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Transition metal-catalyzed syntheses of ‘rod-like’ thioglycoside dimers

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Abstract

Using copper(I)-catalyzed Glaser reaction and palladium-catalyzed Sonogashira reaction, divalent ‘rod-like’ thiomanno-, gluco, galacto, and lactoside clusters were prepared in high yields. © 2000 Elsevier Science Ltd. All rights reserved.

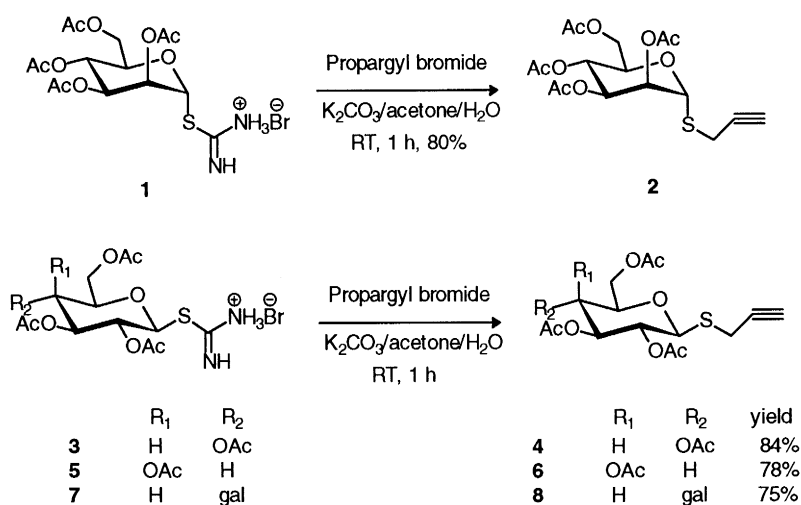
During the last 20 years, tremendous progress has been made in the area of transition metal-mediated organic syntheses. Conjugated acetylenic compounds are very valuable materials for antitumor antibiotics and multinanometer-sized molecular objects.¹ In this respect, homo-coupling between sp and sp carbon atoms and cross-coupling between sp^2 and sp carbon atoms (such as Glaser² and Sonogashira reactions³) as methods to build such compounds have gained great interest. However, much less attention has been paid to reactions with organic sulfur compounds⁴ which have long been known to act as poisons for transition metal catalysts because of their strong coordinating properties. Additionally, these useful reactions have rarely been used in carbohydrate chemistry. Some examples of these reactions have been described by Vasella et al.⁵ in the synthesis of higher oligomers of acetylenosaccharides. Moreover, no such reactions have been applied to thioglycosides, which are of special interest as enzyme inhibitors because they offer the advantage of being resistant to enzymatic hydrolysis, thus being potential inhibitors of glycosidases.⁶

Recently, molecular rods,⁷ which are considered as spacers and construction elements in giant molecules and supramolecular assemblies, have drawn widespread attention. This encouraged us to look for a facile way to build so called ‘rod-like’ carbohydrate dimers. Glaser and Sonogashira reactions make it possible to prepare such kind of sugar rods, where the acetylenic bonds of two carbohydrate moieties are connected to each other or onto an aromatic ring. Such dimers should have more rigid structures that can diminish entropic loss that is usually associated with flexible carbohydrate ligands. Herein, we report the syntheses of divalent ‘rod-like’ thioglycoside clusters by using Glaser and Sonogashira reactions.

The requisite starting material 2-propynyl thio-mannopyranoside **2** was synthesized by the alkylation of the corresponding mannopyranosyl 2-thiopseudourea hydrobromide salt **1**⁸ with 2-propynyl bromide

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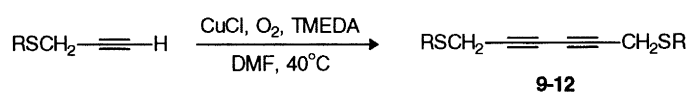
and potassium carbonate in 80% yield. Other acetylenic carbohydrates (glucose **4**, galactose **6**, and lactose **8**) were also prepared from the analogous pseudothioureas **3**, **5**, and **7**⁸ by a procedure similar to that used for **2** in good yields (Scheme 1).



Scheme 1.

Copper(I) halide-catalyzed oxidative coupling of acetylenes represents a convenient way to prepare diynes.⁹ Pyridine or tetramethylethylenediamine (TMEDA) are normally used to solubilize the copper salt and also to facilitate proton abstraction from the terminal alkyne. However, when pyridine was used in homo-coupling of acetylenic thiosugar **2**, the yield was rather low (30%) when compared to the corresponding *O*-mannopyranoside.¹⁰ Addition of more CuCl, or diazabicycloundecene (DBU) had no effect on the yield. The yield could be dramatically increased when TMEDA was used instead of pyridine. In a typical experimental procedure, in a mixture of thiosugar **2** (1 mmol), CuCl (0.3 mmol), and TMEDA (0.6 mmol) in *N,N*-dimethylformamide (10 mL) was bubbled O₂ at 40°C for 2 h. After usual work-up¹¹ and purification by silica gel column chromatography, dimer **9** was obtained in 84% yield. The structure of the product was fully confirmed by NMR and mass spectral analyses.¹¹ This procedure was successfully applied to other thiopropynyl glycosides (**4**, **6**, and **8**) to afford good yields of the corresponding dimers. The results are summarized in Table 1.

