

Microwave-assisted generation of alkoxy radicals and their use in additions, β -fragmentations, and remote functionalizations†‡

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Received 7th March 2006, Accepted 28th March 2006

First published as an Advance Article on the web 9th May 2006

DOI: 10.1039/b603480b

Microwave irradiation (2.45 GHz, 300–500 W) of *N*-(alkoxy)thiazole-2(3*H*)-thiones in low-absorbing solvents affords alkoxy radicals, which were identified by (i) spin adduct formation (EPR-spectroscopy) and (ii) fingerprint-type selectivities in intramolecular additions (stereoselective synthesis of disubstituted tetrahydrofurans), β -fragmentations (formation of carbonyl compounds), and C,H-activation of aliphatic subunits, by δ -selective hydrogen atom transfer. C-Radicals formed from oxygen-centered intermediates were trapped either by Bu₃SnH, L-cysteine ethyl ester, the reduced form of glutathione (reductive trapping), or by bromine atom donor BrCCl₃ (heteroatom functionalization). The results suggest that microwave activation is superior to UV/Vis-photolysis and conductive heating for alkoxy radical generation from *N*-(alkoxy)thiazolethiones. It offers by far the shortest reaction times along with the option to reduce the amount of trapping reagent significantly.

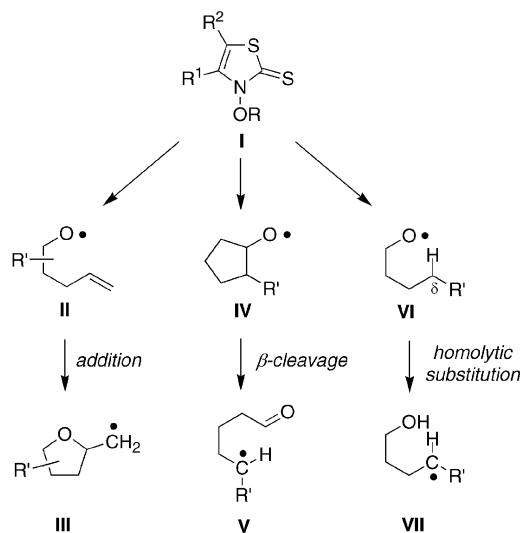
Introduction

The potential of microwaves (2.45 GHz) to increase the rate, selectivity, and efficiency of chemical transformations that proceed *via* polar intermediates has been well documented in the literature.^{1,2} Considerably less, however, is known about the role of microwave activation in radical-based transformations.^{3,4} The issue of selective alkoxy radical formation and a concise study on the chemistry that follows under these conditions has, to the best of our knowledge, not yet been addressed. In view of this background, the present investigation on the feasibility of microwave-induced generation of oxygen-centered radicals starting from *N*-(alkoxy)thiazole-2(3*H*)-thiones **I**^{5–8} has been performed with the aim of documenting the applicability of such intermediates in the three most relevant *O*-radical elementary reactions: (i) intramolecular addition (**II** \rightarrow **III**), (ii) β -fragmentation (**IV** \rightarrow **V**), and (iii) homolytic substitution (**VI** \rightarrow **VII**) (Scheme 1).⁹

Results

1. Synthesis of *N*-(alkoxy)thiazole-2(3*H*)-thiones

O-Alkyl derivatives of *N*-(hydroxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione [MANTTOR **1**: R¹ = CH₃, R² = An (*p*-H₃COC₆H₄)] and *N*-hydroxy-4-(*p*-chlorophenyl)thiazole-2(3*H*)-thione [CPTTOR **2**: R¹ = CP (*p*-ClC₆H₄), R² = H] that were required for conducting spin-trapping experiments (**1a–d**),



Scheme 1 The consequent alkoxy radical chemistry upon microwave activation of *N*-(alkoxy)thiazole-2(3*H*)-thiones **I** [R¹ = CH₃ or *p*-ClC₆H₄ (CP);^{5,6} R² = H or *p*-H₃COC₆H₄ (An); R' = *e.g.* CH₃, C₆H₅].^{7–9}

intramolecular additions (**1e**, **1h**, **2e–h**), β -fragmentations (**1i**, **1j**), and homolytic substitutions (**1k**, **1m**) (Fig. 1), were prepared by selectively *O*-alkylating the corresponding *N*-hydroxythiazole-2(3*H*)-thione tetraethylammonium salt, in an extension of the literature procedures.^{5,6,8,10–12}

2. Microwave-assisted transformations

2.1 Alkoxy radical trapping by 5,5-dimethylpyrrolidine-*N*-oxide (3). The feasibility of alkoxy radical generation upon microwave activation of *N*-(alkoxy)thiazole-2(3*H*)-thiones was verified by heating solutions of 5-(*p*-methoxyphenyl)-4-methyl-substituted heterocycles **1a–d** (*c*₀ = 10^{–2} M) and 5,5-dimethylpyrrolidine-*N*-oxide (**3**) (DMPO) (*c*₀ = 1.8 × 10^{–2} M)

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† Electronic supplementary information (ESI) available: Standard instrumentation, analytical data and microwave-assisted transformations for *N*-(alkoxy)-4-(*p*-chlorophenyl)thiazole-2(3*H*)-thiones (**2**). See DOI: 10.1039/b603480b

‡ Dedicated to Prof. Dr Hartmut Fuess on the occasion of his 65th birthday in recognition of his contributions to structural chemistry and material science.

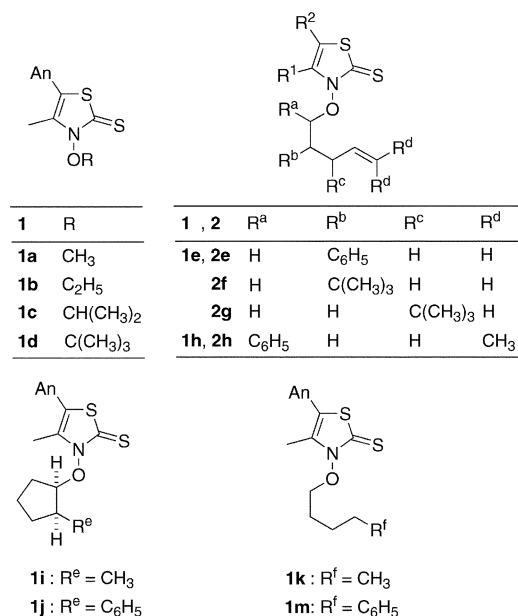
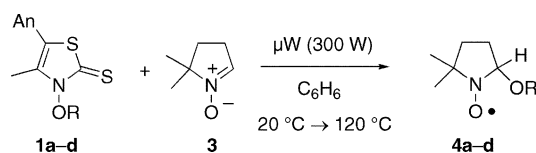


Fig. 1 Numbering of *N*-(alkoxy)thiazole-2(3*H*)-thiones **1** and **2**. An = *p*-H₃COC₆H₄. R¹ = CH₃, R² = An for **1**^{8,10–12} and R¹ = *p*-ClC₆H₄, R² = H for **2**.^{5,6}

in C₆H₆ to 120 °C in a mono-mode microwave device using appropriate vessels, instrumentation, and control units for temperature and pressure regulation (Scheme 2; see Experimental section).[§] EPR-spectra, which were recorded from likewise prepared solutions, showed characteristic signals of spin adducts **4a–d** (for **4b** and **4d** see Fig. 2).¹³ Coupling constants a_N , a_H^β and a_H^γ (Table 1) were calculated on the basis of spectrum simulation and numerical analysis of fitted curves.¹⁴



Scheme 2 Microwave-assisted reaction between *N*-(alkoxy)thiazole-thiones **1a–d** and DMPO (**3**). For indexing of nitroxyl radicals **4** see Table 1.

Table 1 Coupling constants of spin adducts **4a–d** (C₆H₆, 20 °C)

Entry	4	R	<i>g</i>	a_N/G	a_H^β/G	a_H^γ/G
1	a	CH ₃	2.008	12.8	6.6	1.7
2	b	C ₂ H ₅	2.008	12.9	6.9	1.7
3	c	CH(CH ₃) ₂	2.008	12.9	6.3	1.9
4	d	C(CH ₃) ₃	2.008	13.1	9.3	1.5

[§] All microwave-assisted experiments were performed using special glassware and microwave equipment. μW = Microwave irradiation. Chiral *N*-(alkoxy)thiazolethiones **1** and **2** were used as racemates, thus leading to racemic products.

