THIAZOLE AS LEAVING GROUP. THERMAL ELIMINATION FROM THIAZOLYLKETOSES

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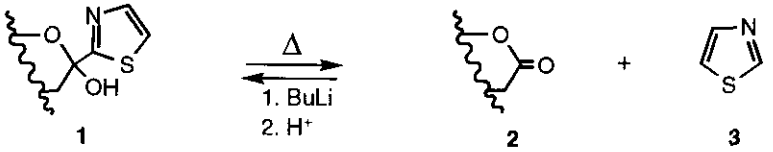
Abstract - Heating thiazolylketofuranoses and -ketopyranoses in refluxing toluene results in the elimination of thiazole and formation of the corresponding sugar lactones in nearly quantitative yield. The same reaction does not occur with 1-*O*-acetyl and 1-*O*-trimethylsilyl derivatives. Also model furyl- and thienyl-ketofuranoses and various thiazolyl alcohols proved to be stable under the above thermolysis conditions. A possible mechanism of the observed thermolysis of thiazolylketoses involves the thiazolium 2-ylide as the actual leaving group.

Central to a great deal of thiazole chemistry and biochemistry is the participation of the thiazolium 2-ylide as a key intermediate in many reaction sequences.[1] The occurrence of this species can be explained as the result of the combined action of the two ring heteroatoms, nitrogen and sulfur. The former initiates the process of formation through quaternization, the latter provides the stabilization through some interaction with the adjacent negatively charged carbon atom.[2] The key role exerted by the thiazole ring through its 2-ylide in the catalytic action of thiamine diphosphate of various carbohydrate based metabolic processes,[3] has been established by Breslow about forty years ago.[4] The same processes were found to be catalyzed also by thiamine itself or by simple thiazolium salts under mild basic conditions.[5] A classical chemical reaction which has been demonstrated to proceed under thiazolium 2-ylide catalysis as well is the coupling of aromatic aldehydes (benzoin condensation)[4,6] or aliphatic aldehydes (benzoin-type condensation).[7] A wide scope reaction occurring through these ylides as intermediates is the umpolung addition of aldehydes to α,β-unsaturated carbonyl compounds (Stetter reaction).[8] A special case of thiazolium 2-ylide generation without base catalysis occurs in the reaction pathway between 2-trimethylsilylthiazole and aldehydes ending up with the formation of 2-hydroxyalkylthiazoles.[9] In this case a desilylation instead of the usual deprotonation reaction takes place in the ylide formation process. Direct observations of thiazolium 2-ylides both in gas phase[10] and solid state[11] have been very recently reported.

We would like to report here a new reaction wherein a thiazolium 2-ylide intermediate can be reasonably postulated. This reaction deals with the thermal elimination of thiazole (**3**) from thiazolyl-ketoses (**1**) to give sugar lactones (**2**) (Scheme 1). While the elimination of a thiazole bearing moiety by carbon-carbon

bond cleavage occurs normally in the final step of the catalytic cycle of the thiamine or thiazolium salts catalyzed processes,[12] the uncatalyzed reaction observed here in neutral thiazole derivatives has no precedents to the best of our knowledge.



Scheme 1

A number of thiazolylketofuranoses and -ketopyranoses (**1**) have been recently made available from work in our laboratory[13] through the addition of 2-lithiothiazole[14] to the corresponding sugar lactones (**2**) (Chart 1). Hence, aiming at the conversion of ketoses (**1**) into *C*-glycosides by reaction with a phosphorane in a Wittig-Michael sequence as described for various aldoses,[15] we treated the thiazolylribofuranose derivative (**1b**) with (2-thiazolyl)carbonylmethylenetriphenylphosphorane (2-TCMP) in refluxing toluene. After 40 h the ribono-lactone (**2b**) was isolated in 50% yield by column chromatography. This observation indicates that the ketose (**1b**) is much less reactive toward 2-TCMP than the corresponding aldose lacking the thiazolyl group at the anomeric carbon[15] and therefore under quite forcing conditions the elimination of thiazole is the major process. Hence the quantitative conversion of **1b** into **2b** was carried out in a preparative scale by heating at 130 °C for 14 h in a closed vial a toluene solution containing 4-Å molecular sieves. Under the same conditions the thiazolylmannofuranose (**1a**), -glucopyranose (**1c**), and -galactopyranose (**1d**) were converted into the corresponding lactones (**2a**), (**2c**), and (**2d**) in almost quantitative yields. The complete thermolysis of the manno-pyranose derivative (**1e**) required heating at 160 °C in cumene as a solvent. The highly volatile thiazole (**3**) was not detected by NMR analysis of any of the above reaction mixtures after the usual workup (see Experimental). On the other hand, parallel experiments carried out with the same ketoses in a sealed NMR tube using DMSO-d_6 or $(CDCl_2)_2$ as the solvent showed the simultaneous formation of lactone and an equimolar amount of thiazole (**3**).

