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Thiazole-Based Synthesis of *C*-Glycosyl Aldehydes

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Key Words: Sugar lactones, sugar aldehydes, *C*-glycosides, thiazole, *C*-glycosidation, formylation

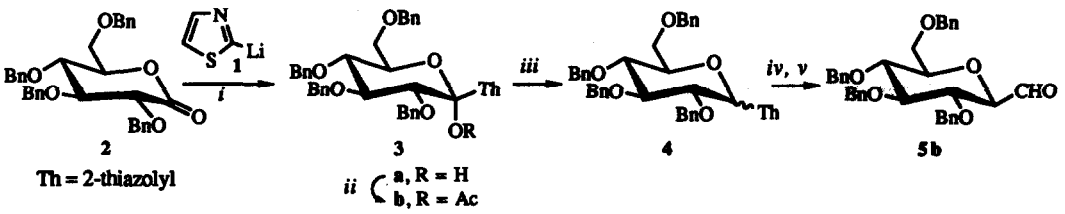
Abstract: *The formylation at the anomeric carbon of the model sugars 2,3,4,6-tetra-O-benzyl-D-glucopyranose and 2,3:5,6-di-O-isopropylidene-D-mannofuranose is carried out by addition of 2-lithiothiazole to the corresponding lactones followed by reductive dehydroxylation and thiazole to formyl deblocking.*

The stereocontrolled installation of a formyl group at the anomeric center of carbohydrates is highly relevant to the synthesis of complex *C*-glycosides[1] (*C*-disaccharides, *C*-glycoproteins, *C*-glycolipids), i.e. stable analogs of naturally occurring sugars which are the subject of increasing interest in carbohydrate chemistry and biochemistry. Crucial to the development of an efficient formylating methodology is the choice of a suitable masked formyl group equivalent. The allenyl group that has been previously employed for that purpose[2] appears to present several disadvantages such as the long reaction time and the very expensive reagent (propargyl trimethylsilane) for its installation and the troublesome cleavage by ozonolysis.[2c] On the other hand the thiazole ring has recently emerged from this[3] and other laboratories[4] work as one of the most convenient formyl group equivalent[5] since it can be incorporated in different types of reagents and easily installed in a variety of substrates, it is stable to a wide range of reaction conditions and is cleaved to aldehyde under mild and neutral conditions. We report herein a thiazole-based synthesis of *C*-glycosyl aldehydes starting from sugar lactones.[6]

The addition of organometallic reagents to protected furanose and pyranose lactones followed by reductive dehydroxylation with silanes has been previously employed to prepare *C*-glycosides.[7] In a similar way, the reaction of 2-lithiothiazole (2-LTT, **1**), generated in situ from 2-bromothiazole and butyl lithium at -78 °C, with tetrabenzylgluconolactone[8] (**2**) afforded exclusively the 2,3,4,6-tetra-*O*-benzyl-β-1-*C*-(2-thiazolyl)-D-glucopyranose[9] (**3a**) in 80 % isolated yield (Scheme 1). Attempts to remove the hydroxyl group by either radical or polar reductive methods gave unsatisfactory results. Hence, anomeric activation was accomplished by conversion (quantitative) of **3a** into the acetyl derivative **3b**. The reduction of this compound with triethylsilane (10 eq.) in the presence of 2.8 eq. of trimethylsilyl triflate (TMSOTf) at room temperature for 15 min afforded a 1 : 1 mixture of α- and β–linked 2-thiazolyl *C*-glycosides **4** (94 %).[10] The lack of diastereofacial selectivity is very likely due to the relatively high temperature that is required for this reaction can proceed to completion.[11] The application of the standard thiazolyl-to-formyl deblocking protocol (*N*-methylation, reduction, hydrolysis)[12] to **4** afforded a 1:1 mixture of α and β *C*-glycosyl aldehydes **5**. Epimerization of the α- to the more stable β-linked isomer was carried out under mild basic conditions.[2c] Hence, the treatment of the above mixture with a 10 % solution of Et_3N in 1:1 *i*-PrOH-CH_2Cl_2 afforded an equilibrium ratio of α/β isomers of

1:20, thus allowing the isolation of the β-formyl glycoside **5b** in 60 % yield.[13] As reported by others[2c], we also observed in this reaction a by-product (3-10 %) arising from β-elimination of the benzyloxy group at the C-2 of the sugar.

