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Photoreactions of *N*-alkoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*)-thiones with L-cysteine derivatives in aqueous solutions

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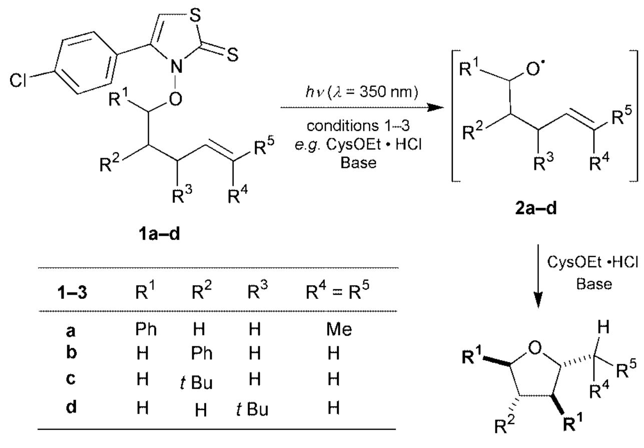
Photolysis of substituted *N*-alkoxythiazolethiones 1 in aqueous solvents furnishes alkoxyl radicals 2 which, upon stereoselective 5-*exo-trig* cyclization, are trapped by water soluble thiols (L-cysteine, L-cysteine ethyl ester, or the reduced form of glutathione, GSH) to afford disubstituted tetrahydrofurans 3 in synthetically useful yields and with satisfactory to excellent diastereoselectivities.

Oxygen radicals are transients in a number of biosyntheses of structurally diverse secondary metabolites.[1–3] In view of the significance of such transformations it is surprising to note that only a limited number of laboratory studies have been performed under biomimetic conditions in order to explore the properties of proposed O-radical key intermediates in water.[4,5] Major drawbacks for adapting standard radical procedures from organic to aqueous solvents originate from an insolubility of the selected reagents such as the radical precursor itself and the trapping reagent, for instance Bu_3SnH.[6] Therefore, we have investigated the feasibility of stereoselective alkoxyl radical reactions in homogeneous and heterogeneous aqueous solvents under neutral (*i.e.* non-oxidative) conditions and disclose our latest results in this communication.

N-Alkoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*)-thiones **1a–d** were selected as O-radical precursors. Thione **1b** had been prepared previously.[6] Heterocycles **1a**, **1c–d** are new compounds which were obtained from the corresponding alkyl chloride (**1a**) or tosylates (**1c**, **1d**) and *N*-hydroxy-*p*-chlorophenylthiazole-2(3*H*)-thione tetraethylammonium salt according to standard procedures.[6]† Thiones **1a–d** themselves are poorly soluble in water. Therefore, all photoreactions of **1** with polar thiols were performed in two phase systems ($C_6H_5CF_3$–H_2O) or in homogeneous mixtures of 1,4-dioxane (hereafter dioxane) and water. Thiols of different polarity and molecular size were selected as hydrogen atom donor: L-cysteine, L-cysteine ethyl ester (as its hydrochloride, L-CysOEt·HCl) and the reduced form of glutathione (GSH, γ-L-glutamyl-L-cysteinylglycine).[7] The selection of $C_6H_5CF_3$ as organic solvent, which is less toxic than benzene, was based on the necessity of direct comparison of the newly obtained data with those from photoreactions of thiones **1** using Bu_3SnH as state of the art reagent.‡ Thus, a solution of 1-phenyl-5-methylhexenoxythiazolethione **1a** and L-CysOEt·HCl in a mixture of $C_6H_5CF_3$–H_2O was treated with a 2 M solution of NaOH and was photolyzed at room temperature in a Rayonet photoreactor (λ_{max} = 350 nm). After complete consumption of **1a**, the pH of the aqueous phase is adjusted to 2 in order to extract residual hydrogen donor into the aqueous phase. The organic layer affords upon workup 68% of 2,5-*trans*-disubstituted tetrahydrofuran **3a** (entry 1, conditions 1, *cis*:*trans* = 30:70) (Scheme 1).‡§

