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Spin trapping of alkoxyl radicals generated from 5-methyl and 5-aryl-3-alkoxy-4-methylthiazole-2(3*H*)-thiones in photochemically induced and microwave-initiated reactions

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ABSTRACT

Methoxyl and isopropoxyl radicals were generated from *N*-alkoxy-4,5-dimethylthiazole-2(3*H*)-thiones ($\lambda_{max}\sim320$ nm) and 5-aryl derivatives (aryl=*p*-XC_6H_4; X=MeO, H, AcNH, Cl) ($\lambda_{max}\sim335$ nm) in photochemically and microwave-induced reactions. Alkoxyl radicals were trapped with dimethylpyrrolidine *N*-oxide and characterized as spin adducts via EPR. Cumyloxyl radicals were liberated in a similar manner from *N*-cumyloxy-5-(4-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione. A noteworthy bathochromic shift was found for the lowest energy transition of *N*-(hydroxy)indeno[2,1-*d*]thiazole-2(3*H*)-thione (λ_{max}=376 nm), if compared to the UV–vis absorption of *N*-hydroxy-4-methyl-5-phenylthiazole-2(3*H*)-thione (λ_{max}=338 nm). Syntheses of alkoxyl radical precursors and procedures for conducting N,O-homolysis are described in a full account.

1. Introduction

The advent of *O*-alkyl thiohydroxamates as sources of oxygen-centered radicals has significantly contributed to current developments in synthetic heteroatom radical chemistry.[1–3] Alkoxyl radical generation from this type of precursor is feasible upon visible light or near UV-excitation, microwave irradiation, or conductive heating in the presence of an initiator.[4,5] The ease of activation thereby gradually decreases along the series of compounds *N*-(alkoxy)-pyridine-2(1*H*)-thiones>*N*-(alkoxy)thiazole-2(3*H*)-thiones (e.g., **1**–**3**)>acyclic *O*-(alkyl)thiohydroxamates.[6–9] Alkoxyl radicals that are liberated under such conditions participate in efficient tin-free chain reactions and have opened new perspectives for C,H-activation,[10,11] stereoselective tetrahydrofuran,[12,13] and tetrahydropyran synthesis,[14] and norbornene functionalization.[15]

N-Alkoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*)-thiones ($\lambda_{max}\sim$ 320 nm, not shown) were for many years the reagents of choice in this laboratory for pursuing mechanistic and synthetic aspects of oxyl radical chemsitry.[3,16] Steric encroachment imposed by the 4-(*p*-chlorophenyl) substituent was found over the years, to hinder formation of tertiary alkoxyl radical precursors, which led to the development of compounds having an aryl group located in position 5, such as in 3-hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**3**). The bathochromic shift exerted by the aromatic substituent onto electronic transitions in heterocycle **3** ($\lambda_{max}\sim334$ nm) raised the question about a control of UV–vis-excitation energies in thiazole-derived cyclic thiohydroxamates in general.[7] In the course of a time-dependent density functional theoretical study on photophysical events leading to N,O-homolysis, a larger set of thiazolethiones was therefore investigated on a computational level. A considerable number of molecules of interest, however, were not included into the original paper, since experimental data for referencing calculated electronic transitions were for reasons of synthetic difficulties not available at that time. Other compounds were included, although their potential to liberate alkoxyl radicals upon photoexcitation had not been verified. Progress in microwave-assisted synthesis of arylpropanones recently opened new perspectives for preparing 5-aryl-3-hydroxy-4-methylthiazolethiones having a moderately electron releasing group (e.g., NHAc in **4**) and an electron withdrawing substituent (e.g., Cl in **5**) located in the aromatic subunit (Fig. 1), in order to complete the series of compounds required for UV–vis spectra correlation. A second input from theory related to a predicted bathochromic shift in case of coplanar arrangement of aryl and thiazole-2(3*H*)-thione entities.[7] Since this arrangement poses a transition structure associated with phenyl group rotation about the C,C-bond connecting both fragments in **2**, a synthesis of 3-(hydroxy)indeno[2,1-*d*]thiazole-2(3*H*)-thione (**6**) was devised for testing theory.

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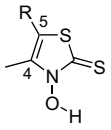
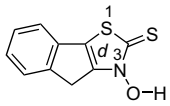


1–5



6

1–5	R
1	CH_3
2	C_6H_5
3	*p*-$(H_3CO)C_6H_4$
4	*p*-$(AcNH)C_6H_4$
5	*p*-ClC_6H_4

Figure 1. Structural formulae and indexing of cyclic thiohydroxamic acids.

The major findings of the present study showed that the location of the lowest energy UV–vis band of *N*-hydroxy and *N*-alkoxy-4-arylthiazole-2(3*H*)-thiones, relevant for inducing N,O-homolysis, was only marginally dependent on the nature of the *p*-substituent. 3-(Hydroxy)indeno[2,1-*d*]thiazole-2(3*H*)-thione (**6**), on the other hand, exhibited a significant bathochromic shift (~38 nm), if compared to derivative **2**. The compound, however, also showed a number of peculiarities, which require future investigation. *N*-Methoxy and isopropoxy derivatives that were prepared from thiohydroxamic acids **1**–**5** furnished alkoxyl radicals upon near UV or microwave excitation. In extension to this methodology, cumyloxyl radicals were generated and trapped. The efficiency of *O*-radical generation was in all instances equivalent, as judged on the basis of EPR spectra of spin adducts. Major results of the study are summarized and discussed in the following sections.

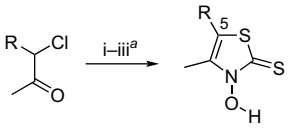
2. Results

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

5-Substituted *N*-(hydroxy)-4-methylthiazole-2(3*H*)-thiones **1**–**5** were prepared in extension to a procedure originally developed for 4-(*p*-chlorophenyl)thiazole-2(3*H*)-thione.[17] The sequence started from 3-substituted propanones (not shown). 2-(4-Chlorophenyl)- and 2-(4-acetylaminophenyl)propan-2-one were prepared from *p*-chloro- and *p*-nitrobenzaldehyde in microwave-assisted nitroaldol condensations or standard procedures thereof.[18,19] Likewise obtained β-nitrostyrenes (not shown) were converted with Fe/HCl [formation of 1-(4-chlorophenyl)propan-2-one] or $Fe/FeCl_2\cdot 4H_2O/Ac_2O$/HOAc [synthesis of 1-(4-acetamidophenyl)propan-2-one] into derived 1-aryl propanones.[20,21] Treatment of the latter with SO_2Cl_2 at 0 °C furnished α-chloroketones **7**–**11** in 65–90% yield.[22] Substitution of *O*-ethyldithiocarbonate for chloride provided α-keto xanthogenates (Table 1, step i), which were treated with hydroxylamine hydrochloride in the presence of pyridine (Table 1, step ii). Vicinal oximino xanthogenates that were formed in the latter reaction underwent efficient 5-*exo*-cyclizations in the presence of KOH in H_2O/CH_2Cl_2 (Table 1, step iii). 5-Substituted *N*-(hydroxy)-4-methylthiazole-2(3*H*)-thiones **1**–**5** were obtained as colorless (**1**) or tan (**2**–**5**) crystalline solids that decomposed (differential thermoanalysis) either prior (e.g., **3**: 158 °C) or after melting (e.g., **1**: mp 88 °C, dec 131 °C).

3-(Hydroxy)indeno[2,1-*d*]thiazole-2(3*H*)-thione (**6**) was prepared from 1-chloro-2-indanone (**12**)[23] in 11% overall yield, according to a similar sequence described for thiones **1**–**5** above (Scheme 1, Table 1). The compound crystallized from petroleum ether/Et_2O as tan solid that decomposed on melting at 148 °C. It was identified via NMR (^1H, ^{13}C, HMBC, HMQC), UV–vis spectroscopy (λ=376 and 267 nm, in MeOH, Fig. 2), and combustion analysis. Thione **6** decomposed rapidly on standing as neat sample at 20 °C or in $CDCl_3$ solution (^1H NMR). Attempts to grow crystals suitable for X-ray diffraction consistently provided 2-oxo-1-indanonoxime.[24]

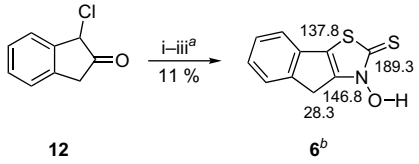
Table 1
Formation of *N*-(hydroxy)thiazole-2(3*H*)-thiones from α-chloroketones



7–11 **1–5**

Entry	R	7–11	1–5 [%]	λ_{max}/nm (lg ε/m^2 mol^{-1})
1	CH_3	**7**	**1**: 74	316 (3.14)[b]
2	C_6H_5	**8**	**2**: 45	338 (3.12)[b]
3	*p*-$(H_3CO)C_6H_4$	**9**	**3**: 66	334 (3.20)[b]
4	*p*-$(AcNH)C_6H_4$	**10**	**4**: 59	336 (3.14)[c]
5	*p*-ClC_6H_4	**11**	**5**: 21	333 (3.21)[c]

[a]Reagents and conditions: (i) potassium *O*-ethyl xanthogenate, acetone, 25 °C, 2 h; (ii) $NH_2OH\cdot HCl$, pyridine, CH_3OH, 0→25 °C, 16 h; (iii) KOH, H_2O, CH_2Cl_2, 0→25 °C, 2 h.
[b] in MeOH.
[c] in EtOH.



