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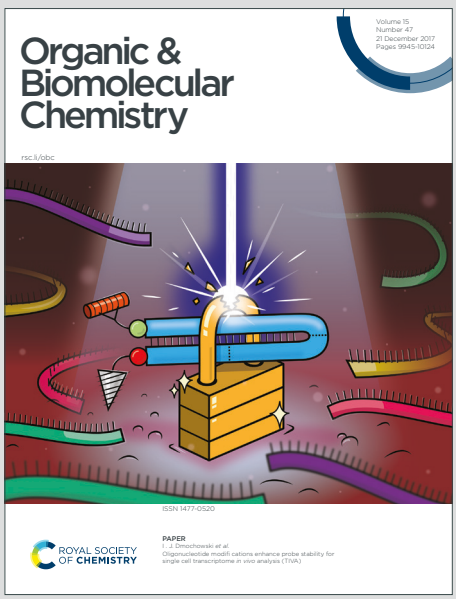

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ARTICLE

Concise synthesis of thiophene *C*-nucleoside analogues bearing sugar residue and aromatic residue through dimerization and sulfur heterocyclization of sugar alkynes and substituted iodoethynylbenzene

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The synthesis of thiophene *C*-nucleoside analogues bearing sugar residue (mono- and disaccharides) and aromatic residue has been achieved by symmetric dimerization of terminal sugar alkynes or unsymmetric dimerization of terminal sugar alkynes and substituted iodoethynylbenzene followed by sulfur heterocyclization in one pot. Homocoupling of terminal sugar alkyne and subsequent sulfur heterocyclization produce thiophene *C*-nucleoside analogues bearing disaccharides. Unsymmetric dimerization of terminal sugar alkyne and substituted iodoethynylbenzene followed by sulfur heterocyclization give those bearing monosaccharide and aromatic residue. This approach is concise, general and mild, which is suitable for structurally diversified pyranosides, furanosides, and acyclic sugars. Thirty-two examples have been given and the corresponding products are obtained in moderate to excellent yields.

Introduction

The therapeutic effect of nucleoside analogues largely depends on their stability in organism, because their catabolism usually includes degradation of nucleosidic linkage. *C*-Nucleoside analogues including "reversed" or "iso-" *C*-nucleoside ones with an aromatic or heteroaromatic moiety directly attached to the carbohydrate through a C-C bond, different from the usual *N*-nucleosides or *O*-glycosides, result in better stability to both acidic and enzymatic hydrolysis, while preserving excellent biological efficacy.[1] These *C*-nucleoside analogues exhibit interesting biological activities. They have proven to be efficient antibiotics,[2] antitumor agents,[3] and inhibitors for diabetes.[4] Figure 1 shows two typical thiophene *C*-nucleoside analogues. Thiophenfurin **1**[5] is a good antitumor agent. It can inhibit the growth of K562 human erythroid leukaemia and LoVo human colon adenocarcinoma, and exhibits substantial activity *in vivo* against L1210 leukaemia. Thiophenfurin also possesses good selectivity towards tumour cells *in vitro* and high-level of conversion to its dinucleotide form.[6] Dinucleotides TFAD, FFAD, and SFAD derived respectively from **1** were found to be an inhibitor of recombinant human inosine 5'-monophosphate dehydrogenase (IMPDH) type I and II.[7] Compound **2** showed remarkable inhibitory activity against hSGLT2 (IC_{50} = 4.0 nM) and good rat UGE effect (1381 mg/d).[8]

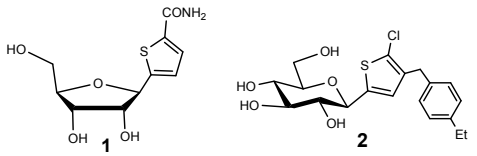

Figure 1 Examples of thiophene *C*-nucleoside analogues possessing biological activities.

