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

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Methoxyl and isopropoxyl radicals were generated from N-alkoxy-4,5-dimethylthiazole-2(3H)-thiones ($\lambda_{max} \sim 320$ nm) and 5-aryl derivatives (aryl=p-XC₆H₄; X=MeO, H, AcNH, Cl) ($\lambda_{max} \sim 335$ 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(3H)-thione. A noteworthy bathochromic shift was found for the lowest energy transition of N-(hydroxy)indeno[2,1-d]thiazole-2(3H)-thione ($\lambda_{max}=376$ nm), if compared to the UV–vis absorption of N-hydroxy-4-methyl-5-phenylthiazole-2(3H)-thione ($\lambda_{max}=338$ nm). Syntheses of alkoxyl radical precursors and procedures for conducting N,O-homolysis are described in a full account.

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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(1H)-thiones>N-(alkoxy)thiazole-2(3H)-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(3H)-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(3H)-thione (3). The bathochromic shift exerted by the aromatic substituent onto electronic transitions in heterocycle 3 ($\lambda_{max} \sim 334$ 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-methyl-thiazolethiones 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(3H)-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(3H)-thione (6) was devised for testing theory.
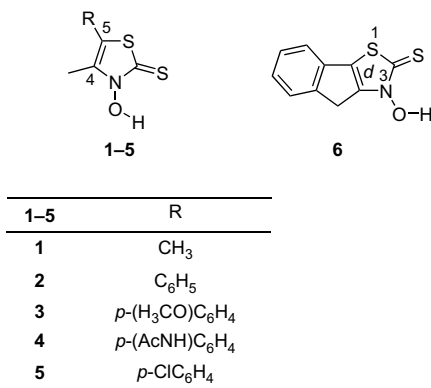
Figure 1. Structural formulae and indexing of cyclic thiohydroxamic acids.

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

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(3H)-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(3H)-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(3H)-thiones

5-Substituted N-(hydroxy)-4-methylthiazole-2(3H)-thiones **1–5** were prepared in extension to a procedure originally developed for 4-(p-chlorophenyl)thiazole-2(3H)-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 nitro-aldol 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$_2$·4H$_2$O/Ac$_2$O/HOAc [synthesis of 1-(4-acetamidophenyl)propan-2-one] into derived 1-aryl propanones.[20,21] Treatment of the latter with SO$_2$Cl$_2$ 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 hydroxyl-amine 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$_2$O/CH$_2$Cl$_2$ (Table 1, step iii). 5-Substituted N-(hydroxy)-4-methylthiazole-2(3H)-thiones **1–5** were obtained as colorless (**1**) or tan (**2–5**) crystalline solids that decomposed (differential thermo-analysis) 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(3H)-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$_2$O as tan solid that decomposed on melting at 148 °C. It was identified via NMR (^{1}H, ^{13}C, HMBC, HMQC), UV–vis spectroscopy (λ=376 and 267 nm, in MeOH, Fig. 2), and combustion

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

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$_2$OH·HCl, pyridine, CH$_3$OH, 0→25 °C, 16 h; (iii) KOH, H$_2$O, CH$_2$Cl$_2$, 0→25 °C, 2 h.
[b] in MeOH.
[c] in EtOH.

analysis. Thione **6** decomposed rapidly on standing as neat sample at 20 °C or in CDCl$_3$ solution (^{1}H NMR). Attempts to grow crystals suitable for X-ray diffraction consistently provided 2-oxo-1-indanonoxime.[24]
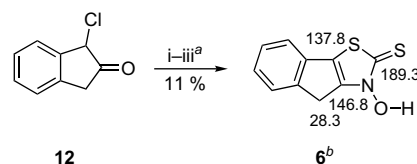
Scheme 1. Preparation of 3-(hydroxy)indeno[2,1-d]thiazole-2(3H)-thione (**6**) from 1-chloro-2-indanone (**12**). Figures in italics refer to selected ^{13}C NMR shift values (CDCl$_3$). (a) Reagents and conditions: (i) potassium O-ethyl xanthogenate, acetone, 25 °C, 2 h (67%); (ii) NH$_2$OH·HCl, pyridine, CH$_3$OH, 0→25 °C, 16 h (94%); (iii) KOH, H$_2$O, CH$_2$Cl$_2$, 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 tetrabutyl-ammonium hydroxide furnished thiohydroxamate tetrabutyl-ammonium 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,
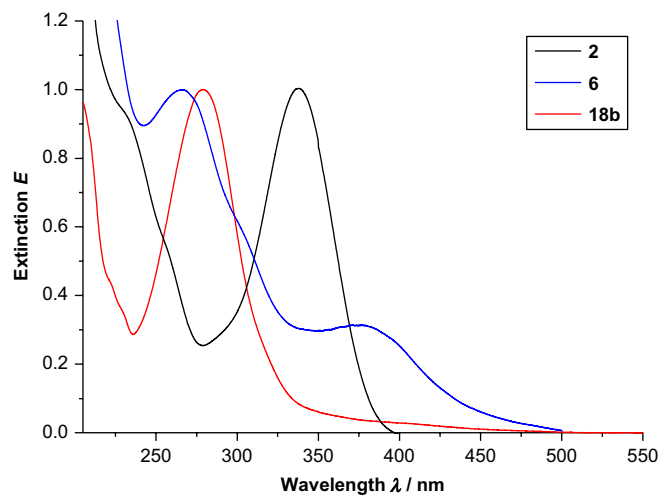

Figure 2. Superposition of normalized electronic spectra of N-hydroxy-4-methyl-5-phenylthiazolethione **2**, indene derivative **6** and 3-(isopropoxy)indeno[2,1-d]thiazole-2(3H)-thione (**18b**) (MeOH, 20 °C).