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Novel syntheses of aryl quinoxaline *C*-nucleoside analogs by mild and efficient three-component sequential reactions†

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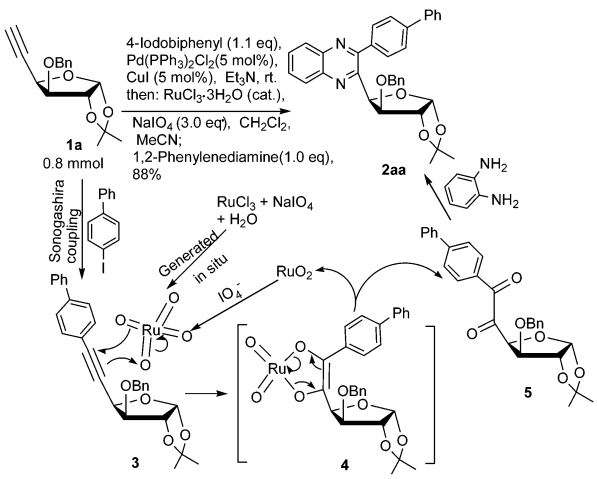
Novel syntheses of *C*-nucleoside analogs with aryl quinoxalines as nucleobase surrogates have been accomplished by mild and efficient three-component sequential reactions in high yields with a wide scope of substrates. The mechanism was clarified by isolation of novel sugar 1,2-diketone derived from oxidation of the corresponding alkyne.

C-Nucleosides and their analogs are the widely studied compounds, in which the C–C bond between the heterocycle and the sugar moiety is resistant to bacterial hydrolases and enables these molecules to interfere with DNA and RNA synthases.[1] Many of these compounds display a potent biological activity.[2] The use of non-natural nucleobases and the designed surrogates to synthesize *C*-nucleoside analogs is a frequently applied approach. Amongst these numerous base analogs, hydrophobic aryl groups and polycyclic aryl groups as nucleobase surrogates are of particular interest due to their biological activities[2a,b] and their use in the extension of the genetic alphabet.[3] Because of the increased propensity to π-stacking and favorable desolvation energy compared to canonical hydrophilic nucleobases, these aryl groups form pairs selectively with the same or other hydrophobic nucleobases in oligonucleotide duplexes.[4] In this way, the aryl *C*-nucleosides have been used to explore base stacking in DNA–DNA duplexes after their incorporation into DNA-oligomers *via* phosphoramidite chemistry or to explore the molecular interactions in DNA–protein recognition processes[5] and the reaction mechanisms of DNA repair enzymes.[6]

The crucial importance of minor-groove interactions of the synthetic nucleobase with the enzyme has been found recently.[7] The triphosphates of hetaryl *C*-nucleosides possessing equivocal nature between hydrophilic and hydrophobic species are therefore the most promising candidates for efficient incorporation into DNA and extension of the duplex.[7a,b,8] Quinoxalines and their derivatives are very important benzoheterocycles, showing a broad spectrum of significant biological activity such as anti-inflammatories,[9] antivirals,[10] antibacterials,[11] kinase inhibitors,[12] anti-HIV[13] and DNA cleaving agents.[14] These have made them privileged structures in combinatorial drug discovery libraries and a number of methods are available for the synthesis of quinoxalines.[15] Although the parent quinoxalines are easily prepared, the corresponding substituted compounds are considerably more challenging. The sugar substituted quinoxaline by the C–C bond (called the quinoxaline *C*-nucleoside) remains sparse. In continuation of our interest in the syntheses of biologically active carbohydrate analogues[16] and *C*-substituted sugar analogues,[17] herein, for the first time, we present a general and efficient synthesis of novel *C*-nucleoside analogs with aryl quinoxalines as nucleobase surrogates.

The terminal sugar alkynes **1a** (Scheme 1) prepared according to the known procedure[18] were initially treated with 4-iodobiphenyl



Scheme 1 The synthesis of **2aa** and the reaction sequence.

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in the presence of $Pd(PPh_3)_2Cl_2$ and CuI at rt under N_2 for 1.5 h. TLC showed the complete conversion of **1a**, indicating that the Sonogashira coupling reaction was finished. The solution was evaporated to remove Et_3N, and then CH_2Cl_2 was added and washed with water. $NaIO_4$, MeCN and catalytic amounts of $RuCl_3{\cdot}3H_2O$ were added and then treated with 1,2-phenylenediamine at rt to give **2aa** in 88% yield.