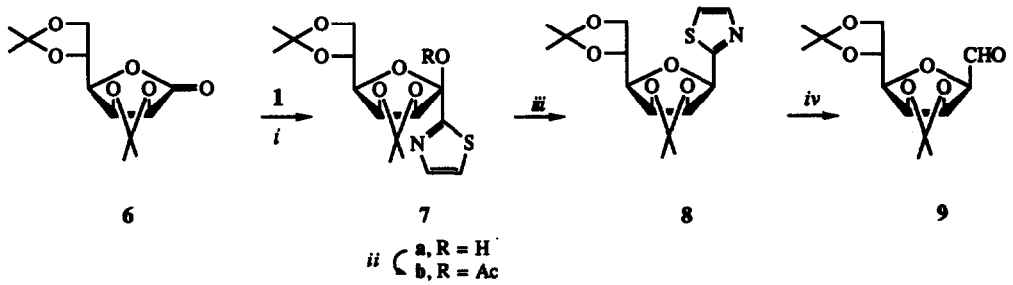
Scheme 1



Reagents and conditions : *i*, THF, -78°C, 1 h; *ii*, Et_3N, Ac_2O, rt, overnight; *iii*, CH_2Cl_2, Et_3SiH (10 eq.), TMSOTf (2.8 eq.), rt, 15 min; *iv*, 1) CH_3CN, MeOTf, 10 min, 2) MeOH, $NaBH_4$, 10 min, 3) CH_3CN-H_2O, $HgCl_2$, 10 min; *v*, *i*-PrOH-CH_2Cl_2, 10% Et_3N, 24 h.

The application of the above methodology to the 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone[14] (**6**) was explored. The addition of 2-LTT (**1**) in THF at -78°C afforded the single diastereomeric hemiketal α-2-thiazolyl mannofuranose[15] **7a** which was isolated in 76 % yield (Scheme 2). The structure of this product was assigned based on the chemical shift value of the hydroxyl group at very low field (δ 5.44 ppm) due to hydrogen bonding with the vicinal O-2 atom. The activation of **7a** as the *O*-acetyl derivative **7b** and the reductive dehydroxylation with Et_3SiH in the presence of TMSOTf afforded exclusively the β-linked 2-thiazolyl *C*-glycoside **8**[16] (92 %) from which the corresponding *C*-glycosyl aldehyde **9**[17] was generated in good yield (78 %). The observed selectivity leading to **8** is consistent with hydride attack to the less hindered face opposite to the acetonide protecting group of an oxycarbenium ion. These results indicate that the methodology is compatible with the presence of rather labile acetonide protecting groups in the sugar.

Scheme 2



Reagents and conditions : see Scheme 1.

In conclusion, we have disclosed a thiazole-based route to two model *C*-pyranosyl and *C*-furanosyl aldehydes. The extension of this methodology to other sugar aldehydes and their homologation to target *C*-glycosides, mainly *C*-disaccharides and *C*-glycosyl amino acids, are under active investigation in our laboratory.