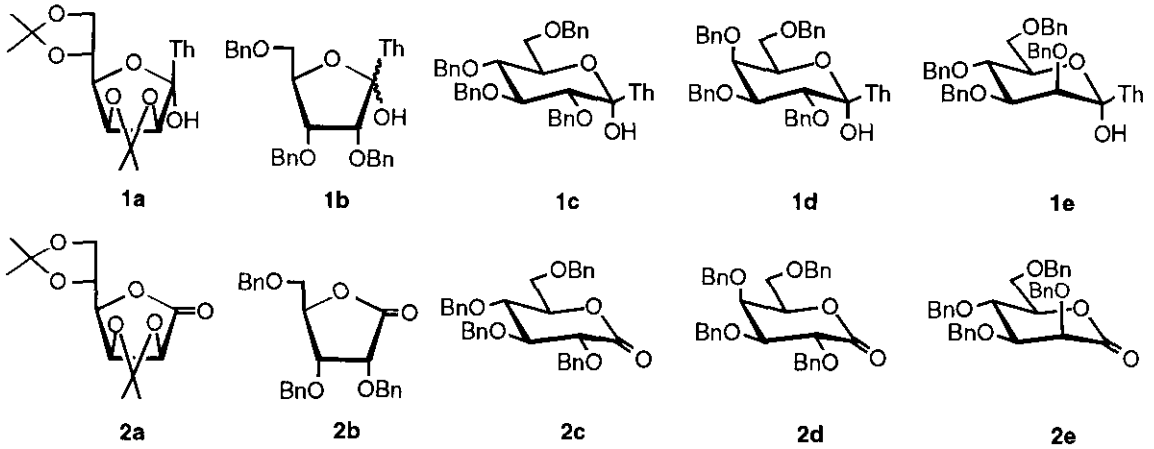
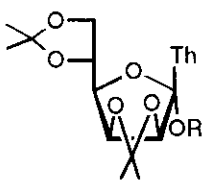
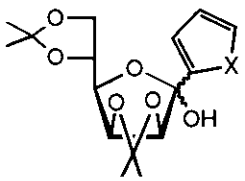


Chart 1. Th = 2-thiazolyl

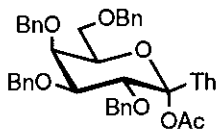
The elimination reaction appeared to be limited to the class of thiazolylketoses (**1**). A set of different compounds (**4-13**) (Chart 2) was recovered unaltered under the above thermolysis conditions. Thus, the thermal stability of anomeric *O*-acetyl and *O*-trimethylsilyl[16] derivatives (**4**), (**5**), and (**8**), and cyclohexanols[17] (**9**) and (**10**) mimicking α and β thiazolylketopyranoses in a chair conformation, demonstrates that the furanose or pyranose hemiketal structure is a prerequisite structural arrangement. This conclusion is supported by the same inertness of the open chain thiazolyl alcohols (**11-13**). Finally, that the reaction is limited to thiazole derivatives is proved by the thermal stability of the furyl- and thienylmannofuranoses (**6**) and (**7**).



4 R = Ac
5 R = $SiMe_3$



6 X = O
7 X = S



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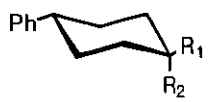
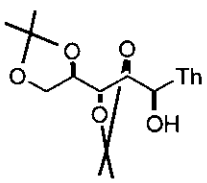


9 R_1 = Th, R_2 = OH
10 R_1 = OH, R_2 = Th



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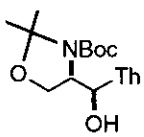

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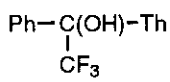

