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A low-temperature, photoinduced thiol–ene click reaction: a mild and efficient method for the synthesis of sugar-modified nucleosides†

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Sugar-modified nucleosides are prime synthetic targets in anticancer and antiviral drug development. Radical mediated thiol–ene coupling was applied for the first time on nucleoside enofuranoside derivatives to produce a broad range of thio-substituted D-*ribo*, -*arabino*, -*xylo* and L-*lyxo* configured pyrimidine nucleosides. In contrast to the analogous reactions of simple sugar exomethylenes, surprisingly, hydrothiolation of nucleoside alkenes under the standard conditions of various initiation methods showed low to moderate yields and very low stereoselectivity. Optimizing the reaction conditions, we have found that cooling the reaction mixture has a significant beneficial effect on both the conversion and the stereoselectivity, and UV-light initiated hydrothiolation of *C*2′-, *C*3′- and *C*4′-exomethylene derivatives of nucleosides at −80 °C proceeded in good to high yields, and, in most cases, in excellent diastereoselectivity. Beyond the temperature, the solvent, the protecting groups on nucleosides and, in some cases, the configuration of the thiols also affected the stereochemical outcome of the additions. The anomalous L-*lyxo* diastereoselectivity observed upon the addition of 1-thio-β-D-gluco- and galactopyranose derivatives onto *C*4′,5′-unsaturated uridines is attributed to steric mismatch between the D-*ribo* *C*4′-radical intermediates and the β-configured 1-thiosugars.

Introduction

The application of nucleosides and nucleic acids in therapy[1] has prompted the development of nucleoside analogues with enhanced chemical and biological properties. The modification of ribose oxygen in nucleosides with other elements such as carbon, nitrogen, fluorine or sulfur is a proven strategy for producing new drug candidates.[2] For example, 5′-thionucleosides are studied as selective inhibitors against essential enzymes,[3] while *C*2′- or *C*3′-branched nucleosides have shown good antitumor or antiviral activity.[2] Ribose modification is also used to control the sugar puckering and thereby increase the nucleic acid resistance.[4] Versatile and stereoselective alteration of the furanose residue in nucleosides is an important challenge for synthetic chemists.

We present here that the thiol–ene click reaction conducted at low temperature represents a generally applicable novel strategy for the efficient modification of nucleosides with various thiol substituents at *C*2′-, *C*3′- and *C*5′-positions.

The radical-mediated addition of thiols to non-activated alkenes,[5] also known as thiol–ene coupling, had widespread application in materials chemistry and chemical biology during the last few years.[6] Due to mild conditions, atom economy and regioselectivity, this process has been extensively utilised in glycochemistry.[7] We and others have reported that sugar-derived alkenes, including endo- and exoglycals, can be employed as acceptor substrates in the photoinitiated thiol–ene chemistry to produce various thiosugars and *S*-linked glycoconjugates in excellent stereoselectivity.[8–10] Although only two examples have emerged in the literature with furanoid alkenes, both demonstrated that hydrothiolation of 3-exomethylene-[8c] and 4-exomethylene-furanosides[9a] showed complete stereoselectivity.

On the basis of the above results, we envisioned the extension of the photoinitiated thiol–ene reaction to nucleoside enofuranoside derivatives.

Results and discussion

We first investigated the addition of 1-propanethiol to the easily available 4′,5′-unsaturated uridine **1**, under previously established standard conditions for the synthesis of *S*-glycoconjugates,[8] irradiating at λ_{max} = 365 nm at room temp-

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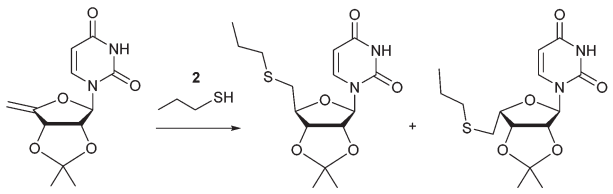
†Electronic supplementary information (ESI) available: Experimental details, characterization of all reported compounds, and copies of NMR spectra for all compounds. See DOI: 10.1039/c7ob02184d

Table 1 Free radical addition of propanethiol to **1** upon various initiation methods[a]



1 **3a** (D-ribo) **3b** (L-lyxo)