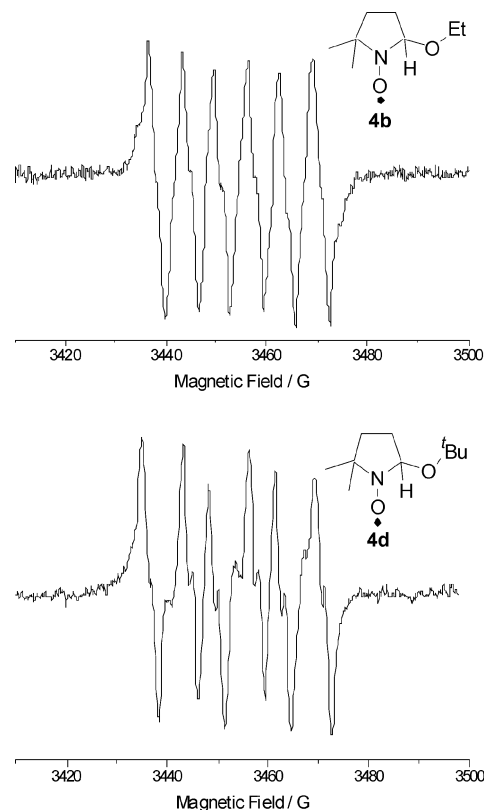


Fig. 2 EPR spectra of spin adducts **4b** (top) and **4d** (bottom) in C₆H₆ (20 °C).

2.2 Bu₃SnH-mediated reactions

(i) **Additions – intramolecular C,O bond formation.** Suitable conditions for pursuing microwave-accelerated syntheses of substituted tetrahydrofurans were established using *N*-(2-phenyl-4-penten-1-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1e**) as a reporter molecule. The compound was converted into 2-phenyl-4-penten-1-al (**6e**, 27%),¹⁵ 2-phenyl-4-penten-1-ol (**7e**, 16%),¹⁶ 5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**9**, 31%),¹⁷ 5-(*p*-methoxyphenyl)-4-methylthiazole (**10**, 2%), and disulfide **11** (5%), if heated to 80 °C for 10 min in a solution of C₆H₅CF₃ using a mono-mode microwave device (Table 2, entry 1). The starting material **1e** was recovered in 52% yield. The stability of thione **1e** decreased considerably if heated in the presence of Bu₃SnH under otherwise identical conditions. Suitable parameters that allowed the complete consumption of *N*-alkenoxy compound **1e** on a reasonable time scale were established by varying the temperature profiles, the tin hydride concentration and amount (data not shown). As a baseline result of this screening, 2.5 equiv. of Bu₃SnH were required in order to convert thione **1e** (within 1 min) into 2-methyl-4-phenyltetrahydrofuran (**5e**, 64%)¹⁸ and the tributyltin adduct **8** (91%), besides minor amounts of the aldehyde **6e** (5%) and alkenol **7e** (2%), as established by ¹H NMR analysis (Table 2, entry 2). The major compounds formed in the latter reaction were isolated in similar but not identical yields from a larger scale experiment (Table 2, entry 2, numbers given in brackets). For comparison, 4.0 equiv. of Bu₃SnH were necessary in order to prepare tetrahydrofuran **5e** (64%, *cis* : *trans* = 88 : 12) from thiazolethione **1e** (within 5–10 min) by conductive

Table 2 Screening for reactivity – microwave-assisted transformations of *N*-(2-phenyl-4-penten-1-oxo)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1e**)^a

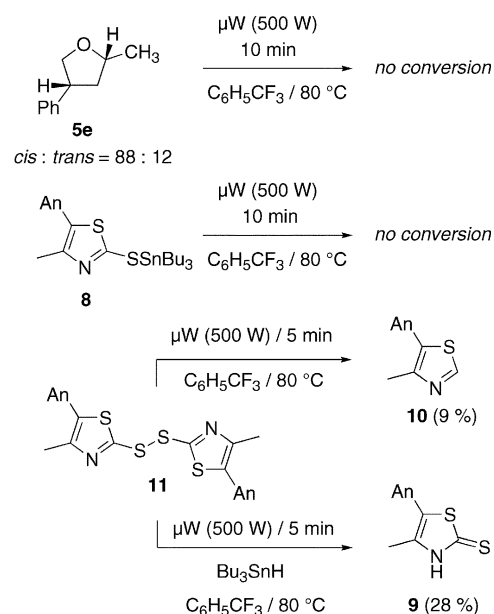
Entry	Bu ₃ SnH (equiv.)	<i>t</i> /min	<i>T</i> /°C	Solvent	5e (%) (<i>cis</i> : <i>trans</i>)	6e (%)	7e (%)	8 (%)	9 (%)	10 (%)	11 (%)
1	0	10 ^b	80	C ₆ H ₅ CF ₃	— ^c	[27]	[16]	—	[31]	[2]	[5]
2	2.5	1.0	80	C ₆ H ₅ CF ₃	64 [53] (88 : 12)	5	2	91 [87]	— ^c	— ^c	— ^c
3	2.0	3.0	60	C ₆ H ₅ CF ₃	56 (88 : 12)	— ^c	— ^c	78	4	— ^c	— ^c
4	2.5	1.5	80	C ₆ H ₆	59 (88 : 12)	— ^c	— ^c	89	3	— ^c	— ^c

^a An = *p*-H₃COC₆H₄. Yields were determined by ¹H NMR, except for the values in square brackets, which are isolated yields. ^b 48% conversion of **1a**.^c Not detected (¹H NMR).

heating (oil bath). If photolyzed for 20 min (350 nm, 30 °C) in a solution of C₆H₅CF₃ and 4.0 equiv. of Bu₃SnH, thione **1e** provided 2-methyl-4-phenyltetrahydrofuran (**5e**, 63%) (data for the latter two experiments is not shown). A decrease of the bulk temperature and the amount of Bu₃SnH slightly reduced the yield of target compound **5e** (Table 2, entry 3, ¹H NMR). Experiments in C₆H₆ (80 °C) took 1.5 min in order to quantitatively convert tetrahydrofuran **1e** in the presence of Bu₃SnH into disubstituted tetrahydrofuran **5e** (Table 2, entry 4). As a standard, the use of 2.0–2.5 equiv. of Bu₃SnH, with C₆H₅CF₃ as solvent, a reaction temperature of 80 °C, a total time of 2.0–2.5 min, and 500 W microwaves were set as optimized conditions in order to perform the succeeding experiments.

Control experiments on the stability of relevant products showed that 2-methyl-4-phenyltetrahydrofuran (**5e**) (*cis* : *trans* = 88 : 12), and 5-(*p*-methoxyphenyl)-4-methyl-2-(tributylstannylsulfanyl)thiazole (**8**) were quantitatively recovered, whereas disulfide **11** afforded 9% 4,5-disubstituted thiazole **10**, if microwave-heated (80 °C) in C₆H₅CF₃, according to ¹H NMR analysis. Treatment of [5-(*p*-methoxyphenyl)-4-methyl-2-thiazyl]disulfide (**11**) with Bu₃SnH under these conditions afforded 28% of thiazolethione **9** (Scheme 3).

In order to obtain additional information on the selectivity of alkoxy radical cyclizations upon microwave activation of *N*-(alkenoxy)thiazolethiones, 4-(*p*-chlorophenyl)-substituted compounds **2e–h** were treated with Bu₃SnH under the established optimized conditions (see Table 2, entry 2). Each of the reactions furnished the corresponding disubstituted tetrahydrofuran **5e–h** (52–70%) and 2-(tributylstannyl)sulfanyl-4-(*p*-chlorophenyl)thiazole **12** (74–93%, ¹H NMR analysis).⁵ *Cis*-diastereoisomers were favored in syntheses of 2,4-substituted heterocycles **5e** (*cis* : *trans* = 88 : 12) and **5f** (*cis* : *trans* = 90 : 10) (Table 3, entries 1–2), whereas *trans*-diastereoisomers were favored in syntheses of 3-(*tert*-butyl)-2-methyltetrahydrofuran (**5g**) (*cis* : *trans* < 2 : 98) and 5-isopropyl-2-phenyltetrahydrofuran (**5h**) (*cis* : *trans* = 30 : 70; Table 3, entries 3–4).^{11,19} Carbonyl compounds (**6e**: 8%, **6f**: 12%, **6g**: 4%, **6h**: 11%; ¹H NMR analysis), and alkenols (**7e**: 5%, **7f**: 7%, ¹H NMR analysis, Table 3) were formed as minor products.¹¹ If repeated

**Scheme 3** Control experiments for investigating product stability under microwave conditions.

on a preparative scale (1 mmol), thiazolethione **2e** provided 61% of 2-methyl-4-phenyltetrahydrofuran (**5e**) (*cis* : *trans* = 88 : 12) and 84% of tributyltin adduct **12** (Table 3, entry 1, numbers in brackets) after purification of the reaction mixture.