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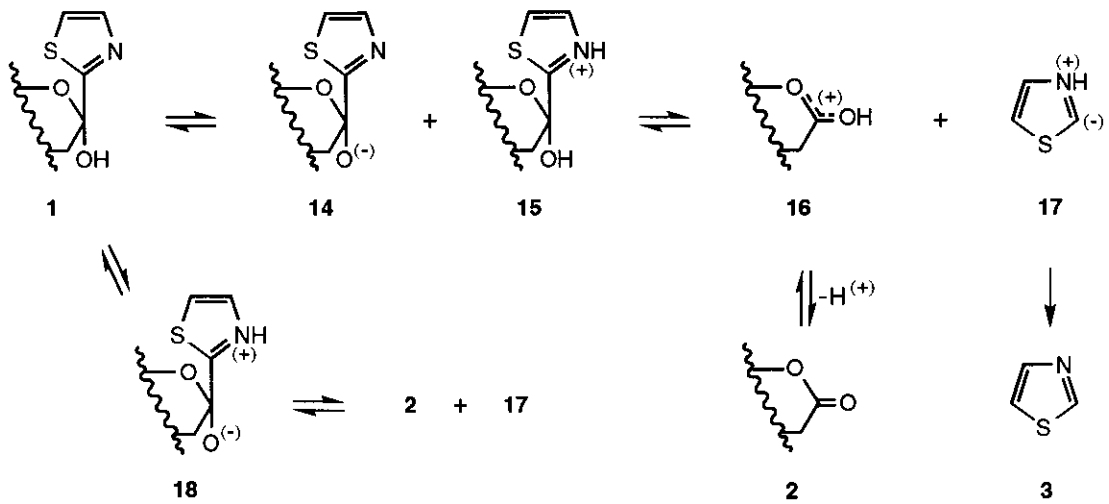
Chart 2. Th = 2-thiazolyl

A simple mechanistic rationale of the conversion of ketoses (**1**) into lactones (**2**) can be now advanced (Scheme 2). The crucial step of the process, *i.e.* the cleavage of the sugar thiazole carbon-carbon bond, should occur through the release of the thiazolium ylide[18] (**17**) from the *N*-protonated thiazolylketose (**15**). The other product of this fragmentation is the protonated sugar lactone (**16**) which enjoys a considerable stabilization through the delocalization of the positive charge on both the exo- and endocyclic oxygen atoms.[19] In this scheme it is assumed that the thiazolium salt (**15**) is formed by a rapid proton exchange[20] between two molecules of **1** . In alternance to the intermediate (**15**), the zwitterion (**18**) arising from either intra- or intermolecular proton exchange processes of **1** can be formed. The release of the thiazolium ylide (**17**) from **18** would give directly the final lactone (**2**). However, the occurrence of the cation (**15**) is supported by a substantial rate increasing by acid catalysis.[21] In fact, complete conversion of the ketose (**1d**) into the corresponding lactone (**2d**) was observed after 5 h heating at 130 °C in toluene containing 3 equiv. of acetic acid, whereas a parallel reaction carried out in the absence of acetic acid showed, after 5 h, the presence of 25% unreacted **1d** and required 12 h to go to completion.



Scheme 2

ACKNOWLEDGEMENTS

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EXPERIMENTAL

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. All solvents were dried over standard drying agents[22] and freshly distilled prior to use. Commercially available powdered 4-Å molecular sieves (50 μm average particle size) were used without further activation. Flash column chromatography[23] was performed on silica gel 60 (230-400 mesh). Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with sulfuric acid. Optical rotations were measured at 20 ± 2 °C in the stated solvent. ^1H (300 MHz) and ^{13}C (75 MHz) NMR were recorded at rt for $CDCl_3$ solutions, unless otherwise specified. Assignments were aided by decoupling and/or homo- and heteronuclear two-dimensional experiments. The structure of compounds (**9**) and (**11**) were determined by X-Ray crystallography.[24] The syntheses of thiazolylketoses[13b] (**1a-e**), acetates[13b] (**4**) and (**8**), furylketose[25] (**6**), aminoalcohol[26] (**12**), and trifluoroalcohol[27] (**13**) have been already reported. 2,3:4,5-Di-*O*-isopropylidene-*aldehydo*-D-arabinose was prepared as described.[28] 2-Bromothiazole and 2-trimethylsilylthiazole are commercially available.

