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Synthesis of thio- and selenoglycosides by cleavage of dichalconides in the presence of zinc/zinc chloride and reaction with glycosyl bromides☆

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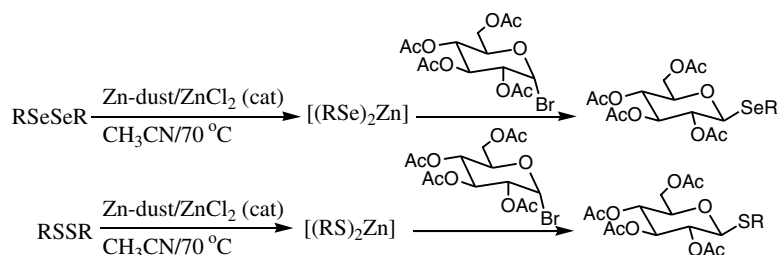
Abstract—A convenient odorless methodology has been devised for the preparation of 1,2-*trans*-thio- and selenoglycosides through zinc-mediated cleavage of disulfides and diselenides and reaction of the thiolate and selenides formed in situ with glycosyl bromides. The yields were excellent in all cases.
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In the last decade, thiosugars have widely been used in biochemical and structural investigations of glycosidases due to their close structural similarity to the natural *O*-glycosides.[1–5] Thioglycosides have found versatile applications in the field of carbohydrate chemistry as very effective and stable glycosyl donors.[6–9] They are also useful intermediates for the preparation of glycosyl fluorides,[10] sulfoxides and sulfones, which are used as glycosyl donors for O- and C-glycosylation.[11–14] The ongoing progress in the syntheses of complex oligosaccharides has been greatly related to the development of newer glycosylation methods exploiting thioglycosides as glycosyl donors. Obviously, there are a number of reports in the literature for the preparation of thioglycosides. The most often employed protocol for thioglycoside preparation is the treatment of glycosyl acetates with alkyl/aryl thiols or alkyl/aryl thiotrimethylsilanes in the presence of a Lewis acid.[15–20] These methods suffer from a number of drawbacks, such as, the necessity of working with malodorous and toxic thiols and formation of anomerized products. Another method for the preparation of 1,2-*trans*-thioglycosides uses *S*-glycosyl isothiouronium salts generated from glycosyl halides as the starting compounds.[21,22] Although this method gives a comparatively odorless protocol, it requires pre-generation of *S*-glycosyl isothiouronium salts from relatively unstable glycosyl halides and in general this method does not allow for the preparation of aryl thioglycosides.

Scheme 1.

Table 1. Zinc mediated cleavage of dichalconides and reaction with glycosyl bromides towards the formation of 1,2-*trans*-thio- and selenoglycosides

Entry	Dichalconides	Glycosyl bromides **1**	Products **2**	Time[a] (min)	Temperature (°C)	Yield[b] (%)	Ref.
a	PhSSPh			25	70	92	35
b	PhSSPh			30	70	90	36
c	PhSSPh			20	70	88	37
d	PhSSPh			45	70	92	38
e	PhSSPh			25	70	85	39
f	(p-CH$_3$C$_6$H$_4$)$_2$S$_2$			25	70	90	40
g	(p-CH$_3$C$_6$H$_4$)$_2$S$_2$			30	70	92	40
h	(p-CH$_3$C$_6$H$_4$)$_2$S$_2$			20	70	87	40
i	(p-CH$_3$C$_6$H$_4$)$_2$S$_2$			25	70	85	40
j	(C$_6$H$_5$CH$_2$)$_2$S$_2$			25	70	85	41
k	(C$_6$H$_5$CH$_2$)$_2$S$_2$			25	70	90	41
l	(C$_6$H$_5$CH$_2$)$_2$S$_2$			25	70	90	42
m	(C$_6$H$_5$CH$_2$)$_2$S$_2$			45	70	86	—
n	(p-NO$_2$C$_6$H$_4$CH$_2$)$_2$S$_2$			40	70	92	—
o	(p-NO$_2$C$_6$H$_4$CH$_2$)$_2$S$_2$			40	70	95	43
p	PhSeSePh			45	70	92	26

Table 1 (continued)

Entry	Dichalconides	Glycosyl bromides **1**	Products **2**	Time[a] (min)	Temperature (°C)	Yield[b] (%)	Ref.
q	PhSeSePh			45	70	90	—
r	PhSeSePh			40	70	90	23
s	PhSeSePh			45	70	88	26
t	PhSeSePh			40	70	85	26
u	PhSSPh			60	70	56[c]	46
v	PhSeSePh			60	70	50[c]	47

[a] After formation of the thiolate or selenide anion.
[b] Isolated yield.
[c] With some of the β-isomer (~10%).

