Cyclopentyl and Carbohydrate Derivatives of *N*-Hydroxy-4-methylthiazole-2(*3H*)-thione: Synthesis by Mitsunobu Reaction and Highly Selective Photochemical Conversion into Aldehydes

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Abstract: Substituted *N*-cyclopentoxy- and carbohydrate-derived thiazole-2(3H)-thiones **3** were prepared from alcohols **2** or from 2,3:5,6-di-*O*-isopropylidene mannose in the presence of PPh₃, diethyl azodicarboxylate (DEAD), and *N*-hydroxy-4-methylthiazole-2(3H)-thione (**1**). Alkoxyl radical precursors **3** were photoreacted with hydrogen atom donors to afford substituted aldehydes **7** or formyl esters **10–11** via highly regioselective alkoxyl radical fragmentations.

Key words: alkoxyl radical, carbohydrate, β -cleavage, Mitsunobu reaction, thiazolethione

The unsubstituted cyclopentoxyl radical undergoes a regioselective β -C-C cleavage which leads to the ω -formylbutyl radical.¹ It is a reversible reaction with the equilibrium shifted towards the acyclic intermediate since the cyclopentane ring strain of ~ 26 kJ mol^{-1} is relieved by the ring opening reaction and a strong C–O π -bond is formed at the expense of a C–C σ -bond. The kinetics of this radical rearrangement have been thoroughly investigated by Beckwith and Hay.² In open chain alkoxyl radicals the regioselectivity of β -C–C cleavage is generally governed by thermochemical effects. According to theoretical studies by Houk et al. the same guidelines should apply for cyclic systems.³ Experimental evidences for such radical based transformations under neutral (i.e. non oxidative) conditions, however, are rare in the literature.⁴ Selected examples of ring opening reactions of anomeric oxyl radicals have only recently been been studied by Suárez et al.⁵ In view of this issue we have addressed two aspects of oxygen radical induced C-C-cleavages: (i) a versatile and short access to substituted N-cyclopentoxy-4-methylthiazolethiones **3** as alkoxyl radical precursors (Table 1) and (ii) a concise study on the regioselectivity of β -C-C fission in substituted cyclopentoxyl radicals and in carbohydrate-derived radicals (Table 2).

We have applied the Mitsunobu-reaction⁶ for the synthesis of *N*-alkoxy 4-methylthiazole-2(3H)-thiones **3** since these radical precursors have recently been successfully applied for synthetic purposes.⁷ Based on structural analogy to the chosen substrates, cyclopentanol (**2a**) was selected for elucidation of suitable conditions for the synthesis of **3**. Our experiments showed that the conversion of **2a** with diethyl azodicarboxylate, PPh₃, and *N*-hydroxy-4-methylthiazole-2(3H)-thione (**1**) affords *N*-cyclopentoxythiazolethione **3a** in 79% yield, if benzene

is used as solvent (Table 1, entry 1).⁸ Neither a change in solvents to CH_2Cl_2 , THF, or CH_3NO_2 , nor the use of diisopropyl azodicarboxylate or bis(1,1,1-trichloro)ethyl azodicarboxylate led to an improvement of yields for thione **3a**. A comparison with the hitherto "best yield" (87%) for the synthesis of *N*-cyclopentoxythiazolethione **3a** from cyclopentyl tosylate in a phase transfer-catalyzed alkylation of **1**⁹ indicates that the new method is highly competitive and certainly more convenient since it safes an additional step.¹⁰





Besides cyclopentanol (1a), 1,2-*trans*-disubstituted derivatives 2b and 2c were reacted with DEAD, PPh₃ and acid 1 in benzene to afford the corresponding diastereomerically pure *cis*-substituted *N*-cyclopentoxy-substituted thiones 3b and 3c in good yields (Table 1, entries 2 and 3). Substrates with two vicinal substituents adjacent to the reactive C–O bond, for example the four different diastereomers of 2-phenyl 5-methyl substituted cyclopentanols $2d-g^{11}$ are sterically significantly more demanding which caused a severe drop in yields of *O*-radical precursors (synthesis of 3d, 3f; Table 1, entries 4, 6).¹² Syntheses of compounds **3e** and **3g** using the conditions which are given in Table 1 failed, presumably due to competing elimination reactions leading to phenyl substituted cyclopentenes¹³. Relative configurations of all di- or trisubstituted *N*-cyclopentoxy derivatives **3** were established by NOE-experiments.