12 **6**[b]

Scheme 1. Preparation of 3-(hydroxy)indeno[2,1-*d*]thiazole-2(3*H*)-thione (**6**) from 1-chloro-2-indanone (**12**). Figures in italics refer to selected ^{13}C NMR shift values ($CDCl_3$). (a) Reagents and conditions: (i) potassium *O*-ethyl xanthogenate, acetone, 25 °C, 2 h (67%); (ii) $NH_2OH\cdot HCl$, pyridine, CH_3OH, 0→25 °C, 16 h (94%); (iii) KOH, H_2O, CH_2Cl_2, 0→25 °C, 2 h (25%). (b) λ_{max}/nm (lg ε)=376 (2.45), ε in m^2 mol^{-1}.

Deprotonation of thiohydroxamic acids **1**–**6** with tetrabutylammonium hydroxide furnished thiohydroxamate tetrabutylammonium salts as tan powders (not shown). Alkylation of the latter with methyl or isopropyl *p*-toluenesulfonate in anhydrous DMF at 25 °C occurred selectively at oxygen to furnish *O*-esters **13a**–**17a** (R^1=CH_3; Table 2, entries 1–5) and **13b**–**17b** [R^1=$CH(CH_3)_2$; Table 2, entries 6–10] as colorless to tan solids in 45–82% yield. Since the reaction between *N*-(hydroxy)indeno[2,

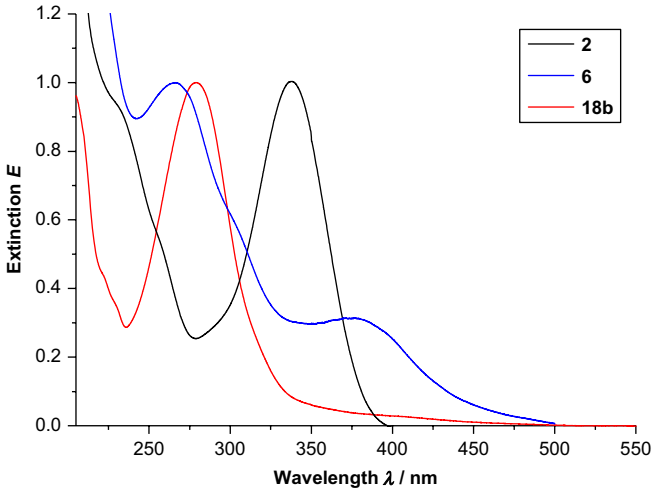
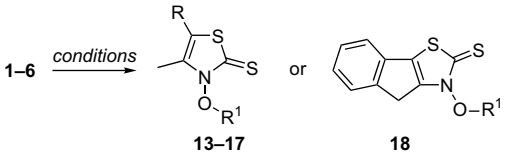


Figure 2. Superposition of normalized electronic spectra of *N*-hydroxy-4-methyl-5-phenylthiazolethione **2**, indene derivative **6** and 3-(isopropoxy)indeno[2,1-*d*]thiazole-2(3*H*)-thione (**18b**) (MeOH, 20 °C).

Table 2
O-Alkylation of cyclic thiohydroxamic acids **1**–**6**



13–17 **18**

Entry	**1**–**6**[a]	R^1	Conditions[b]	**13**–**18**/%	λ_{max}/nm (lg ε/m^2 mol^{-1})
1	**1**	CH_3	iv, v	**13a**: 68	321 (3.16)[c]
2	**2**	CH_3	iv, v	**14a**: 45	333 (3.28)[c]
3	**3**	CH_3	iv, v	**15a**: 64	333 (3.30)[c]
4	**4**	CH_3	iv, v	**16a**: 64	336 (3.22)[d]
5	**5**	CH_3	iv, v	**17a**: 59	335 (3.28)[d]
6	**1**	$CH(CH_3)_2$	iv, vi	**13b**: 82	322 (3.14)[c]
7	**2**	$CH(CH_3)_2$	iv, vi	**14b**: 62	334 (3.27)[c]
8	**3**	$CH(CH_3)_2$	iv, vi	**15b**: 73	335 (3.29)[c]
9	**4**	$CH(CH_3)_2$	iv, vi	**16b**: 53	337 (3.21)[d]
10	**5**	$CH(CH_3)_2$	iv, vi	**17b**: 71	337 (3.21)[d]
11	**6**	$CH(CH_3)_2$	iv, vii	**18b**: 9	279 (3.25)[c]
12	**3**	$C(CH_3)_2C_6H_5$	viii	**15c**: 15	337 (3.26)[c]

[a] For indexing of compounds **1**–**5** see Table 1.
[b] iv: NBu_4OH, CH_3OH, 25 °C; v: $TsOCH_3$, DMF, 25 °C; vi: ^{i}PrOTs, DMF, 25 °C; vii: ^{i}PrCl, DMF 25 °C; viii: 2-phenyl-2-propanol, DIC, CuCl, CH_2Cl_2.
[c] in MeOH.
[d] in EtOH.

1-*d*]thiazole-2(3*H*)-thione tetrabutylammonium salt and ^{i}PrOTs in DMF consistently provided a mixture of *N*-isopropoxy compound **18d** and unspent tosylate that was not separable in our hands, 2-chloropropane was used as alternative alkylating reagent (Table 2, entry 11). This modification allowed to obtain pure thione **18b** as brown oil. Its electronic spectrum (λ>200 nm) showed a broad and featureless band at λ=279 nm with a tail end reaching to ~420 nm (Fig. 2). *N*-(Cumyloxy)thiazolethione **15c** was isolated as a tan crystalline solid in gram quantities starting from *N*-(hydroxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**3**), 2-phenyl-2-propanol, diisopropyl carbodiimide and CuCl in a solution of anhydrous CH_2Cl_2 (Table 1, entry 12).[25–27]

2.2. Photochemically induced and microwave-initiated transformations

Solutions of *N*-(alkoxy)thiazolethiones **13**–**17** (c_o=10^{-2} M) and 2-dimethylpyrrolidine-*N*-oxide (DMPO; c_o=1.8×10^{-2} M) in C_6H_6 were subjected to microwave irradiation (1 min, 300 W, monomode apparatus)[†] in sealed tubes at 120 °C. EPR spectra recorded from solutions prepared from decomposition of *N*-(methoxy) thiazolethiones **13a**–**17a** and *N*-isopropoxy derivatives **13b**–**17b** provided signals at *g*=2.0081–2.0082 G (e.g., Fig. 3). Spectra simulation[28,29] and numerical analysis of fitted curves allowed to determine coupling constants a_N, a_H^β, and a_H^γ (Table 3, entries 1–10), which were diagnostic for spin adducts **19a** and **19b** (Table 3, Fig. 3).[30] Microwave heating of *N*-(cumyloxy)thiazolethione **15c** under similar conditions furnished a signal at *g*=2.0080 G showing larger a_H^β and a smaller a_H^γ value while a_N was approximately constant, thus pointing to cumyloxyl radical trapping by DMPO. Spectra similar to those from microwave experiments were recorded from solutions prepared by irradiating (λ=350 nm) *N*-(isopropoxy)thiazolethiones **13b**–**17b** for 1 min in C_6H_6 at 25 °C in the presence of DMPO (Table 3, entries 6–10). Photolysis of *N*-(isopropoxy)indenothiazolethione **18b** under such conditions consistently furnished an EPR signal at *g*=2.0082. Data analysis led

[†] The use of specialized microwave equipment for conducting microwave-assisted transformations is strongly advised.