In order to clarify this mechanism, the reaction was stopped by evaporating the reaction mixture to dryness before 1,2-phenylenediamine was added. Fortunately, the product 1,2-diketone **5** (Scheme 1) was isolated. In this way, the reactants undergo a Sonogashira coupling reaction, with subsequent oxidation followed by condensation as the three main steps. The reaction sequence starts with $Pd(PPh_3)_2Cl_2$ and CuI catalyzed coupling between **1a** and 4-iodobiphenyl to produce sugar biphenyl alkyne **3**. RuO_4 generated *in situ* from catalytic amounts of $RuCl_3$, H_2O and an excess of sodium periodate attacks the triple bond of **3** to form the intermediate **4**. The sugar 1,2-diketone **5** is produced after elimination of RuO_2 from **4**. The RuO_2 is subsequently oxidized by IO_4^- to give RuO_4 which participates in the next oxidation recycle. The condensation of **5** with 1,2-phenylenediamine gives the desired product **2aa**. The structures of **2aa** and **5** were characterized by ^1H NMR, ^{13}C NMR, DEPT-135, 2D NMR, HRMS and IR spectra.

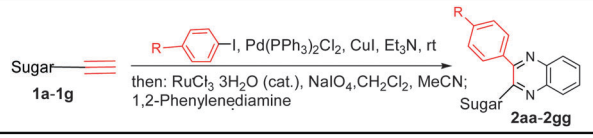
In the optimization studies for the synthesis of **2aa** from **1a**, we found that the best results for the Sonogashira coupling reaction were obtained with 1.1 equivalent of 4-iodobiphenyl, 1.0 equivalent of **1a** and 5 mol% of $Pd(PPh_3)_2Cl_2$ and CuI each. The reaction was complete within 1.5 h at rt. Increasing the reaction temperature diminished the yield, probably due to the deprotection of 1,2-*O*-isopropylidene in the presence of $Pd(PPh_3)_2Cl_2$ and CuI as Lewis acid. For conversion of sugar alkyne into sugar 1,2-diketone, although the oxidation system for diarylalkynes has been presented,[19] the elevated temperature, prolonged reaction time and acidic media are not suitable for the sugar alkyne having sensitive functional groups. Hitherto, no oxidation of sugar alkyne into the corresponding 1,2-diketone has been reported. In order to get a mild oxidation system suitable for **3** and the other fragile sugar alkynes, we used the isolated intermediate **3** as the starting material to explore the oxidation system. DMSO as an oxidant was used in the presence of 5–10 mol% of Lewis acid (Table 1, entries 1–3). Only a trace of **5** was produced using the two different palladium catalysts at 80 °C and 30% yield was obtained when $FeBr_3$ was used as a catalyst. Prolonged reaction time and increasing the reaction temperature resulted in the complicated reactions. $KMnO_4$ and H_5IO_6 as oxidants also did not work well and **5** was generated in 28–40% yield, respectively (Table 1, entries 4–6). We were pleased to find that $RuCl_3{\cdot}3H_2O/NaIO_4$ was a very efficient oxidation system for converting **3** into **5** at rt (Table 1, entries 7–9). It was optimized and a yield of 90% was finally

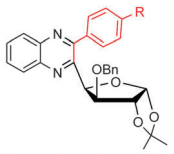
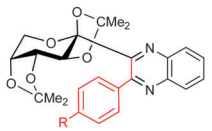
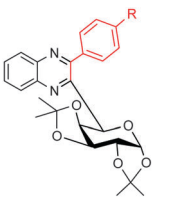
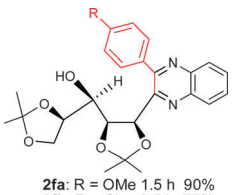
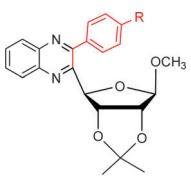
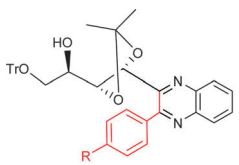
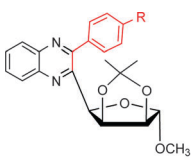
Table 1 The oxidation of **3** to **5** under various conditions[a]

Entry	Oxidation system	*T* (°C)	Time	Yield[a] (%)
1	$PdCl_2$, DMSO	80	4 h	Trace
2	PdI_2, DMSO	80	4.5 h	Trace
3	$FeBr_3$, DMSO	80	2 h	30
4	$KMnO_4$, H_2O, MeCN	60	2 h	28
5	$KMnO_4$, H_2O, acetone	60	2 h	35
6	H_5IO_6, MeOH	60	2 h	40
7	$RuCl_3{\cdot}3H_2O$, $NaIO_4$, H_2O, CH_2Cl_2	rt	15 min	65
8	$RuCl_3{\cdot}3H_2O$, $NaIO_4$, H_2O, MeCN	rt	10 min	72
9	$RuCl_3{\cdot}3H_2O$, $NaIO_4$, H_2O, CH_2Cl_2, MeCN	rt	5 min	90[b]

[a] Isolated yield. [b] The reaction was performed on a 0.5 mmol scale using $RuCl_3{\cdot}3H_2O$ (1.3 mol%) and $NaIO_4$ (3.0 equiv.) in the tricomponent solvent (H_2O/CH_2Cl_2/MeCN = *ca.* 1 : 10 : 5).