The conditions which are given in Table 1 were applied to prepare mannosyl thiazolethione **3h** (31%, Figure) from 2,3:5,6-di-*O*-isopropylidene- α -D-mannofuranose. For reasons which are unclear at the moment, the synthesis of glucosyl thiazolethione **3i** from 2,3,4,6-tetra-*O*-acetyl- β -D-glucose failed. This compound, however, is readily available from 2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranosyl bromide and acid **1** in 72% yield using the phase transfer alkylation method.⁹



Figure Yields of mannosyl thizaolthione **3h** and glucosyl thiazolethione **3i**. [a] Mitsunobu reaction.^{6,12} [b] Phase transfer alkylation.⁹

In the second part of this study, thiazolethiones **3** (Table 1, Figure) and reactive hydrogen donors, either Bu₃SnH or $(Me_3Si)_3SiH$ (for Y–H: $c_0 = 0.18$ M; 3.7 equiv.), were dissolved in C₆H₆ or C₆D₆ and were photolyzed 30 min at room temperature in a Rayonet[®] apparatus ($\lambda = 350$ nm, Table 2).¹⁴ Analytical data (¹H NMR) from the crude reaction mixture indicated, that only aldehydes which originated from α – β -cleavage, e.g. compounds **6b**–**d**, were obtained from these experiments. Alcohols **2** which could have been formed by a direct trapping of **4** and carbonyl compounds from the alternative α – ϵ -fission, were absent. Except of volatile hexanal (**6b**) (NMR, GC analysis, Table 2, entries 1,2) all products were purified by column chromatography.

The data in Table 2 confirm the well-known preference of *O*-radical mediated β -C–C-cleavages to afford the most stabilized of all possible intermediate carbon radicals. For further mechanistic discussions it should be noted that a possible reverse reaction $\mathbf{5} \rightarrow \mathbf{4}$ has been omitted from the illustration in Table 2, since it has not yet been investigated. Thus, 2-phenyl substituted radicals $4\mathbf{c}$ and $4\mathbf{d}$ regioselectively afford substituted benzyl radicals $5\mathbf{c}$ and $5\mathbf{d}$ as intermediates which are then trapped by Bu₃SnH to yield aldehydes $6\mathbf{c}$ and $6\mathbf{d}$. We were surprised to note, that the 2-methyl substituted radical reacts similar selectively to afford hexanal ($6\mathbf{b}$) as single detectable product.¹⁵
 Table 2
 Photolysis of N-Alkoxy-4-methylthiazole-2(3H)thiones 3



(a) The configuration at C^{α} in **2** in this Scheme is opposite to those of alcohols **2** which were used for the synthesis of radical precurors **3**. (b) Photoreaction in *o*-C₆H₄Cl₂; the yield was determined by GC using *n*-tetradecane as internal standard.

(c) Photoreaction in C_6D_6 , the yield was measured by NMR using anisole as internal standard.

(d) Photoreaction in C_6H_6 . – $Y = Bu_3Sn$ or $(Me_3Si)_3Si$, Tz = 4-methyl thiazyl-3-sulfanyl.