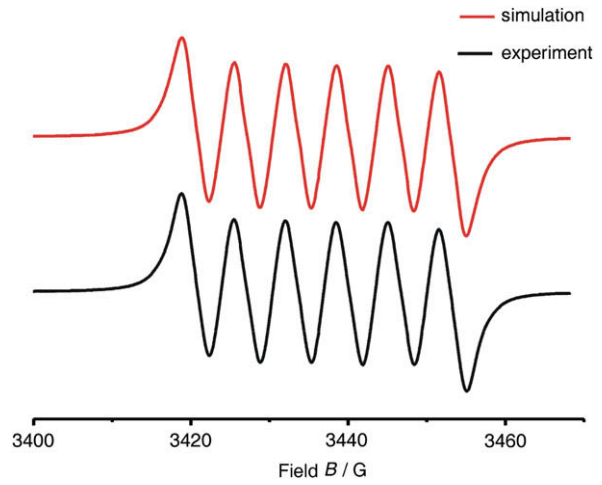


Figure 3. EPR spectrum of 2-isopropoxy-substituted nitroxyl radical **19b** recorded from a photolyzed solution of thione **15b** and DMPO in C_6H_6 at 20 °C.

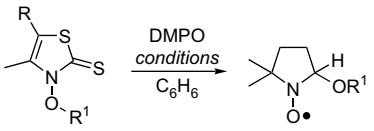
to coupling constants of a_N=12.7 G, a_H^β=8.8 G, and a_H^γ=1.4 G, which were distinctively different from values recorded for **19b** in experiments starting from thiones **13b**–**17b**.

3. Discussion

3.1. Preparation and properties of *N*-(alkoxy)thiazole-2(3*H*)-thiones

The established synthesis of *N*-(hydroxy)thiazole-2(3*H*)-thiones[17,31,32] was modified in the present study, starting from α-chloroketones instead of α-bromoketones. The former were less severe lachrymators and provided higher yields of purer α-haloketones **7**–**12**. Sufficiently pure material for α-chlorination of 1-(4-chlorophenyl)propan-2-one was obtained via the nitroolefin pathway (see Section 5). Alternative approaches using arene-substitution (starting from chlorobenzene)[33] or organometallic reactions (starting from *p*-chlorophenylacetic acid)[34–36] were not successful in our hands. The unexpectedly low yield in the final step of *N*-(hydroxy)indenothiazolethione synthesis was attributed to an inherent lability of compound **6** toward base. If treated, for instance, with NEt_4OH in a solution of CH_3OH, as

Table 3
Spin adduct formation from thiones **13**–**17** and DMPO



13–17 **19**

Entry	**13**–**18**	Conditions[a]	**19**[b]	*g*	a_N/G	a_H^β/G	a_H^γ/G
1	**13a**	MW	**19a**	2.0081	12.8	6.5	1.7
2	**14a**	MW	**19a**	2.0082	12.8	6.7	1.7
3	**15a**	MW	**19a**	2.0081	12.8	6.5	1.7
4	**16a**	MW	**19a**	2.0081	12.8	6.5	1.6
5	**17a**	MW	**19a**	2.0082	12.7	6.3	1.6
6	**13b**	MW/*hν*	**19b**	2.0081/2.0081	13.0/13.0	6.4/6.5	1.8/1.7
7	**14b**	MW/*hν*	**19b**	2.0082/2.0082	13.0/13.0	6.5/6.5	1.7/1.7
8	**15b**	MW/*hν*	**19b**	2.0080/2.0080	12.9/13.0	6.3/6.5	1.9/1.7
9	**16b**	MW/*hν*	**19b**	2.0081/2.0080	13.0/13.1	6.5/6.5	1.7/1.7
10	**17b**	MW/*hν*	**19b**	2.0081/2.0080	12.9/13.0	6.5/6.5	1.7/1.7
11	**15c**	MW	**19c**	2.0080	13.1	9.3	1.5

[a] MW: 300 W, 120 °C, *hν* (λ=350 nm), 25 °C.
[b] indexing for spin adducts **19**: **a** for R^1=CH_3, **b** for R^1=$CH(CH_3)_2$, **c** for R^1=$C(C_6H_5)(CH_3)_2$.

required for the synthesis of isopropyl ester **18b**, acid **6** not only got deprotonated but also underwent secondary transformations, which have so far not been fully explored.[24]

^{13}C NMR resonances of the thiocarbonyl group in *N*-hydroxy compounds **1**–**6** ($CDCl_3$) showed a gradual shift along the sequence 168.5 (**1**, R=CH_3) <169.3 (**2**, R=C_6H_5) <170.2 (**5**, R=*p*-$ClC_6H_4CH_3$) <172.0 (**3**, R=*p*-$MeOC_6H_4$) <175.9 [**4**, R=*p*-(AcNH)C_6H_4] <189.2 (**6**). Although the origin of the underlying effect is not known, the location of $\delta_{C=S}$ for **6** was similarly noteworthy as its lowest energy UV–vis band (λ_{max}=376 nm, in MeOH), in particular if compared to compound **2** (λ_{max}=338 nm, in MeOH). In view of the existing information from computational and X-ray crystallographic work[7] it seemed reasonable to assume that the most significantly populated conformer of 5-phenyl-4-methylthiazolethione **2** showed a twist of ~40° between phenyl and thiazolethione entities. The π-system in indenothiazolethione **6**, on the other hand, is expected to be planar. The bathochromic shift of ~38 nm observed for the UV–vis absorption of fused tricyclic compound **6** therefore should reflect a smaller HOMO–LUMO gap due to more extensive π-electron delocalization, compared to 5-phenylthiazolethione **2**. The present study also clarified that 5-aryl for 5-methyl substitution in *N*-(hydroxy)thiazole-2(3*H*)-thiones causes a bathochromic shift of ~20 nm. *p*-Substituent variation, on the other hand, from OMe, NHAc, H, to Cl was not associated with notable UV–vis spectral changes (Tables 1 and 2).

Selective O-alkylation of *N*-(hydroxy)thiazolethione tetrabutylammonium salts was attainable using hard alkylating reagents (alkyl tosylates and chlorides). The yields gradually decreased along the sequence of introduced alkyl groups ^{i}Pr>Me>cumyl.[11,13,15,16] Although the yield of tertiary thiohydroxamic acid *O*-ester **15c** did not exceed 15%, it should be noted that alternative pathways starting from cumyl halides, or 2-phenyl-2-propanol/acid combinations, and a variety of thiohydroxamate salts, had completely failed so far.

On storage in flasks exposed to conventional laboratory illumination at 20 °C, stability of thiones gradually fell along the series of ester substituents CH_3>$CH(CH_3)_2$≫$C(C_6H_5)(CH_3)_2$. Primary/secondary thiazolethiones **13a**/**b**–**17a**/**b** therefore were kept in the dark (e.g., in amber colored flasks) at 20 °C, whereas tertiary derivative **15c** preferentially was stored in a freezer (−20 °C).

3.2. Identification of reactive intermediates

Photochemical and microwave-induced activation of *N*-(alkoxy)thiazolethiones **13**–**17** furnished derived alkoxyl radicals as judged on the basis of spin-trapping experiments and subsequent EPR analysis. Although the use of alternative solvents, such as α,α,α-trifluorotoluene, for synthetic purposes generally is favored, trapping reactions were preferentially conducted in C_6H_6 (e.g., Fig. 3). The latter choice and the use of 5 mm diameter cuvettes increased signal to noise ratio considerably. Likewise obtained spectra were assigned to spin adducts **19a**–**c** on the basis of *g*-values and diagnostic changes observed in going from methoxy via isopropoxy to cumyloxy substitution. Differences in terms of rate and efficiency of alkoxyl radical generation from *N*-(alkoxy)thiazolethione under such conditions were not evident from the present data. Since *N*-(alkoxy)- and *N*-(alkenoxyl)-5-(*p*-methoxyphenyl)-4-methylthiazolethiones, for example, **15a**–**c** and derivatives thereof, have already been successfully applied in a number of alkoxyl radical-based investigations, it is expected that derivatives of thiones **13**–**14**, and **16**–**17** will show similar utility for such purposes. This circumstance is particularly of interest for solid phase tethering of derivatives of *p*-acetamido-substituted thiazolethiones,[37] which, in addition to the chemistry of *N*-(hydroxy)indeno[2,1-*d*]thiazole-2(3*H*)-thione (**6**), is being pursued at the moment in this laboratory.

4. Conclusion

5-Methyl- (λ_{max}=318 nm) and 5-aryl (aryl=*p*-XC_6H_4; X=MeO, H, AcNH, Cl) (λ~331–336 nm) substituted *N*-hydroxy-4-methylthiazole-2(3*H*)thiones **1**–**5** were prepared in synthetically useful yields and quantities. The general approach was successfully adapted for the synthesis of *N*-(hydroxy)indeno[2,1-d]thiazole-2(3*H*)-thione (**6**) (λ_{max}=376 nm). O-Alkylation of thiohydroxamic acids was feasible, with the efficiency gradually decreasing along the sequence of introduced alkyl group ^{i}Pr>Me>cumyl. *N*-Alkoxy-4-methylthiazole-2(3*H*)thiones **13**–**17** afforded alkoxyl radicals, if photolyzed (λ=350 nm, 1 min, 20 °C) or activated in a monomode microwave instrument (1 min, 120 °C) in the absence of AIBN, as evident from spin-trapping experiments and subsequent EPR analysis. These findings are expected open perspectives for new developments in synthetic and mechanistic alkoxyl radical chemistry.