Alternatively we found that tetrahydrofuran **3a** could be prepared in similar yields from thione **1a** in a homogeneous mixture of dioxane and water by application of L-CysOEt·HCl as hydrogen atom donor and neat Na_2CO_3 as base (entry 1, conditions 2, 64%, *cis*:*trans* = 30:70). Other organic cosolvents such as CH_3CN, acetone, or MeOH, were found to be inferior to dioxane. In a third experiment, 53% of tetrahydrofuran **3a** was obtained from the photoreaction of thiazolethione **1a** and GSH in dioxane–H_2O (entry 1, conditions 3, 53%, *cis*:*trans* = 30:70). These findings indicate, that efficient stereoselective alkoxyl radical cyclizations in homogeneous aqueous solvents are feasible. However, it is essential to use 10 equiv. of L-cysteine derivatives as hydrogen atom donors at the given concentration level, since lower thiol strengths lead to the formation of alkoxyl radical-derived alcohols besides the corresponding carbonyl compounds in 1:1 molar ratios. Compared to the corresponding Bu_3SnH-mediated reactions the yields decrease only slightly whereas stereoselectivities are not affected by the change in solvent.‡

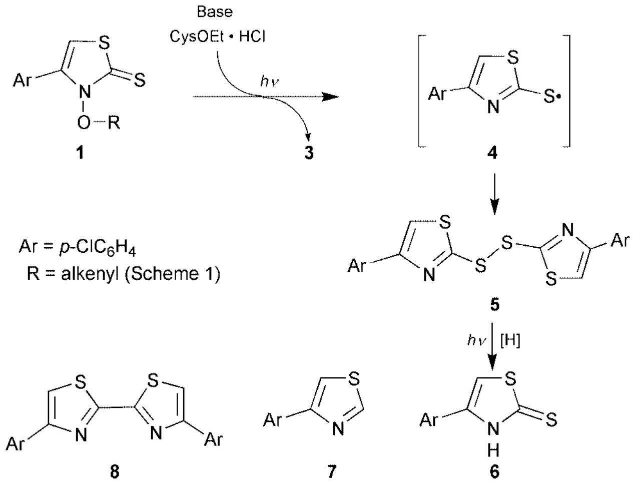
The best conditions 1–3 (Scheme 1) were subsequently applied for experiments using 2-phenylpentenyloxythiazolethione **1b** (entry 2) and derivatives **1c–d** (entries 3–4). Photoreactions using 2-substituted 4-pentenyloxythiazolethiones **1b** and **1c** afforded *cis*-2,4-disubstituted tetrahydrofurans **3b** and **3c** as major products which is in line with the general guidelines of stereoselective 5-*exo-trig* alkoxyl cyclizations[8–10] and with the Beckwith–Houk model[11] for carbon radical ring closure reactions (entries 2 and 3). The observed high stereoselectivity for the formation of 4-*tert*-butyl-2-methylte-



1–3	R^1	R^2	R^3	$R^4 = R^5$
a	Ph	H	H	Me
b	H	Ph	H	H
c	H	*t* Bu	H	H
d	H	H	*t* Bu	H

Entry	1	Yields 3a–d [%] (*cis* : *trans*) conditions 1[a]	conditions 2[b]	conditions 3[c]
1	1a	68 (30 : 70)	64 (30 : 70)	53 (30 : 70)
2	1b	50 (88 : 12)	52 (88 : 12)	34 (88 : 12)
3	1c	71 (90 : 10)	66 (90 : 10)	60 (90 : 10)
4	1d	68 (<2 : >98)	64 (<2 : >98)	47 (<2 : >98)

Scheme 1 Stereoselective synthesis of disubstituted tetrahydrofurans **3** from *N*-alkoxythiazolethiones **1** and L-cysteine derivatives. L-CysOEt HCl = L-cysteine ethyl ester hydrochloride, GSH = γ-L-glutamyl-L-cysteinylglycine. [a] Conditions 1: $C_6H_5CF_3$–H_2O = 4/1 (v/v), 2 M NaOH, L-CysOEt HCl. [b] Conditions 2: dioxane–H_2O = 4/1 (v/v), L-CysOEt HCl, Na_2CO_3. [c] Conditions 3: dioxane–H_2O = 4/1 (v/v), GSH.§



Scheme 2 Formation of thiazoles **5–8** from *N*-alkoxythiazolethiones **1**.

trahydrofuran **3c** from the corresponding alkenoxyl radical **2c** (entry 3, *cis*:*trans* = 90:10) is considered to originate from beneficial steric effects of the *tert*-butyl substituent. This interpretation is supported by a noteworthy 2,3-*trans*-selectivity for the formation of 3-*tert*-butyl-2-methyltetrahydrofuran **3d** from the corresponding thiazolethione **1d** (entry 4).[7,10,11]

