Tetrahedron Letters 53 (2012) 5231–5234

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# *ortho*-Alkynylphenyl thioglycosides as a new type of glycosylation donors under the catalysis of Au(I) complexes

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ARTICLE INFO

*Article history:*
Received 8 June 2012
Revised 6 July 2012
Accepted 13 July 2012
Available online 20 July 2012

*Keywords:*
Gold(I) catalyst
Glycosylation
Thioglycoside
*ortho*-Alkynylphenyl thioglycoside
Orthoester

ABSTRACT

*ortho*-Alkynylphenyl thioglycosides, prepared readily via Sonagashira coupling of *ortho*-bromophenyl thioglycosides with alkynes, could undergo glycosidation effectively under the catalysis of a gold(I) complex.



New glycosylation methods are still in great demand to tackle the synthesis of complex oligosaccharides and glycoconjugates in efficient and economical manners.[1] Recently, C–C triple bond, installed in the anomeric leaving group, has been employed as a trigger for glycosylation.[2–5] Especially, we disclosed that glycosyl *ortho*-alkynylbenzoates were excellent glycosylation donors under the catalysis of a gold(I) complex.[4] This new protocol has shown great advantages in the glycosylation of substrates susceptible to acid and electrophiles.[5] On the other hand, thioglycosides have been used as one of the most versatile types of donors in glycosylation, because they are sufficiently stable to allow various protecting group manipulations while they can be activated effectively to undergo glycosidation in the presence of many thiophilic reagents.[6] Nevertheless, the requirement of a stoichiometric amount of the electrophilic reagents as promoters turns out to be a major drawback. Thus, we envision *ortho*-alkynylphenyl thioglycosides as privileged new donors, providing they could undergo glycosidation under the mild gold(I)-catalyzed conditions while remain the stability of thioglycosides. Herein we report the preliminary results on the preparation and donor properties of *ortho*-alkynylphenyl thioglycosides.

*ortho*-Alkynylphenyl thioglycosides **2a–c** were synthesized conveniently via Sonagashira coupling of *ortho*-bromophenyl thioglycosides **1a–c** with 1-hexyne in high yields (Scheme 1).[7] *ortho*-Bromophenyl thioglycosides **1a–c** were readily prepared from the corresponding glycosyl acetates with *ortho*-bromo-thiophenol in the presence of $BF_3{\cdot}Et_2O$, or from glycosyl bromides in the presence of $K_2CO_3$ in acetone as reported.[8]

The glycosidic coupling reactions of perbenzyl *ortho*-hexynylphenyl thioglycoside **2a** with cholesterol **3a** were firstly examined in the presence of a variety of the gold(I) complexes. As shown in Table 1, with $PPh_3AuOTf$ or [Btz-Au-$PPh_3$]OTf as the catalyst (0.1 equiv), the reaction of **2a** (1.2 equiv) and **3a** (1.0 equiv) in the presence of 4 Å molecular sieves in dry $CH_2Cl_2$ proceeded smoothly, providing the desired glycoside **4** in >90% yields within 30 min (entries 3 and 4). However, similar reactions with $PPh_3AuNTf_2$ or $PPh_3AuSbF_6$ as the catalyst led to the coupled glycoside **4** in only moderate yields, in that *C*-glycoside **5**[9] was isolated unexpectedly in 30% and 46% yields, respectively (entries 1 and 2). The formation of **5** could be explained by a [1,3]-sigmatropic rearrangement of a benzothiophene sulfonium ion intermediate (Fig. 1).[10]

With [Btz-Au-$PPh_3$]OTf as the catalyst, the coupling of *ortho*-hexynylphenyl thioglycoside **2a** with 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranoside (**3b**) and *n*-pentenol (**3c**) under similar conditions provided the corresponding glycosides **6** and **7** in excellent yields (Table 2 entries 1 and 2). Expectedly, no $\alpha/\beta$ selectivity was attained in the absence of a neighboring participating group (in donor **2a**). With peracetyl *ortho*-hexynylphenyl thioglucopyranoside **2b** as the donor, the reactions with **3a–c** under similar conditions, however, led to a mixture of the corresponding β-glycoside and orthoester in favor of the latter (entries 3–5). The coupling of *ortho*-hexynylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside **2c** with cholesterol **3a** led to the desired

