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Photoinduced Thiol−Ene Coupling as a Click Ligation Tool for Thiodisaccharide Synthesis

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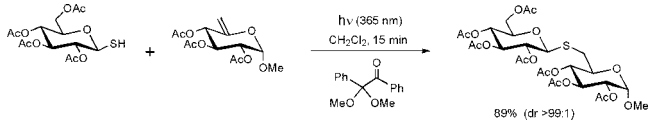

The high efficiency and selectivity of the thiol−ene radical reaction has been validated by the photoinduced coupling of anomeric sugar thiols with sugar alkenes to give 1,6-linked *S*-disaccharides in good to excellent yields (76−92%) and high diastereoselectivities (up to 99%). The reaction appears to be well-qualified as an exemplar click process.

In the quest for carbohydrate mimics to be used as probes in biological studies and leads for new therapeutics, *C*- and *S*-glycosides are focused synthetic targets of great relevance. The sulfur derivatives, however, are quite attractive candidates because they represent the smallest step away from natural *O*-glycosides in the backbone space.[1] In fact, the convenient choice of sulfur over carbon to replace oxygen at the glycosidic center is supported by similar conformational space adopted by *S*-glycosides and *O*-glycosides,[2] while the differences existing between the C−S and C−O bond lengths as well as the C−S−C and C−O−C bond angles result in small variation between the positions of the carbon atoms of the glycosidic linkage. Moreover, S-linked oligomers display lower susceptibility to enzymatic hydrolysis because the rate of hydrolysis of the thioglycosidic bond by glycohydrolases is several orders of magnitude slower than that of the corresponding *O*-glycosides.[3] The resistance of the thioglycosidic bond to cleavage has been ascribed to the low proton affinity of sulfur, resulting in inefficient general acid catalysis to the departing leaving moiety.[4] Most thio-oligosaccharide chemical syntheses[5] exploit the low basicity and high nucleophilicity of sulfur and employ a sugar thiol or thiolate anion in a reaction with another carbohydrate bearing a suitable leaving group. Other methods include glycosylation of thiosugar acceptors with activated glycosyl donors and Michael additions of sugar thiolates to α,β-unsaturated systems. Notably, however, the photochemical/thermal addition of sugar thiols to sugar alkenes is not included in the list of employed reactions. The centenary old thiol−ene coupling (TEC)[6] is known to proceed by a radical mechanism[7] to give an anti-Markovnikov sulfide adduct in very high yield. The special features that make TEC a formidable linking process in polymer and bioorganic chemistry have been highlighted in a recent paper from our laboratory.[8] These include high efficiency, total atom economy, orthogonality to a broad range of reagents, and compatibility with water and oxygen. Therefore, in very recent times, TEC has been reported as an exemplar case of click process[9] according to the concept formulated some years ago by Sharpless and co-workers.[10] However, while there has been an extensive use of this reaction in polymer chemistry,[11] only a few and recent applications in bioorganic chemistry have been reported.[12] Hence we envisaged the assembly of thiodisaccharides by this ligation tool as an opportunity to validate its synthetic potential as well as provide a new and general entry to these important carbohydrate mimics.

Initially, we set out to synthesize the *S*-disaccharide **3** under optimized conditions by using the readily available (see Supporting Information) peracetylated glucosyl thiol **1a** and the diacetonide-protected galactose-derived alkene **2a** as the reagents (Scheme 1).