2,3:5,6-Di-*O*-isopropylidene-1-*C*-(2-thiazolyl)-1-*O*-trimethylsilyl-α-D-mannofuranose (**5**). Route *a*. A solution of **1a** (138 mg, 0.4 mmol) and Et_3N (280 μL, 2.0 mmol) in anhydrous CH_2Cl_2 (4 mL) was treated with trimethylsilyl triflate (108 μL, 0.6 mmol) at rt for 15 min, then concentrated. The residue was eluted from a short column of silica gel with 3:1 cyclohexane-AcOEt (containing 0.1% of Et_3N) to give (**5**) (143 mg, 86%) as a low-melting solid; $[\alpha]_D$ = +70.7 ° (*c* 1, $CHCl_3$). ^1H NMR: δ 7.85 and 7.35 (2 d, 2 H, *J* = 3.2 Hz, Th), 4.94 (dd, 1 H, *J* = 3.7 and 5.8 Hz, H-3), 4.87 (d, 1 H, *J* = 5.8 Hz, H-2), 4.52 (dt, 1 H, *J* = 5.7 and 6.5 Hz, H-5), 4.28 (dd, 1 H, *J* = 3.7 and 6.5 Hz, H-4), 4.18 (d, 2 H, *J* = 5.7 Hz, 2 H-6), 1.49,

1.43, 1.31, and 1.24 (4 s, 12 H, 4 Me), 0.01 (s, 9 H, $SiMe_3$). ^{13}C NMR: δ 168.6, 142.6, and 120.0 (Th), 112.7 and 108.9 (2 O-C-O), 106.1 (C-1), 88.4 (C-4), 79.9 (C-2), 79.7 (C-3), 73.2 (C-5), 66.2 (C-6), 26.7, 25.5, 25.3, and 24.0 (4 Me), 0.8 ($SiMe_3$). Anal. Calcd for $C_{18}H_{29}NO_6SSi$: C, 52.02; H, 7.03; N, 3.37. Found: C, 52.28; H, 7.16; N, 3.21.

Route *b*. To a stirred, cooled (0 °C) solution of lactone (**2a**) (130 mg, 0.5 mmol) and 2-trimethylsilylthiazole (160 µL, 1.0 mmol) in anhydrous THF (5 mL) was added in one portion tris(dimethylamino)sulfonium difluorotrimethylsilicate (14 mg, ~0.05 mmol; purchased from Fluka, ~90% pure). The yellow solution was stirred at 0 °C for an additional 1 h, then diluted with 1 M phosphate buffer at pH = 7 (4 mL), warmed to rt, partially concentrated, diluted with H_2O (2 mL), and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give a 4.5:1 mixture of **5** and its β anomer (190 mg, ~92%) contaminated by trace amounts of byproducts (NMR analysis).

A solution of this crude mixture in 9:1 MeOH-H_2O (5 mL) was treated at rt for 1 h with tetrabutylammonium fluoride hydrate (130 mg, ~0.5 mmol), then partially concentrated, diluted with H_2O (5 mL), and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 1.5:1 cyclohexane-AcOEt to afford pure **1a** [137 mg, 80% from **2a**].

2,3:5,6-Di-*O*-isopropylidene-1-*C*-(2-thienyl)-α,β-D-mannofuranose (**7**). To a stirred, cooled (0 °C) solution of butyllithium (1.5 mL of a 1.6 M solution in hexanes, 2.4 mmol) was added dropwise a solution of thiophene (190 µL, 2.4 mmol; distilled from KOH immediately before use) in anhydrous THF (2 mL). The solution was kept at rt for 30 min, then cooled to -70 °C. To the stirred solution was added dropwise a solution of **2a** (516 mg, 2.0 mmol) in anhydrous THF (2 mL). The mixture was allowed to warm to -30 °C in 1 h, then poured into a 1 M phosphate buffer at pH = 7 (20 mL), and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 3:1 cyclohexane-AcOEt (containing 0.1% of Et_3N) to give **7** (615 mg, 90%) as a mixture of anomers and open-chain hydroxy ketone. ^1H NMR (selected data for the α-D-anomer): δ 7.34 (dd, 1 H, *J* = 1.0 and 5.0 Hz, thienyl H-5), 7.18 (dd, 1 H, *J* = 1.0 and 3.6 Hz, thienyl H-3), 7.02 (dd, 1 H, *J* = 3.6 and 5.0 Hz, thienyl H-4), 4.95 (dd, 1 H, *J* = 3.9 and 5.7 Hz, H-3), 4.68 (d, 1 H, *J* = 5.7 Hz, H-2), 4.49 (ddd, 1 H, *J* = 5.2, 6.1, and 7.0 Hz, H-5), 4.31 (dd, 1 H, *J* = 3.9 and 7.0 Hz, H-4), 4.16 (dd, 1 H, *J* = 6.1 and 8.8 Hz, H-6a), 4.11 (dd, 1 H, *J* = 5.2 and 8.8 Hz, H-6b), 2.80 (s, 1 H, OH). Anal. Calcd for $C_{16}H_{22}O_6S$: C, 56.12; H, 6.48. Found: C, 56.41; H, 6.37.