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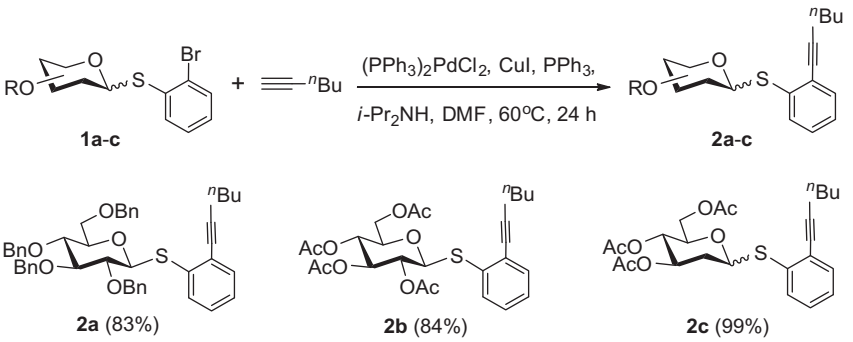
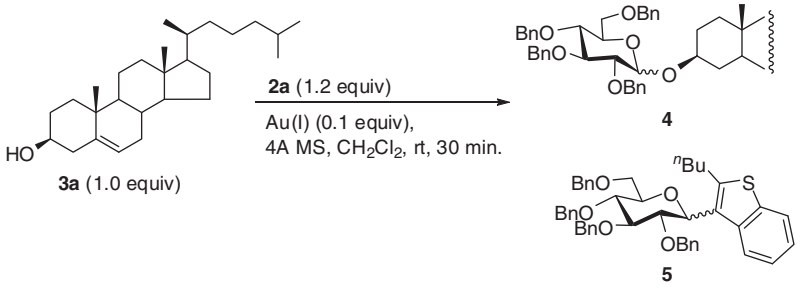
http://dx.doi.org/10.1016/j.tetlet.2012.07.059




**Scheme 1.** Preparation of *ortho*-hexynylphenyl thioglycosides **2a–c**.

**Table 1**
Coupling of *ortho*-hexynylphenyl thioglycoside **2a** with cholesterol **3a** under the catalysis of Au(I) complexes




| Entry | Au(I) complex | **4** (Yield; $\alpha/\beta$ ratio[a]) | **5** (Yield; $\alpha/\beta$ ratio[a]) |
|---|---|---|---|
| 1 | $PPh_3AuNTf_2$ | 66% (1:1) | 30% (1:1) |
| 2 | $PPh_3AuSbF_6$ | 48% (1:1) | 46% (1:1) |
| 3 | $PPh_3AuOTf$ | 95% (1:1) | Trace |
| 4 | [Btz-Au-$PPh_3$]OTf | 90% (1:1) | Trace |

[a] The $\alpha/\beta$ ratio was determined by isolated yields. Btz = benzotriazole.