As photoinduced bioorganic thiol−ene couplings have been carried out under a variety of conditions, we started performing our model reaction at room temperature and without deoxy-

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SCHEME 1

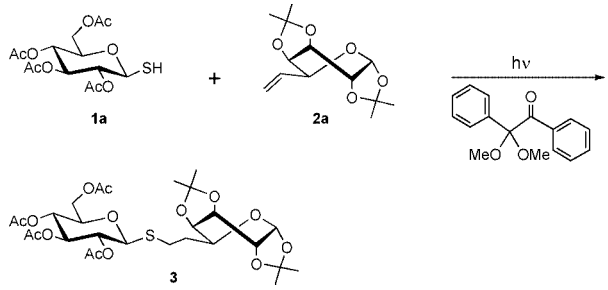

TABLE 1. Photoinduced Reactions of Thiol 1a with Alkene 2a

entry	**1a**:**2a** ratio[a]	PI[b] (%)	solvent	time (min)	λ_{max} (nm)	conv[c] (%)	**3**[d] (%)
1	1.1:1	15	MeOH	960	420	25	14
2	1.5:1	10	MeOH	480	420	25	20
3	3.0:1	15	MeOH	960	420	50	42
4	1.0:1	50	MeOH	60	365	50	46
5	1.2:1	50	MeOH	60	365	>97	79
6	1.3:1	50	MeOH	60	365	>97	91
7	3.0:1	50	MeOH	60	365	>97	79
8	1.3:1	25	MeOH	60	365	>97	61
9	1.3:1	50	MeOH	30	365	>97	78
10	1.3:1	50	MeOH	15	365	>97	81
11	1.3:1	50	MeOH	60	365	>97	83
12	1.2:1	10	MeOH	15	365	>97	75
13	1.2:1	10	CH_2Cl_2	15	365	>97	80
14	1.2:1	10	$PhCH_3$	15	365	>97	81
15	1.2:1	10	−−	15	365	>97	89
16	1.3:1	50	MeOH	540	sun light	>97	77

[a] Reactions were performed on a 0.05 M scale. [b] Photoinitiator 2,2-dimethoxy-2-phenylacetophenone (DPAP). [c] Reacted alkene determined by ^{1}H NMR analysis of the crude mixture. [d] Isolated yield of pure **3**.

genation by irradiation with a UV−visible lamp (λ_{max} = 420 nm, 40 W) in the presence of 2,2-dimethoxy-2-phenylacetophenone (DPAP) as the photoinitiator (Table 1).

Runs 1−3 carried out in MeOH with thiol/ene ratios of 1.1:1, 1.5:1, and 3:1 afforded **3** in low to moderate isolated yields even after several hours irradiation. Small amounts of **3** were observed in the crude reaction mixtures by NMR analysis. Hence, different conditions were applied. Irradiation of a 1:1 mixture of thiol−ene by a household UVA lamp (λ_{max} = 365 nm, 4 × 15 W) in a glass vial still afforded the product **3** in moderate yield (run 4). With our great delight, however, when the thiol/ene ratio from 1.2:1 to 1.3:1 and then to 3:1 (runs 5−7) was increased, the yields of isolated **3** were good to excellent. Significantly, the ^{1}H NMR spectra of the crude reaction mixtures, as shown in Figure 1, and analysis of the peaks in the region between 5.8 and 6.0 ppm corresponding to the alkene protons clearly showed that, at a thiol/ene 1:1 ratio, unreacted alkene was still present, whereas at 1.2:1 ratio, the alkene was quantitatively transformed into the *S*-disaccharide **3**. Notably, the NMR spectrum of the latter reaction mixture was almost identical to that of pure **3**, the only significant impurity being the 1,1′-diglucosyldisulfide (GlcSSGlc) arising from the homocoupling of thiol **1a**. Similar results were obtained by decreasing the amount of photoinitiator DPAP from 50 to 10 mol % and reducing the irradiation time from 60 to 15 min (runs 9−12). In this context, it was also established that in the absence of DPAP no coupling reaction took place even after 7 h irradiation. Finally, it was demonstrated that the reaction could be performed in aprotic solvents such as CH_2Cl_2 and toluene (runs 13 and