5. Experimental

5.1. General

Standard instrumentation and general remarks have been disclosed previously.[13] 3-Chlorobutan-2-one (**7**), 1-phenylpropan-2-one, and 1-(*p*-methoxyphenyl)propan-2-one were commercially available. 1-Chloro-1-phenylpropanone (**8**) (88%),[22,32] 1-chloro-1-(*p*-methoxyphenyl)propanone (**9**) (93%),[22] 1-chloro-2-indanone (**12**),[23] 3-(ethoxythiocarbonylsulfanyl)-2-butanone,[38] *N*-methyl-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**15a**), and *N*-isopropoxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**15b**)[4,7] were prepared according to published procedures.

5.1.1. Microwave and EPR instrumentation

Discover® (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, temperature measurement via IR sensor. 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.

5.2. *N*-(Hydroxy)thiazole-2(3*H*)-thiones

5.2.1. Nitrostyrenes

5.2.1.1. 1-Nitro-4-(2-nitro-propenyl)-benzene. A solution of *p*-nitrobenzaldehyde (49.4 g, 359 mmol), nitroethane (28.1 g, 359 mmol) and piperidine (8.1 mL) in toluene was refluxed for 16 h using a Dean-Stark trap. The solvent was removed under reduced pressure. The remaining viscous dark red oil was taken up in CH_2Cl_2 (400 mL) and washed with H_2O (2×125 mL) and aq HCl (1 M, 2×75 mL). The aqueous phase was extracted with CH_2Cl_2 (200 mL). Combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The remaining red solid was crystallized from CH_2Cl_2/pentane. Yield: 48.0 g (231 mmol, 71%). Mp: 112–113 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46 (s, 3H), 7.59 (d, 2H, *J*=8.0 Hz), 8.09 (s, 1H), 8.32 (d, 2H, *J*=8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 124.2, 130.6, 130.9, 139.0, 148.2, 150.3. MS (EI) *m*/*z* 208 (M^+, 0.04), 208 (6), 161 (19), 132 (21), 115 (100). Anal. Calcd for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N 13.46; Found: 51.63; H, 3.75; N 13.54.

5.2.1.2. 1-Chloro-4-(2-nitro-propenyl)-benzene[39]. A suspension of *p*-chloro-benzaldehyde (7.15 g, 50.9 mmol), piperidine (0.4 mL, 4 mmol) and nitroethane (3.5 mL, 44.6 mmol) was heated in a closed vessel in a microwave device (1 min, 300 W, 120 °C). The reaction mixture was cooled afterward to 22 °C. The heating-cooling cycle was repeated for 6 consecutive times. The reaction

mixture was afterward allowed to stand for 24 h at 0 °C, whereupon a brown solid crystallized. The solids were removed by filtration, washed with cold (0 °C) EtOH, and dried to afford 1-chloro-4-(2-nitro-propenyl)benzene as a yellow solid (5.80 g, 29.3 mmol, 58% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.43 (s, 3H), 7.35–7.37 (m, 2H), 7.41–7.44 (m, 2H), 8.02 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 129.2, 130.8, 131.1, 132.1, 136.0, 148.1. MS (EI) *m*/*z* 199, 197 (M^+) (13:4), 150 (17), 139 (15), 116 (49), 115 (100), 103 (14).

5.2.2. Arylpropan-2-ones

5.2.2.1. 1-(4-Acetamidophenyl)propan-2-one. A slurry obtained from 4-nitro-(2-nitropropenyl)benzene (20.0 g, 96 mmol), Fe powder (75.0 g, 1.34 mol, ~325 mesh), HOAc (250 mL), and Ac_2O (500 mL) was heated to reflux while $FeCl_2\cdot(H_2O)_4$ (5.0 g) was carefully added in small portions. The suspension was mechanical stirred for 4 h. The gray suspension was filted through a pad of cellite. The residue was washed with H_2O (3×50 mL) and aq concd HCl (10 mL). The pH of the filtrate was adjusted to 0 °C using aq HCl (37%). The acidic aqueous phase was extracted with CH_2Cl_2 (2×100 mL). Combined organic washings were dried ($MgSO_4$) and concentrated under reduced pressure. The remaining volatiles (H_2O, acids, Ac_2O) were removed at 5 mbar/150 °C to furnish a solid that was dissolved in CH_2Cl_2 (100 mL) and washed with an aqueous solution of KOH (2.5 M, 2×75 mL) in H_2O (150 mL). The organic layer was kept. Combined aqueous washings were extracted with CH_2Cl_2 (100 mL). Combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to furnish 1-(4-acetamidophenyl)propan-2-one as bright yellow solid (13.5 g, 70 mmol, 73% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.99 (s, 3H), 2.06 (s, 3H), 3.64 (s, 2H), 7.06 (d, 2H, J_H=4.0 Hz), 7.47 (d, 2H, J=8.0), 9.89 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.7, 29.5, 50.5, 120.4, 130.1, 130.2, 137.1, 168.5, 206.7. MS (EI) *m*/*z* 191 (M^+, 10), 148 (26), 106 (100), 77 (9). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N 7.32; Found: C, 68.12; H, 6.65; N 7.24.

5.2.2.2. 1-(4-Chlorophenyl)propan-2-one[21]. 1-Chloro-4-(2-nitroprop-1-enyl)-benzene (20.8 g, 106 mmol), Fe powder (44.0 g, 794 mmol, ~325 mesh), and $FeCl_2\cdot(H_2O)_4$ (1.80 g, 14.4 mmol) were suspended in H_2O/EtOH [375 mL, 4/3 (v/v)]. The reaction mixture was mechanical stirred and heated to 70 °C. Aq HCl [37% (*w*/*w*), 25 mL] was added and stirring was continued for 6.5 h. The hot suspension was filtered under suction. The solids were washed with boiling EtOH (200 mL). Combined filtrate and washing were concentrated under reduced pressure to furnish an aqueous solution, which was extracted with Et_2O (3×100 mL). Combined etheral washings were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by distillation (bp 79–82 °C, 0.4 mbar) to yield 1-(4-Chlorophenyl)propan-2-one as yellowish oil (8.74 g, 51.8 mmol, 49% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.18 (s, 3H), 3.68 (s, 2H), 7.11–7.15 (m, 2H), 7.29–7.33 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.5, 50.2, 129.0, 130.9, 132.8, 133.2, 205.7.

5.2.3. 2-Haloketones

General method. A solution of $SOCl_2$ (1.1 equiv) in CH_2Cl_2 (1.5 mL/mmol) was added in a dropwise manner over a period of 5 min to an ice-cooled solution of a substituted propan-2-one (1 equiv) in CH_2Cl_2 (0.5 mL/mmol). The reaction mixture was stirred at 0 °C for 2 h. The resulting red solution was washed with H_2O (2×0.5 mL/mmol) and $NaHCO_3$ (saturated aqueous solution, 2×0.25 mL/mmol), dried ($MgSO_4$), and concentrated under reduced pressure.

5.2.3.1. 1-Chloro-1-(4-acetamidophenyl)propan-2-one (10). 1-Chloro-1-(4-acetamidophenyl)propan-2-one was obtained as a yellow solid (12.1 g; 54 mmol, 76% yield). It was used without further purification. An analytical pure sample was obtained via chromatographic purification of the crude product [SiO_2, petroleum ether/Et_2O=3/1 (v/v), R_f=0.47]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.22 (s, 3H), 2.34 (s, 3H), 5.31 (s, 1H), 7.37 (m, 2H, J=12.0 Hz), 7.54 (m, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.6, 26.1, 66.3, 120.5, 127.3, 128.9, 135.5, 169.2, 200.4. Anal. Calcd for $C_{11}H_{12}ClNO_2$: C, 58.54; H, 5.36; N 6.21; Found: C, 58.84; H, 5.56; N 6.45.