A search for a substitute for Bu₃SnH for possible future synthetic applications of microwave-assisted alkoxy radical reactions under reductive conditions showed that derivatives of the α -amino acid cysteine, *i.e.* L-cysteine ethyl ester hydrochloride (L-CysOEt·HCl) or the reduced form of glutathione (GSH), were adequate for this purpose.²⁰ Since both compounds are water-soluble, transformations between *N*-(2-phenylpentenoxy)thiazolethione **2e** and GSH, or the reagent combination of L-CysOEt·HCl and NaOH, were conducted in 1,4-dioxane–H₂O (2 : 1, v/v), to provide

Table 3 Conversion of *N*-(alkoxy)-4-(*p*-chlorophenyl)thiazolethiones **2e–h** in the presence of Bu₃SnH under microwave conditions^a

Entry	2, 5–7	R ^a	R ^b	R ^c	R ^d	5 (%) (<i>cis</i> : <i>trans</i>)	6 (%)	7 (%)	12 (%)
1	e	H	C ₆ H ₅	H	H	70 [61] (88 : 12)	8	5	93 [84]
2	f	H	C(CH ₃) ₃	H	H	54 (90 : 10) ^b	12	7	74
3	g	H	H	C(CH ₃) ₃	H	52 (<2 : 98) ^{b,c}	4	— ^d	81
4	h	C ₆ H ₅	H	H	CH ₃	58 (30 : 70)	11	— ^d	88

^a CP = *p*-ClC₆H₄; 2.0–2.5 equiv. Bu₃SnH. Yields of compounds **5–7** and **12** were determined by ¹H NMR, except for the values in square brackets, which are isolated yields. ^b GC. ^c *Cis*-**5g** was not detected (¹H NMR). ^d Not detected (¹H NMR).

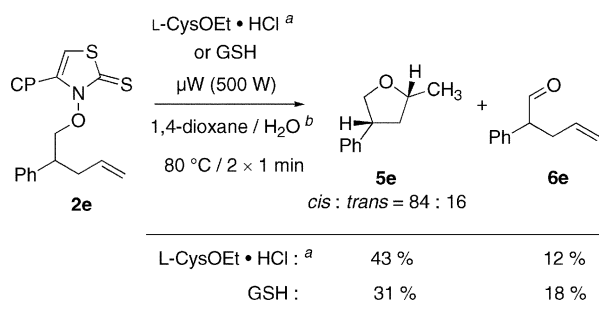
2-methyl-4-phenyltetrahydrofuran (**5e**) in 31% yield (with GSH as the hydrogen atom donor) or 43% yield (with L-CysOEt·HCl, Scheme 4). Both syntheses provided minor amounts (12–18%) of 2-phenylpentenal (**6e**) as a side product (Scheme 4). No evidence (TLC and ¹H NMR) for formation of the expected adduct of the L-cysteine-derived *S*-radical to the thione sulfur in **2e** was evident from the crude reaction mixtures. On a qualitative basis, thiazole-

derived products resembled those specified for the conversion of thione **1e** in the absence of Bu₃SnH (Table 2).²⁰

(ii) **β-C,C-cleavage – formation of carbonyl compounds.** *N*-(*Cis*-2-methylcyclopentoxo)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1i**) afforded hexanal (**13i**, 78%) (GC), 2-(tributylstannyl)sulfanylthiazole (**8**, 96%) and a small amount of 5-(*p*-methoxyphenyl)-4-methylthiazole (**10**), if treated for 1 min at 70 °C in a solution of C₆H₅CF₃ with Bu₃SnH (3.0 equiv.) in a mono-mode microwave device (Table 4, entry 1). In order to prevent loss of aldehyde **13i** due to evaporation, the temperature was constrained to 70 °C in this experiment. The same conditions were applied to prepare 4-phenylpentanal (**13j**, 42%)²¹ (¹H NMR), and tributyltin adduct **8** (93%) from *cis*-2-phenylcyclopentoxo-substituted thiazolethione **1j** and Bu₃SnH (Table 4, entry 2).

2.3 BrCCl₃-mediated reactions

(i) **Additions – 5-*exo*-trig bromocyclizations.** The feasibility of heteroatom-trapping of alkoxyl radical reaction products²² under microwave conditions was explored using BrCCl₃ as the heteroatom donor and *N*-(alkenoxy)-5-(*p*-methoxyphenyl)-4-methylthiazolethiones **1e** and **1h** as *O*-radical sources. Based



Scheme 4 The use of water-soluble thiols as reactive hydrogen atom donors in tetrahydrofuran syntheses starting from *N*-(2-phenyl-4-penten-1-oxo)thiazolethione **2e** (CP = *p*-ClC₆H₄). ^a Addition of 9 equiv. of NaOH required. ^b 2 : 1, v/v.

Table 4 Formation of aldehydes from 2-substituted *N*-(cyclopentoxo)thiazolethiones **1i** and **1j** and Bu₃SnH

Entry	1, 13	R ^c	13 (%)	8 (%)	10 (%)
1	i	CH ₃	78 ^b	96	4 ^c
2	j	C ₆ H ₅	42	93	— ^c

^a An = *p*-H₃COC₆H₄; 3.0 equiv. of Bu₃SnH. Yields were determined by ¹H NMR, unless otherwise noted. ^b GC. ^c Not detected (¹H NMR).

Table 5 Microwave-assisted conversion of *N*-(alkenoxy)thiazolethiones **1e** and **1h** in the presence of BrCCl₃^a

Entry	1, 6, 7, 14	R ^a	R ^b	R ^d	14 (%) (<i>cis</i> : <i>trans</i>)	6 (%)	7 (%)	15 (%)
1	e	H	C ₆ H ₅	H	68 [62] (88 : 12)	18	12	84 [79]
2	h	C ₆ H ₅	H	CH ₃	51 (30 : 70)	15	16	76

^a An = *p*-H₃COC₆H₄; 3.0 equiv. of BrCCl₃; 3.0–5.0 equiv. of AIBN. Yields were determined by ¹H NMR, except for the values in square brackets, which are isolated yields.

on results from a supplementary study (data not shown), AIBN (3.0 equiv.) had to be added, in order to drive the bromination reactions to completion within 2 min. Application of these parameters furnished 2-bromomethyl-4-phenyltetrahydrofuran (**14e**,²³ 68%, *cis* : *trans* = 88 : 12), aldehyde **6e** (18%), alkenol **7e** (12%) and 5-(*p*-methoxyphenyl)-4-methyl-2-(trichloromethylsulfanyl)thiazole (**15**, 84%) from *N*-(alkenoxy) compound **1e** (Table 5, entry 1; ¹H NMR analysis).²⁴ If repeated on a 1 mmol scale, bromomethyltetrahydrofuran **14e** (62%, *cis* : *trans* = 88 : 12), and trichloromethyl adduct **15** (79%) were isolated as analytically pure samples after chromatographic work up of the reaction mixtures (Table 5, entry 1, figures in square brackets). In order to compare the efficiency of microwave activation, conductive heating, and photochemical reactions for initiating *O*-radical reactions starting from *N*-(alkoxy)thiazolethiones, two further experiments were performed. Under thermal conditions, (5–10 min of heating in an oil bath at 80 °C in C₆H₅CF₃), 10–15 equiv. of AIBN and 5.0 equiv. of BrCCl₃ were necessary for converting thione **1e** into bromocyclization product **14e** (55%, *cis* : *trans* = 88 : 12). In the photochemically induced reaction, 2-bromomethyl-4-phenyltetrahydrofuran (**14e**, 59%, *cis* : *trans* = 88 : 12) was prepared upon irradiating (350 nm, 30 °C) a solution of *N*-(2-phenylpentenoxy)thiazolethione **1e** and 5.0 equiv. of BrCCl₃ in C₆H₅CF₃ for 20 min (data for the latter two experiments is not shown).

In a final bromocyclization experiment, a solution of *N*-(5-methyl-1-phenyl-4-hexen-1-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1h**) in C₆H₅CF₃ was heated under optimized microwave conditions to afford 2-(1-bromo-1-methylethyl)-5-phenyltetrahydrofuran (**14h**, 51%, *cis* : *trans* = 30 : 70),²² 5-methyl-1-phenyl-4-hexen-1-one (**6h**, 15%), the derived alkenol **7h** (16%) and trichloromethylsulfanylthiazole **15** (76%) (Table 5, entry 2).