Table 1
Cu(I)-catalyzed homo-coupling reactions of 2-propynyl glycosides



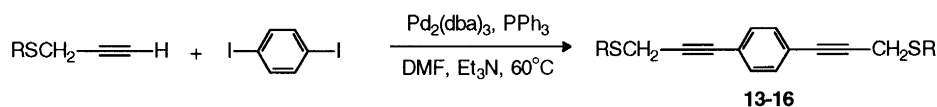
Entry	R	Reaction Time (h)	Product	Yield (%)
1	Man (2)	2	9	84
2	Glc (4)	2	10	80
3	Gal (6)	2	11	85
4	Lac (8)	3	12	82

In order to further increase the interglycosidic distance, while maintaining the rigidity within the linker, palladium-catalyzed Sonogashira cross-coupling between alkynes and aryl iodides was next considered.

The Sonogashira coupling reaction between 2-propynyl thio-mannopyranoside **2** and 1,4-diiodobenzene was investigated by using Pd₂(dba)₃, CuI, and PPh₃ in DMF and Et₃N solution (1:1, v/v) under nitrogen at room temperature for 1 h. The sulfur-containing compound **2** showed not to poison the palladium catalyst. The cross-coupling dimer **13** was formed in 82% yield. However, the oxidative homo-coupling of acetylenic mannopyranoside **2** to symmetrical diyne **9** (10% yield) was also catalyzed under such conditions. The separation of the diyne from the desired product was very difficult because of their close polarity.

To reduce the side reaction, some methods such as strict exclusion of oxygen¹² or slow addition of alkyne¹³ could be used. Copper(I) iodide was a particularly effective cocatalyst to facilitate the coupling and to allow the reaction to occur at room temperature. A likely assumption was that a copper alkynylide was formed. We thought this intermediate could cause the side reaction. So the modified Sonogashira reaction without addition of copper salt was carried out. In a typical reaction, treatment of 2-propynyl thio-mannopyranoside **2** (1 mmol) and 1,4-diiodobenzene (0.45 mmol) in a degassed solution of DMF and Et₃N (1:1, v/v) in the presence of Pd₂(dba)₃ (0.05 mmol) and PPh₃ (0.1 mmol) at 60°C under nitrogen atmosphere for 2 h afforded the desired dimer **13** in 95% yield. No diyne was found under these conditions. To demonstrate the scope of this new application, we also examined Sonogashira coupling of diiodobenzene with other carbohydrates (**4**, **6**, and **8**). All of them provided good yields of dimer **13–16** in yields ranging from 89% to 93%. The results are summarized in Table 2.

Table 2
Palladium-catalyzed Sonogashira coupling of 2-propynyl glycosides



Entry	R	Reaction Time (h)	Product	Yield (%)
1	Man (2)	2	13	95
2	Glc (4)	2	14	90
3	Gal (6)	2	15	93
4	Lac (8)	4	16	89

In conclusion, copper(I)-catalyzed Glaser reaction and palladium-catalyzed Sonogashira reaction have been applied toward the synthesis of divalent ‘rod-like’ thioglycoside clusters. The reactions are general, high yielding, and compatible with the usual acetate protecting groups.

Acknowledgements

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11. Work-up procedure: the reaction mixture was poured into water (10 mL). The mixture was extracted with dichloromethane (2×10 mL). The combined organic phases were washed with water, dried over anhydrous sodium sulfate, and concentrated under vacuum. All new compounds showed satisfactory NMR (Bruker AMX 500 MHz) and mass spectral data. Selected data for compound **9**: FAB: calcd for C₃₄H₄₂O₁₈S₂ 802.2. Found 803.2 (M+1); ¹H NMR (CDCl₃) δ 5.37 (d, 2H, J_{1,2} 1.4 Hz, H-1), 5.29 (dd, 2H, J_{2,3} 3.4 Hz, H-2), 5.25 (dd, 2H, J_{4,5} 9.7 Hz, H-4), 5.13 (dd, 2H, J_{3,4} 10.0 Hz, H-3), 4.27–4.22 (m, 4H, H-6a, H-5), 4.02 (m, 2H, H-6b), 3.42 (ABq, 2H, J 16.7 Hz, -SCH_AC≡), 3.27 (ABq, 2H, -SCH_BC≡), 2.10, 2.02, 1.98, 1.91 (s, 24H, OAc's); ¹³C NMR (CDCl₃) δ 170.4, 169.6, 169.5, 169.4 (C=O's), 81.5 (C-1), 73.6 (-C≡C), 70.1 (C-2), 69.5 (C-3), 69.3 (C-5), 67.8 (-C≡C), 66.0 (C-4), 62.1 (C-6), 20.7, 20.7, 20.6, 20.5 (OAc's), 18.9 (-CH₂C≡).
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