***Z*- and *E*-4-Phenyl-1-(2-thiazolyl)cyclohexanol (9 and 10).** To a stirred, cooled (-78 °C) solution of butyllithium (6.9 mL of a 1.6 M solution in hexanes, 11.0 mmol) in anhydrous Et_2O (15 mL) was added in 20 min a solution of freshly distilled 2-bromothiazole (990 µL, 11.0 mmol) in anhydrous Et_2O (5 mL) and stirring was continued for an additional 30 min at -78 °C. To the yellow solution was added in 20 min a solution of 4-phenylcyclohexanone (1.74 g, 10.0 mmol) in anhydrous THF (15 mL). The mixture was stirred for 30 min at -78 °C, then allowed to warm to -60 °C in 30 min, and poured into a 1 M phosphate buffer at pH = 7 (100 mL). The layers were separated, and the aqueous layer was extracted

with CH_2Cl_2 (2 x 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with CH_2Cl_2-Et_2O (from 30:1 to 10:1) to give first **9** (0.41 g, 16%) as a solid; mp 174-175 °C (from AcOEt-cyclohexane). ^{1}H NMR: δ 7.74 (d, 1 H, J = 3.2 Hz, Th), 7.36-7.19 (m, 6 H, Ph, Th), 2.82 (s, 1 H, OH), 2.68 (tt, 1 H, J = 3.4 and 11.5 Hz, H-4), 2.22-1.86 (m, 8 H). Anal. Calcd for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40. Found: C, 69.59; H, 6.51; N, 5.50.
Eluted second was **10** (1.37 g, 53%) as a solid; mp 103-104 °C (from cyclohexane). ^{1}H NMR: δ 7.78 and 7.36 (2 d, 2 H, J = 3.2 Hz, Th), 7.31-7.16 (m, 5 H, Ph), 2.70 (tt, 1 H, J = 3.4 and 11.5 Hz, H-4), 2.69 (s, 1 H, OH), 2.56-2.48 and 2.06-1.79 (2 m, 8 H). Anal. Found: C, 69.68; H, 6.57; N, 5.52.

(1*R*,2*R*,3*S*,4*S*)-2,3:4,5-Di-*O*-isopropylidene-1-(2-thiazolyl)-1,2,3,4,5-pentahydroxy pentane (11). To a stirred, cooled (0 °C) solution of 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose (230 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (5 mL) was added 2-(trimethylsilyl)thiazole (240 μL, 1.5 mmol). The solution was kept overnight at rt, then concentrated. The residue was dissolved in THF (5 mL) and treated at rt for 1 h with tetrabutylammonium fluoride hydrate (260 mg, ~1.0 mmol), then diluted with H_2O (10 mL), and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give a crude 5:1 mixture of **11** and its C-1 epimer. The residue was eluted from a column of silica gel with 19:1 CH_2Cl_2-acetone (containing 0.2% of Et_3N) to afford first (1*S*,2*R*,3*S*,4*S*)-2,3:4,5-di-*O*-isopropylidene-1-(2-thiazolyl)-1,2,3,4,5-pentahydroxy-pentane contaminated by **11** (37 mg, ~12%); ^{1}H NMR: δ 7.80 and 7.33 (2 d, 2 H, J = 3.2 Hz, Th), 5.15 (dd, 1 H, J = 2.4 and 9.5 Hz, H-1), 4.50 (dd, 1 H, J = 2.4 and 7.4 Hz, H-2), 4.20-3.85 (m, 4 H), 3.44 (d, 1 H, J = 9.5 Hz, OH), 1.40, 1.36, and 1.30 (3 s, 12 H, 4 Me).
Eluted second was **11** (180 mg, 57%) as a solid; mp 122-123 °C (from AcOEt-cyclohexane); $[\alpha]_D$ = +18.4 ° (*c* 0.7, $CHCl_3$). ^{1}H NMR: δ 7.80 and 7.36 (2 d, 2 H, J = 3.2 Hz, Th), 5.10 (dd, 1 H, J = 3.7 and 6.5 Hz, H-1), 4.24-3.87 (m, 5 H), 3.89 (d, 1 H, J = 3.7 Hz, OH), 1.44, 1.38, and 1.35 (3 s, 12 H, 4 Me). ^{13}C NMR: δ 170.8, 142.7, and 119.7 (Th), 110.6 and 110.3 (2 O-C-O), 87.8, 79.3, 76.1, and 72.6 (C-1, C-2, C-3, C-4), 67.3 (C-5), 26.8, 26.6, 26.0, and 24.9 (4 Me). Anal. Calcd for $C_{14}H_{21}NO_5S$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.52; H, 6.65; N, 4.36.