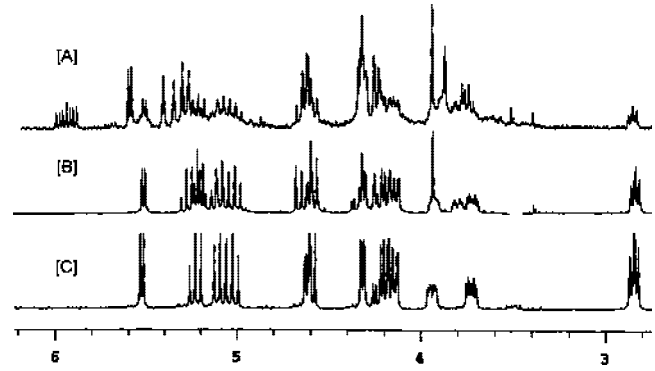

FIGURE 1. ^{1}H NMR spectra [A] and [B] of the crude reaction mixtures after photolysis of **1a** and **2a**: [A] **1a/2a** 1.0:1 ratio (50% conversion), [B] **1a/2a** 1.2:1 ratio (>97% conversion). [C] Spectrum of pure isolated product **3**.

14) with the same efficiency as in MeOH. Remarkably, disulfide GlcSSGlc did not form in CH_2Cl_2, thus allowing the recovery of residual **1a** by chromatography. In addition to the convenience of performing reactions under aerobic conditions and in normal laboratory glassware, the practicability and fidelity of the process were validated by it being carried out under solvent-free conditions (run 15) or sunlight irradiation (run 16). On the other hand, attempts to perform the reaction with the reagents floating on water[13] were unsuccessful because the waxy thiol **1a** and the oily alkene **2a** mixed together to form a material that stuck to the wall of the reaction vial. Under these conditions, the product **3** was obtained in only 50% isolated yield.

With the identification of suitable reaction conditions, the substrate scope of TEC for *S*-disaccharide synthesis was explored. To this aim, representative sugar thiols and alkenes all featuring acetyl or isopropylidene protective groups were considered, and the results of their photoinitiated reactions are collected in Table 2. Coupling of peracetylated glucosyl thiol **1a** with hex-5-enopyranosides **2b**,**c** and pent-4-enofuranoside **2d** proceeded rapidly and completely as monitored by NMR analysis to give the corresponding *S*-disaccharides **4**−**6** in high isolated yields and diastereoselectivities (entries 1−3). Notably, these products are exact *S*-disaccharide isosteres of natural *O*-disaccharides. Given the chain-reaction-type mechanism of TEC,[7] the formation of the stereoisomers **4**−**6**[14] can be explained by invoking the formation of thioalkyl radical intermediates **A**, **B**, and **C**, all featuring trans arrangements of the substituents on the C4−C5 bond. It can be envisaged that these intermediates expose the less hindered face to a molecule of thiol from which they abstract a H• radical in the final and irreversible locking step (Figure 2). Next, the effect of the anomeric configuration of the sugar thiol on the efficiency of the coupling reaction was tested by examining the reactions of the peracetylated α- and β-mannosyl derivatives **1b** and **1c** with alkenes **2a** and **2c** (entries 4−7). While the reaction of the α-anomer **1b** with **2c** in standard 1.2:1 ratio afforded the product **8** as a single diastereoisomer in high yield (entry 5), the reaction of **1b** with **2a** and the reactions of **1c** with **2a** and **2c** (entries 4,