Entry	Thiol equiv.	Initiation	Solvent	*T*	Time	D-*Ribo* : L-*lyxo*[b]	Yield[c] (%)
1	3	DPAP, *hν*[d]	Toluene	rt	3 × 15 min	2 : 1	60
2	6	DPAP, *hν*[d]	Toluene	rt	3 × 15 min	2 : 1	69
3	8	AIBN	Toluene	120 °C	6 h	1.5 : 1	54
4	3	Et_3B	CH_2Cl_2	rt	2 days	2 : 1	38
5	3	Et_3B, catechol	CH_2Cl_2	rt	4 h	2 : 1	59
6	4	TiO_2, *hν*[e]	CH_2Cl_2	rt	2 days	2 : 1	7
7	2	DPAP, *hν*[d]	Toluene	−30 °C	3 × 15 min	4 : 1	88
8	2	DPAP, *hν*[d]	Toluene	−80 °C	3 × 15 min	5 : 1	89
9	2	DPAP, *hν*[d]	Toluene–MeOH	−80 °C	3 × 15 min	6.3 : 1	88
10[f]	2	Et_3B, catechol	CH_2Cl_2–MeOH	−80 to −20 °C	24 h	2.5 : 1	64

[a] The reactions were carried out on a 0.2–0.5 mmol scale. [b] Ratio of products determined by ^1H NMR. [c] Overall yield of products isolated by column chromatography and the low yield was caused by low conversion of **1**. [d] Irradiation by UV light (λ_{max} = 365 nm), the reaction was carried out in a borosilicate vessel without any caution to exclude air or moisture. [e] Irradiation by visible light using a 100 W domestic light bulb. [f] Kept in the refrigerator overnight.

erature in the presence of the cleavable photoinitiator 2,2-dimethoxy-2-phenylacetophenone (DPAP) (Table 1, entries 1 and 2). According to our expectation,‡ thiol **2** added exclusively across the exocyclic double bond of the furanose residue providing the 5′-*S*-propyl derivative **3**. However, a low level of diastereoselectivity (2 : 1 D-*ribo* : L-*lyxo* ratio) was observed and the yield was only 69% even with 6 equiv. of thiol due to incomplete conversion of **1**. This result was surprising because Dondoni and Marra described excellent yield and exclusive *ribo*-selectivity for hydrothiolation of the methyl β-D-riboside counterpart of **1** with a slight excess of thiols.[9a] To evaluate if the yield and the stereoselectivity can be influenced by the initiation methods, the reaction was repeated under various conditions including thermal initiation with AIBN, photoredox activation in the presence of TiO_2 [11] or using Et_3B[12] as the radical initiator (Table 1, entries 3–6).

Unfortunately, neither the yield nor the selectivity could be increased. The Et_3B–catechol reagent system, which was developed for the hydrothiolation of allylic double bonds,[12a] showed similar efficacy to the UV-initiated reaction (entries 5 and 1). The other initiation methods proved to be less efficient, due to the low conversion of **1** (entries 4 and 6) and the thermal activation even slightly eroded the D-*ribo* diastereoselectivity (entry 3). Next, the temperature effect on the photoinduced addition was studied. To our great delight, both the stereoselectivity and the yield could substantially be improved by cooling even with a much lower thiol excess (entries 7–9). At −30 °C, an 88% overall yield was achieved with 2 equiv. of thiol, and the stereoselectivity was increased to a 4 : 1 D-*ribo* : L-*lyxo* ratio. By cooling the reaction mixture to −80 °C the selectivity reached the 5 : 1 D-*ribo* : L-*lyxo* ratio in toluene and the use of a toluene–MeOH 1 : 1 solvent mixture led to an even higher D-*ribo* selectivity. Although the cooling was also beneficial for the Et_3B–catechol-mediated addition (entry 10), the reaction was very sluggish at −80 °C, and the overall efficacy was inferior to that of the photoinitiated reaction.

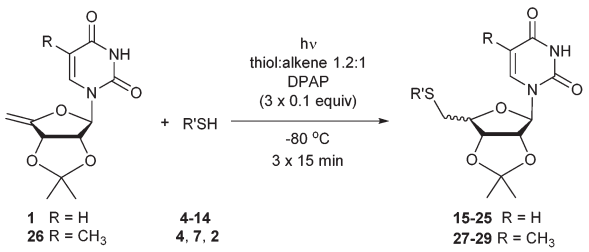
After optimizing the conditions of the thiol–ene addition, the substrate scope was investigated. First, compound **1** was reacted with a variety of thiols, including 1-thiosugars **4** and **5**, amino acid derivatives **6**, **7** and **9**, sulfonic acid salt **8** and dithiol **10**, at −80 °C with a 1.2 : 1 thiol : ene ratio (Table 2, entries 1–12).