According to the data which are reported in Scheme 1 it is obvious that heterogeneous and homogeneous conditions 1 and 2 (Scheme 1), which demand L-CysOEt·HCl as hydrogen atom donor and a suitable base, are superior to the GSH for preparing tetrahydrofurans **3** from thiones **1**. It is worth mentioning, that GSH requires the presence of water in order to deliver its hydrogen atom to cyclized *O*-radicals, although GSH is partially soluble in pure dioxane. Similar observations were made for free amino acid L-cysteine as hydrogen atom donor which affords almost identical yields and selectivities of **3** as GSH does (not shown in Scheme 1). Further, syntheses of tetrahydrofurans **3** fail if photolyses of thiones **1** and GSH are performed in heterogeneous mixtures. For example, the photoreaction of radical precursor **1b** and GSH in $C_6H_5CF_3$–H_2O affords 2-phenylpent-4-en-1-ol (34%) and the corresponding aldehyde 2-phenylpent-4-enal (21%) as sole products.

In almost every photochemical run, formation of a colorless to yellowish precipitate was observed. This material was soluble in acetone, but less soluble in diethyl ether. It was shown to be a mixture of strongly UV-absorbing compounds which were characterized as different primary and secondary photoproducts presumably of the starting thiones **1** (Scheme 2). Expected addition products of either glutathionyl or cysteinyl radicals to the thiocarbonyl group in parent thiones **1a–d** were surprisingly absent in the reaction mixtures.[6] According to control experiments it is likely that the disulfide **5** is formed as primary product which then undergoes further absorption of UV light to afford both 4-(*p*-chlorophenyl)thiazole-2(3*H*)-thione (**6**) and thiazole **7** besides the bisthiazole **8**. Evidence for this assumption is derived from products obtained after photodecomposition of disulfide **5** at λ = 350 nm in dioxane–water (4:1, v/v) which affords 43% of thiazole **7** and 16% of thiazolethione **6**. It is interesting to note that the thiazole-derived photoproducts **5–8** (Scheme 2) are identical to those isolated from photochemical studies using the parent acid of **1**, *i.e.* *N*-hydroxy-4-(*p*-chlorophenyl)thiazolethione, as hydroxyl radical source for DNA-strand break in photobiological studies.[12]

In conclusion, we have demonstrated that L-cysteine-derivatives, *e.g.* L-CysOEt, or the tripeptide GSH can be applied as useful radical traps for the stereoselective formation of disubstituted tetrahydrofurans **3** *via* an alkoxyl radical pathway in aqueous solvents. These investigations point to the feasibility of *O*-radical reactions using *N*-alkoxythiazole-2(3*H*)-thiones, *e.g.* derivatives of **1**, under biomimetic conditions. Further work is in progress in order to pursue *O*-radical chemistry in water as the sole solvent.

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Notes and references

† Satisfactory analytical data were obtained for all new compounds in this study: thiazolethiones **1a**, **1c**, and **1d**, and tetrahydrofurans **3c** and **3d**.

‡ For comparison, yields of tetrahydrofurans **3** from photoreactions of **1** and Bu_3SnH in $C_6H_5CF_3$ were determined. Figures in brackets denote the *cis–trans* ratios: **3a**: 93% (30:70), **3b**: 60% (88:12), **3c**:97% (90:10), **3d**:88% (<2:>98).

§ In a typical run thiazolethione **1** (1 mmol) was dissolved in the organic solvent ($C_6H_5CF_3$ or 1,4-dioxane, 20 ml). L-CysOEt·HCl (10 mmol) and a base (9 mmol, see Scheme 1), or GSH, or L-cysteine (10 mmol) were dissolved in water (5 mL). Both solutions were combined while stirring to afford the reaction mixture which was photolyzed at ambient temperature in a Rayonet® photoreactor (λ = 350 nm). Upon complete consumption of **1** (*ca.* 30 min), the colorless to yellowish precipitate was filtered-off and the remaining solution was worked up as follows. For reactions with CysOEt in $C_6H_5CF_3$–H_2O, 2 M HCl was added with agitation to adjust to pH 2 in the aqueous phase. Subsequently, phases were separated and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic phases were dried with $MgSO_4$ and concentrated *in vacuo*. The product **3** was purified by column chromatography (SiO_2, petroleum ether–Et_2O = 2:1, v/v). If dioxane is used as solvent, the organic solvent is first evaporated from the reaction mixture. Subsequently, diethyl ether was added (20 mL) to the aqueous phase and tetrahydrofurans **3** were isolated as described above.

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