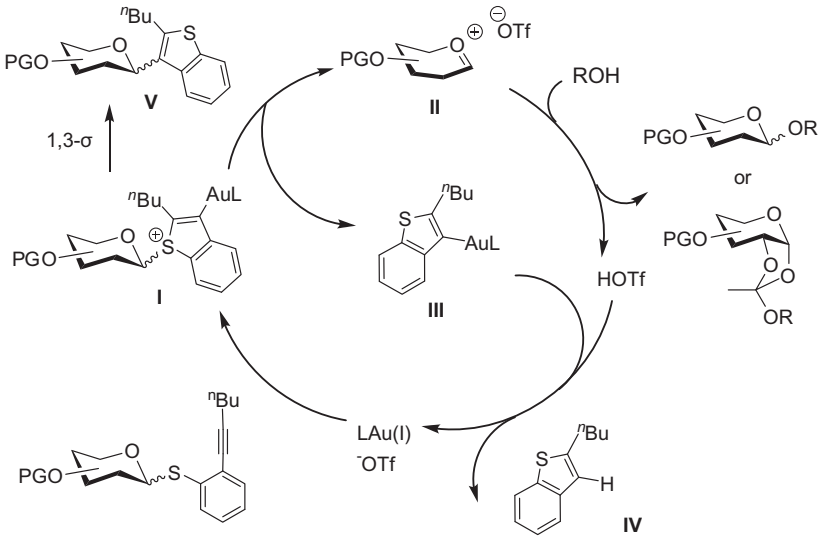
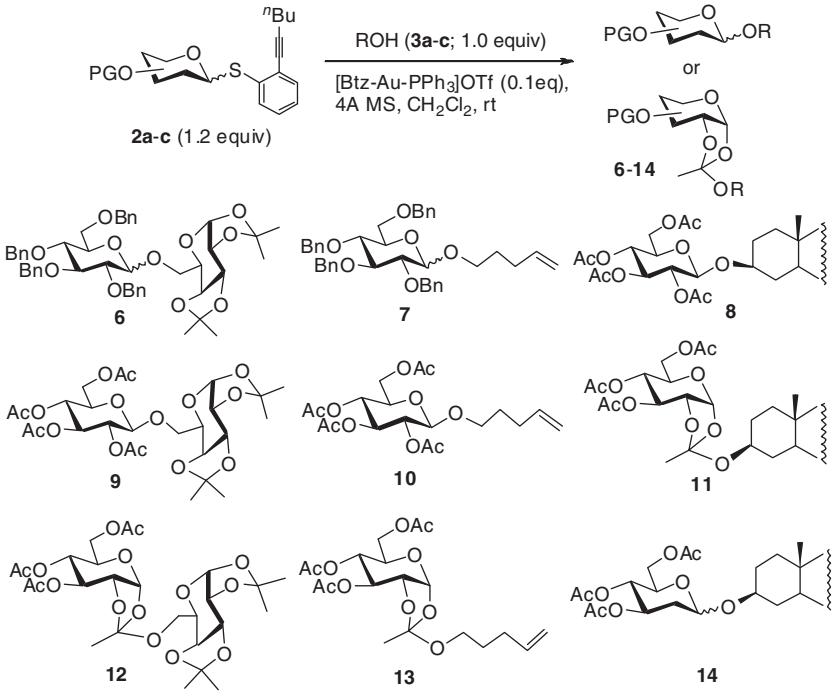



**Figure 1.** Mechanistic rational for the present glycosidic coupling of *ortho*-hexynylphenyl thioglycosides with alcohols under the catalysis of [Btz-Au-$PPh_3$]OTf.

glycoside **14** nearly quantitatively, albeit in moderate α/β selectivity (entry 6).

A mechanistic rational for the present glycosylation reaction is depicted in Figure 1. Thus, activation of the C–C triple bond positioned in the *ortho*-alkynylphenyl thioglycoside with a gold(I) complex leads to the formation of glycosyl benzothiophene sulfonium ion **I**. Departure of benzothiophene-3-yl-gold(I) complex **III** from **I** leaves behind the glycosyl oxocarbenium ion **II**, which can undergo glycosidation or orthoester formation.[11] Protonolysis of the Au–C bond in **III** regenerates the Au(I) catalyst;[12] the consumption

**Table 2**
Glycosidic coupling of *ortho*-hexynylphenyl thioglycosides (**2a–c**) with alcohols (**3a–c**) under the catalysis of [Btz-Au-$PPh_3$]OTf[a]




| Entry | Donor | Acceptor | Product | Time | Yield (%) | Ratio ($\alpha/\beta$) |
|---|---|---|---|---|---|---|
| 1 | **2a** | **3b** | **6** | 30 min | 96 | 1:1.5[c] |
| 2 | **2a** | **3c** | **7** | 30 min | 96 | 1:1.2[c] |
| 3 | **2b** | **3a** | **8**/**11** = 7:92[b] | 30 min | 99 | 0:1 |
| 4 | **2b** | **3b** | **9**/**12** = 11:78[c] | 30 min | 99 | 0:1 |
| 5 | **2b** | **3c** | **10**/**13** = 9:90[c] | 30 min | 99 | 0:1 |
| 6 | **2c** | **3a** | **14** | 2 h | 99 | 2.9:1[c] |

[a] For a typical procedure: To a stirred mixture of thioglucoside **2a** (86 mg, 0.12 mmol), 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranoside **3b** (26 mg, 0.10 mmol), and 4Å MS in $CH_2Cl_2$ (2 mL) at rt was added [Btz-Au-$PPh_3$]OTf (7 mg, 0.01 mmol). After stirring at rt for 0.5 h (as monitored by TLC), the mixture was filtered through a Celite and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 8:1) to provide glycoside **6** (75 mg, 96%, $\alpha/\beta$ 1:1.5).
[b] The ratio was determined by isolated yields.
[c] The ratio was determined by $^1$H NMR spectroscopic measurement of the crude products.

of the proton (from alcohol ROH) ensures the inherent neutral conditions for the reaction.[4d] Alternatively, [1,3]-sigmatropic rearrangement of the glycosyl benzothiophene sulfonium intermediate **I** followed by protodeauration leads to the benzothiophene 3C-glycoside (e.g., **5**).[10]

In summary, we have shown that *ortho*-alkynylphenyl thioglycosides can be prepared easily and can be employed as glycosyl donors for glycosidation under the catalysis of [Btz-Au-$PPh_3$]OTf or $Ph_3PAuOTf$. The scope and applications of this new glycosylation protocol is a subject of further studies.