5.2.3.2. 1-Chloro-1-(4-chlorophenyl)propan-2-one (11). In extension of the general method, the reaction mixture was stirred an additional 12 h at 22 °C. 1-Chloro-1-(4-chlorophenyl)propan-2-one was obtained as a viscious oil (10.3 g, 50.9 mmol, 78% yield) and was used without further purification. An analytical pure sample was obtained via chromatographic purification of the crude product [SiO_2, petroleum ether/Et_2O=3/1 (v/v), R_f=0.61]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ=2.24 (s, 3H), 5.30 (s, 1H), 7.36–7.39 (m, 4H).^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.8, 65.5, 129.2, 129.3, 133.5, 135.3. MS (EI) *m*/*z* 206, 204, 202 (M^+, 1.4:8.5:13.7), 169, 167 (8.5:24), 161, 160, 159 (10:65:100), 89 (76). Anal. Calcd for $C_9H_8Cl_2O$: C, 53.29; H, 3.97; Found: C, 53.29; H, 3.99.

5.2.4. Preparation of xanthogenates

General method. To a suspension of potassium *O*-ethyldithiocarbonate (1 equiv) in acetone (1 mL/mmol) was added a solution of a haloketone (**7**–**11**) (1 equiv) in acetone (1 mL/mmol) over a period of 15 min at 20 °C. The reaction mixture was stirred for 2 h at 20 °C. The solvent was evaporated under reduced pressure. H_2O (1 mL/mmol) was added. The brown solution was extracted with Et_2O (2×2 mL/mmol). Combined organic washings were dried ($MgSO_4$) and concentrated under reduced pressure to furnish a crude material that was sufficiently pure for succeeding transformations. An analytical pure sample was obtained via chromatographic purification of the crude product (SiO_2).

5.2.4.1. 1-(Ethoxythiocarbonylsulfanyl)-1-(4-methoxyphenyl)-2-propanone. Yield: 25.8 g (91.0 mmol, 91%); yellow solid [R_f=0.66 petroleum ether/Et_2O=1/1 (v/v), eluent used for chromatography: petroleum ether/Et_2O=2/1 (v/v)]. UV (EtOH) λ_{max} (lg ε/m^2 mol^{-1}) 278 (3.37), 223 (3.42) nm. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40 (t, 3H, J=7.1 Hz), 2.27 (s, 3H), 3.80 (s, 3H), 4.60 (q, 2H, J=7.1 Hz), 5.57 (s, 1H), 6.84–6.91 (m_c, 2H), 7.21–7.23 (m_c, 2H). ^{13}C NMR ($CDCl_3$, 63 MHz) δ 14.1, 29.1, 55.7, 64.3, 70.8, 115.1, 124.1, 130.7, 160.0, 201.5, 213.0. MS (EI) *m*/*z* 284 (7), 251 (20), 163 (100), 77 (19), 43 (21). Anal. Calcd for $C_{13}H_{16}O_3S_2$: C, 54.90; H, 5.67; Found: C, 54.88; H, 5.65.

5.2.4.2. 1-(Ethoxythiocarbonylsulfanyl)-1-(4-acetamidophenyl)-2-propanone. Extractions were performed with CH_2Cl_2 instead of Et_2O. Yield 10.9 g (35 mmol, 92%) of a yellow solid [R_f=0.12 (Et_2O)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37 (t, 3H, J=7.09 Hz), 2.25 (s, 3H), 4.58 (q, 2H, J=7.10 Hz), 5.59 (s, 1H), 7.27–7.28 (m, 2H), 7.31–7.33 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 28.8, 63.8, 70.7, 129.4, 130.5, 131.5, 135.0, 201.0 (*C*=O), 212.2 (*C*=S). MS (CI) *m*/*z* 312 ($M+H^+$, 20), 226 (4), 218 (9), 190 (100). Anal. Calcd for $C_{14}H_{17}NO_3S_2$: C, 53.99; H, 5.50; N 4.50; Found: C, 54.09; H, 5.56; N 4.46.

5.2.4.3. 1-(Ethoxythiocarbonylsulfanyl)-1-(4-chlorophenyl)-2-propanone. The crude material was treated with petroleum ether (30–50 °C, 10 mL) and kept at 0 °C for 48 h, to furnish a yellow solid that was collected by filtration and dried (4.48 g, 15.6 mmol, 96% yield). R_f=0.34 [Et_2O/pentane=3/1 (v/v)]. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.37 (t, 3H, J=7.09 Hz), 2.25 (s, 3H), 4.58 (q, 2H, J=7.10 Hz), 5.59 (s, 1H), 7.27–7.28 (m, 2H), 7.31–7.33 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.7, 28.8, 63.8, 70.7, 129.4, 130.5, 131.5, 135.0, 201.0 (*C*=O), 212.2 (*C*=S). MS (EI) *m*/*z* 290, 288 (M^+, 0.1:0.3), 257, 255 (38:100), 228 (27), 200 (30), 185 (38), 157 (98). Anal. Calcd for $C_{12}H_{13}ClO_2S_2$: C, 49.90; H, 4.54; Found: C, 50.12; H, 4.40.

5.2.4.4. 1-(Ethoxythiocarbonylsulfanyl)-2-indanone. According to the general procedure, a solution of 1-chloro-2-indanone[23] (7.10 g, 42.6 mmol) in acetone (40 mL) was added to a suspension of potassium-*O*-ethyldithiocarbonat (6.83 g, 42.6 mmol) in acetone (70 mL) at 20 °C. The crude product was recrystallized (Et_2O, pentane). Yield: 7.22 g (28.6 mmol, 67%), dark red solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (t, 3H, J=7.2 Hz), 3.65 (d, 1H, J=22.4 Hz), 3.72 (d, 1H, J=22.4 Hz), 4.58 (m_c, 2H), 5.24 (s, 1H), 7.32–7.34 (m, 3H), 7.42–7.44 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.4, 42.8, 57.2, 70.9, 124.8, 125.1, 128.0, 128.7, 136.9, 137.5, 209.4, 211.2 (*C*=S). MS (EI) *m*/*z* 252 (M^+, 19), 163 (100), 103 (63).

5.2.5. (Ethoxythiocarbonylsulfanyl)alkanone oximes

General method. To an ice-cooled suspension of a ethoxythiocarbonylsulfanyl propanone (section 5.2.4) (1 equiv) and $NH_2OH{\cdot}HCl$ (1.1 equiv) in MeOH (0.5 mL/mmol) was added pyridine (1.25 equiv). The reaction mixture was stirred for 16 h at 20 °C. The solvent was evaporated under reduced pressure to furnish a residue that was taken up in Et_2O (4 mL/mmol). The organic phase was washed successively with aq 0.5 N HCl (2 mL/mmol) and H_2O (2 mL/mmol) and dried ($MgSO_4$). The solvent was removed under reduced pressure. The residue was purified by recrystallization or chromatography.

5.2.5.1. 3-(Ethoxythiocarbonylsulfanyl)-2-butanone oxime. Yield: 9.65 g (46.5 mmol, 93%), colorless solid from petroleum ether/Et_2O=3/1 (v/v); mp 55 °C; R_f=0.77 [petroleum ether/Et_2O=3/1 (v/v)]. UV (EtOH) λ_{max} (lg ε/m^2 mol^{-1}) 280 (3.43), 220 (3.33) nm. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.42 (t, 3H, J=7.2 Hz), 1.52 (d, 3H, J=7.1 Hz), 1.96 (s, 3H), 4.51 (q, 1H, J=7.2 Hz), 4.65 (q, 2H, J=7.2 Hz), 8.7 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.1, 13.7, 17.9, 49.5, 70.2, 157.2, 212.7. MS (EI) *m*/*z* 207 (M^+, 2), 174 (100), 86 (20), 42 (53). Anal. Calcd for $C_7H_{13}NO_2S_2$: C, 40.58; H, 6.32; N, 6.76; Found: C, 40.71; H, 5.96; N, 6.58.

5.2.5.2. 1-(4-Methoxyphenyl)-1-(ethoxythiocarbonylsulfanyl)-2-propanone oxime. Yield: 12.9 g (43.2 mmol, 86%), yellow solid from CH_3OH; mp 86 °C; R_f=0.50 [petroleum ether/Et_2O=3/1 (v/v)]. UV (EtOH) λ_{max} (lg ε/m^2 mol^{-1}) 282 (3.47), 224 (3.63) nm. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.38 (t, 3H, J=7.1 Hz), 1.90 (s, 3H), 3.80 (q, 2H, J=7.1 Hz), 5.50 Hz (s, 1H), 6.82–6.90 (m_c, 2H), 7.26–7.33 (m_c, 2H). ^{13}C NMR ($CDCl_3$, 63 MHz) δ 13.5, 13.7, 55.3, 57.4, 70.2, 114.3, 128.0, 129.8, 156.0, 159.4, 212.1. MS (EI) 299 (M^+, 1), 178 (100), 146 (40), 77 (17), 51 (5). Anal. Calcd for $C_{13}H_{17}NO_3S_2$: C, 52.15; H, 5.73; N, 4.68; Found: C, 52.23; H, 5.44; N, 4.68.