Several thiophene *C*-nucleosides and their analogues were obtained during the synthesis of aryl *C*-nucleosides or ary *C*-glycosides (Figure 2). A mixture of thienyl α- and β-*C*-nucleosides were obtained by the reaction of protected D-ribose with lithium salt of thiophene followed by intramolecular cyclisation of the corresponding 1,4-diols under Mitsunobu conditions,[9] or catalyzed by $Yb(OTf)_3$[10] and *p*-TsOH[11]. Lemaire group synthesized 2-thienyl β-D-glucopyranoside by the reaction of perpivaloylated glucopyranosyl bromide with thienylzinc in toluene/*n*-dibutyl ether during the synthesis of *C*-aryl glycosides,[12] and later they synthesized 2- and 3-thienyl α-D-glucopyranoside *via* syn opening of perpivaloylated 1,2-anhydroglucal with thienylzinc.[13] This group prepared 2- and 3-thienyl β-isomers using perpivaloylated α-D-glucopyranosyl bromide reacting with thienylzinc or thienylzinc

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bromide, during the study of Friedel−Crafts fashion substitution of glucoside bromide and arylzinc reagents.[14] Lee and his coworkers synthesized substituted thienyl β-*C*-glucopyranosides by lithium halogen exchange of iodothiophene or bromothiophene derivatives followed by the addition of a lithiated thiophene derivatives to gluconolactone to yield lactols, which were reduced by $Et_3SiH/BF_3{\cdot}OEt_2$ and deprotected.[15] Some compounds showed inhibitory activities *in vitro* against SGLT2. Imamura[16] and Migaud[17] employed the similar strategy to synthesize 2-(4-methoxybenzyl)-4-thienyl β-*C*-glucopyranoside and 2-cyano-5-thienyl *C*-nucleoside from D-gluconolactone and D-ribonolactone, respectively. Gagné also obtained a mixture of thienyl α- and β-D-glucopyranoside by $Ni(COD)_2$/*t*Bu-Terpy catalyzed coupling of acetyl protected α-D-glucopyranosyl bromide with thienylzinc halide·LiCl (halide = Br, I).[18] Recently, Molander reported the general synthesis of "reverse" aryl *C*-glycosides and used this method to synthesize two "reverse" thiophene *C*-nucleoside analogues *via* Ni/photoredox dual catalysis and dihydropyridyl saccharide motifs as radical precursors.[19] However, the available methods and strategies are restricted to very few sugar substrates. Thiophene *C*-nucleoside analogues remain sparse, and they were usually obtained incidentally in the synthesis of aryl *C*-glycosides. The development of a general, modular, and simple synthetic method remains an unsolved challenge, especially the methods that would preserve the anomeric carbon to produce nonclassical, "reversed" or "iso-" *C*-nucleoside analogues are particularly scarce, although they may have increased enzymatic stability and exhibit attractive biological properties. In continuation of our interest in the syntheses of biologically active carbohydrate analogues[20] and *C*-substituted sugar analogues,[21] herein, we present the synthesis of thiophene *C*-nucleoside analogues bearing sugar residue (mono- and disaccharides) and aromatic residue through sequential reactions in one pot.

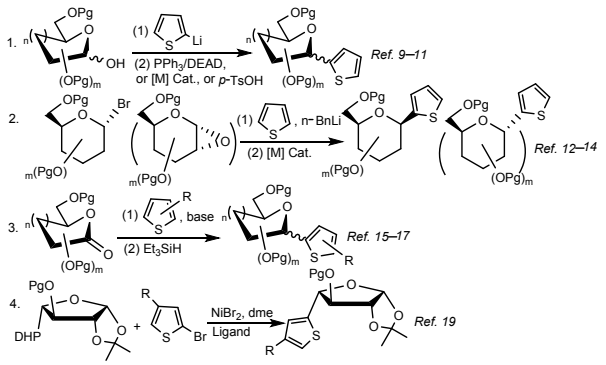
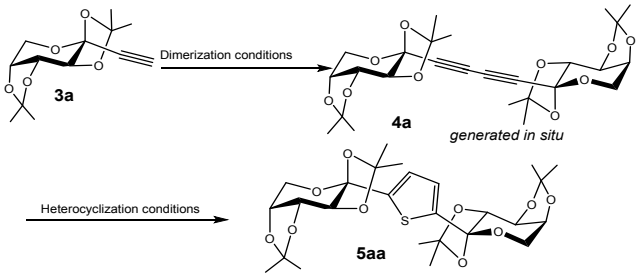


Figure 2 Previous methods for the synthesis of thiophene *C*-nucleoside analogues.