(ii) **Homolytic substitution – remote functionalization.** Heating of a solution of *N*-(1-pentoxy)-5-(*p*-methoxyphenyl)-4-methylthiazolethione **1k**, AIBN (3.0 equiv.), and BrCCl₃ (5.0 equiv.) in C₆H₅CF₃ for 2.5 min in a mono-mode microwave instrument provided 4-bromopentan-1-ol (**16k**,⁶ 64%) (¹H NMR; Table 6, entry 1). In a similar way, 4-bromo-4-phenylbutan-1-ol (**16m**,²⁵ 37%) was obtained from thione **1m** (¹H NMR; Table 6, entry 2). Attempts to purify phenyl-substituted δ-bromohydrin **16m** by chromatography (SiO₂, petroleum ether–Et₂O = 1 : 1, v/v) resulted in a quantitative conversion of the bromoalcohol into 2-phenyltetrahydrofuran.²⁶ The heterocyclic subunit of radical precursors **1k** and **1m** was transformed in both reactions into 5-(*p*-methoxyphenyl)-4-methyl-2-(trichloromethylsulfanyl)thiazole (**15**, 81% from **1k** and 82% from **1m**) and bisthiazyl disulfide **11** (3%).

Table 6 Formation of δ-bromohydrins **16** from *N*-(alkoxy)thiazolethiones **1**^a

Entry	1, 16	R ^f	AIBN (equiv.)	16 (%)	15 (%)	11 (%)
1	k	CH ₃	2.0	64	81	3
2	m	C ₆ H ₅	4.0	37	82	3

^a An = *p*-H₃COC₆H₄; 5.0 equiv. of BrCCl₃. Yields were determined by ¹H NMR.

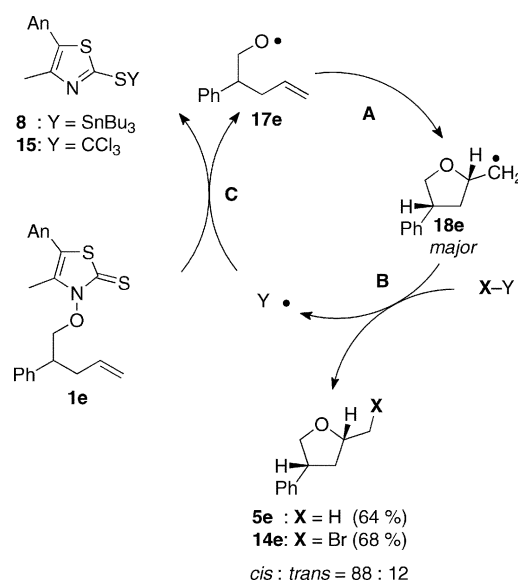
Discussion

(i) Alkoxy radical precursors

The synthesis of *N*-substituted thiazolethiones **1** and **2** was performed according to established procedures or extensions thereof.^{6,8} The selectivity of product formation and the associated yields followed trends that have been discussed in detail for structurally related derivatives of compounds **1** and **2**.^{6,9} In view of the severe difficulties noted in earlier reports of preparing tertiary *O*-alkyl derivatives of cyclic thiohydroxamates,^{5,6,27} the newly developed synthesis of *N*-(*tert*-butoxy)thiazolethione **1d** deserves a comment. The compound was finally obtained in 25% yield using *O*-*tert*-butyl-*N,N*-diisopropylisourea²⁸ as the alkylating reagent. This procedure is under current investigation in order to improve its yield and scope.

(ii) N,O-Cleavage, alkoxy radical generation, and radical chain mechanism

If dissolved in a low-absorbing solvent and heated in microwave device (2.45 GHz), *N*-(alkoxy)-5-(*p*-methoxyphenyl)-4-methylthiazolethiones **1** undergo N,O-homolysis to furnish primary, secondary, or tertiary alkoxy radicals, as shown by the formation of spin adducts **4**. The latter intermediates were identified by their characteristic *g*-values, magnitudes of the hyperfine coupling constants a_N , a_H^β , and a_H^γ , and (decisively) by the changes of EPR-parameter by gradually increasing the steric encroachment at the γ -position (Table 1).¹³ The yields of spin adducts **4a–d** were not quantified, and therefore the efficiency of N,O-homolyses in thiones **1a–d** under such conditions remained unclear. In order to determine this crucial parameter, *N*-(2-phenyl-4-penten-1-oxy)thiazolethione **1e**, as a reporter molecule, was microwave-irradiated in a mono-mode microwave instrument (500 W, 80 °C).^{29–31} Approximately half of this compound decomposes within 10 min at 80 °C to afford 2-phenyl-4-pental (6e), 2-phenyl-4-penten-1-ol (7e), and a total of three thiazole derivatives (Table 2). Although it is tempting to interpret these findings in terms of alkoxy radical generation and subsequent disproportionation, the mechanism that leads to formation of products **6e**, **7e**, and thiazole derivatives **9–11** has not hitherto been known. The fact that no 5-*exo*-trig cyclization products were detected (¹H NMR) points to a non-radical fragmentation mechanism, which requires future investigation. Selective N,O-fragmentation by the alkoxy radical mechanism, however, is attainable by adding reactive atom-transfer reagents to microwave-irradiated solutions of, e.g., thiones **1e** or **2e**, as documented by the formation of 2-methyl-4-phenyltetrahydrofuran (**5e**) and tributyltin adducts **8** or **12** (using Bu₃SnH as mediator).⁹ The synthesis of these compounds under such conditions is considered to occur by a chain mechanism (Scheme 5). Experimental evidence to support this interpretation originate from (i) results of spin-trapping experiments, (ii) stereochemical preferences for formation of major cyclization products of **5e–h**, which follow the guideline for the 4-penten-1-oxyl radical ring closure that is distinctively different from selectivities in polar cyclizations,³² and (iii) the mass balance between tributyltin adducts **8** and **12** and cyclic ethers **5e–h**. The sequence is considered to start by thermal activation of, for instance, *N*-(2-phenyl-4-penten-1-oxy)thiazolethione **1e**. Alkoxy radical release furnishes intermediate **17e**, which selectively cyclizes



Scheme 5 Elementary reactions for the formation of 2-methyl-4-phenyltetrahydrofuran (**5e**) and 2-bromomethyl-4-phenyltetrahydrofuran (**14e**) in radical chain reactions starting from *N*-(2-phenyl-4-penten-1-oxy)thiazolethione **1e**. Step A: 5-*exo*-trig cyclization. Step B: hydrogen (Bu₃SnH) or bromine atom transfer (BrCCl₃) onto cyclized radical **18e**. Step C: addition of the chain carrying the Y• radical (Bu₃Sn• or •CCl₃) to a second molecule of thione **1e**. X–Y = H–SnBu₃, Br–CCl₃.

in a 5-*exo*-trig manner in a fast, kinetically controlled reaction to afford cyclized radical **18e**.¹⁸ Trapping of tetrahydrofuryl-2-methyl radical **18e** with Bu₃SnH (see also section (iii) in the Discussion) provides 2-methyl-4-phenyltetrahydrofuran (**5e**) and radical Bu₃Sn•. The tin radical adds to the C=S group in **1e** to afford an adduct (not shown) that undergoes N,O-homolysis, thus leading to the formation of tributylstannylsulfanyl-substituted thiazole **8** and a second *O*-radical **17e**.

(iii) Hydrogen atom trapping

Bu₃SnH (BDE Sn–H = 326.4 kJ mol^{–1})³³ in a solution of C₆H₅CF₃ was the most effective mediator for performing alkoxy radical reactions in this study. Application of this reagent furnished disubstituted tetrahydrofurans (intramolecular additions) or aldehydes (β -fragmentations) without the necessity to add AIBN for the complete consumption of *O*-radical precursor **1** or **2**.⁹ A change of hydrogen donor to water-soluble non-toxic thiols (BDE S–H: e.g. *n*-PrS–H = 365.7 kJ mol^{–1})³⁴ offers the benefit to apply an aqueous solvent at the expense of a slightly reduced yield of cyclic ether **5e**.²⁰

(iv) Bromine atom trapping

Bromine atom trapping experiments (BDE Cl₃C–Br = 231 \pm 4 kJ mol^{–1})³⁵ required the use of at least 2.0 equiv. of AIBN, in order to prepare organobromine compounds in synthetically useful yields. By considering its decomposition parameters, it is obvious that the azo compound cannot be completely consumed within the time span applied for converting thiones **1** and **2** into target compounds **14** or **16** under microwave conditions.³⁶ Results from additional experiments indicated that the only detectable spin adduct that is formed in a microwave-heated solution

of *N*-(methoxy)-5-(*p*-methoxyphenyl)-4-methylthiazolethione **1a**, AIBN, and DMPO (**3**) in $\text{C}_6\text{H}_5\text{CF}_3$ ($T_{\text{max}} = 120^\circ\text{C}$) originates from $\cdot\text{C}(\text{CH}_3)_2\text{CN}$ addition to the nitrene (not shown in Table 1). On the other hand, no products of $\text{C}(\text{CH}_3)_2\text{CN}$ addition to sulfur, similar to structures of sulfides **8**, **12**, **15**, were detected in any of the bromination reactions. The role of AIBN in these reactions therefore has to be restricted to $\cdot\text{CCl}_3$ radical generation from BrCCl_3 . A second pathway that provides $\cdot\text{CCl}_3$ radicals is associated with the closing homolytic substitution step of the synthesis of bromocyclization products **14** (Scheme 5) or δ -bromohydrins **16**. If a bimolecular rate law for $\cdot\text{CCl}_3$ addition to the $\text{C}=\text{S}$ π -bond in *N*-(alkoxy)thiazole-2(3*H*)-thiones applies, the radical concentration is the key for controlling the rate of this process in order to make it fit into the kinetic scheme of the proposed chain mechanism (Scheme 5).⁹ The propensity of the $\cdot\text{CCl}_3$ radical to carry a chain reaction in thiohydroxamate-based free radical brominations has been well documented in the literature.^{22,37} In view of the fact that 2.0 equiv. of AIBN (and sometimes more) are required in order to obtain the yields of organobromine compounds that are listed in Tables 5 and 6, it is, however, unlikely that a very efficient chain reaction is maintained under these conditions.