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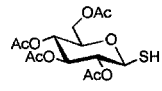
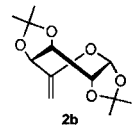
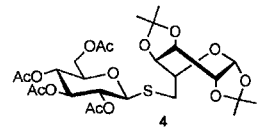
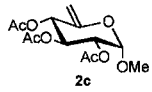
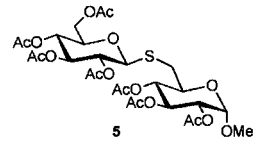
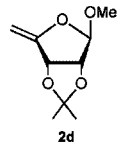
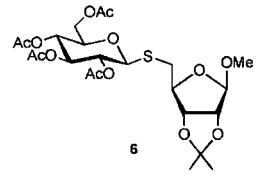
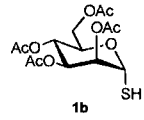
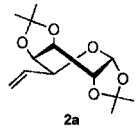
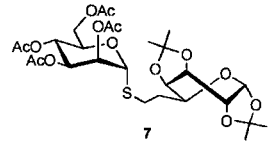
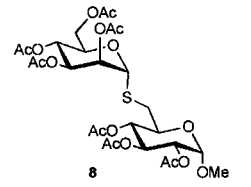
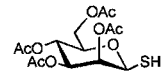
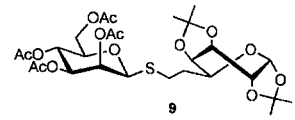
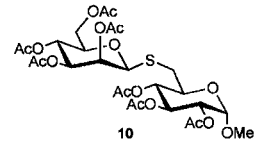
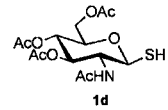
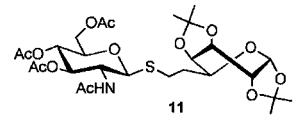
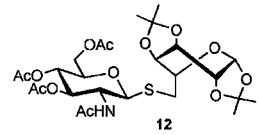
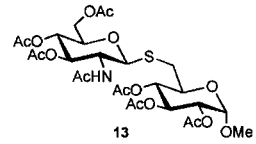
(14) The configuration of the newly formed stereocenters was assigned on the basis of the $J_{4,5}$ values (**4** and **5**) or by the presence of nOe between H1 and H4 (**6**). The ^{1}H NMR data of the known compounds *epi*-**4** (Tian, Q.; Zhang, S.; Yu, Q.; He, M.-B.; Yang, J.-S. *Tetrahedron* **2007**, *63*, 2142) and **5** (El Ashry, E. S. H.; Awad, L. F.; Abdel Hamid, H. M.; Atta, A. I. *Synth. Commun.* **2006**, *36*, 2769) matched quite well those reported in the literature.

TABLE 2. Reaction of Thiols 1 with Alkenes 2 To Give *S*-Disaccharides

Entry	Thiol	Alkene	1 : 2 ratio	Product	Yield and dr [b]
1	 **1a**	 **2b**	1.2 : 1	 **4**	82%, 75 : 25
2	**1a**	 **2c**	1.2 : 1	 **5**	89%, >99 : 1
3	**1a**	 **2d**	1.2 : 1	 **6**	92%, >99 : 1
4	 **1b**	 **2a**	3.0 : 1	 **7**	76%
5	**1b**	**2c**	1.2 : 1	 **8**	89%, >99 : 1
6	 **1c**	**2a**	3.0 : 1	 **9**	80%
7	**1c**	**2c**	3.0 : 1	 **10**	85%, 97 : 3
8	 **1d**	**2a**	1.2 : 1	 **11**	77%
9	**1d**	**2b**	1.2 : 1	 **12**	83%, 66 : 34
10	**1d**	**2c**	1.2 : 1	 **13**	84%, 94 : 6

[a] All reactions were performed in CH_2Cl_2 (0.05 M) with irradiation at λ_{max} 365 nm in the presence of DPAP (10 mol %). [b] Yields and diastereomeric ratios (dr) determined on isolated product.

6, and 7) required a thiol/ene ratio of 3:1 in order to give good yields of the corresponding coupling products **7**, **9**, and **10**.[15] Efficient and stereoselective reactions were also observed by coupling 2-acetamido-2-deoxyglucosyl thiol **1d** with alkenes **2a**−**c** (entries 8−10), thereby providing evidence on TEC compatibility with carbohydrate fragments containing the *N*-

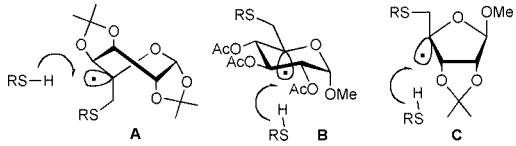


FIGURE 2. Postulated intermediates **A**, **B**, and **C** leading to the *S*-disaccharides **4**, **5**, and **6**, respectively.

acetylamino group and which are found within biologically important oligosaccharide natural products.