The second unexpected result from our data was the fact that no alcohols 2 were discovered by NMR or by GC in the crude reaction mixtures. After consumption of 1 equiv of Bu₃SnH in photoreactions of 3, a final concentration of Bu₃SnH of 0.13 M should remain. According to kinetic data from the literature this concentration is sufficient to convert the cyclopentoxyl radical ($R^{\beta} = R^{\varepsilon} = H$ in Table 2) into a 1: 2 mixture of cyclopentanol (1a) and pentanal under *pseudo*-first order conditions.² However, the fact that no alcohols 2b-f were obtained in our experiments means that either ring opening reactions in substituted cyclopentoxyl radicals 2b-f are faster than the hydrogen atom transfer from the stannane to the cyclopentoxyl radical, or the rate constant of 5-exo-trig cyclizations of radicals **5b**-**f** is substantially slower than the reference value of the ω -formylbutyl radical.

In a final set of experiments, mannosyl thiazolethione **3h** and glucosyl derivative **3i** were photoreacted with $Bu_3SnH [c_o(Bu_3SnH) = 0.18 \text{ M}, 3.7 \text{ equiv.}]$ to afford via β -C-C cleavage of the intermediate *O*-radicals (not shown in Scheme 1) either symmetrically substituted arabinitol derivative **7** or the unsymmetrically substituted arabinitol **8** in excellent yields (Scheme).



Scheme Photochemical conversion of carbohydrate-derived thiazolethiones **3h** and **3i** into arabinitol derivatives **7** and **8**.

In summary, we have applied the Mitsunobu reaction for the first time in the synthesis of *N*-alkoxythiazole-2(3H)thiones **3** from substituted cyclopentanols **2** and a mannose derivative (i.e. lactol). These compounds **3** serve as efficient alkoxyl radical precursors which were applied in the photochemical synthesis of aldehydes **6** under mild and neutral conditions.