We were pleased to find that the addition of thiols to the exomethylene moiety of **1** occurred with good to excellent yields (71–92%) and, except for the 1-thiosugar cases, with high levels of D-*ribo* diastereoselectivity. The reaction was compatible with the carboxylic acid function (entries 7, 8 and 10) and with the sensitive Fmoc group (entry 8) and in most cases reached completion with the slight excess thiol applied. In this context, this method is a mild and economic alternative to the conventional nucleophilic substitution which generally requires strong basic conditions and a higher excess thiol.§

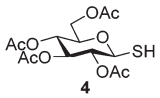
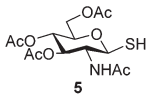
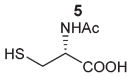
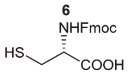
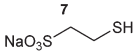
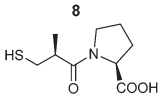
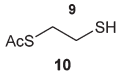
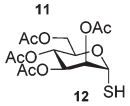
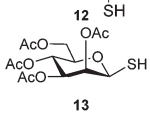
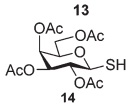
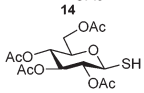
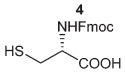
‡ As terminal double bonds react much faster than the internal ones and conjugated double bonds are nonreactive under thio-click conditions (see ref. 6*a* and *c*) chemoselective addition to the exocyclic double bond was expected.

§ We have studied the synthesis of **17** and **18** by nucleophilic substitution starting from the corresponding 5′-deoxy-5′-iodo uridine derivative. Compound **17** could be prepared in 76% yield with 4 equiv. of **6** in the presence of Cs_2CO_3. However, analogous reactions of **7** using various bases gave **18** in a yield of up to 20%.

Table 2 Photoinduced addition of various thiols to 4′-enofuranoside uridine and ribothymidine at low temperature



1 R = H, **26** R = CH_3 — **4-14**, **4**, **7**, **2** — **15-25** R = H, **27-29** R = CH_3

Entry	Thiol	Solvent	Product	D-*Ribo* : L-*lyxo*[a]	Yield[b] (%)
1[c]	 **4**	Toluene, rt	**15**	1.1 : 1	87
2		Toluene	**15**	1 : 1	89
3		Toluene–MeOH	**15**	1 : 3	88
4		MeOH	**15**	1 : 2	81
5	 **5**	Toluene–MeOH, rt	**16**	1 : 1.25	77
6		Toluene–MeOH	**16**	1 : 4.5	80
7[d]	 **6**	Toluene–MeOH	**17**	10 : 1	92
8	 **7**	Toluene–MeOH	**18**	10 : 1	89
9	 **8**	MeOH–DMF 5 : 1	**19**	14 : 1	85
10	 **9**	MeOH	**20**	6 : 1	91
11[c]	 **10**	Toluene	**21**	6 : 1	71
12[c]		Toluene : MeOH	**21**	6 : 1	70
13[d]	 **11**	Toluene, rt	**22**	3 : 1	58
14[d]		Toluene, −40 °C	**22**	2 : 1	62
15	 **12**	Toluene, rt	**23**	3.5 : 1	60
16		Toluene	**23**	8 : 1	89
17	 **13**	Toluene, rt	**24**	1.2 : 1	56
18		Toluene	**24**	1 : 1	72
19		Toluene–MeOH	**24**	1 : 1	66
20	 **14**	Toluene, rt	**25**	1 : 1.6	68
21		Toluene	**25**	1 : 1.6	80
22		Toluene–MeOH	**25**	1 : 3.5	78
23	 **4**	Toluene–MeOH	**27**	1 : 2.5	80
24	 **7**	Toluene–MeOH	**28**	5 : 1	64
25	 **2**	Toluene	**29**	5 : 1	59
26[e]		Toluene	**29**	5 : 1	78

[a] Ratio of products determined by ^{1}H NMR. [b] Overall yield of products isolated by column chromatography. [c] 1.5 equiv. of thiol was used. [d] 6 equiv. of thiol was used. [e] 3 equiv. of thiol was used.

Surprisingly, the addition of 1-thio-β-D-glucose **4** in toluene, either at room temperature or at −80 °C, proceeded with a complete lack of stereoselectivity, while running this reaction in MeOH or in a MeOH–toluene mixture at −80 °C, a modest L-*lyxo* selectivity was observed (entries 1–4). Addition of the 2-acetamido-1-thio-β-D-glucopyranose derivative **5** onto **1** also showed an L-*lyxo* selectivity which reached the 4.5 : 1 L-*lyxo* : D-*ribo* ratio at −80 °C (entries 5 and 6). We assumed that this opposite stereoselectivity was caused by the higher steric demand of the glycosyl thiols relative to the primary