## Acknowledgments

This work was financially supported by the Ministry of Science and Technology of China (2012ZX09502-002) and the National Natural Science Foundation of China (20932009 and 20921091).

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7. A general procedure for the preparation of *ortho*-hexynylphenyl thioglycosides. A mixture of **1a** (356 mg, 0.5 mmol), $(PPh_3)_2PdCl_2$ (70 mg, 0.1 mmol), CuI (19 mg, 0.1 mmol), $PPh_3$ (52 mg, 0.2 mmol), and *i*-$Pr_2NH$ (2 mL) in DMF (4 mL), after carefully degassed, was stirred for 30 min under $N_2$ at room temperature before 1-hexyne (0.3 mL, 2.5 mmol) was introduced. After stirring at 60 °C for 24 h, the resulting mixture was diluted with $CH_2Cl_2$. The organic phase was washed with saturated $NH_4Cl$ and saturated $NaHCO_3$, respectively, and was then dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 15:1) to afford **2a** (295 mg, 83%) as a yellow solid: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.70–7.56 (m, 1H), 7.45–7.14 (m, 21H), 7.09 (dd, $J$ = 5.6, 3.6 Hz, 2H), 4.94 (dd, $J$ = 14.2, 10.4 Hz, 2H), 4.84 (dd, $J$ = 10.4, 4.8 Hz, 3H), 4.70 (d, $J$ = 10.0 Hz, 1H), 4.64–4.47 (m, 3H), 3.85–3.77 (m, 1H), 3.78–3.51 (m, 5H), 2.39 (t, $J$ = 7.0 Hz, 2H), 1.59–1.39 (m, 4H), 0.87 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.6, 138.4, 138.2, 138.1, 137.7, 132.5, 128.8, 128.6, 128.6, 128.5, 128.3, 128.1, 127.9, 127.83, 127.80, 127.7, 126.0, 124.2, 97.3, 86.8, 86.0, 81.1, 79.2, 78.6, 77.9, 76.0, 75.6, 75.2, 73.6, 69.2, 30.8, 22.2, 19.5, 13.7; HR-ESIMS ($m/z$) calcd for $C_{46}H_{48}O_5S$ $[M+Na]^+$ 735.3115, found 735.3124. Compound **2b**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.48 (d, $J$ = 7.6 Hz, 1H), 7.39 (d, $J$ = 7.2 Hz, 1H), 7.25–7.13 (m, 2H), 5.26 (t, $J$ = 9.2 Hz, 1H), 5.11 (t, $J$ = 9.6 Hz, 2H),