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References and Notes

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- (8) Typical procedure: A 10 mL Schlenk flask was charged with *N*-hydroxy-4-methylthiazole-2(3*H*)thione (1) (221 mg, 1.50 mmol), dry C_6H_6 (5 mL), triphenylphosphine (525 mg, 2.00 mmol), alcohol 2 (1 mmol) and a magnetic stirring bar. After cooling in an ice bath DEAD (0.33 mL, 366 mg, 2.10 mmol) was added dropwise through a rubber septum cap during a period of 5 min with agitation. Stirring of the brownish-red solution was continued at 20 °C for 36 h. Afterwards the reaction mixture was diluted with CH_2Cl_2 (10 mL) and extracted with 2 M aqueous NaOH (10 mL). The aqueous phase was washed CH_2Cl_2 (2 × 10 mL) and the combined organic phases are dried (MgSO₄) and concentrated in vacuo to afford a brown oil which was purified by column chromatography (SiO₂).¹²
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- (12) Thiazolethiones 3b-i are new compounds. Characteristic analytical data are provided for two examples: N-(cis-2phenylcyclopentoxy)-4-methylthiazole-2(3H)-thione cis-(3c): colorless solid; yield: 577 mg (66%); dec. 123 °C (DTA; differential thermoanalysis); $R_{\rm f} = 0.42$ [petroleum ether/ diethyl ether = 1/1(v/v)]; ¹H NMR (CDCl₃, 250 MHz): $\delta = 1.68 - 2.40$ (m, 6 H, 3'-H-5'-H), 1.94 (d, 3 H, ${}^{4}J = 1.2$ Hz, 4-CH₃), 3.32 (ddd, 1 H, ${}^{3}J$ = 7.3 Hz, 6.3 Hz, 4.0 Hz, 2'-H), 5.99 (dt, 1H, ${}^{3}J_{d} = 4.0$ Hz, ${}^{3}J_{t} = 1.0$ Hz, 1'-H), 6.05 (q, 1 H, 5-H, ${}^{4}J = 1.2$ Hz, 5-H), 7.19–7.39 (m, 3 H, 3"-5"-H), 7.46–7.52 (m, 2 H, 2"-H, 5"-H).¹³C NMR (CDCl₃, 250 MHz): $\delta = 13.5, 21.7,$ 28.3, 29.6, 50.2, 88.5, 102.8, 126.4, 126.5, 128.0, 128.5, 128.6, 128.8, 138.4, 181.3. UV/VIS (EtOH) : λ_{max} (lg ϵ) = 320 nm (3.920); C₁₅H₁₇NOS₂ (291.4): calcd. C 61.82, H 5.88, N 4.81, S 22.00; found C 61.56, H 5.74, N 4.66, S 21.81. N-(2,3:5,6-Di-O-isopropyliden-β-D-mannofuranosyl)-4methylthiazole-2(3H)-thione (3i): colorless solid; yield 464 mg (31%); $[\alpha]_{20}^{D} = -35.2$ (*c* 1.0 in CHCl₃); mp 87 °C (dec.); $R_{\rm f} = 0.51$ [petroleum ether/diethylether/methanol = 10/10/1 (v/v/v)]; ¹H NMR (CDCl₃, 250 MHz): $\delta = 1.37$ (s, 3 H, 7'-CH₃) or 8'-CH₃), 1.39 (s, 3 H, 7'-CH₃ or 8'-CH₃), 1.41 (s, 3 H, 7'-CH₃ or 8'-CH₃), 1.56 (s, 3 H, 7'-CH₃ or 8'-CH₃), 2.31 (d, 3 H, ${}^{4}J = 1.2$ Hz, 4-CH₃), 3.66 (dd, 1 H, ${}^{3}J = 6.7$ Hz, 3.7 Hz, 4'-H), 4.01–4.16 (m, 2 H, 6'-H), 4.46 (dt, 1 H, ${}^{3}J_{t} = 1.2$ Hz, ${}^{3}J_{d} = 6.7$ Hz, 5'-H), 4.76 (dd, 1 H, ${}^{3}J = 6.0$ Hz, 3.7 Hz, 3'-H), 5.05 (dd, 1H, ${}^{3}J = 6.0$ Hz, 4.0 Hz, 2'-H), 5.85 (d, 1 H, ${}^{3}J = 4.0$ Hz, 1'-H), 6.12 (q, 1 H, ${}^{4}J$ = 1.2 Hz, 5-H); ${}^{13}C$ NMR (CDCl₃, 63 MHz): $\delta = 13.8, 24.8, 25.2, 25.8, 26.8, 66.4, 73.1, 77.1, 78.7, 78.9,$ 101.8, 104.9, 109.3, 114.0, 139.0, 180.2. UV/VIS (EtOH) : λ_{max} (lg ϵ) = 318 nm (3.897); C₁₆H₂₃NO₆S₂ (389.5): calcd. C 49.34, H 5.95, N 3.60, S 16.47; found C 49.37, H 5.81, N 3.40, S 16.19.
- (13) For example, 10% of a 6: 1 mixture of 1-phenyl-3-methyl cyclopentene and 1-methyl-3-phenyl cyclopentene (see Wolinsky, J. *J. Org. Chem.* 1976, *41*, 754–750) were isolated besides 85% of alcohol 2g from the reaction of 2g, PPh₃, DEAD, and thiazolethione 1.

(14) A 10 mL Schlenk flask was charged with *N*-alkoxy-4methylthiazole-2(3*H*)thione **3** (0.5 mmol) and dry C_6H_6 (10 mL). The reaction vessel was sealed with a rubber septum and cooled to liquid nitrogen temperature. After thorough evaporation the flask was flushed with argon and Bu₃SnH (0.48 mL, 531 mg, 1.83 mmol) was added. The reaction mixture was degassed by three consecutive freeze-pump-thaw cycles and then thermostated in a water bath to 18 °C. The solution was photolyzed for 30 min in a Rayonet[®] apparatus ($\lambda = 350$ nm). Afterwards, the solvent was evaporated in vacuo and the remaining oil purified by column chromatography (SiO₂). $R_{\rm f}$ -values of selected products: 0.57 (**6c**) 0.66 (**6d**), both: petroleum ether/methyl *tert*-butyl ether 3/1 (v/v), 0.62 (**7**) in petroleum ether/ methyl *tert*-butyl ether 1/1 (v/v).

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