(v) Comparison between radical precursors and methods for initiating alkoxyl radical reactions

According to the results of the present study, microwave irradiation is a powerful method for activating *N*-(alkoxy)thiazolethiones by the alkoxyl radical pathway. Its use offers the advantage to cut reaction times by a factor of about 10 and to lower the required amount of trapping reagent by a factor of approximately 2, if compared to the parameters applied in experiments initiated by conductive heating or UV/Vis photolysis. The *O*-radical selectivities observed in microwave-assisted transformations consistently agreed with those measured in related studies.^{9,22} *The observed microwave effect is therefore restricted to the alkoxyl radical-forming step.* Whereas AIBN is generally required for initiating thermally induced alkoxyl radical generation from *N*-(alkoxy)thiazolethiones **1** or **2** by conductive heating, its use under microwave conditions was restricted to bromination reactions. Free radical bromocyclizations that proceed in the absence of additional AIBN, however, are attainable. In this case the reaction between a given *N*-(alkoxy)thiazolethione **1** or **2** and BrCCl_3 has to be initiated using an appropriate light source.^{22,38}

The differences between the ability of *N*-(alkoxy)-5-(*p*-methoxyphenyl)-4-methylthiazolethiones **1** and 4-(*p*-chlorophenyl)-substituted derivatives **2** to afford products of alkoxyl radical-based transformations were small (see ESI†). In the present study, the use of 5-(*p*-methoxyphenyl)-4-methylthiazolethiones **1** was favored, due their more efficient synthetic access, improved characteristics, and reliable performance in 5-*exo*-trig cyclizations, β -fragmentations, and remote functionalizations.

As a final remark, it is worth mentioning that a removal of O_2 using freeze–pump–thaw cycles (with Ar as inert gas), which was a prerequisite for obtaining adequate yields in thermally (conductive heating) or photochemically-induced reactions, *was not necessary for successfully performing synthetic alkoxyl radical chemistry under microwave conditions.* None of the latter experiments were performed under Ar.

Conclusions

Microwave activation constitutes a significant improvement for the generation of *O*-radicals from *N*-(alkoxy)thiazolethiones. The intermediates formed in the present study underwent efficient cyclizations (synthesis of disubstituted tetrahydrofurans), β -fragmentations (formation of carbonyl compounds), and C_H -activation of aliphatic subunits by δ -selective hydrogen atom transfer under mild and neutral conditions. The advantage of the microwave method originates from considerably shorter reaction times and the use of smaller amounts of trapping reagents. It is compatible with aqueous and organic solvents, without the necessity to perform radical-based transformation in an inert gas atmosphere.

Experimental

1. General remarks

Standard instrumentation and general remarks have been disclosed previously (see also ESI†).²²

Microwave and EPR instrumentation. The following microwave equipment was used: A MLS–Ethos® 1600 mono-mode instrument (Milestone) [500 W, quartz glass vessel (length 15 cm, diameter 2 cm), equipped with a 20 bar excess pressure valve, stirring device, cooling fan, and temperature measurement by fiber optics], and a Discover® instrument (CEM) [300 W, quartz glass vessel (length 9 cm, inside diameter 1.3 cm) equipped with a 20 bar excess pressure valve, stirring device, cooling fan, and temperature measurement by an IR sensor; mode: power time]. EPR spectra were recorded with an ESP 300 spectrometer (Bruker) operating in the X-band mode at 15 mW microwave power and a modulation amplitude of 1.0 G at 20°C .

Materials. NEt_4OH (25% solution in MeOH, w/w), Bu_3SnH , BrCCl_3 , α,α' -azobis(isobutyronitrile) (AIBN) were obtained from commercial sources and were used as received (Fluka, Merck, Lancaster). *N*-(Hydroxy)-4-(*p*-chlorophenyl)thiazole-2(3*H*)-thione tetraethylammonium salt,⁸ *N*-(hydroxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt,⁸ 2-phenyl-4-penten-1-yl *p*-toluenesulfonate,¹⁸ 1-chloro-5-methyl-1-phenyl-4-hexene,¹⁹ *n*-pentyl *p*-toluenesulfonate,¹⁹ *trans*-2-methylcyclopentyl *p*-toluenesulfonate,²¹ *trans*-2-phenylcyclopentyl *p*-toluenesulfonate,²¹ 2-(1,1-dimethylethyl)-4-penten-1-yl *p*-toluenesulfonate,¹¹ 3-(1,1-dimethylethyl)-4-penten-1-yl *p*-toluenesulfonate,¹¹ *N*-methoxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1a**),⁸ and *N*-(ethoxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1a**)⁶ were prepared according to published procedures. 4-Phenyl-1-butyl *p*-toluenesulfonate was prepared from the corresponding alcohol by adapting a general procedure for the preparation of alkyl tosylates.³⁹ All solvents and reagents were purified following recommended standard procedures.⁴⁰ Petroleum ether refers to the fraction boiling in the range $45\text{--}55^\circ\text{C}$.

2. Synthesis of *N*-(alkoxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thiones

General procedure. A round-bottomed flask was charged with *N*-(hydroxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt (0.84 g, 2.20 mmol), an

appropriate alkyl chloride or tosylate (2.20 mmol), and DMF (7 mL) under argon to exclude moisture. The reaction mixture was stirred for 4–6 days at 20 °C in the dark. Afterwards, it was diluted with *tert*-butyl methyl ether (30 mL). H₂O (30 mL) was added and the phases were separated. The aqueous layer was extracted with *tert*-butyl methyl ether (3 × 20 mL). The combined organic phases were washed with a saturated aqueous solution of NaHCO₃ and brine (10 mL each). After drying (MgSO₄), the solvent was removed under reduced pressure to furnish an oil, which was purified by chromatography (SiO₂, petroleum ether–Et₂O).

***N*-(Isopropoxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (1c).** Yield: 0.47 g (73%) from 2-propyl tosylate (0.47 g, 2.20 mmol); *R*_f = 0.40 (SiO₂, petroleum ether–Et₂O = 2 : 1, v/v), light orange powder. C₁₄H₁₇NO₂S₂ (295.42) requires C 56.92, H 5.80, N 4.74, S 21.71; found C 56.81, H 5.93, N 4.86, S 21.34; δ_H (250 MHz; CDCl₃) 1.38 (d, *J* = 6.1, 6 H, CH₃), 2.29 (s, 3 H, CH₃), 3.83 (s, 3 H, OCH₃), 5.50 (sept., *J* = 6.1, 1 H, OCH₃), 6.94 (d, *J* = 8.8, 2 H, Ar–H), 7.24 (d, *J* = 8.8, 2 H, Ar–H); δ_C (63 MHz; CDCl₃) 12.7 (CH₃), 20.6 (CH₃), 25.4, 55.4 (OCH₃), 78.6 (OCH), 114.3, 114.5, 119.3, 122.7, 129.9, 130.4, 133.4, 159.9, 179.2 (C=S); λ_{max} (EtOH)/nm (lg ε) 334 (4.48), 258 sh; *m/z* (EI, 70 eV) 295 [M⁺] (55%), 237 [C₁₁H₁₁NOS₂⁺] (100), 178 [C₁₀H₁₀SO⁺] (35).