Results and discussion

Because the coupling of terminal alkyne is a useful reaction and is tolerant of many functional groups to construct molecules,[22] we envisioned the dimerization of the terminal sugar alkyne and subsequent sulfur heterocyclization of the corresponding disaccharides 1,3-butadiyne generated in situ to form thiophene ring in one pot, thus affording thiophene *C*-nucleoside analogues having two sugars. Sugar alkyne **3a** (scheme 1) having two acidic sensitive and sterically hindered isopropylidene was employed to explore this synthetic method, and the conditions for dimerization of **3a** and sulfur heterocyclization of **4a** were optimized respectively. Initially, various reaction conditions for dimerization of **3a** were examined. When the homocoupling of **3a** was carried out under Eglington conditions in the presence of copper(II) acetate in pyridine (Table 1, entry 1),[23] the disaccharides 1,3-butadiyne **4a** was not obtained and most of starting material **3a** was recovered except a small amount of decomposition. When the Hay coupling conditions[24] were applied to **3a** with O_2 in the presence of catalytic amounts of bidentate ligand TMEDA and copper(I) chloride (entry 2), yield of **4a** was low and many side products were present. The Sonogashira coupling conditions were then used for this homocoupling.[25] The influence of various factors on the homocoupling of **3a** was investigated. When the reaction was performed in CH_3CN and Et_2NH at rt using $PdCl_2(PPh_3)_2$/CuI as catalysts, **4a** was produced in 66% yield (entry 3). The change of base Et_2NH to Et_3N improved the reaction(entries 4-7). When the reaction was carried out in CH_3CN and Et_3N, **4a** was afforded in 73% yield (entry 4). THF is superior to CH_3CN, giving **4a** in 85% yield (entry 5). The change of solvent to DMF largely improved the dimerization. The dimer **4a** was obtained in 93% yield at rt in the presence of 2 mol% of $PdCl_2(PPh_3)_2$ and CuI each in DMF and Et_3N (entry 6). Increasing the temperature caused the decrease of the yield (entry 7).



Scheme 1 Synthesis of thiophene *C*-nucleoside analogues bearing disaccharides **5aa**

Table 1 Dimerization of **3a** to form **4a**[a]

3a → (Dimerization conditions) → **4a**

Entry	catalyst	Base	Solvent	T (°C)	Yield (%)[b]
1	$Cu(OAc)_2$		Pyridine	60	-
2	CuCl	TMEDA	acetone	50	48
3	$PdCl_2(PPh_3)_2$, CuI	Et_2NH	CH_3CN	rt	66
4	$PdCl_2(PPh_3)_2$, CuI	Et_3N	CH_3CN	rt	73
5	$PdCl_2(PPh_3)_2$, CuI	Et_3N	THF	rt	85
6	$PdCl_2(PPh_3)_2$, CuI	Et_3N	DMF	rt	93
7	$PdCl_2(PPh_3)_2$,	Et_3N	DMF	60	89

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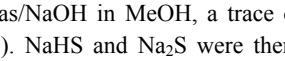
CuI

[a]Reaction conditions: 0.6 mmol of **3a**, 0.6 mmol of $Cu(OAc)_2$, 3 ml of Pyridine, 0.03 mmol of CuCl and TMDEA each, 5 ml of acetone, 0.012 mmol of $PdCl_2(PPh_3)_2$ and CuI each, 3 ml of CH_3CN and THF each, 1.5 ml of DMF, 0.5 ml of Et_2NH and Et_3N each. [b]Isolated yield.