As in the case of thioglycosides, selenoglycosides have also been used in carbohydrate chemistry for the preparation of oligosaccharides, C-glycosides, glycoconjugates, etc.[23–25] Selenoglycosides can be selectively activated in the presence of thioglycosides, which make them attractive in oligosaccharide synthesis.[26] In general, selenoglycosides are prepared by treating halides with selenium under sodium borohydride reduction conditions[27,28] or by treating glycosyl acetate with arylselenol derived from the hypophosphorus acid reduction of diphenyldiselenide in the presence of BF₃·OEt₂.[26,29–31] In both the cases, there are similar drawbacks as in the case of thioglycoside preparation including the use of malodorous reagents and incompatibility of base labile protecting groups under sodium borohydride reaction conditions. Therefore, there is an urgent need to develop an odorless, convenient and general reaction protocol for the preparation of thio- and selenoglycosides. Organometallic reactions have attracted considerable attention in synthetic organic chemistry.[32,33] Recently, we noted a report on the preparation of diorganyl selenides using zinc mediated cleavage of diaryl diselenides followed by reaction of the selenide anions formed in situ with alkyl halides.[34] We envisioned that a similar zinc mediated cleavage of disulfides and diselenides and reaction of the thiolate and selenide anions formed in situ with glycosyl bromide could furnish thio- and selenoglycosides under generalized one-pot reaction conditions thereby avoiding the use of any malodorous reagents. In this letter, we wish to report our findings on the treatment of zinc with disulfides/diselenides followed by reaction of the thiolate/selenide anions formed

in situ with glycosyl bromides to furnish thio- and selenoglycosides via an odorless, generalized reaction with high stereoselectivity (Scheme 1).

In a first set of experiments, diphenyl disulfide was treated with an equimolar quantity of zinc-dust in CH₃CN at 70 °C for several hours to generate zinc thiolate but no reaction occurred even after 24 h. In order to activate the zinc, a catalytic amount of fused ZnCl₂ was added to the reaction mixture, which was placed in a preheated oil bath at 70 °C. As expected the reaction started immediately and the reaction mixture became turbid in 45 min indicating the formation of zinc thiolate. To the turbid reaction mixture, a solution of acetobromo-D-glucose (1.5 equiv) in CH₃CN was added and the reaction was allowed to stir at the same temperature. After 20 min, TLC showed complete consumption of acetobromo-D-glucose and formation of a new compound corresponding to phenyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside. After further experimentation, by varying the quantity of zinc-dust from 0.5 to 1.5 equiv with respect to diphenyldisulfide, it was observed that initial reaction of an equimolar mixture of diphenyldisulfide and zinc-dust in the presence of a catalytic quantity of fused ZnCl₂ followed by addition of glycosyl bromide (2.0 equiv) furnished 1,2-trans-thioglycosides in excellent yields. Similar reaction conditions were applied for the preparation of 1,2-trans-selenoglycosides using diphenyl diselenides (Scheme 1). In the case of diselenide, it took slightly longer to form the selenide in comparison to disulfide cleavage. The findings on the cleavage of disulfides and diselenides with zinc-dust

and concomitant reaction of the thiolates and selenide anions formed, in situ with a variety of glycosyl bromides towards the formation of thio- and selenoglycosides are listed in Table 1. It is worth mentioning that the procedure can be employed for the preparation of sialic acid 2-thio- and 2-selenoglycosides. The use of other common solvents; for example, CH_2Cl_2, $CHCl_3$, THF, DMF and nitromethane did not produce the same results as with acetonitrile.

A typical experimental procedure is as follows: To a solution of diaryl or diaralkyldisulfide or diaryl diselenide (1.0 mmol) in CH_3CN (5.0 ml) was added zinc-dust (66.0 mg, 1.0 mmol) followed by fused $ZnCl_2$ ($\sim$25 mg). The reaction mixture was placed in a pre-heated oil bath at 70 °C for 45 min during which time the reaction mixture became turbid indicating the formation of zinc-thiolate or selenide. A solution of per-O-acetylated glycosyl bromide (2.0 mmol) in CH_3CN (5.0 ml) was added to the turbid reaction mixture which was then stirred at 70 °C for the appropriate time as indicated in Table 1. After completion of the reaction (TLC; hexane/EtOAc 1:1), the reaction mixture was concentrated under reduced pressure and the crude mass was dissolved in CH_2Cl_2 (25.0 ml). The organic layer was washed with aq $NaHCO_3$ solution and water dried (Na_2SO_4) and evaporated to dryness. The crude products were purified over SiO_2 using hexane–EtOAc as eluant to furnish pure aryl and aralkyl thio- and selenoglycosides, the structures of which were confirmed from their NMR and mass spectra. All the known compounds prepared gave acceptable ^{1}H NMR and ^{13}C NMR spectra that matched the reported data. It is noteworthy that only 1,2-trans-thio- and selenoglycosides were formed under the reaction conditions without formation of any anomerized product.[44] During the preparation of this manuscript, a report appeared in the literature using $RuCl_3$ catalyzed cleavage of diselenides in the presence of zinc.[45] However, the present protocol should be considered as the cheaper alternative as well as a general method for the preparation of thio- and selenoglycosides in high yield.