***N*-(2-Phenyl-4-penten-1-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (1e).** Yield: 0.87 g (67%) from 2-phenyl-4-penten-1-yl tosylate (0.70 g, 2.20 mmol); *R*_f = 0.35 (SiO₂, petroleum ether–Et₂O = 2 : 1, v/v), colorless solid (petroleum ether–Et₂O), mp 69 °C (DTA), dec. 105 °C (DTA); C₂₂H₂₃NO₂S₂ (397.57) requires C 66.47, H 5.83, N 3.52, S 16.13; found C 66.31, H 5.97, N 3.48, S 15.87; δ_H (400 MHz; CDCl₃) 1.96 (s, 3 H, CH₃), 2.54 (ddd, *J* = 1.4, 8.1, 14.2, 1 H), 2.73 (ddd, *J* = 1.1, 6.1, 13.1, 1 H), 3.29 (ddt, *J* = 6.3, 7.5, 13.6, 1 H), 3.83 (s, 3 H, OCH₃), 4.50 (t, *J* = 7.5, 1 H), 4.76 (dd, *J* = 6.3, 7.6, 1 H), 5.00 (dd, *J* = 1.9, 12.2, 1 H), 5.07 (dd, *J* = 1.8, 17.1, 1 H), 5.74 (dddd, *J* = 6.9, 10.4, 13.9, 17.2, 1 H), 6.91 (m_c, 2 H, Ar–H), 7.16 (m_c, 2 H, Ar–H) (m_c = centred multiplet), 7.22–7.30 (5 H, m, Ph); δ_C (100 MHz; CDCl₃) 11.6 (CH₃), 36.5, 44.4, 55.4 (OCH₃), 79.2, 114.5, 117.1, 122.5, 127.0, 128.0, 128.5, 129.8, 135.4, 140.8, 159.9, 178.7 (C=S); *m/z* (EI, 70 eV) 237 [C₁₁H₁₁NOS₂⁺] (5%), 222 (1), 131 (78), 91 (100).

***N*-(5-Methyl-1-phenyl-4-hexen-1-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (1h).** Yield: 0.94 g (52%) from 1-chloro-5-methyl-1-phenyl-4-hexene (0.46 g, 2.20 mmol); *R*_f = 0.35 (SiO₂, petroleum ether–Et₂O = 3 : 1, v/v), yellowish solid, mp 78–80 °C; C₂₄H₂₇NO₂S₂ (425.61) requires C 67.73, H 6.39, N 3.29, S 15.07, found C 67.78, H 6.48, N 3.48, S 15.37; δ_H (400 MHz; CDCl₃) 1.48 (s, 3 H, CH₃), 1.59 (s, 3 H, CH₃), 1.68 (s, 3 H), 2.03–2.19 (m, 4 H), 3.79 (s, 3 H, OCH₃), 5.09 (dt, *J* = 1.2, 5.2, 1 H), 6.09 (dd, *J* = 6.2, 8.0, 1 H), 6.85 (d, *J* = 6.2, 2 H, Ar–H), 7.01 (d, *J* = 7.0, 2 H, Ar–H), 7.34–7.40 (m, 5 H, Ph); δ_C (100 MHz; CDCl₃) 12.6 (CH₃), 18.1, 24.7, 26.1, 32.3, 86.5, 114.8, 123.5, 129.0, 129.2, 129.6, 130.0, 130.3, 134.2, 137.2, 180.0 (C=S); *m/z* (EI, 70 eV) 188 [C₁₃H₁₆O⁺] (13%), 105 (100), 77 (38).

***N*-(1-Pentoxo)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (1i).** Yield: 0.72 g from 1-pentyl tosylate (0.53 g, 2.20 mmol); *R*_f = 0.35 (SiO₂, petroleum ether–Et₂O = 2 : 1, v/v), colorless solid (petroleum ether), mp 50 °C (DTA), dec. 114 °C (DTA); C₁₆H₂₁NO₂S₂ (323.48) requires C 59.41, H 6.54, N 4.33, S

19.82; found C 59.64, H 6.42, N 4.34, S 19.48; λ_{max} (EtOH)/nm (lg ε) 336 (4.76); δ_H (400 MHz; CDCl₃) 0.94 (t, *J* = 7.2, 3 H), 1.41 (ddd, *J* = 6.9, 7.7, 14.7, 2 H), 1.53–1.45 (m, 2 H), 1.85 (dd, *J* = 6.8, 13.5, 2 H), 2.32 (s, 3 H, CH₃), 3.83 (s, 3 H, OCH₃), 4.45 (t, *J* = 6.7, 2 H), 6.94 (m_c, 2 H, Ar–H), 7.22 (m_c, 2 H, Ar–H); δ_C (100 MHz; CDCl₃) 12.4 (CH₃), 14.3, 22.9, 27.9, 28.2, 55.8 (OCH₃), 76.8, 114.7, 119.7, 123.0, 130.2, 132.6, 160.3, 179.1 (C=S); *m/z* (EI, 70 eV) 323 [M⁺] (28%), 307 (7), 237 (74), 221 (11), 178 (19), 146 (18), 70 (21).

***N*-(4-Phenyl-1-butoxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (1j).** Yield: 0.85 g (44%) from 0.67 g of 4-phenyl-1-butyl tosylate; *R*_f = 0.40 (SiO₂, petroleum ether–Et₂O = 2 : 1, v/v), colorless solid (petroleum ether), mp 71 °C (DTA), dec. 116 °C (DTA); C₂₁H₂₃NO₂S₂ (385.55) requires C 65.42, H 6.01, N 3.63, S 16.63; found C 64.85, H 5.89, N 3.68, S 16.35; δ_H (400 MHz; CDCl₃) 1.88 (m_c, 4 H), 2.30 (s, 3 H, CH₃), 2.72 (t, *J* = 7.1, 2 H), 3.84 (s, 3 H, OCH₃), 4.45 (t, *J* = 5.9, 2 H), 6.94 (m_c, 2 H, Ar–H), 7.22 (m_c, 2 H, Ar–H), 7.18–7.32 (m, 5 H, Ph–H); δ_C (100 MHz; CDCl₃) 12.4 (CH₃), 27.8, 27.9, 31.3, 55.8 (OCH₃), 76.4, 114.9, 119.7, 122.9, 126.3, 128.7, 128.8, 130.2, 132.5, 142.2, 160.3, 179.1 (C=S); *m/z* (EI, 70 eV) 237 [C₁₁H₁₁NOS₂⁺] (2%), 222 (1), 148 (8), 104 (100), 91 (43).

***N*-(Cis-2-methylcyclopentoxo)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (1k).** Yield: 0.75 g (77%) from *trans*-2-methylcyclopentyl tosylate (0.56 g); *R*_f = 0.30 (SiO₂, petroleum ether–Et₂O = 3 : 1, v/v), yellowish solid (petroleum ether–Et₂O), mp 62 °C (DTA), dec. 106 °C (DTA); C₁₇H₂₁NO₂S₂ (335.49) requires C 60.86, H 6.31, N 4.18, S 19.11; found C 60.60, H 6.45, N 4.12, S 18.59; λ_{max} (EtOH)/nm (lg ε) 338 (4.11), 230 (4.15); δ_H (400 MHz; CDCl₃) 1.27 (s, 3 H, CH₃), 1.62 (m_c, 1 H), 1.70 (m_c, 1 H), 1.78 (m_c, 1 H), 1.87–1.97 (m, 1 H), 1.92 (m_c, 1 H), 1.98 (m_c, 1 H), 2.22–2.15 (m, 1 H), 2.30 (s, 3 H, CH₃), 3.83 (s, 3 H, OCH₃), 5.62 (dt, *J* = 4.8, 4.9, 1 H), 6.94 (m_c, 2 H, Ar–H), 7.24 (m_c, 2 H, Ar–H); δ_C (100 MHz; CDCl₃) 12.5 (CH₃), 13.6, 21.9, 29.6, 31.4, 39.3, 55.4 (OCH₃), 89.8, 114.5, 119.3, 122.7, 129.8, 133.6, 159.8, 179.3 (C=S); *m/z* (EI, 70 eV) 335 [M⁺] (27%), 237 (100), 151 (15), 98 (42).