The next task was to explore the method for heterocyclization of **4a** to **5aa**. Cyclization of alkynes have been applied in the synthesis of various heterocyclic compounds with high-atom efficiency,[26] but were usually performed in the presence of strong acid or lewis acid at high temperature. These reaction conditions were unsuitable for disaccharides 1,3-butadiynes due to their instability in acidic medium, especially at high temperature. Therefore, heterocyclization of disaccharides 1,3-butadiyne **4a** using different types of sulfur sources were examined in neutral or basic medium. When **4a** was treated by H_2S gas/NaOH in MeOH, a trace of **5aa** was produced (Table 2, entry 1). NaHS and Na_2S were then employed as sulfur sources. The heterocyclization of **4a** with NaHS didn't produce **5aa** in DMF at rt. Increasing the temperature to 80 ^{0}C gave a trace of product, but KOH promoted the reaction, giving **5aa** in 55% yield (entries 2-4). The change of solvent to DMSO and THF didn't improve the reaction (entries 5-6). When the heterocyclization with $Na_2S{\cdot}9H_2O$ was carried out in DMF, no desired product **5aa** was obtained (entry 7), which is similar to the case of NaHS. However, the presence of KOH led to **5aa** in 90% yield (entry 8). The change of solvent to DMSO gave the similar result (entry 9). The other solvents such as Dioxane, THF, and MeOH are inferior to DMF or DMSO, resulting in **5aa** in 40-55% yields (entries 10-12).

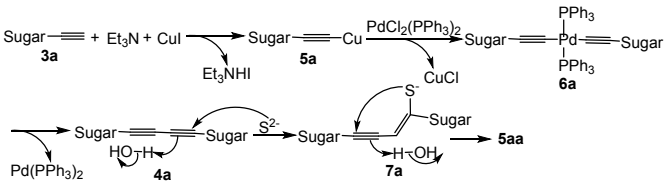
Table 2 Sulfur heterocyclization of **4a** to **5aa** under various conditions[a]



Entry	sulfur reagent	Base	Solvent	T (°C)	Yield (%)[b]
1	H_2S gas	NaOH	MeOH	reflux	trace
2	NaHS		DMF	rt	-
3	NaHS		DMF	80	trace
4	NaHS	KOH	DMF	80	55
5	NaHS	KOH	DMSO	80	50
6	NaHS	KOH	THF	reflux	45
7	$Na_2S{\cdot}9H_2O$		DMF	60	-
8	$Na_2S{\cdot}9H_2O$	KOH	DMF	60	90
9	$Na_2S{\cdot}9H_2O$	KOH	DMSO	60	85
10	$Na_2S{\cdot}9H_2O$	KOH	Dioxane	60	40
11	$Na_2S{\cdot}9H_2O$	KOH	THF	60	53
12	$Na_2S{\cdot}9H_2O$	EtOH	MeOH	reflux	55

[a]Reaction conditions: 0.40 mmol of **4a**, 1.0 mmol of sulfur reagent (except H_2S gas), 0.80 mmol of NaOH, 0.12 mmol of KOH, 2 ml of solvent. [b]Isolated yield.

A plausible mechanism for the formation of **5aa** from **3a** is proposed as shown in Scheme 2. The reaction of **3a** with CuI in the presence of Et_3N gives intermediate **5a**. Then the substitution reaction of Pd(Ⅱ) with **5a** occurs to afford bis-(triphenylphosphine) dialkynylpalladium **6a** and CuCl. Intermediate **6a** undergoes reductive elimination to produce disaccharides 1,3-diyne **4a**. Nucleophilic attack of Na_2S on **4a** followed by abstraction of H^+ from H_2O yields **7a**. Intermediate **7a** undergoes intramolecular nucleophilic cyclisation reaction and then abstraction of H^+ from H_2O to form the desired product **5aa**.



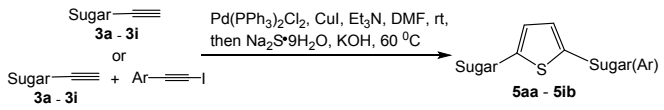
Scheme 2 The proposed mechanism for the formation of **5aa** from **3a**.