thiols **6–10**. To examine this assumption, the bulky 2-methylpropane-2-thiol **11** was reacted with **1**.¶ Unexpectedly, a relatively high D-*ribo* selectivity (3 : 1 D-*ribo* : L-*lyxo* ratio) was observed at room temperature, which, however, decreased by cooling to a 2 : 1 D-*ribo* : L-*lyxo* ratio (entries 13 and 14). Although this result confirmed that the direction of the H-abstraction by the *C*-4′ centered radical intermediate can be influenced not only by the temperature but also the bulkiness of the thiol, it did not explain the *lyxo*-selectivity observed with the thiosugars **4** and **5**. Next, alkene **1** was reacted with the 1-thio-α-D-mannopyranose derivative **12** and the β-thiosugars **13** and **14** (entries 15–22). To our great surprise, the addition of the α-thiosugar **12** occurred with a significant D-*ribo* selectivity at rt which was further increased to a 8 : 1 D-*ribo* : L-*lyxo* ratio when the reaction was carried out at −80 °C. However, similar reactions with the β-congener **13** either at rt or −80 °C proceeded with a complete lack of stereoselectivity, while the addition of the 1-thio-β-D-galactopyranose **14** followed the stereoselectivity of the *gluco*-epimers **4** and **5**. These results clearly demonstrate that the anomeric configuration of the thiosugars exerts a profound effect on the stereochemical outcome of the addition which can also be modified slightly by the solvent and by the *C*2 configuration. To the best of our knowledge, it has not been observed before that the configuration of the thiols can affect the stereochemical outcome of the thiol–ene coupling.

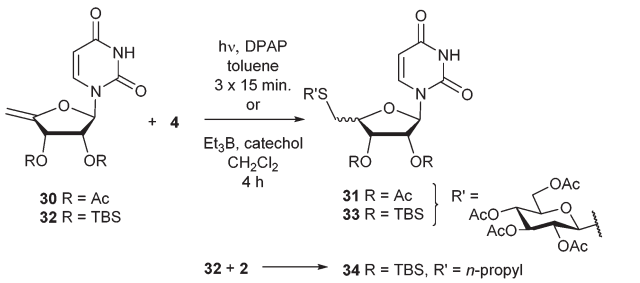
The thiol–ene reactions of ribothymidine **26** (Table 2, entries 23–26) showed the same stereoselectivity trends as observed with the uridine analogue **1**. The addition of 1-thioglucose **4** showed a slight L-*lyxo* selectivity, while a significant D-*ribo* preference was observed with the primary thiols **2** and **7**. Although the yields were slightly lower with ribothymidine than uridine, they still remained in a preparatively useful range.

To determine if the protecting groups on the alkene were able to influence the stereochemical outcome of the addition, the uridine derivatives **30** and **32** were reacted with thiol **4**, initially at room temperature. Similar to the analogous reaction of **1**, a lack of stereoselectivity was observed with the acetyl-protected alkene **30**, moreover, the yields were low (Table 3, entries 1 and 2). Interestingly, the reaction of the *tert*-butyldimethylsilyl-protected **32** with **4** showed a remarkable ~4 : 1 L-*lyxo* selectivity at rt, applying either the UV-irradiation or the Et_3B–catechol-mediated conditions (Table 3, entries 4 and 5). Repeating the photoinitiated reaction at −80 °C, an increased 6 : 1 L-*lyxo* : D-*ribo* dr was achieved in an excellent 98% overall yield (entry 6). The addition of 1-propanethiol onto **32** proceeded with a 2.5 : 1 L-*lyxo* preference at room temperature. However, the cooling again favoured the formation of the D-*ribo* isomer, as observed in the reactions of **1** with primary thiols and led to the complete loss of stereoselectivity at −80 °C (Table 3, entries 7 and 8).

To further study the alkene scope, compounds **35**, **38** and **41** were subjected to thiol–ene reactions. First, **35** bearing the exocyclic double bond at position *C*2′ was hydrothiolated with **2** and **4** (Table 4). In contrast to the *C*4′ exomethylene case, the addition reactions across the *C*2′-positioned double bond showed the same trend of D-*arabino* selectivity using either the primary thiol **2** or the sugar thiol **4**. Although a fairly good

¶Due to the low reactivity of the *t*-butylthiyl radical formed (see ref. 8*c*), a higher excess of 2-methylpropane-2-thiol was required for the efficient thiol–ene reaction.