Thermal elimination of thiazole from ketoses 1. A mixture of **1a-d** (0.1 mmol), activated 4-Å powdered molecular sieves (0.10 g), and toluene (2 mL) was stirred in a screw-capped vial at 130 °C (oil-bath temperature) for 14 h, then cooled to rt, diluted with CH_2Cl_2, filtered through a pad of Celite, and concentrated to afford quantitatively almost pure **2a-d** (^{1}H NMR analysis).
Under the above conditions the ketose (**1e**) gave a 4:1 mixture of unreacted **1e** and lactone (**2e**). When the reaction was performed at 160 °C for 14 h in cumene as the solvent, a ~9:1 mixture of **2e** and its epimer (**2c**) was obtained in quantitative yield (^{1}H NMR analysis).

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14. Although 2-lithiothiazole is more conveniently prepared from 2-bromothiazole as described in ref. 13b, the same reagent can be also obtained from unsubstituted thiazole (**3**) as shown in Scheme 1.
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16. The synthesis of this compound has been recently described by fluoride ion mediated addition of 2-trimethylsilylthiazole to the lactone (**2a**) (R. Csuk and M. Schaade, *Tetrahedron*, 1994, **50**, 3333). However, the reported NMR data were not in agreement with those of the compound that we have prepared here by silylation of the ketose (**1a**). Hence, we repeated the literature procedure and

obtained different results both in the product distribution and configurational assignments. Instead of only one anomer as reported, both anomers were formed in 4.5:1 ratio. The configuration of these products was assigned by comparison of the $\delta_{C\text{-}1}$ values in their ^{13}C NMR spectra (downfield chemical shifts have been observed for the ketofuranose anomers having the C-1–O-1 and C-2–O-2 bonds in a trans orientation; see: refs. 13b and 25, and A. Boschetti, L. Panza, F. Ronchetti, G. Russo, and L. Toma, *J. Chem. Soc., Perkin Trans. 1*, 1988, 3353). The major product resulted to be the α anomer, identical to the compound obtained by silylation of **1a** . Thus, the compound isolated by Csuk and Schaade appears not to be **5** but the β anomer.

17. As expected from the results in ref. 12, the conversion of **9** and **10** into 4-phenylcyclohexanone was achieved through their *N*-methylthiazolium triflates. The removal of the thiazole ring as the 2-ylide from these salts occurred at rt in 30 min upon treatment with 1 equiv. of DBU. On the other hand, without the addition of base the thermal elimination of the thiazole moiety was not observed after 20 h at 120 °C. It is worth noting that *N*-methylthiazolium triflates of **1a** and **1d** afforded quantitatively the corresponding lactones (**2a**) and (**2d**) by heating at 130 °C for only 15 min.
18. The attempts to trap the ylide (**17**) with an electrophile by performing the thermal elimination in neat benzaldehyde were unsuccessful.
19. A less stable protonated ketone or aldehyde has to be generated, along with the ylide (**17**), if an analogous reaction pathway is followed by tertiary or secondary alcohols such as **9-13** .
20. Although the anomeric (hemiacetalic) hydroxyl group of sugars is slightly more acidic ($\Delta pK_a \approx 1$) than the non-anomeric ones (B. Capon and W. G. Overend, *Adv. Carbohydr. Chem.*, 1960, **15**, 11), this feature does not seem to be important for the thermal elimination of thiazole. In fact, the alcohol (**13**) bearing the strong electron-withdrawing trifluoromethyl group is stable upon prolonged heating as the much less acidic alcohols (**9-12**) (pK_a (CH_3OH) = 15.5; pK_a (CF_3CH_2OH) = pK_a (glucose) = 12.4).
21. Compounds (**9**) and (**10**) were recovered unchanged after heating at 120 °C for 20 h in the presence of 3 equiv. of acetic acid.
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