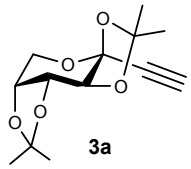
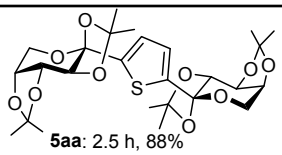
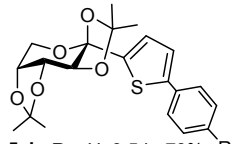
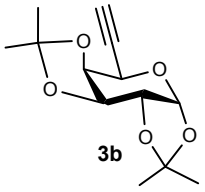
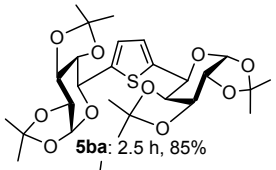
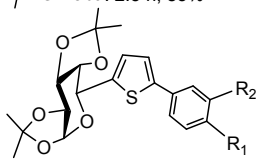
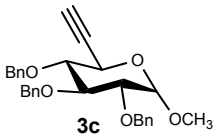
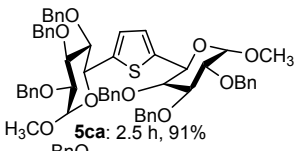
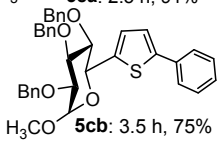
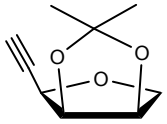
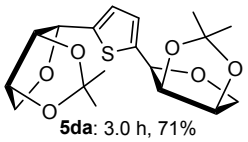
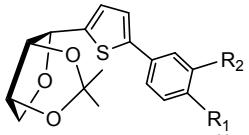
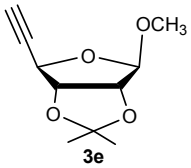
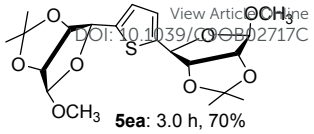
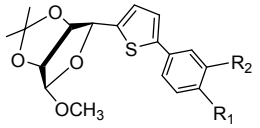
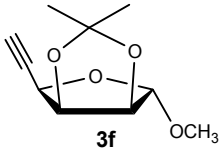
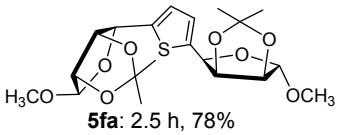
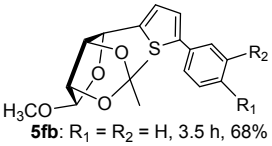
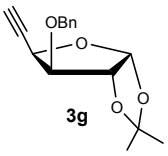
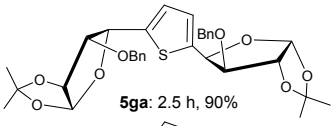
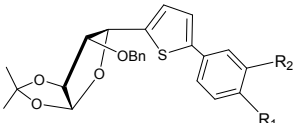
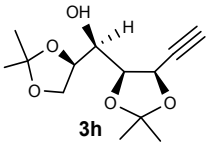
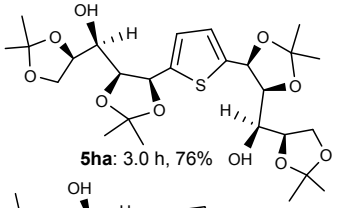
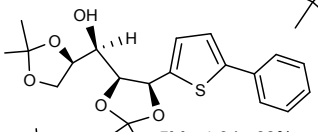
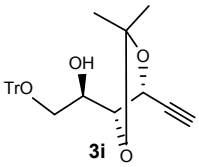
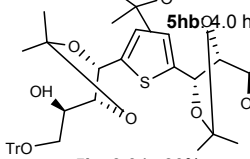
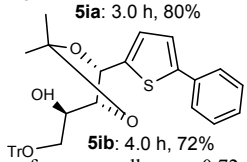
After finishing optimization studies, attempts to perform the dimerization of **3a** and sulfur heterocyclization of the intermediate **4a** in one pot was successful. Specifically, when the dimerization of **3a** was finished under optimal conditions, the mixture was filtered by diatomaceous earth. The solution of mother liquid, $Na_2S{\cdot}9H_2O$ and KOH was heated under optimal conditions to give **5aa** in 88% yield (Table 3, entry 1). This one-pot approach was also successfully applied to the synthesis of thiophene *C*-nucleoside analogues bearing monosaccharide by unsymmetric dimerization of terminal sugar alkynes and iodides followed by sulfur heterocyclization. When **3a** was employed to couple with iodoethynylbenzene, 1-iodoethynyl-4-methylbenzene, and 1-fluoro-4-iodoethynylbenzene followed by sulfur heterocyclization, respectively, the corresponding products **5ab, 5ac,** and **5ad** were given in 73%, 80% and 70% yields (Table 3, entry 1). The electron-donating CH_3 is superior to the electron-withdrawing F, giving **5ac** in higher yield. The yields of the compounds **5ab, 5ac**, and **5ad** having monosaccharide were lower than **5aa** bearing disaccharides due to the side reaction of homocoupling of sugar alkyne **3a** and homocoupling of iodides.