5.2.5.3. 1-(4-Acetamidophenyl)-1-(ethoxythiocarbonylsulfanyl)-2-propanone oxime. A AcOEt/CH_2Cl_2 2/1 (v/v) mixture was used for extraction instead Et_2O. Yield: 3.42 g (11 mmol, 75%), yellow solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.37 (t, 3H, J=7.1 Hz), 1.89 (s, 3H), 2.17 (s, 3H), 4.59 (q, 2H, J=6.9 Hz), 5.50 (s, 1H), 7.32 (d, 2H, J=8.4 Hz), 7.46 (d, 2H, J=8.4 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.7, 14.3, 24.6, 57.5, 70.3, 120.2 (2C), 129.4, 132.2, 137.9, 155.9, 168.9, 212.0 (*C*=S). MS (CI) *m*/*z* 327 (M+H$^+$, 6), 293 (12), 277 (11), 231 (31), 205 (100).

5.2.5.4. 1-(4-Chlorophenyl)-1-(ethoxythiocarbonylsulfanyl)-2-propanone oxime. In modification of the general procedure, 2 equiv of $NH_2OH{\cdot}HCl$ were used. The reaction mixture was stirred for 1 h at 0 °C and for 2.5 h at 22 °C. Yield of 1-(4-chlorophenyl)-1-(ethoxythiocarbonylsulfanyl)-2-propanone oxime: 3.14 g (10.3 mmol, 80%) as a red oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.90 (s, 3H), 4.60 (q, 2H, J=7.10 Hz), 5.52 (s, 1H), 7.30–7.32 (m, 2H), 7.33–7.34 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.7, 13.8, 57.6, 70.5, 129.0, 130.1, 134.3, 135.2, 155.9 (*C*=O), 211.7 (*C*=S). MS (EI) *m*/*z* 272, 270 (1:3), 227, 225 (1:3), 182 (18), 146 (8), 115 (30), 76 (100).

5.2.5.5. 3-(Ethoxythiocarbonylsulfanyl)-1-indanone oxime. To a solution of 1-(ethoxythiocarbonylsulfanyl)-2-indanone (5.00 g, 19.8 mmol) and $H_2NOH{\cdot}HCl$ (4.13 g, 59.4 mmol) in MeOH (70 mL) and CH_2Cl_2 (30 mL) were added a few drops of pyridine at 0 °C. The mixture was stirred for 3 h at 20 °C and worked up according to the general procedure. Yield: 5.00 g (18.7 mmol, 94%) dark red oil. An analytically pure sample was obtained upon purification of the crude product by chromatography [SiO_2, petroleum ether/Et_2O=2/1 (v/v), R_f=0.60)] to furnish the title compound as orange oil, which solidified, if stored at −18 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, 3H, J=7.2 Hz), 3.89 (d, 2H, J=4.4 Hz), 4.68 (m_c, 2H), 5.97 (s, 1H), 7.27–7.31 (m, 3H), 7.44–7.45 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 33.6, 54.2, 71.1, 124.9, 125.5, 128.2, 129.3, 138.8, 139.3, 162.4, 213.0 (*C*=S). MS (EI) *m*/*z* 267 (M^+, 4), 178 (14), 146 (100). Anal. Calcd for $C_{12}H_{13}NO_2S_2$: C, 53.91; H, 4.90; N, 5.24; Found: C, 53.86; H, 4.96; N, 5.48.

5.2.6. Cyclization of (ethoxythiocarbonylsulfanyl)alkanone oximes

General method. To an ice-cooled solution of KOH (4 equiv) in H_2O (4 mL/mmol) was added a solution of the corresponding (ethoxythiocarbonyl-sulfanyl)acetoneoxime (1 equiv) in CH_2Cl_2 (3.5 mL/mmol). The reaction mixture was stirred for 2 h at 20 °C H_2O (1 mL/mmol) was added and the phases were separated. The aqueous phase was extracted twice with light petroleum (each 0.3 mL/mmol) and acidified to pH 2 with concd HCl. The aqueous phase was extracted five times with CH_2Cl_2 (each 1 mL/mmol). Combined organic phases were dried ($MgSO_4$). The solvent was evaporated under reduced pressure. The residue was recrystallyzed from light petroleum/Et_2O.

5.2.6.1. N-(Hydroxy)-4,5-dimethylthiazole-2(3H)-thione (1). Yield: 4.26 g (26.5 mmol, 88%), colorless solid from petroleum ether/Et_2O=3/1 (v/v); mp: 88 °C, 133 °C dec R_f=0.05 [petroleum ether/Et_2O=1/1 (v/v)]. UV (MeOH) λ_{max} (lg ε/m^2 mol^{-1}) 316 (3.14). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.22 (q, 3H, J=0.9 Hz, 5-CH_3), 2.27 (q, 3H, J=0.9 Hz, 4-CH_3), 9.8 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$, 63 MHz) δ 11.0, 11.7, 114.8, 130.8, 168.5. MS (EI) *m*/*z* 161 (M^+, 100), 144 (50), 85 (59), 59 (35). Anal. Calcd for $C_5H_7NOS_2$: C, 37.28; H, 4.38; N, 8.69; Found: C, 37.63; H, 4.53; N, 8.46. HRMS (ESI): calcd 160.9971(2), found 160.9969.

5.2.6.2. N-(Hydroxy)-5-phenyl-4-methylthiazole-2(3H)-thione (2). Yield: 5.66 g (25.5 mmol, 14%), tan solid from Et_2O; mp: 141 °C. UV (MeOH) λ_{max} (lg ε/m^2 mol^{-1}) 338 (3.12). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46 (s, 3H, CH_3), 7.34–7.38 (m, 2H, Ph-H), 7.39–7.47 (m, 3H, Ph-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.1, 119.5, 128.6, 128.9, 129.2, 129.9, 130.2, 169.3. *m*/*z* (CI): 224 (M+H$^+$, 100), 208 (5), 148 (3), 130 (1). Anal. Calcd for $C_{10}H_9NOS_2$: C, 53.78; H, 4.06; N, 6.27; Found: C, 53.69; H, 4.11; N, 6.42.

5.2.6.3. N-(Hydroxy)-5-(4-methoxyphenyl)-4-methylthiazole-2(3H)-thione (3). Yield: 6.23 g (24.9 mmol, 83%), tan solid from CH_3OH; mp 158 °C, decomp.; R_f=0.05 [petroleum ether/Et_2O=1/1 (v/v)]. UV (MeOH) λ_{max} (lg ε/m^2 mol^{-1}) 334 (3.20), 250 (3.12) nm. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.43 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.93–7.00 (m_c, 2H, Ar-H), 7.24–7.31 (m_c, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 63 MHz) δ 12.0, 55.4, 114.7, 119.5, 122.1, 129.8, 130.0, 160.2, 169.2. MS (EI) *m*/*z* 253 (M^+, 100), 177 (45), 77 (18), 63 (11). HRMS (ESI) $C_{11}H_{11}NO_2S_2$: calcd 253.0231, found: 253.0236(1).

5.2.6.4. N-(Hydroxy)-5-(4-acetamidophenyl)-4-methylthiazole-2(3H)-thione (4). Yield: 2.20 g (8 mmol, 85%), tan solid; mp 135 °C dec. UV (EtOH) λ_{max} (lg ε/m^2 mol^{-1}) 335 (3.14). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.06 (s, 3H, 6-H), 2.28 (s, 3H, HNCOCH_3), 7.37 (d, 2H, J=8.7 Hz, 3′-H and 5′-H), 7.68 (d, 2H, $^3J_{H,H}$=8.6 Hz, 2′-H und 6′-H), 10.15 (s, 1H, -N*H*), 12.32 (s, 1H, -O*H*). ^{13}C NMR (DMSO-d_6, 100 MHz)

δ 12.1 (CH_3), 23.8 ($HNCOCH_3$), 116.7 (5-C), 119.0 (3′-C und 5′-C), 124.2 (4′-C), 128.4 (2′-C und 6′-C), 133.9 (4-C), 139.2 (1′-C), 168.3 ($HNCOCH_3$), 175.9 (*C*=S). MS (CI) *m*/*z* 281 ($M+H^+$, 100), 265 (10), 249 (8), 221 (27). Anal. Calcd for $C_{12}H_{12}N_2O_2S_2$: C, 51.41; H, 4.31; N, 9.99; Found: C, 51.30; H, 4.31; N, 9.46.