***N*-(Cis-2-phenylcyclopentoxo)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (1m).** Yield: 0.87 g (53%) from *trans*-2-phenylcyclopentyl tosylate (0.70 g); *R*_f = 0.35 (SiO₂, petroleum ether–Et₂O = 2 : 1, v/v), yellow solid (petroleum ether–Et₂O), mp 85 °C (DTA), dec. 100 °C (DTA); C₂₂H₂₃NO₂S₂ (397.56) requires C 66.47, H 5.83, N 3.52, S 16.13; found C 66.22, H 5.93, N 3.40, S 15.85; λ_{max} (EtOH)/nm (lg ε) 338 (4.14), 232 (4.16); δ_H (400 MHz; CDCl₃) 1.94 (s, 3 H, CH₃), 1.84–2.38 (m, 6 H), 3.34 (ddd, *J* = 4.4, 7.2, 1 H), 3.82 (s, 3 H, OCH₃), 6.01 (t, *J* = 3.9, 1 H), 6.91 (m_c, 2 H, Ar–H), 7.13 (m_c, 2 H, Ar–H), 7.21 (m_c, 1 H, Ph), 7.32 (m_c, 2 H, Ph), 7.50 (m_c, 2 H, Ph); δ_C (100 MHz; CDCl₃) 12.6 (CH₃), 22.3, 29.4, 30.3, 50.7, 55.8 (OCH₃), 89.2, 114.8, 123.1, 126.9, 128.4, 129.2, 130.2, 134.0, 138.9, 160.2, 180.1 (C=S); *m/z* (EI, 70 eV) 397 [M⁺] (0.1%), 160 (45), 118 (17), 104 (100), 91 (22).

***N*-(*Tert*-butoxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (1d).** A solution of *tert*-butanol (74.1 mg, 1.00 mmol) and diisopropyl carbodiimide (139 mg, 1.10 mmol, 0.17 mL) was treated with CuCl (2.00 mg, 20.2 μmol) and stirred for 24 h at 20 °C. This mixture was treated at –40 °C with a solution of *N*-(hydroxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (0.38 g, 1.50 mmol) in CH₂Cl₂ (2 mL). Stirring was continued for 24 h at 20 °C. The solids were removed by

filtration to afford a clear solution, which was concentrated under reduced pressure. The residue was purified by chromatography (SiO_2 , petroleum ether– Et_2O = 2 : 1, v/v) to afford 77.8 mg (25%) of *N*-(*tert*-butoxy)thiazolethione **1d**. R_f = 0.31 (petroleum ether– Et_2O = 2 : 1, v/v); $\text{C}_{15}\text{H}_{19}\text{NO}_2\text{S}_2$ (309.44) requires C 58.22, H 6.19, N 4.53, S 20.72; found C 58.21, H 6.02, N 4.36, S 20.38; δ_{H} (400 MHz; CDCl_3) 1.63 (s, 9 H, 2-H), 2.31 (s, 3 H, 4'- CH_3), 3.83 (s, 3 H, O- CH_3), 6.94 (m, 2 H, Ar-H), 7.25 (m, 2 H, Ar-H); δ_{C} (100 MHz; CDCl_3) 14.2 (CH_3), 28.9, 55.4 (OCH_3), 91.9, 114.5, 119.3, 123.0, 129.9, 134.3, 159.8, 182.5; m/z (EI, 70 eV) 309 [M^+] (21%), 253 [$\text{C}_{11}\text{H}_{11}\text{NO}_2\text{S}_2^+$] (100), 160 [$\text{C}_{10}\text{H}_{10}\text{NO}^+$] (30), 77 [C_6H_5^+] (7), 57 [C_4H_9^+] (11).

3. Microwave-assisted transformations

Temperature programs (TPs). For reactions using the MLS–Ethos[®] 1600 instrument (500 W, stirring device and cooling fan turned on): **TP1** (reactions in C_6H_6): 20 \rightarrow 80 $^\circ\text{C}$ (1.5 min), T_{iso} = 80 $^\circ\text{C}$ (1.0 min), 80 \rightarrow 20 $^\circ\text{C}$ (3.0 min). **TP2** (reactions in $\text{C}_6\text{H}_5\text{CF}_3$): 20 \rightarrow 80 $^\circ\text{C}$ (1.5 min), T_{iso} = 80 $^\circ\text{C}$ (for reaction times refer to Schemes and Tables), 80 \rightarrow 20 $^\circ\text{C}$ (5.0 min). **TP3**: (reactions in $\text{C}_6\text{H}_5\text{CF}_3$): 20 \rightarrow 60 $^\circ\text{C}$ (1.0 min), T_{iso} = 60 $^\circ\text{C}$ (3.0 min), 60 \rightarrow 20 $^\circ\text{C}$ (3.0 min). **TP4** (reactions in $\text{C}_6\text{H}_5\text{CF}_3$): 20 \rightarrow 70 $^\circ\text{C}$ (1.0 min), T_{iso} = 70 $^\circ\text{C}$ (1.0 min), 70 \rightarrow 20 $^\circ\text{C}$ (3.0 min). **TP5** (reactions in 1,4-dioxane– H_2O): 20 \rightarrow 80 $^\circ\text{C}$ (1.0 min), T_{iso} = 80 $^\circ\text{C}$ (1.0 min), power off (1 min), T_{iso} = 80 $^\circ\text{C}$ (1.0 min), 80 \rightarrow 20 $^\circ\text{C}$ (3.0 min). For reactions using the CEM-Discover[®] instrument (300 W, stirring device and cooling fan turned on): **TP6** (reactions in C_6H_6): 30 s reaction time, which includes heat ramp 20 \rightarrow 120 $^\circ\text{C}$.

Experiments analyzed by ^1H NMR spectroscopy. (i) **Bu_3SnH as trapping reagent.** In a typical run, an *N*-(alkoxy)-4-(*p*-chlorophenyl)thiazole-2(3*H*)-thione (**2**) (0.054 mmol) was dissolved in C_6H_6 (1 mL) or $\text{C}_6\text{H}_5\text{CF}_3$ (1 mL). Bu_3SnH (36 μL , 0.14 mmol) was added to the reaction mixture. The reaction vessel was closed, placed into the microwave device, and irradiated according to TP 1–4. The solvent was evaporated under reduced pressure to afford a residue, which was taken up with CDCl_3 (0.6 mL). Anisole (8.6 mg, 0.08 mmol) was added as internal standard. The yields of reaction products (Tables 2–4) were deduced from the relative intensities of proton resonances, referenced to the anisole OCH_3 signal (^1H NMR). Control experiments, which were performed in C_6D_6 using TP 1, gave identical results, within experimental error. (ii) **BrCCl_3 as trapping reagent.** *N*-(Alkoxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1**) (0.054 mmol) was dissolved in $\text{C}_6\text{H}_5\text{CF}_3$ (1 mL). BrCCl_3 (3.0 equiv., 0.16 mmol, 16 μL) and AIBN (3.0 equiv., 0.48 mmol, 79 mg) were added. The reaction vessel was closed, placed into the microwave device, and irradiated according to TP 2. The solvent was evaporated under reduced pressure to afford a residue, which was taken up with CDCl_3 (0.6 mL). Anisole (8.6 mg, 0.08 mmol) was added as internal standard. The yields of reaction products (Tables 2–4) were deduced from the relative intensities of proton resonances, referenced to the anisole OCH_3 signal (^1H NMR). Control experiments, which were performed in C_6D_6 using TP 1, gave identical results, within experimental error.

Experiments analyzed by GC. (i) **Bu_3SnH as trapping reagent.** In a typical run, an *N*-(alkoxy)-5-(*p*-methoxyphenyl)-4-

methylthiazole-2(3*H*)-thione (**1**) (50 μmol) and a defined amount of *n*-tetradecane (internal standard) were dissolved in $\text{C}_6\text{H}_5\text{CF}_3$ (1 mL). Bu_3SnH (2.0 equiv., 36 μL , 0.14 mmol) was added to the mixture. The reaction vessel was closed, placed into the microwave device and irradiated according to TP 4. The reaction mixture was immediately analyzed by GC. For yields refer to Tables 3 and 4. (ii) **L-Cysteine derivatives as hydrogen atom donors.** A quartz glass vessel equipped with a 20 bar pressure valve was charged with *N*-(2-phenyl-4-penten-1-oxy)-4-(*p*-chlorophenyl)thiazole-2(3*H*)-thione (**2e**) (26.4 mg, 0.068 mmol), L-cysteine ethyl ester hydrochloride (0.126 g, 0.68 mmol), NaOH (27.2 mg, 0.61 mmol), 1,4-dioxane (1 mL), and H_2O (0.5 mL). The vessel was closed and irradiated according to TP 5. The reaction mixture was analyzed by GC as described previously.²⁰ The yields of 2-methyl-4-phenyltetrahydrofuran (**5e**) and 2-phenyl-4-pentenal (**6e**) are compiled in Scheme 4. The reaction between *N*-alkoxythiazolethione **2e** and the reduced form of glutathione (0.209 g, 0.68 mmol) and thiazolethione **2e** was conducted and analyzed as in the previous experiment.