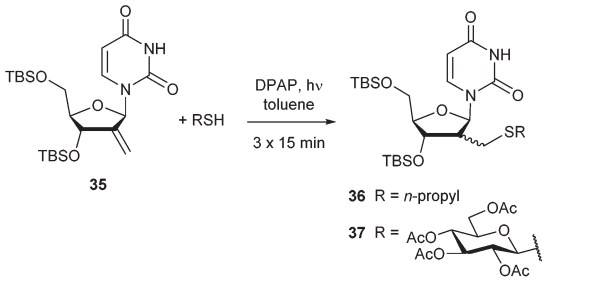
Table 3 Hydrothiolation of 4′-methyleneuridine derivatives bearing different protecting groups



Entry	Alkene	Thiol	Initiation	*T*	D-*Ribo* : L-*lyxo*[a]	Yield[b] (%)
1	**30**	**4**	DPAP, *hν*	rt	1.1 : 1	56[c]
2	**30**	**4**	Et_3B, catechol	rt	1.1 : 1	54
4	**32**	**4**	DPAP, *hν*	rt	1 : 3.7	77
5	**32**	**4**	Et_3B, catechol	rt	1 : 3.5	82
6	**32**	**4**	DPAP, *hν*	−80 °C	1 : 6	98
7	**32**	**2**	DPAP, *hν*	rt	1 : 2.5	59
8	**32**	**2**	DPAP, *hν*	−80 °C	1 : 1	67

[a] Ratio of products determined by ^{1}H NMR. [b] Overall yield of products isolated by column chromatography.

Table 4 Hydrothiolation of 2′deoxy-2′-methyleneuridine



Entry	Thiol	Product	*T*	D-*Arabino* : D-*ribo*[a]	Yield[b] (%)
1	**2**	**36**	rt	4 : 1	39
2	**2**	**36**	−80 °C	12.5 : 1	68
3	**4**	**37**	rt	5 : 1	68[c]
4	**4**	**37**	−80 °C	10 : 1	89

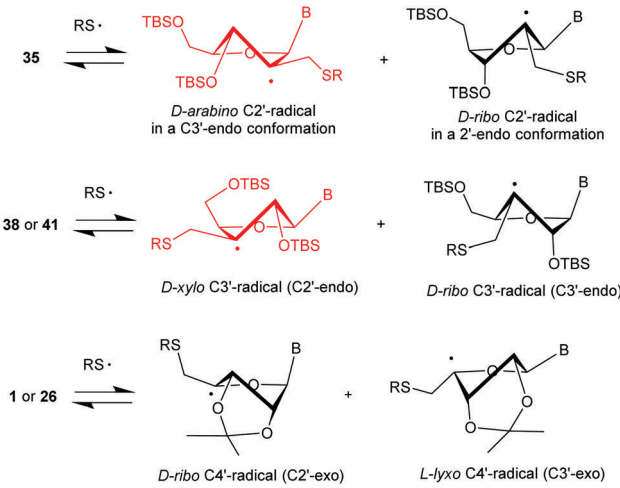
[a] Ratio of products determined by ^{1}H NMR. [b] Overall yield of products isolated by column chromatography. [c] Similar results were obtained with Et_3B–catechol.

level of diastereoselectivity was observed in favour of the D-*arabino* isomer at room temperature with both thiols, the yields were only moderate (Table 4, entries 1 and 3). We were pleased to find that running the reactions at −80 °C significantly improved the yields and also the levels of diastereoselectivity (Table 4, entries 2 and 4).

Finally, the *C3′*-exomethylene derivatives **38** and **41** were reacted with thiols **2**, **4** and **12** (Table 5).

Surprisingly, propanethiol **2** did not react with either of the alkenes at room temperature. However, to our great delight, performing the reactions at −80 °C led to the formation of the addition products **39** and **42** with fair yields and excellent D-*xylo* selectivities (entries 1 and 4). Addition of the β-1-thioglucose **4** across the *C3′*-exomethylene moiety also proceeded with a D-*xylo* selectivity in all cases (entries 2, 3, 5 and 6). The low level of diastereoselectivity observed at rt was increased to a 90–96% range by cooling, however, the yields remained moderate (entries 2 *vs.* 3 and 5 *vs.* 6). Finally, the α-thiosugar **12** was reacted with **41** in order to study if the anomeric configuration exerts an effect on the stereochemical outcome of the reaction (entry 7). In this case, the anomeric configuration did not make any difference in the diastereoselectivity, and the addition of both the α-thiosugar **12** and the β-thiosugar **4** onto **41** occurred at an excellent level of D-*xylo* selectivity providing the corresponding products **43** and **44** in the same 50 : 1 D-*xylo* : D-*ribo* ratio (entries 6 and 7).

The source of the stereoselectivity in the thiol–ene coupling of exocyclic alkenes is the preferred H-abstraction by the carbon-centered radical from the thiol into an axial position.[6d,13] We assume that the reactions presented herein proceed through the equatorial radicals depicted in Scheme 1, and the stereochemical outcome of the reactions is controlled by the relative stability of the radical pairs. Our results suggest that the proportion of the more stable radical intermediate and thus the level of stereoselectivity in a given reaction can be greatly increased by cooling the reaction to −80 °C.