5.2.6.5. N-(Hydroxy)-5-(4-chlorophenyl)-4-methylthiazole-2(3H)-thione (5). Yield: 641 mg (2.23 mmol, 59%), tan solid; mp 140–141 °C. UV (EtOH) λ_{max} ($\lg \varepsilon/m^2\,mol^{-1}$) 334 (3.21) nm. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.44 (s, 3H, 4-CH_3), 7.28–7.30 (m, 2H, Ph-H), 7.41–7.43 (m, 2H, Ph-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.3, 118.3, 128.6, 129.6, 130.0, 131.3, 135.2, 170.2. MS (CI) *m*/*z* 258 ($M+H^+$, 100), 222 (7), 205 (3). Anal. Calcd for $C_{10}H_8ClNOS_2$: C, 46.82; H, 3.10; N, 5.40; Found: C, 46.60; H, 3.13; N, 5.43.

5.2.6.6. N-(Hydroxy)-(4H)-indeno[2,1-d]thiazole-2(3H)-thione (6). A solution of 1-(ethoxythiocarbonylsulfanyl)-2-indane oxime (2.86 g, 10.7 mmol) in CH_2Cl_2 (10 mL) was added to KOH (1.20 g, 21.4 mmol) in H_2O (23 mL) at 0 °C. The mixture was stirred 2 h at 20 °C. CH_2Cl_2 und H_2O were added until two clear phases were obtained. The solution was worked up according to general procedure 5.6.2. The crude product was purified by recrystallization (Et_2O). Yield: 580 mg (2.62 mmol, 25% yield) tan solid. UV (MeOH) λ_{max} ($\lg \varepsilon/m^2\,mol^{-1}$) 376 (2.45), 267 (2.91). ^1H NMR ($CDCl_3$, 400 MHz) δ 3.85 (s, 2H, CH_2), 7.43–7.47 (m, 1H, Ar-H), 7.52–7.54 (m, 1H, Ar-H), 7.65–7.69 (m, 1H, Ar-H), 7.87–7.89 (m, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3 (CH_2), 124.7 (Ar-C), 126.9 (Ar-C), 128.1 (Ar-C), 136.1 (Ar-C), 137.8, 146.8, 155.2, 189.3 (*C*=S); MS (EI) *m*/*z* 221 (M^+, 4), 205 (36), 146 (33), 103 (63). Anal. Calcd for $C_{10}H_7NOS_2$: C, 54.28; H, 3.19; N, 6.33; Found: C, 54.36; H, 3.28; N, 6.41.

5.3. *N*-(Hydroxy)thiazole-2(3*H*)-thione tetralkylammonium salts

General method. To a solution of a *N*-(hydroxy)thiazole-2(3*H*)thione **1**–**6** (1.10 mmol) in MeOH (2 mL) was added a solution of NEt_4OH or NBu_4OH in MeOH (1.10 mmol, 0.73 mL, 1.5 M) at 20 °C. The solvent was evaporated under reduced pressure to furnish a residue that was freeze-dried (12 h).

5.4. *N*-(Alkoxy)thiazole-2(3*H*)-thiones

General method. *N*-(Hydroxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)thione tetraalkylammonium salt (1.00 mmol) was disolved in anhydrous DMF (2 mL). An alkyl tosylate or alkyl halide (1.00–1.10 mmol) was added. The reaction mixture was stirred for 12 h at 20 °C. Water (10 mL) was added. The aqueous phase was extracted with Et_2O (3×5 mL). Combined organic washings were dried ($MgSO_4$) and concentrated under reduced pressure to furnish a crude product, which was purified by recrystallization or chromatography. For synthesis of *N*-cumyloxythiazolethione **15c** see section 5.5.

5.4.1. N-(Methoxy)-4,5-dimethylthiazole-2(3H)thione (13a)

From CH_3OTs (172 mg, 1.00 mmol); yield: 0.13 g (0.68 mmol, 68% yield), tan solid from CH_3OH. Mp 54 °C. R_f=0.45 [petroleum ether/Et_2O=2/1 (v/v)]. UV (MeOH) λ_{max} ($\lg \varepsilon/m^2\,mol^{-1}$) 321 (3.16) nm. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.12 (q, 3H, *J*=0.9 Hz, CH_3), 2.19 (q, 3H, *J*=0.9 Hz, CH_3), 4.13 (s, 3H, $NOCH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.3, 12.4, 63.9, 115.0, 132.6, 178.6244 (3.38). MS (EI) *m*/*z* 175 (M^+, 100), 144 (12), 85 (44). Anal. Calcd for $C_6H_9NOS_2$: C, 41.12; H, 5.18; N, 7.99; Found: C, 41.24; H, 5.24; N, 8.06.

5.4.2. N-(Isopropoxy)-4,5-dimethylthiazole-2(3H)thione (13b)

From ^{i}PrOTs (236 mg, 1.05 mmol); yield: 175 mg (862 μmol, 82%), colorless solid from petroleum ether/Et_2O=1/1 (v/v). Mp 83 °C. R_f=0.37 [petroleum ether/Et_2O=1/1 (v/v)]. UV (MeOH) λ_{max} ($\lg \varepsilon/m^2\,mol^{-1}$) 322 (3.14) nm. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (d, 6H, *J*=6.2 Hz, $CH(CH_3)_2$), 2.12 (d, 3H, *J*=0.8 Hz, 4-CH_3), 2.14 (d, 3H, *J*=0.8 Hz, CH_3), 5.46 [sept, 1H, *J*=6.2 Hz, $CH(CH_3)_2$]. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.5, 12.1, 20.5, 78.2, 114.3, 133.8, 178.7. MS (CI) *m*/*z* 204 ($M+H^+$, 100), 190 (39), 162 (39), 145 (15). Anal. Calcd for $C_8H_{13}NOS_2$: C, 47.26; H, 6.44; N, 6.89; Found: C, 47.54; H, 6.53; N, 6.75.

5.4.3. N-(Methoxy)-5-phenyl-4-methylthiazole-2(3H)thione (14a)

From CH_3OTs (194 mg, 1.04 mmol); yield: 108 mg (455 μmol, 45%), tan solid from petroleum ether/Et_2O=1/1 (v/v); mp: 86 °C; R_f=0.31 [pentane/Et_2O=1/1 (v/v)]. UV (MeOH) λ_{max} ($\lg \varepsilon/m^2\,mol^{-1}$) 333 (3.28) nm. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.39 (s, 3H, CH_3), 4.23 (s, 3H, OCH_3), 7.31–7.34 (m, 2H, Ph-H), 7.36–7.46 (m, 3H, Ph-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.1 (CH_3), 63.7 ($NOCH_3$), 119.4, 128.5, 128.7, 129.1, 130.3, 132.5, 178.9 (*C*=S). MS (EI) *m*/*z* 237 (M^+, 100), 207 (97), 173 (29), 162 (23), 147 (91), 130 (61), 121 (66), 115 (73), 103 (59), 77 (58). Anal. Calcd for $C_{11}H_{11}NOS_2$: C, 55.67; H, 4.67; N, 5.90; Found: C, 55.99; H, 4.70; N, 5.99.

5.4.4. N-(Isopropoxy)-5-phenyl-4-methylthiazole-2(3H)thione (14b)

From ^{i}PrOTs (201 mg, 936 μmol); yield: 169 mg (637 μmol, 62%), tan solid from petroleum ether/Et_2O=1/1 (v/v). R_f=0.52 [petroleum ether/Et_2O=1/1 (v/v)]. Mp 100 °C. UV (MeOH) λ_{max} ($\lg \varepsilon/m^2\,mol^{-1}$) 334 (3.27) nm. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 [d, 6H, *J*=6.4 Hz, $CH(CH_3)_2$], 2.33 (s, 3H, CH_3), 5.52 [sept, 1H, *J*=6.0 Hz, $CH(CH_3)_2$], 7.31–7.34 (m, 2H, Ph-H), 7.35–7.45 (m, 3H, Ph-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.8 (CH_3), 20.5, 78.6 [$NOCH(CH_3)_2$], 119.2, 128.5, 128.6, 129.1, 130.6, 134.1, 179.6 (*C*=S). MS (CI) *m*/*z* 266 ($M+H^+$, 100), 252 (16), 224 (10), 207 (15), 190 (1), 147 (1). Anal. Calcd for $C_{13}H_{15}NOS_2$: C, 58.83; H, 5.70; N, 5.28; Found: C, 59.03; H, 5.69; N, 5.25.