Preparative scale transformations. (i) **In the absence of additional trapping reagents.** A quartz glass vessel equipped with a 20 bar pressure valve was charged with *N*-(2-phenyl-4-penten-1-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1e**) (0.40 g, 1.01 mmol). $\text{C}_6\text{H}_5\text{CF}_3$ (10 mL) was added. The vessel was closed and irradiated according to TP 2 (T_{iso} = 10 min). The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2 , petroleum ether–*tert*-butyl methyl ether = 9 : 1, v/v) and thiazoles **9–11** to furnish 2-phenyl-4-pentenal (**5e**) (43.7 mg, 27%, R_f = 0.48), 2-phenyl-4-penten-1-ol (**6e**) (26.2 mg, 16%, R_f = 0.19 for petroleum ether–ethyl acetate = 9 : 1, v/v). 5-(*p*-Methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**9**). Yield: 0.24 g (31%); R_f = 0.72 (SiO_2 , petroleum ether–acetone = 2 : 1, v/v), colorless crystals (MeOH); $\text{C}_{11}\text{H}_{11}\text{NOS}_2$ (237.33) requires C 55.67, H 4.67, N 5.90, S 27.02; found C 55.43, H 4.51, N 5.75, S 26.13. HR MS calcd. 237.0282, found 237.0282; λ_{max} (EtOH)/nm (lg ϵ) 284 (4.23); δ_{H} (250 MHz; CDCl_3) 2.31 (s, 3 H, CH_3), 3.84 (s, 3 H, OCH_3), 6.94 (d, J = 8.6, 2 H, Ar-H), 7.25 (d, J = 8.6, 2 H, Ar-H); δ_{C} (63 MHz; CDCl_3) 33.7 (CH_3), 36.6, 55.4, 114.4, 130.0, 159.8, 171.5; m/z (EI, 70 eV) 237 [M^+] (100), 222 (17), 178 (5), 163 (14). 5-(*p*-Methoxyphenyl)-4-methylthiazole (**10**). Yield: 4.1 mg (2%); R_f = 0.54 (SiO_2 , petroleum ether–acetone = 2 : 1, v/v), colorless powder (petroleum ether– Et_2O); $\text{C}_{11}\text{H}_{11}\text{NOS}$ (205.28) requires C 64.36, H 5.40, N 6.82, S 15.62; found C 64.96, H 5.23, N 6.54, S 15.47; HR MS calcd. 205.0561, found 205.0563; δ_{H} (250 MHz; CDCl_3) 2.55 (s, 3 H, CH_3), 3.86 (s, 3 H, OCH_3), 6.97 (d, J = 8.9, 2 H, Ar-H), 7.37 (d, J = 8.9, 2 H, Ar-H), 8.77 (s, 1 H); δ_{C} (63 MHz; CDCl_3) 15.5 (OCH_3), 55.4 (CH_3), 107.9, 114.3, 123.4, 130.5, 146.8, 149.9, 159.7; m/z (EI, 70 eV) 205 [M^+] (100), 190 (44), 178 (11), 163 (23). 2,2'-Bis[5-(*p*-methoxyphenyl)-4-methylthiazyl]disulfide (**11**). Yield: 4.8 mg (5%). Yellow needles (MeOH); R_f = 0.63 (SiO_2 , petroleum ether– Et_2O = 5 : 1, v/v); $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_2\text{S}_4$ (472.65) requires C 55.91, H 4.27, N 5.93, S 27.13; found: C 55.27, H 4.08, N 5.36, S 27.02; HR MS calcd. 472.0408, found 472.0407; λ_{max} (EtOH)/nm (lg ϵ) 330 nm (4.37), 300sh (4.12); δ_{H} (250 MHz; CDCl_3) 2.46 (s, 6 H, CH_3), 3.84 (s, 6 H, OCH_3), 6.94 (d, J = 8.3, 4 H, Ar-H), 7.33 (4 H, d, J 8.3, Ar-H). m/z (EI, 70 eV) 472 [M^+] (20), 237 (100), 205 (9), 178 (23), 163 (28). (ii) **Bu_3SnH as hydrogen atom donor.** A quartz glass vessel equipped with a

20 bar pressure valve was charged with *N*-(2-phenyl-4-penten-1-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1e**) (0.40 g, 1.01 mmol), C₆H₅CF₃ (10 mL), and Bu₃SnH (0.53 mL, 2.02 mmol). The vessel was closed and irradiated according to TP 2. The solvent was evaporated under reduced pressure to furnish a residue, which was purified by column chromatography (SiO₂, petroleum ether–Et₂O = 2 : 1, v/v) to afford 2-methyl-4-phenyl tetrahydrofuran (**5e**) (86.8 mg, 53%) as colorless liquid (*cis*-**5e** : *trans*-**5e** = 88:12), and 5-(*p*-methoxyphenyl)-4-methyl-2-(*tri-n*-butylstannylsulfanyl)thiazole (**8**). Yield: 0.46 g (87%). *R*_f = 0.45 (SiO₂, petroleum ether–Et₂O = 5 : 1, v/v), colorless oil; C₂₃H₃₇NOS₂Sn (526.39) requires C 52.48, H 7.08, N 2.66, S 12.18; found C 52.23, H 7.45, N 2.54, S 11.27; HR MS calcd. 527.1339, found 527.1338; λ_{max} (EtOH)/nm (lg ε) 318 (4.17); δ_H (250 MHz; CDCl₃) 0.94 (t, *J* = 7.3, 9 H, CH₃), 1.35 (m_c, *J* = 7.3, 8.3, 12 H, CH₂CH₂), 1.62 (m_c, *J* = 8.3, 6 H, CH₂), 2.32 (s, 3 H, CH₃), 3.83 (s, 3 H, OCH₃), 6.91 (d, *J* = 8.8, 2 H, Ar–H), 7.29 (d, *J* = 8.8, 2 H, Ar–H); δ_C (63 MHz; CDCl₃) 13.7 (CH₃), 15.9 (CH₂Sn), 27.1 (CH₂), 28.6 (CH₂), 55.3 (CH₃), 107.8, 114.0, 114.2, 124.8, 130.2, 158.9, 171.6 (2 × C); *m/z* (EI, 70 eV) 526 [M⁺] (0.2%), 470 [M⁺ – C₄H₉] (100), 356 (34), 237 (18), 204 (9), 177 (8).

(iii) In the presence of BrCCl₃. A quartz glass vessel equipped with a 20 bar pressure valve was charged with *N*-(2-phenyl-4-penten-1-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1e**) (0.40 g, 1.01 mmol), C₆H₅CF₃ (10 mL), BrCCl₃ (3.03 mmol, 0.3 mL), and AIBN (3.03 mmol, 497 mg). The vessel was closed and irradiated according to TP 2 with *T*_{iso} extended to 2.5 min. The solvent was concentrated under reduced pressure and purified by column chromatography (SiO₂) to furnish 2-bromomethyl-4-phenyltetrahydrofuran (**14e**) (151.0 mg, 62%) as a colorless liquid [*R*_f = 0.45 (SiO₂, petroleum ether–*tert*-butyl methyl ether = 9 : 1, v/v)] and 5-(*p*-methoxyphenyl)-4-methyl-2-(trichloromethylsulfanyl)thiazole (**15**). Yield: 0.28 g (79%). *R*_f = 0.77 (SiO₂, petroleum ether–acetone = 4 : 1, v/v), yellowish crystals (MeOH). C₁₂H₁₀Cl₃NOS₂ (354.70) requires C 40.63, H 2.84, N 3.95, S 18.08; found C 40.27, H 2.77, N 3.75, S 16.52; HRMS: calcd. 352.9269, found 352.9269; λ_{max} (CH₃CN)/nm (lg ε) 324 (4.33); δ_H (250 MHz; CDCl₃) 2.59 (s, 3 H, CH₃), 3.86 (s, 3 H, OCH₃), 6.99 (d, *J* = 7.5, 2 H, Ar–H), 7.41 (d, *J* = 7.5, 2 H, Ar–H); δ_C (63 MHz; CDCl₃) 16.3 (CH₃), 55.4 (OCH₃), 114.4, 123.0, 130.6, 141.6, 150.3, 160.1, 182.5; *m/z* (EI, 70 eV) 354 [M⁺] (15), 236 (100), 177 (42).

Spin-trapping experiments in the presence of DMPO (**3**).

A quartz vessel was charged with a solution of *N*-(alkoxy)thiazolethiones **1a–d** (*c*₀ = 10^{–2} M) and DMPO (*c*₀ = 1.8 × 10^{–2} M) in anhydrous C₆H₆. The solution was purged with Ar (5 min). The vessel was crimped, irradiated according to TP 6, and placed in the cavity of the EPR spectrometer. The EPR data are compiled in Table 1.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (Grant Ha1705/5–2 and Graduiertenkolleg 690: Elektronendichte-Theorie und Experiment). We thank Prof. Dr U. Holzgrabe for providing access to the MLS–Ethos® 1600 microwave device, Dr E. Heller for helpful discussions, and CEM for providing the Discover® device.

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