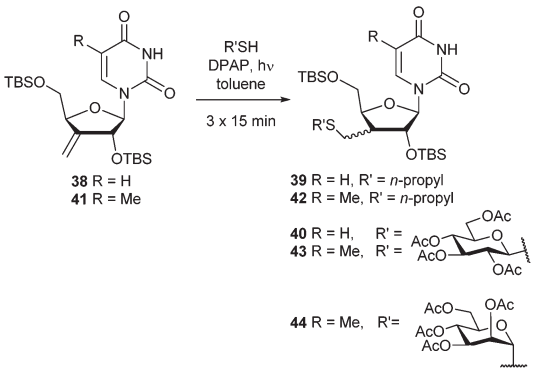


Scheme 1 Equatorial *C2′*, *C3′* and *C4′* radical intermediates formed in the first, reversible step of the thiol–ene reactions. All-equatorial radicals are highlighted in red.

In the case of the *C2′*- and *C3′*-exomethylene derivatives, the reactions preferably go through the more stable radicals possessing an all-equatorial substitution pattern, leading to the observed D-*arabino*-selectivity from the *C2′*-alkene **35** and the D-*xylo*-selectivity from the *C3′*-alkenes **38** and **41** (Scheme 1). Although the participation of the less stable D-*ribo*-configured *C2′*- and *C3′*-radicals is not negligible in the room-temperature reactions, which explains the low/moderate levels of diastereoselectivity at rt, it can be significantly suppressed by cooling resulting in the observed excellent diastereoselectivities.

For the 4′-exomethylene derivatives **1**, **26**, **30** and **32**, the stereochemical outcome of the reactions can be influenced by many factors including the solvent, the protecting groups and the size and configuration of the thiols. Our results demonstrate that the low-temperature reactions of **1** and **26** with primary thiols, as well as with the 1-thiomannose derivative **12**, preferentially go through the D-*ribo C4′*-radical, existing in the *C2′-exo* ($^3T_2$) conformation, leading to the good D-*ribo*-selectivities. We assume that the anomalous stereochemical results observed with the bulky thiol **11** and the β-D-*gluco*-configured 1-thiosugars (**4**, **5**, **13** and **14**) can be explained by the steric congestion of the carbon-centered radicals and, possibly, by a steric mismatch between the thiosugars and the D-*ribo* configured *C4′*-radicals formed from **1**, **26** or **32**.[14] Due to this steric mismatch, the L-*lyxo* radicals participate in the H-abstraction step in an increased extent compared to the reactions of primary thiols, thus leading to the increased ratio of the L-*lyxo* isomer in the products.

Table 5 Photoinitiated hydrothiolation of *C3′*-methylene derivatives of uridine (**38**) and ribothymidine (**41**)



Entry	Alkene	Thiol	Product	*T*	DXylo : D-*ribo*[a]	Yield[b]
1[c]	**38**	**2**	**39**	−80 °C	50 : 1	75%
2[d]	**38**	**4**	**40**	rt	3 : 1	26%
3[d]	**38**	**4**	**40**	−80 °C	17 : 1	49%
4[c,d]	**41**	**2**	**42**	−80 °C	12.5 : 1	39%
5[d]	**41**	**4**	**43**	rt	2 : 1	27%
6[d]	**41**	**4**	**43**	−80 °C	50 : 1	30%
7	**41**	**12**	**44**	−80 °C	50 : 1	60%

[a] Ratio of products determined by ^{1}H NMR. [b] Overall yield of products isolated by column chromatography. [c] No reaction observed at room temperature. [d] Unreacted starting compounds were recovered.

The most unusual finding of our study is the beneficial effect of cooling on the degree of conversion of the thiol–ene click reaction. Recent kinetic analysis of thiol–ene coupling has revealed the importance of the stability of the carbon-centered radical intermediate, which directly influences not only the activation barrier of the hydrogen abstraction step but also the reversibility of the propagation (thiyl addition) step.[15] In our case, the reaction can be accomplished through several radicals of different stabilities, and the reaction path involving the most stable radical is preferred at low temperature. We assume that the equilibrium of the rapidly reversible propagation step lies toward the product (carbon-centered radical) in a greater extent for a more stable radical than for a less stable one. The other beneficial effect of cooling is that it significantly suppresses the disulfide formation from the thiyl radical, which is one of the undesired termination steps of the thiol–ene coupling. Thereby, the excess thiol applied can substantially be reduced at low temperature.

Conclusion

In conclusion, we have demonstrated that the low-temperature photoinitiated thiol–ene reaction provides a facile approach to various sugar-modified nucleosides including 5′-thiosubstituted D-*ribo* or L-*lyxo* derivatives, as well as valuable *C*2′- and *C*3′-branched compounds with D-*arabino*- or D-*xylo* configuration.