In summary, an odorless general methodology has been developed for the preparation of a series of 1,2-trans-thio- and selenoglycosides through zinc mediated reduction of diaryl and diarylalkyl disulfides and diselenides followed by reaction of glycosyl bromides with the thiolates and selenides generated in situ. The fast, stereoselective formation of 1,2-trans thio- and selenoglycosides without formation of anomerized products and avoiding the use of toxic and malodorous thiols and selenols under neutral reaction conditions makes this protocol better than existing methodologies in this area.

Acknowledgements

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44. **Spectral data for compounds, which are not reported earlier**: *Benzyl 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside* (**2m**): Yield 86%; White solid, mp 138.2 °C; $[\alpha]_D^{25}$ +6.6 (*c* 1.5, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz): $\delta = 7.83$–7.74 (m, 4H, aromatic protons), 7.28–7.16 (m, 5H, aromatic protons), 5.79 (t, $J = 9.9$ Hz each, 1H, H-3), 5.30 (d, $J = 10.5$ Hz, 1H, H-1), 5.16 (t, $J = 9.6$ Hz, 1H, H-4), 4.42 (t, $J = 9.9$ Hz, 1H, H-2), 4.30 (dd, $J = 12.3$ and 4.3 Hz, 1H, H-6$_a$), 4.13 (d, $J = 12.6$ Hz, 1H, H-6$_b$), 3.86 (Abq, $J = 12.6$ Hz each, 2H, SCH$_2$), 3.6–3.5 (m, 1H, H-5), 2.12, 2.04, 1.85 (3s, 9H, 3COCH$_3$); ^{13}C NMR (CDCl$_3$, 50 Hz): $\delta = 171.0$, 170.4, 169.8, 167.7 (2C), 137.1–124.1 (aromatic carbons), 80.7, 76.2, 71.8, 69.2, 62.6, 53.9, 34.6, 21.1, 21.0, 20.8; IR (KBr): 1757, 1713, 1379, 1252, 1222, 1092, 1038, 720 cm^{-1}; ESI-MS: $m/z = 564$ [M+Na]. Anal. Calcd for C$_{27}$H$_{27}$NO$_9$S (541): C, 59.88; H, 5.03%. Found: C, 59.70; H, 5.25%.

p-Nitrobenzyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (**2n**): Yield 92%; Yellow oil. $[\alpha]_D^{25}$ −37 (*c* 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz): $\delta = 8.18$ (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.5$ Hz, 2H), 5.16 (t, $J = 9.0$ Hz each, 1H), 5.10–5.0 (m, 2H), 4.38 (d, $J = 8.0$ Hz, 1H), 4.27 (dd, $J = 9.0$ and 4.5 Hz, 1H), 4.14 (dd, $J = 12.0$ and 3.8 Hz, 1H), 4.0 (dd, $J = 13.2$ Hz each, 2H), 3.73–3.65 (m, 1H), 2.10, 2.05, 2.03, 2.01 (4s, 12H); ^{13}C NMR (CDCl$_3$, 50 Hz): δ 170.7, 170.3, 169.7 (2C), 147.6, 145.3, 130.3 (2C), 124.1 (2C), 82.2, 76.4, 73.9, 70.1, 68.6, 62.5, 33.1, 21.0, 20.9, 20.8 (2C); IR (Neat): 1752, 1522, 1348, 1225, 1042 cm^{-1}; ESI-MS: m/z 522 [M+Na]. Anal. Calcd for C$_{21}$H$_{25}$NO$_{11}$S (499): C, 50.50; H, 5.04%. Found: C, 50.25; H, 5.30%.

Phenyl 2, 3,4,6-tetra-O-acetyl-1-seleno-β-D-galacto-pyranoside (**2q**): Yield 90%; Oil; $[\alpha]_D^{25}$ +7.2 (*c* 1.5, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz): $\delta = 7.63$ (d, $J = 7.2$ Hz, 2H, aromatic protons), 7.33–7.26 (m, 3H, aromatic protons), 5.40 (d, $J = 2.7$ Hz, 1H, H-4), 5.26 (t, $J = 9.6$ and 9.9 Hz, 1H, H-2), 5.02 (dd, $J = 9.6$ and 3.3 Hz, 1H, H-3), 4.90 (d, $J = 9.9$ Hz, 1H, H-1), 4.19–4.06 (m, 2H, H-6$_{ab}$), 3.92–3.88 (m, 1H, H-5), 2.09, 2.07, 2.03, 1.96 (4s, 12H, 4COCH$_3$); ^{13}C NMR (CDCl$_3$, 50 Hz): $\delta = 170.7$, 170.5 (2C), 169.9, 135.2–128.1 (aromatic carbons), 82.2, 75.8, 72.1, 68.4, 67.7, 62.0, 21.3, 21.1, 20.9 (2C); IR (Neat): 2926, 1748, 1654, 1370, 1225, 1052, 771 cm^{-1}; ESI-MS: $m/z = 511$ [M+Na]. Anal. Calcd for C$_{20}$H$_{24}$O$_9$Se (488): C, 49.29; H, 4.96%. Found: 49.14; H, 5.15%.

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