4.93 (d, *J* = 10.2 Hz, 1H), 4.25 (dd, *J* = 12.2, 5.6 Hz, 1H), 4.14 (d, *J* = 12.2 Hz, 1H), 3.83–3.70 (m, 1H), 2.45 (t, *J* = 7.0 Hz, 2H), 2.07 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.67–1.56 (m, 2H), 1.51 (dt, *J* = 14.7, 7.3 Hz, 2H), 0.96 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.7, 170.3, 169.5, 169.3, 135.6, 132.9, 130.1, 128.2, 127.1, 125.6, 97.4, 84.9, 78.4, 75.9, 74.1, 70.0, 68.5, 62.43, 30.8, 22.2, 20.83, 20.79, 20.73, 20.71, 19.5, 13.7; HR-ESIMS (*m*/*z*) calcd for $C_{26}H_{32}O_9S$ $[M+Na]^+$ 543.1659, found 543.1673. Compound **2c–β**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.49 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.39 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.24–7.14 (m, 2H), 5.07–4.98 (m, 3H), 4.25 (dd, *J* = 12.2, 5.8 Hz, 1H), 4.12 (dd, *J* = 12.1, 2.4 Hz, 1H), 3.71 (ddd, *J* = 9.6, 5.6, 2.4 Hz, 1H), 2.53 (ddd, *J* = 12.8, 5.2, 2.0 Hz, 1H), 2.47 (t, *J* = 7.0 Hz, 2H), 2.10–2.02 (m, 9H), 1.96 (dd, *J* = 18.3, 6.4 Hz, 1H), 1.61 (ddd, *J* = 13.8, 9.2, 4.8 Hz, 3H), 1.57–1.45 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.8, 170.4, 169.9, 136.2, 132.8, 129.9, 128.1, 126.9, 125.2, 97.3, 80.9, 78.5, 76.1, 71.9, 69.1, 62.9, 36.3, 30.8, 22.1, 21.0, 20.89, 20.86, 19.4, 13.7. Compound **2c–α**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.52 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.40 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.24–7.14 (m, 2H), 5.85 (d, *J* = 5.6 Hz, 1H), 5.38 (ddd, *J* = 11.6, 9.2, 5.4 Hz, 1H), 5.03 (t, *J* = 9.6 Hz, 1H), 4.53 (ddd, *J* = 10.1, 4.8, 2.1 Hz, 1H), 4.32 (dd, *J* = 12.4, 4.8 Hz, 1H), 3.96 (dd, *J* = 12.4, 2.0 Hz, 1H), 2.48 (dd, *J* = 13.6, 6.6 Hz, 3H), 2.27 (ddd, *J* = 13.6, 12.0, 6.0 Hz, 1H), 2.14–1.96 (m, 11H), 1.70–1.59 (m, 2H), 1.57–1.46 (m, 3H), 0.97 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.7, 170.1, 170.0, 136.1, 132.9, 130.5, 128.2, 126.9, 125.8, 96.8, 81.9, 78.7, 69.7, 69.5, 69.0, 62.3, 35.5, 30.8, 22.1, 21.0, 20.8, 19.4, 13.7.

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9. *Compound **5–β***: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.10 (bs, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.44–6.98 (m, 20H), 6.94–6.85 (m, 2H), 5.02–4.87 (m, 3H), 4.76–4.57 (m, 3H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.26 (d, *J* = 10.4 Hz, 1H), 4.15–3.75 (m, 5H), 3.65 (dd, *J* = 26.8, 10.0 Hz, 2H), 3.07–2.89 (m, 1H), 2.78 (bs, 1H), 1.74–1.60 (m, 2H), 1.45–1.32 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); HR-ESIMS (*m*/*z*) calcd for $C_{46}H_{48}O_5S$ $[M+Na]^+$ 735.3115, found 735.3110. Compound **5–α**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.00–7.89 (m, 1H), 7.78–7.69 (m, 1H), 7.41-7.17 (m, 18H), 7.15–7.05 (m, 4H), 6.72 (d, *J* = 7.2 Hz, 2H), 5.50 (d, *J* = 2.4 Hz, 1H), 4.79 (d, *J* = 11.4 Hz, 1H), 4.63 (d, *J* = 11.4 Hz, 1H), 4.60–4.50 (m, 3H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.28–4.18 (m, 1H), 4.15–4.05 (m, 2H), 4.00–3.92 (m, 2H), 3.78 (d, *J* = 3.2 Hz, 2H), 3.70 (t, *J* = 2.6 Hz, 1H), 2.91 (dt, *J* = 15.4, 7.8 Hz, 1H), 2.78 (dt, *J* = 15.2, 7.8 Hz, 1H), 1.67–1.48 (m, 2H), 1.351.25 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 143.7, 140.0, 138.7, 138.6, 138.3, 138.2, 137.7, 128.6, 128.5, 128.4, 128.23, 128.17, 128.12, 128.03, 127.95, 127.8, 127.63, 127.57, 124.2, 123.7, 123.3, 121.7, 82.6, 80.8, 76.6, 74.3, 73.6, 72.9, 72.7, 71.3, 70.3, 34.1, 29.1, 22.8, 14.0; HR-ESIMS (*m*/*z*) calcd for $C_{46}H_{48}O_5S$ $[M+Na]^+$ 735.3115, found 735.3100.
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12. *Benzothiophene **IV***: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.76 (d, *J* = 8.0 Hz,1H),7.65(d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 1H), 6.99 (s, 1H), 2.90 (t, *J* = 7.4 Hz, 1H), 1.73 (q, *J* = 14.8, 7.2 Hz, 2H), 1.40 (m, 2H), 0.95(t, *J* = 7.6 Hz, 3H).