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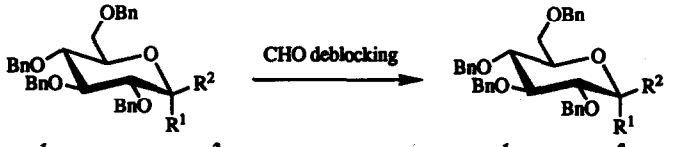
9. The configuration was *inter alia* assigned on the basis of the characteristic chemical shift of H-3 (See Nicotra, F. ; Panza, L.; Russo, G. *Tetrahedron Lett.* **1991**, *32*, 4035). **3a**: mp 96°C (hexane-ethyl acetate); $[\alpha]_D$ +10.8 ($CHCl_3$) ; ^1H NMR (300 MHz, $CDCl_3$), selected data δ : 3.72 (dd, 1 H, $J_{6,5}$ = 1.6, $J_{6,6'}$ = 11.6 Hz, H-6), 3.83 (dd, 1 H, $J_{6',5}$ = 4.2 Hz, H-6'), 3.86 (dd, 1 H, $J_{4,3}$ = 9.0, $J_{4,5}$ = 10.0 Hz, H-4), 4.01 (d, 1 H, $J_{2,3}$ = 9.0 Hz, H-2), 6.08 (dd, 1 H, H-3), 4.16-4.24 (ddd, 1 H, H-5), 4.58 (s, 1 H, O*H*), 7.4 and 7.8 (2 d, 2 H , *J*= 3.2, thiazole).
10. Anomerically pure **4a** and **4b** were isolated by flash chromatography (30:1 toluene-acetone).
    4a: syrup, $[\alpha]_D$ +38.3 ($CHCl_3$) ; ^1H NMR (300 MHz, $CDCl_3$) δ : 3.66 (dd, 1 H, $J_{5,6}$ = 2.0, $J_{6,6'}$ = 10.6 Hz, H-6), 3.73 (dd, 1 H, $J_{6',5}$ = 3.3 Hz, H-6'), 3.79 (dd, 1 H, $J_{4,3}$ = 8.7, $J_{4,5}$ = 10.0 Hz, H-4), 3.96 (ddd, 1 H, H-5), 4.03 (dd, 1 H, $J_{2,1}$ = 6.0, $J_{2,3}$ = 8.7 Hz, H-2), 4.3 (dd, 1 H, H-3), 4.47 and 4.62 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.50 and 4.81 (2 d, 2 H, *J* = 10.7 Hz, PhCH_2), 4.68 and 4.76 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.80 and 4.95 (2 d, 2 H, *J* = 11.3 Hz, PhCH_2), 5.29 (d, 1 H, H-1), 7.05-7.40 (m, 21 H, 4 Ph and thiazole), 7.85 (d, 1 H, *J* = 3.1 Hz, thiazole).
    4b: mp 113°C (hexane-ethyl acetate), $[\alpha]_D$ +10.4 ($CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ 3.62-3.88 (m, 6 H, H-2, H-3, H-4, H-5, H-6, H-6'), 4.15 and 4.52 (2 d, 2 H, *J* = 10.1 Hz, PhCH_2), 4.56 and 4.62 (2 d, 2 H, *J* = 11.5 Hz, PhCH_2), 4.60 and 4.86 (2 d, 2 H, *J* = 10.8 Hz, PhCH_2), 4.71 (m, 1 H, H-1), 4.89 and 4.95 (2 d, 2 H, *J* = 10.8 Hz, PhCH_2), 7.00-7.40 (m, 20 H, 4 Ph), 7.40 and 7.84 (2 d, 2 H, *J* = 3.1 Hz, thiazole).

