd, *J* = 1.6 Hz, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 4.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.53, 144.21 (q, *J* = 34.0 Hz), 136.59, 133.28, 132.87, 131.38, 124.78, 120.07, 119.60 (q, *J* = 275.0 Hz), 35.52; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.23 (s, 3F); HRMS (ESI): m/z calcd for $C_{10}H_6F_3ClN_2NaO^+$ $[M+Na]^+$ 285.0013. Found 284.9999.

1,6,7-trimethyl-3-(trifluoromethyl)quinoxalin-2(1*H*)-one (3s): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3s** (81% yield, 62.4 mg) as light yellow solid, m. p. = 148-150°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (s, 1H), 7.14 (s, 1H), 3.71 (s, 3H), 2.45 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.79, 144.39, 142.76 (q, *J* = 33.3 Hz) 133.89, 132.73, 131.47, 129.42, 120.17 (q, *J* = 274.4 Hz), 114.44, 29.05, 20.96, 19.17; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -69.90 (s, 3F); HRMS (ESI): m/z calcd for $C_{24}H_{22}F_6N_4O_2Na^+$ $[2M+Na]^+$ 535.1539. Found 535.1558.

6,7-difluoro-1-methyl-3-(trifluoromethyl)quinoxalin-2(1*H*)-one (3t): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3t** (83% yield, 65.5 mg) as white solid, m. p. = 134-135°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82 (dd, *J* = 8.0 Hz, *J* = 9.6 Hz, 1H), 7.21 (dd, *J* = 6.8 Hz, *J* = 12.0 Hz, 1H), 3.71 (s,

3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.71 (dd, *J* = 14.4 Hz, *J* = 257.8 Hz), 150.09, 146.22 (dd, *J* = 14.0 Hz, *J* = 248.8 Hz), 143.32 (q, *J* = 34.0 Hz), 131.35 (d, *J* = 9.0 Hz), 126.06 (d, *J* = 6.9 Hz), 118.60 (q, *J* = 274.9 Hz), 118.24 (dd, *J* = 2.6 Hz, *J* = 18.2 Hz), 101.75 (d, *J* = 23.2 Hz), 28.72; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.25 (s, 3F), -124.08 (d, *J* = 22.56 Hz, 1F), -139.53 (d, *J* = 22.56 Hz, 1F); HRMS (ESI): m/z calcd for $C_{10}H_5F_5N_2NaO^+$ $[M+Na]^+$ 287.0214. Found 287.0202.

6,7-dichloro-1-methyl-3-(trifluoromethyl)quinoxalin-2(1*H*)-one (3u): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3u** (51% yield, 45.5 mg) as yellow solid, m. p. = 156-158°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (s, 1H), 7.51 (s, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.92, 144.06 (q, *J* = 34.3 Hz), 137.17, 132.80, 131.31, 128.73, 127.71, 144.06 (q, *J* = 275.1 Hz), 114.56, 28.46; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.25 (s, 3F); HRMS (ESI): m/z calcd for $C_{10}H_5Cl_2F_3N_2NaO^+$ $[M+Na]^+$ 318.9623. Found 318.9627.

6-bromo-1,7-dimethyl-3-(trifluoromethyl)quinoxalin-2(1*H*)-one (3v): he crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3v** (62% yield, 59.6 mg) as light yellow solid, m. p. = 156-158°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82 (s, 1H), 7.60 (d, *J* = 2.8 Hz, 1H), 3.70 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.26, 144.07 (q, *J* = 33.9 Hz), 134.75, 133.31, 132.44, 131.25, 129.96, 119.84 (q, *J* = 274.8 Hz), 117.66, 29.26, 22.32; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.12 (s, 3F); HRMS (ESI): m/z calcd for $C_{11}H_8F_3BrN_2KO^+$ $[M+K]^+$ 358.9404. Found 358.9406.

7-bromo-1,6-dimethyl-3-(trifluoromethyl)quinoxalin-2(1*H*)-one (3w): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1 as an eluent) to afford the product **3w** (50% yield, 48.3 mg) as pale yellow solid, m. p. = 212-214°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (s, 1H), 7.25 (s, 1H), 3.72 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.43, 144.42, 143.92 (q, *J* = 33.9 Hz), 134.42, 133.74, 129.99, 120.15, 119.77 (q, *J* = 274.9 Hz), 115.31, 29.23, 24.13; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.12 (s, 3F); HRMS (ESI): m/z calcd for $C_{11}H_8F_3BrN_2NaO^+$ $[M+Na]^+$ 342.9664. Found 342.9646.

3-(trifluoromethyl)-2*H*-benzo[b][1,4]oxazin-2-one (3x): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1 as an eluent) to afford the product **3x** (43% yield, 27.8 mg) as white solid, m. p. = 64-65°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.93 (dd, *J* = 1.2 Hz, *J* = 8.0 Hz, 1H), 7.73-7.69 (m, 1H), 7.51-7.47 (m, 1H), 7.41 (dd, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.49, 147.43, 141.53 (q, *J* = 36.4 Hz), 134.67, 130.86, 129.40, 126.45, 118.93 (q, *J* = 275.1 Hz), 116.87; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.08 (s, 3F); HRMS (ESI): m/z calcd for $C_9H_5F_3NO_2^+$ $[M+H]^+$ 216.0267. Found 216.0248.

3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)quinoxalin-2(1*H*)-one (3y): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1 as an eluent) to afford the product **3y** (81% yield, 83.6 mg) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (dd, *J* = 0.8 Hz, *J* = 8.4 Hz, 1H), 7.73-7.62 (m, 2H), 7.47-7.43 (m, 1H), 5.76 (s, 2H), 3.37-3.69 (m, 2H), 0.97-0.93 (m, 2H), -0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.29, 145.56 (q, *J* = 33.8 Hz), 134.96, 134.88, 133.01, 132.46, 126.32, 121.28 (q, *J* = 275.0 Hz), 116.85, 72.98, 69.03, 19.41, -0.01; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.04 (s, 3F); HRMS (ESI): m/z calcd for $C_{15}H_{19}F_3SiN_2NaO_2^+$ $[M+Na]^+$ 367.1060. Found 367.1045.

Acknowledgements

We acknowledge the financial support from the National Natural Science Foundation of China (Grant No. 21776056), the Natural Science Foundation of Hebei Province (CN) (Grant No. B2018202253, B2016202393, B2015202284) and the Program for the Top Young Innovative Talents of Hebei Province (CN) (Grant No. BJ2017010).

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10.1002/adsc.201800863

FULL PAPER

Direct C-H Trifluoromethylation of Quinoxalin-2(1*H*)-ones under Transition-Metal-Free Conditions

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