The low or moderate stereoselectivity observed at rt upon hydrothiolation of the *C*2′- and *C*3′-exomethylene nucleosides **35**, **36** and **41** could be greatly increased by cooling, and the corresponding *C*2′-branched D-arabinosyl and the *C*3′-branched D-xylosyl derivatives could be produced with good to excellent selectivity.

Our study revealed that the stereoselectivity of the thiol–ene coupling of the 4′,5′-unsaturated nucleosides is not easy to predict, probably due to the comparable stability of the corresponding D-*ribo* and L-*lyxo* radical intermediates. Nevertheless, good levels of D-*ribo* selectivity could be achieved in the low-temperature reactions of the isopropylidene-protected uridine **1** with primary thiols. Interestingly, the β-configured thiosugars did not follow this trend, instead, they tend to react with an L-*lyxo* selectivity at low temperature.

Besides enhancing the stereoselectivity, the low temperature also enhances the yield of the thiol–ene coupling, assumedly, by exerting a beneficial effect on the overall kinetics of the reaction.

The investigation of the scope and potential of the low-temperature thiol–ene coupling on purine nucleosides and on sugar-alkenes with an endocyclic double bond is underway.

Experimental

General information

2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-glucopyranose (**4**),[16] 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranose (**5**),[17] *N*-(9-fluorenylmethoxycarbonyl)-L-cysteine (**7**),[18] *S*-(2-mercaptoethyl)thioacetate (**10**),[19] 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranose (**12**),[20] 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-mannopyranose (**13**),[20] and 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranose (**14**)[21] were prepared according to the literature procedures. 2,2-Dimethoxy-2-phenylacetophenone (DPAP) and thiols **2**, **6–9** and **11** were purchased from Sigma Aldrich Chemical Co. and used without further purification. The synthesis of nucleoside enofuranosides **1**, **26**, **30**, **32**, **35**, **38** and **41** is described in the ESI.† Optical rotations were measured at room temperature with a PerkinElmer 241 automatic polarimeter. TLC was performed on a Kieselgel 60 F_{254} (Merck) with detection by UV-light (254 nm) and immersing into sulfuric acid ammonium-molybdate solution or 5% ethanolic sulfuric acid followed by heating. Flash column chromatography was performed on Silica gel 60 (Merck 0.040–0.063 mm). Organic solutions were dried over anhydrous Na_2SO_4 or $MgSO_4$, and concentrated under vacuum. The ^{1}H NMR (360 and 400 MHz) and ^{13}C NMR (90 and 100 MHz) spectra were recorded on Bruker DRX-360 and Bruker DRX-400 spectrometers at 25 °C. Chemical shifts are referenced to Me_4Si (0.00 ppm for ^{1}H) and to the residual solvent signals ($CDCl_3$: 77.2, DMSO-d_6: 39.5, CD_3OD: 49.0 for ^{13}C). Two-dimensional COSY and ^{1}H–^{13}C HSQC experiments were used to assist NMR assignments and 2D ROESY spectra were used for configurational assignments. MALDI-TOF MS analyses of the compounds were carried out in the positive reflectron mode using a BIFLEX III mass spectrometer (Bruker, Germany) equipped with delayed-ion extraction. 2,5-Dihydroxybenzoic acid (DHB) was used as a matrix and $F_3CCOONa$ as a cationising agent in DMF. ESI-TOF MS spectra were recorded by using a microTOF-Q type QqTOFMS mass spectrometer (Bruker) in the positive ion mode using MeOH as the solvent. Elemental analysis (C, H, N and S) was performed on an Elementar Vario MicroCube instrument.

The photoinitiated reactions were carried out in a borosilicate vessel by irradiation with a Hg-lamp giving maximum emission at 365 nm, without any caution to exclude air or moisture.

Representative example for the photoinduced addition of thiols to alkenes at −80 °C in the presence of DPAP

2′,3′-*O*-Isopropylidene-5′-*S*-*n*-propyl-5′-thiouridine (3a) and 1-(2′,3′-*O*-isopropylidene-5′-*S*-*n*-propyl-5′-thio-α-L-lyxofuranosyl) uracil (3b). To a solution of alkene **1** (90 mg, 0.3 mmol) and thiol **2** (0.6 mmol, 2 equiv., 60 μL) in toluene (1 mL) 2,2-dimethoxy-2-phenylacetophenone (7.7 mg, 0.03 mmol) was added. The reaction mixture was cooled to −80 °C and irradiated with UV light for 15 min. After 15 min DPAP (7.7 mg, 0.03 mmol) dissolved in toluene (0.3 mL) was added, and the mixture was cooled to −80 °C and irradiated for another 15 min. The addition of DPAP and irradiation at this temperature was repeated once more. Then the solution was concentrated and the crude product was purified by flash column chromatography (gradient elution 8 : 2 → 7 : 3 *n*-hexane–acetone) to give a 5 : 1 mixture of **3a** and **3b** (103 mg, 89%). A second flash column chromatography (95 : 5 CH_2Cl_2–acetone)

of the diastereomeric mixture gave pure **3a** (R_f = 0.31, 7 : 3 *n*-hexane–acetone) as a colourless syrup and pure **3b** (R_f = 0.30, 7 : 3 *n*-hexane–acetone) as a colourless syrup.