Table 2 The scope of substrates for the syntheses of various aryl quinoxaline *C*-nucleoside analogs[a]



Entry	Product yield[b], time	Entry	Product yield[b], time
1	 **2aa**: R = Ph 3 h 88% **2ab**: R= CN 4 h 73% **2ac**: R = Cl 3.3 h 75% **2ad**: R = H 3 h 86%	5	 **2ea**: R = F 4 h 71% **2eb**: R = Cl 4.5 h 71% **2ec**: R = H 4 h 83% **2ed**: R= CN 5 h 70% **2ee** :R = Ph 3.5 h 81%
2	 **2ba**: R = Cl 4.5 h 76% **2bb**: R = Ph 3.5 h 89% **2bc**: R = H 3.5 h 88%	6	 **2fa**: R = OMe 1.5 h 90% **2fb**: R = Cl 2.5 h 77% **2fc**: R = H 2 h 85% **2fd**: R = CN 3 h 72% **2fe**: R = F 3 h 74% **2ff**: R = Me 2 h 89% **2fg**: R = Ph 2 h 84% **2fh**: R = Br 3 h 75%
3	 **2ca**: R= CN 3 h 72% **2cb**: R = Cl 2.5 h 76% **2cc**: R = H 2 h 86% **2cd**: R = Ph 2 h 88%	7	 **2ga**: R = OMe 3.5 h 84% **2gb**: R = Cl 4 h 74% **2gc**: R = H 3 h 80% **2gd**: R = CN 4.5 h 70% **2ge**: R = F 4 h 73% **2gf**: R = Me 3 h 83% **2gg**: R = Ph 2.5 h 83%
4	 **2da**: R = Ph 2.5 h 88% **2db**: R = Cl 3.5 h 75% **2dc**: R = H 3 h 86% **2dd**: R = CN 4 h 73%		

[a] Reaction conditions: 0.81 mmol of aryl iodide, 0.8 mmol of terminal sugar alkyne, 5 mol% of each $Pd(PPh_3)_2Cl_2$ and CuI, 3 ml of Et_3N, 4 ml of CH_2Cl_2, 2 ml of MeCN, 1.3% mol of $RuCl_3{\cdot}H_2O$, 2.4 mmol of $NaIO_4$, 0.81 mmol of 1,2-phenylenediamine, rt. [b] Isolated yield.

attained in the presence of 1.3 mol% of $RuCl_3 \cdot 3H_2O$ and 3.0 equivalent of $NaIO_4$ by use of tricomponent solvent of H_2O, CH_2Cl_2 and MeCN (*ca.* 1 : 10 : 5) within 5 min.

To explore the generality of this method and to synthesize various aryl quinoxaline *C*-nucleoside analogs, various terminal sugar alkynes and substituted aryl iodides were used to perform this sequence, which were summarized in Table 2 (the structures of **1a–1g** are shown in pages 2–4 in the ESI†). The sequence proceeds smoothly to give the corresponding products in high yields. All the aryl iodides having electron-donating, electron-withdrawing and electron-neutral substituents can be used throughout this reaction sequence without difficulties. Generally, aryl iodide with electron-withdrawing substituents gives the lowest yield (for example R = CN, Table 2, entry 1, entries 3–7) and that having electron-donating groups is superior to the others (for example entry 6, **2fa**, **2ff**). All the sugar alkynes can be coupled efficiently to produce the aryl quinoxaline *C*-nucleoside analogs. However, D-fructose derived **1e** takes longer reaction time and gives lower yield (Table 2, entry 5) than that of the other cyclic sugar alkynes, probably due to the steric hindrance of di-*O*-isopropylidene. The acyclic sugar alkyne **1g** has a less clean reaction and gives lower yield than **1f**, because of the bulky triphenylmethyl group at the 4′-position and its easy deprotection in the presence of Lewis acid. All the new compounds were characterized by ^{1}H NMR, ^{13}C NMR, DEPT-135, 2D NMR, HRMS and IR.

In summary, novel syntheses of *C*-nucleoside analogs with aryl quinoxalines as nucleobase surrogates have been accomplished from various terminal sugar alkynes by mild and efficient sequential Sonogashira coupling/oxidation/condensation reactions in high yields. This method has a wide scope of substrates including various substituted aryl iodides as well as cyclic and acyclic terminal sugar alkynes. The reaction mechanism was clarified by isolation of the novel product, the first example of oxidation of sugar alkyne into the corresponding 1,2-diketone. In addition, these aryl quinoxaline *C*-nucleoside analogs are optically pure. They are the precursors of the tetrahydroquinoxaline derivatives which have also shown great potential for drug development. Thus, a lot of optically pure tetrahydroquinoxaline derivatives can be obtained if these quinoxaline *C*-nucleoside analogs are hydrogenated.

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