Although we were aware that benzyl protective groups were quite labile under shortwave UV irradiation in thiol−ene experiments,[16] conditions were sought to perform reactions with *O*-benzylated substrates. Unfortunately, the NMR spectra of the crude reaction mixture obtained from 2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl thiol (**1e**) and the model alkene **2a** in the presence of 10 mol % of DPAP showed the formation of decomposition products only.

In conclusion, we believe that this work validates the potential of the thiol−ene coupling in a topical field of glycochemistry directed toward the construction of carbohydrate mimics such as *S*-glycosides. This new synthesis of 1,6-linked *S*-disaccharides being operationally simple and chemically efficient should find its own place in the repertoire of valuable synthetic procedures leading to these unnatural carbohydrates. Finally, the implementation of the thiol−ene coupling using multifunctionalized reagents such as carbohydrates demonstrated once more its chemoselectivity. Hence the definition of photoclick reaction appears to be appropriate.

At present, it seems premature to compare the value of this ligation tool to that of the quintessential click reaction represented by the copper(I)-catalyzed azide alkyne cycloaddition.[17] In the event, however, the thiol−ene reaction would score a point for it being promoted by the most innocuous, inexpensive, and green catalyst such as irradiation at close to visible light or even by sunlight. This might provide numerous opportunities in chemistry-related fields such as chemical biology and medicinal chemistry.

Experimental Section

Thiodisaccharide 6. The reaction was carried out in a glass vial (diameter = 1 cm; wall thickness = 0.65 mm), sealed with a natural rubber septum, located 2.5 cm away from the UVA lamp. To a solution of **1a** (47 mg, 0.13 mmol) and **2d** (21 mg, 0.11 mmol) in dry CH_2Cl_2 (2.2 mL) was added DPAP (3.3 mg, 0.013 mmol). The solution was irradiated at rt for 15 min under magnetic stirring, then concentrated. The residue was eluted from a column of silica gel with cyclohexane/AcOEt (from 2:1 to 1:1) to give **6** (55 mg, 92%) as a colorless syrup: $[\alpha]_D = -40.7$ (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz) δ 5.24 (dd, 1H, $J_{2',3'} = J_{3',4'} = 9.3$ Hz, H-3′), 5.08 (dd, 1H, $J_{1',2'} = 10.2$ Hz, H-2′), 5.07 (dd, 1H, $J_{4',5'} = 10.0$ Hz, H-4′), 4.86 (s, 1H, H-1), 4.75 (dd, 1H, $J_{2,3} = 5.9$ Hz, $J_{3,4} = 3.6$ Hz, H-3), 4.62 (d, 1H, H-1′), 4.56 (d, 1H, H-2), 4.24 (dd, 1H, $J_{5',6'a} = 5.1$ Hz, $J_{6'a,6'b} = 12.5$ Hz, H-6′a), 4.13 (ddd, 1H, $J_{4,5a} = 8.3$ Hz, $J_{4,5b} = 6.0$ Hz, H-4), 4.12 (dd, 1H, $J_{5',6'b} = 2.5$ Hz, H-6′b), 3.70 (ddd, 1H, H-5′), 3.32 (s, 3H, OMe), 3.10 (dd, 1H, $J_{5a,5b} = 13.8$ Hz, H-5a), 2.87 (dd, 1H, H-5b), 2.08, 2.06, 2.03, and 2.01 (4 s, 12H, 4 Ac), 1.49 and 1.37 (2 s, 6H, 2 Me); ^{13}C NMR δ 170.6 (C), 170.2 (C), 169.34 (C), 169.28 (C), 112.6 (C), 107.1 (CH), 85.1 (CH), 83.6 (CH), 79.9 (CH), 79.5 (CH), 75.8 (CH), 73.9 (CH), 69.9 (CH), 68.2 (CH), 62.1 (CH_2), 54.6 (CH_3), 28.0 (CH_2), 26.0 (CH_3), 25.1 (CH_3), 20.6 (2 CH_3), 20.5 (2 CH_3); ESI-MS (550.57) 568.7 ($M + NH_4$)$^+$. Anal. Calcd for $C_{23}H_{34}O_{13}S$: C, 50.17; H, 6.22. Found: C, 49.83; H, 6.29.