11. The preference for the axial addition of hydride to the oxycarbenium ions leading to β-linked C-glycosides is generally observed at low temperature (ref. 7) with this silane. The structure of the silane was found to have an influence on the stereoselectivity of the reduction. Under identical conditions, phenyldimethylsilane gave a 2:1 mixture in favor of the unexpected α (axial) product **4a**. For a similar observation see ref. 7b.
12. Dondoni, A.; Marra, A.; Perrone, D. *J. Org. Chem.* **1993**, *58*, 275. In this case, better yield has been obtained using mercury(II) chloride instead of copper(II) chloride.
13. The pure β-isomer **5b** was also obtained from its thiazole-masked precursor **4b** by the usual deblocking procedure[12] (76% yield). In a similar way was the α-isomer **5a** generated from **4a** although it was contaminated by 10 % of **5b** (72% total yield).
    5a: syrup, ^{1}H NMR (300 MHz, $CDCl_3$), selected data, δ : 4.40 (d, 1 H, $J_{1,2}$ = 6.0 Hz, H-1), 9.98 (s, 1 H, CHO).
    5b: syrup, ^{1}H NMR (300 MHz, $CDCl_3$) selected data, δ : 3.48–3.58 (m, 1 H, H-5), 3.58–3.80 (m, 5 H, H-1, H-2, H-3, H-4, H-6), 3.84 (dd, 1 H, $J_{5,6'}$ = 9.1 Hz, H-6'), 9.65 (d, 1 H, $J_{CHO,1}$ = 1.6 Hz, CHO).
    Attempts to purify **5a** by flash chromatography failed due to major decomposition and partial epimerization to **5b**.



4a R^1 = 2-thiazolyl, R^2 = H
4b R^1 = H, R^2 = 2-thiazolyl

5a R^1 = CHO, R^2 = H
5b R^1 = H, R^2 = CHO

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15. **7a**: mp 140°C (hexane-ethyl acetate), $[\alpha]_D$ +43.6 ($CHCl_3$) ; ^{1}H NMR (300 MHz, $CDCl_3$) δ : 1.31, 1.40, 1.47 and 1.50 (4 s, 12 H, 4 CH_3), 4.08 (dd, 1 H, $J_{6,5}$ = 5.0, $J_{6,6'}$ = 8.3 Hz, H-6), 4.14 (dd, 1 H, $J_{6',5}$ = 5.8 Hz, H-6'), 4.32 (dd, 1 H, $J_{4,3}$ = 4.1, $J_{4,5}$ = 7.5 Hz, H-4), 4.48 (ddd, 1 H, H-5), 4.79 (d, 1 H, $J_{2,3}$ = 5.8 Hz, 5.03 (dd, 1 H, H-3), 5.44 (s, 1 H, OH), 7.46 and 7,8 (2 d, 2 H, J = 3.2 Hz, thiazole).
16. **8**: syrup, $[\alpha]_D$ +52.8 ($CHCl_3$) ; ^{1}H NMR (300 MHz, $CDCl_3$) δ : 1.31, 1.41, 1.46 and 1.48, (4 s, 12 H, 4 CH_3), 3.78 (dd, 1 H, $J_{4,3}$ = 3.5, $J_{4,5}$ = 7.0 Hz, H-4), 4.16 (d, 2 H, $J_{5,6}$ = 5.6 Hz, 2 H-6) 4.51 (dt, 1 H, H-5), 4.91 (dd, 1 H, $J_{3,2}$ = 5.6 Hz, H-3), 4.99 (dd, 1 H, $J_{2,1}$ = 3.5 Hz, H-2), 5.05 (d, 1 H, H-1), 7.36 and 7.81 (2 d, 2 H, J = 3,3 Hz, thiazole).
17. **9**: syrup, ^{1}H NMR (300 MHz, $CDCl_3$) δ : 1.31, 1.39, 1.46 and 1.47, (4 s, 12 H, 4 CH_3), 3.65 (dd, 1 H, $J_{4,3}$ = 3.2, $J_{4,5}$ = 7.6 Hz, H-4), 4.02 (dd, 1 H, $J_{1,2}$ = 4.3, $J_{1,CHO}$ = 1.0 Hz, H-1) 4.08-4.18 (m, 2 H, H-6, H-6'), 4.45 (ddd, 1 H, $J_{5,6}$ = $J_{5,6'}$ = 5.3 Hz, H-5), 4.83 (dd, 1 H, $J_{3,2}$ = 5.4 Hz, H-3), 5.06 (dd, 1 H, H-2), 9.64 (d, 1 H, CHO).

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