To examine the scope and generality of this synthetic method and to synthesize more thiophene *C*-nucleoside analogues, the structurally diversified terminal sugar alkynes were employed to perform this one-pot procedure. The results were shown in Table 3. The pyranosides **3a**, **3b**, and **3c** gave the corresponding thiophene *C*-nucleoside analogues in moderate to excellent yields (entries 1-3). **3c** afforded **5ca** in 91% yield, which is higher than the products **5aa** and **5ba**, probably due to that the benzyl protected sugar is more stable than the isopropylidene protected ones, thus resisting the decomposition. Next, the scope of substrates was expanded to furanosides such as **3d**, **3e**, **3f**, and **3g**. The corresponding products were obtained in 65%-90% yields. **3g** was superior to the other furanosides, giving the corresponding products in higher yields. When the scope was extended to acyclic sugars such as **3h** and **3i**, the corresponding products were produced in 68-80% yields. In general, the yields of thiophene *C*-nucleoside analogues bearing disaccharides are higher than those of the ones having monosaccharides. All the products were characterized by ^{1}H NMR, ^{13}C NMR, DEPT-135, 2D NMR, HRMS, and IR.

Table 3 Synthesis of structurally diversified thiophene *C*-nucleoside analogues bearing sugar residue (mono- and

disaccharides) and aromatic residue [a].



Entry	Terminal sugar alkynes	Product, Time, Yield[b]
1	 3a	 **5aa**: 2.5 h, 88%  **5ab**: R = H, 3.5 h, 73% **5ac**: R = CH_3, 3.0 h, 80% **5ad**: R = F, 4.0 h, 70%
2	 3b	 **5ba**: 2.5 h, 85%  **5bb**: R_1= R_2 = H, 3.5 h, 69% **5bc**: R_1 = CH_3, R_2 = H, 3.0 h, 75% **5bd**: R_1 = H, R_2 = F, 4.0 h, 69%
3	 3c	 **5ca**: 2.5 h, 91%  **5cb**: 3.5 h, 75%
4	 3d	 **5da**: 3.0 h, 71%  **5db**: R_1 = R_2 = H, 3.5 h, 70% **5dc**: R_1 = CH_3, R_2 = H, 3.0 h, 75% **5dd**: R_1 = F, R_2 = H, 4.0 h, 70% **5de**: R_1 = H, R_2 = F, 4.0 h, 70%
5	 3e	 **5ea**: 3.0 h, 70%  **5eb**: R_1 = H, R_2 = H, 3.5 h, 66% **5ec**: R_1 = CH_3, R_2 = H, 3.0 h, 70% **5ed**: R_1 = H, R_2 = F, 4.0 h, 65%
6	 3f	 **5fa**: 2.5 h, 78%  **5fb**: R_1 = R_2 = H, 3.5 h, 68% **5fc**: R_1 = CH_3, R_2 = H, 3.0 h, 70% **5fd**: R_1 = F, R_2 = H, 3.5 h, 65% **5fe**: R_1 = H, R_2 = F, 3.5 h, 65%
7	 3g	 **5ga**: 2.5 h, 90%  **5gb**: R_1 = R_2 = H, 3.5 h, 72% **5gc**: R_1 = F, R_2 = H, 3.5 h, 70% **5gd**: R_1 = H, R_2 = F, 3.5 h, 70%
8	 3h	 **5ha**: 3.0 h, 76%  **5hb**: 4.0 h, 68%
9	 3i	 **5ia**: 3.0 h, 80%  **5ib**: 4.0 h, 72%