Thiodisaccharide 7. To a solution of **1b** (54.5 mg, 0.15 mmol) and **2a** (12.5 mg, 0.05 mmol) in dry CH_2Cl_2 (1 mL) was added DPAP (3.8 mg, 0.015 mmol). The solution was irradiated at rt for 30 min under magnetic stirring, then concentrated. A solution of the residue in pyridine (0.3 mL) and Ac_2O (0.3 mL) was kept at rt for 30 min, then concentrated. The yellow residue was eluted from a column of silica gel with CH_2Cl_2/Et_2O (from 4:1 to 2:1) to give **7** (23.5 mg, 76%) as a syrup: $[\alpha]_D = -133.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz) δ 5.72 (dd, 1H, $J_{3',4'} = J_{4',5'} = 9.5$ Hz, H-4′), 5.69−5.63 (m, 2H, H-2′, H-3′), 5.38 (d, 1H, $J_{1,2} = 5.0$ Hz, H-1), 5.22 (br s, 1H, H-1′), 4.61 (ddd, 1H, $J_{5',6'a} = 5.0$ Hz, $J_{5',6'b} = 2.2$ Hz, H-5′), 4.45 (dd, 1H, $J_{6'a,6'b} = 12.3$ Hz, H-6′a), 4.42 (dd, 1H, $J_{2,3} = 2.3$ Hz, $J_{3,4} = 8.0$ Hz, H-3), 4.22 (dd, 1H, H-6′b), 4.12 (dd, 1H, H-2), 3.95 (ddd, 1H, $J_{4,5} = 1.8$ Hz, $J_{5,6a} = 10.0$ Hz, $J_{5,6b} = 3.3$ Hz, H-5), 3.65 (dd, 1H, H-4), 2.73 (ddd, 1H, $J_{6a,7a} = 5.9$ Hz, $J_{6b,7a} = 10.0$ Hz, $J_{7a,7b} = 12.6$ Hz, H-7a), 2.56 (ddd, 1H, $J_{6a,7b} = J_{6b,7b} = 5.5$ Hz, H-7b), 2.20 (dddd, 1H, $J_{6a,6b} = 13.5$ Hz, H-6a), 1.62 (dddd, 1H, H-6b), 1.77, 1.65, 1.63, and 1.59 (4 s, 12H, 4 Ac), 1.61, 1.41, 1.12, and 1.02 (4 s, 12H, 4 Me); ^{13}C NMR δ 170.7 (C), 170.0 (C), 169.8 (C), 169.6 (C), 109.1 (C), 108.5 (C), 96.5 (CH), 81.7 (CH), 72.9 (CH), 71.1 (CH), 70.9 (CH), 70.5 (CH), 69.5 (CH), 68.7 (CH), 66.3 (CH), 65.3 (CH), 62.3 (CH_2), 29.2 (CH_2), 26.9 (CH_2), 26.00 (CH_3), 25.97 (CH_3), 25.0 (CH_3), 24.3 (CH_3), 20.9 (CH_3), 20.7 (2 CH_3), 20.6 (CH_3); ESI-MS (620.66) 638.7 ($M + NH_4$)$^+$. Anal. Calcd for $C_{27}H_{40}O_{14}S$: C, 52.25; H, 6.50. Found: C, 52.53; H, 6.42.

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Supporting Information Available: Experimental procedures and physical data of **3**, **4**, **5**, and **8**−**13**, copies of the ^{1}H and ^{13}C NMR spectra of **3**, **4**, **6**, **7**, and **9**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Using the reagents in 1.2:1 ratio, the products were isolated in low yields: **7** (44%), **9** (20%), **10** (25%).

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