5.4.5. N-(Methoxy)-5-(4-acetamidophenyl)-4-methylthiazole-2(3H)thione (16a)

From CH_3OTs (677 mg, 2.41 mmol); yield: 453 mg (1.53 mmol, 64%), tan solid. R_f=0.21 [Et_2O/AcOEt=1/1 (v/v)]. Mp 130 °C (dec). UV (EtOH) λ_{max} $\lg \varepsilon/m^2\,mol^{-1}$) 336 (3.22) nm. ^1H NMR (DMSO-d_6, 400 MHz) δ 2.06 (s, 3H, CH_3), 2.34 (s, 3H, $HNCOCH_3$), 4.14 (s, 3H, $NOCH_3$), 7.37 (d, 2H, *J*=8.8 Hz), 7.68 (d, 2H, *J*=8.8 Hz), 10.14 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 12.0, 24.1, 63.7, 117.7, 119.4 (2C), 124.2, 128.8 (2C), 133.1, 139.8, 168.7, 177.0 (*C*=S). MS (CI) *m*/*z* 295 ($M+H^+$, 100), 279 (61), 233 (40), 192 (33). Anal. Calcd for $C_{13}H_{14}N_2O_2S_2$: C, 53.04; H, 4.79; N, 9.52; Found: C, 52.76; H, 4.86; N, 8.98.

5.4.6. N-(Isopropoxy)-5-(4-acetamidophenyl)-4-methylthiazole-2(3H)thione (16b)

From ^{i}PrOTs (430 mg, 2.01 mmol); yield: 341 mg (1.06 mmol, 53%), tan solid. Mp 153–154 °C dec. UV (EtOH) λ_{max} ($\lg \varepsilon/m^2\,mol^{-1}$) 337 (3.21) nm. ^1H NMR (DMSO-d_6, 400 MHz) δ 1.32 [d, 6H, *J*=6.4 Hz,-CH(CH_3)$_2$], 2.06 (s, 3H, CH_3), 2.32 (s, 3H, $HNCOCH_3$), 5.29 [sept, 1H, *J*=6.2 Hz, $CH(CH_3)_2$], 7.39 (d, 2H, *J*=8.8 Hz), 7.68 (d, 2H, *J*=8.8 Hz, 2′-H und 6′-H), 10.13 (s, 1H, -N*H*). ^{13}C NMR (DMSO-d_6, 400 MHz) δ 12.4, 20.0, 23.8, 78.8, 117.4, 119.0 (2C), 124.0, 128.5, 133.9, 139.4, 168.4, 177.4 (*C*=S). MS (CI) *m*/*z* 323 ($M+H^+$, 100), 307 (33), 265 (23), 233 (9). Anal. Calcd for $C_{15}H_{18}N_2O_2S_2$: C, 55.87; H, 5.63; N, 8.69; Found: C, 55.96; H, 5.82; N, 8.52.

5.4.7. N-(Methoxy)-5-(4-chlorophenyl)-4-methylthiazole-2(3H)thione (17a)

From CH_3OTs (768 mg, 4.57 mmol); yield: 553 mg (0.68 mmol, 59%), colorless solid. Mp 117–118 °C. R_f=0.29 [petroleum ether/Et_2O=5/2 (v/v)]. UV (EtOH) λ_{max} ($\lg \varepsilon/m^2\,mol^{-1}$) 335 (3.28) nm. ^1H NMR ($CDCl_3$, 600 MHz) δ 2.36 (s, 3H, CH_3), 4.22 (s, 3H,

NOCH_3), 7.24–7.26 (m, 2H), 7.40–7.41 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.2, 63.9, 118.1, 128.8, 129.5, 129.9, 133.0, 134.9, 179.0 (*C*=S). MS (CI) *m*/*z* 272 ($M+H^+$, 100), 241 (12), 236 (8). Anal. Calcd for $C_{11}H_{10}ClNOS_2$: C, 48.79; H, 3.54; N, 5.08; Found: C, 48.61; H, 3.71; N, 5.15.

5.4.8. N-(Isopropoxy)-5-(4-chlorophenyl)-4-methylthiazole-2(3H)thione (17b)

From ^{i}PrOTs (283 mg, 1.32 mmol); yield: 257 mg (857 μmol, 71%), tan solid. Mp 121–122 °C. R_f=0.45 [petroleum ether/Et_2O=2/1 (v/v)]. UV (EtOH) λ_{max} (lg ε/m^2 mol^{-1}) 337 (3.21) nm. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 [d, 6H, *J*=6.3 Hz, CH(CH_3)$_2$], 2.23 (s, 3H, CH_3), 5.45–5.43 [sept., 1H, *J*=6.3 Hz, C*H*(CH$_3$)$_2$], 7.26–7.28 (m, 2H, Ar-H), 7.39–7.41 (m, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.7, 20.5, 76.7, 117.6, 129.0, 129.3, 129.6, 129.7, 134.5, 170.2 (*C*=S). MS (CI) *m*/*z* 300 ($M+H^+$, 100), 286 (14), 258 (9), 241 (17). Anal. Calcd for $C_{13}H_{14}ClNOS_2$: C, 52.24; H, 4.71; N, 4.67; Found: C, 52.07; H, 4.73; N, 4.66.

5.4.9. N-(Isoproxy)-(4H)-indeno[2,1-d]thiazole-2(3H)-thione (18b)

From 2-chloropropane (132 mg, 1.68 mmol); yield: 40.6 mg (9%), brown oil from pentane/Et_2O 1/1 (v/v). R_f=0.49 [pentane/Et_2O=1/1 (v/v)]. UV (MeOH) λ_{max} (lg ε/m^2 mol^{-1}) 279 (3.25) nm. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 [d, 6H, *J*=6.3 Hz, -CH(CH_3)$_2$], 3.81 (s, 2H, CH_2), 4.71 [sept, 1H, *J*=6.3 Hz, C*H*(CH$_3$)$_2$], 7.42 (m_c, 1H, Ar-H), 7.49 (m_c, 1H, Ar-H), 7.64 (m_c, 1H, Ar-H), 7.89 (m_c, 1H, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 28.9 (CH_2), 78.4 [OCH(CH$_3$)$_2$], 124.5, 126.7, 127.9, 135.7, 137.9, 146.8, 153.3, 189.5 (C=S).

5.5. *N*-(1-Methyl-1-phenyleth-1-oxy)-5-(p-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (15c)

A slurry of *tert*-butanol [2.44 g (17.9 mmol)], diisopropyl carbodiimide [2.26 g (17.9 mmol)] und CuCl [35.4 mg (0.34 mmol)] in anhydrous CH_2Cl_2 (5 mL) was stirred for 24 h at 25 °C. A solution of *N*-(hydroxy)thiazolethione **3** [5.00 g (19.7 mmol)] in anhydrous CH_2Cl_2 (40 mL) was added at −78 °C. The mixture was stirred for 60 h (at 20 °C). Solids were removed by filtration. The filtrate was collected and concentrated under reduced pressure. The residue was purified by chromatography [SiO_2, pentane/Et_2O=2/1 (v/v)] to furnish 1.01 g (15%) *N*-cumyloxythiazolethione **15c** as tan cristalline solid, R_f=0.29 [SiO_2, petroleum ether/Et_2O=2:1 (v/v)]. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.57 (s, 3H, CH_3), 2.03 (s, 6H, 2 CH_3), 3.80 (s, 3H, OCH_3), 6.88 (m_c, 2H, Ar-H), 7.12 (m_c, 2H, Ar-H), 7.33–7.36 (m, 1H, Ph-H), 7.38–7.41 (m, 2H, Ph-H), 7.59 (m_c, 2H, Ph-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 27.6, 55.4 (OCH_3), 92.6, 114.4, 118.8, 122.8, 125.7, 128.3, 128.4, 129.8, 134.6, 144.6, 159.7, 182.3 (C=S). MS (EI) *m*/*z* 253 (16), 177 (6), 118 (100), 43 (42), 91. Anal. Calcd for $C_{20}H_{21}NO_2S_2$: C, 65.42; H, 6.01; N, 3.63; Found: C, 64.85; H, 5.89; N, 3.68.

5.6. Photochemically induced reactions

General Procedure. All reactions were carried out in a RPR-Rayonet® Photo Reactor (Southern New England) equipped with 16×350 nm lamps (21 W). For the EPR-experiments 1 mL of a solution of the corresponding thiazolthione (0.01 M^{-1}) and 20 μL DMPO in C_6H_6 was irradiated for 1 min at 22 °C.

5.7. Microwave-initiated transformations

All reactions were carried out in a CEM Discover® single mode microwave instrument in a closed vessel. For the EPR-experiments DMPO (20 μL) was added to a solution of the an *N*-(alkoxy)-thiazolthione in C_6H_6 (1 mL, 0.01 M^{-1}) and the mixture heated for 1 min (MW power 300 W, T_{max}: 120 °C, p_{max}10 bar).

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Supplementary data

^{13}C NMR spectra of selected compounds (4 pages). Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2008.09.006.

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