*Compound **3a** (D-ribo product).* ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.89 (s, 1H, N*H*), 7.37 (d, J = 8.1 Hz, 1H, H-6 uracil), 5.75 (d, J = 8.1 Hz, 1H, H-5 uracil), 5.69 (d, $J_{1',2'}$ = 2.2 Hz, 1H, H-1′), 4.99 (dd, $J_{2',3'}$ = 6.6 Hz, $J_{1',2'}$ = 2.2 Hz, 1H, H-2′), 4.82 (dd, $J_{2',3'}$ = 6.6 Hz, $J_{3',4'}$ = 4.2 Hz, 1H, H-3′), 4.27 (td, $J_{4',5'}$ = 6.1 Hz, $J_{3',4'}$ = 4.3 Hz, 1H, H-4′), 2.92–2.80 (m, 2H, H-5′a,b), 2.55 (t, J = 7.5 Hz, 2H, $CH_3CH_2CH_2$), 1.63 (dt, J = 14.7 Hz, J = 7.4 Hz, 2H, $CH_3CH_2CH_2$), 1.57 (s, 3H, i-propylidene C*H*$_3$), 1.36 (s, 3H, i-propylidene C*H*$_3$), 0.98 (t, J = 7.3 Hz, 3H, $CH_3CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.8, 150.1 (2C, 2 × *C*O uracil), 142.5 (1C, C-6 uracil), 114.7 (1C, i-propylidene C_q), 102.7 (1C, C-5 uracil), 94.2 (1C, C-1′), 86.7 (1C, C-4′), 84.5 (1C, C-2′), 83.2 (1C, C-3′), 35.1 (1C, $CH_3CH_2CH_2$), 34.5 (1C, C-5′), 27.2, 25.4 (2C, 2 × i-propylidene *C*H$_3$), 23.0 (1C, $CH_3CH_2CH_2$), 13.5 (1C, $CH_3CH_2CH_2$); MALDI-TOF MS: m/z calcd for $C_{15}H_{22}N_2NaO_5S$ $[M + Na]^+$ 365.114, found 365.119.

*Compound **3b** (L-lyxo product).* ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.31 (s, 1H, N*H*), 7.22 (d, J = 8.0 Hz, 1H, H-6 uracil), 5.73 (dd, J = 8.1 Hz, J = 1.8 Hz, 1H, H-5 uracil), 5.36 (s, 1H, H-1′), 5.24 (d, $J_{2',3'}$ = 6.0 Hz, 1H, H-2′), 4.99 (dd, $J_{2',3'}$ = 5.9 Hz, $J_{3',4'}$ = 3.9 Hz, 1H, H-3′), 4.59 (td, $J_{4',5'}$ = 6.8 Hz, $J_{3',4'}$ = 3.9 Hz, 1H, H-4′), 2.88–2.76 (m, 2H, H-5′a,b), 2.57 (td, J = 7.2 Hz, J = 0.8 Hz, 2H, $CH_3CH_2CH_2$), 1.65–1.57 (m, 2H, $CH_3CH_2CH_2$), 1.52 (s, 3H, i-propylidene C*H*$_3$), 1.36 (s, 3H, i-propylidene C*H*$_3$), 0.99 (t, J = 7.3 Hz, 3H, $CH_3CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.7, 150.8 (2C, 2 × *C*O uracil), 143.7 (1C, C-6 uracil), 113.3 (1C, i-propylidene C_q), 102.5 (1C, C-5 uracil), 97.4 (1C, C-1′), 85.8 (1C, C-4′), 85.5 (1C, C-2′), 81.6 (1C, C-3′), 35.1 (1C, $CH_3CH_2CH_2$), 31.1 (1C, C-5′), 26.4, 24.9 (2C, 2 × i-propylidene *C*H$_3$), 23.1 (1C, $CH_3CH_2CH_2$), 13.6 (1C, $CH_3CH_2CH_2$); ESI-TOF MS: m/z calcd for $C_{15}H_{22}N_2NaO_5S$ $[M + Na]^+$ 365.114, found 365.122.

Conflicts of interest

There are no conflicts of interest to declare.

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