[a]Reaction condition: 0.60 mmol of sugar alkyne, 0.72 mmol of iodoethynylbenzene, 0.012 mmol of $PdCl_2(PPh_3)_2$ and CuI each, 0.5 ml of Et_3N, 1.5 ml of DMF, 1.5 mmol of $Na_2S·9H_2O$, 0.18 mmol of KOH. [b]Isolated yield.

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Conclusions

In summary, we report the synthesis of thiophene *C*-nucleoside analogues having sugar residue (mono- and disaccharides) and aromatic residue by symmetric dimerization of terminal sugar alkyne or unsymmetric dimerization of terminal sugar alkyne and iodode followed by sulfur heterocyclization in one pot. Homocoupling of terminal sugar alkyne and subsequent sulfur heterocyclization produce thiophene *C*-nucleoside analogues with disaccharides. Unsymmetric dimerization of terminal sugar alkyne and iodide followed by sulfur heterocyclization gives thiophene *C*-nucleoside analogues with monosaccharides. The synthetic approach was concise, simple, and general. The structurally diversified substrates which include pyranosides, furanosides, and acyclic sugars have been examined. 32 examples have been given and the corresponding products are given in moderate to excellent yields.

Experimental Section

General

Commercially available reagents were used without purification. Commercially available solvents were dried by standard procedures prior to use. Nuclear magnetic resonance spectra were recorded on a 400 MHz spectrometer, and the chemical shifts are reported in δ units, parts per million (ppm), relative to residual chloroform (7.28 ppm) in the deuterated solvent. The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, and m = multiplet. Coupling constants, J, are reported in hertz (Hz). The ^{13}C NMR spectra are reported in ppm relative to $CDCl_3$ (77.0 ppm).

General procedure for the synthesis of 5aa-5ib:

A mixture of sugar alkyne (0.60 mmol), or sugar alkyne (0.60 mmol) and iodoethynylbenzene (0.72 mmol), $PdCl_2(PPh_3)_2$ (0.012 mmol), CuI (0.012 mmol), Et_3N (0.5 mL) and DMF (1.5 mL) was stirred under air atmosphere at rt until TLC indicated the disappearance of sugar alkyne. The mixture was filtered by diatomaceous earth. $Na_2S{\cdot}9H_2O$ (1.5 mmol) and KOH (0.18 mmol) was added to the mother liquid, and the solution was heated at 60 ^{0}C until TLC showed the completion of the reaction. Then it was evaporated to dryness and the residue was dissolved in EtOAc (25 mL), washed with water (2×5 mL) and brine (5 mL), dried over Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography to give the desired products.

Conflicts of interest

There are no conflicts to declare.

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Concise synthesis of thiophene *C*-nucleoside analogues bearing sugar residue and aromatic residue through dimerization and sulfur heterocyclization of sugar alkynes and substituted iodoethynylbenzene

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The synthesis of thiophene *C*-nucleoside analogues bearing mono- and disaccharides has been achieved by symmetric dimerization of terminal sugar alkynes or unsymmetric dimerization of terminal sugar alkynes and substituted iodoethynylbenzene followed by sulfur heterocyclization in one pot.