New Methods for the Introduction of Substituents into Thiazoles

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New methods for the regioselective introduction of substituents into thiazoles have been developed using thiazole, 2-phenylthiazole and 4,5-dimethylthiazole as representative thiazoles. Improved halogenation methods, displacement of hydroxy groups in combination with dehalogenation at C-5 yield all eight possible 2-phenyl-4-halo-, 5-halo- and 4,5-dihalo-thiazoles in which halogen is chlorine and bromine. Peracid oxidation of the thiazoles gives the corresponding thiazole 3-oxides. These are not activated towards halogenation but are deprotonated with sodium hydride. The anions formed react with electrophiles such as paraformaldehyde, 2,2-dimethylpropanal, 2,2-dimethylpropanoyl chloride, hexachloroethane, tetrabromomethane, and dimethyl disulfide leading to the introduction of carbon substituents, halogen, and methylthio groups. In these reactions, the reactivity of the thiazole ring positions decreases in the order 2 > 5 > 4. Monoselectivity is low when halogen and methylthio groups are introduced since these substituents enhance the acidity of adjacent ring protons. 2-Phenyl-4,5-dihalothiazole 3-oxides lose the 5-halogen when treated with sulfite ion. Trimethyloxonium tetrafluoroborate *O*-methylates thiazole 3-oxides. Thiazole *N*-oxides also react with acetyl chloride and phosphorus oxychloride to afford chlorothiazoles in a non-selective manner. Phosphorus trichloride deoxygenates thiazole 3-oxides.

Substituents have been introduced into the thiazole ring by electrophilic substitution, nucleophilic substitution, or metalation followed by reaction with an electrophile. In thiazole, like in pyridine, the nitrogen atom deactivates the ring towards electrophilic attack. Most electrophilic substitution reactions take place in strongly acidic media in which the thiazole nitrogen is protonated. This leads to a further decrease in reactivity toward electrophilic substitution. Smooth substitution usually requires the presence of activating electron-releasing groups. The 5-position is more prone to substitution than the 4-position while the 2-position is far less susceptible to electrophilic attack.[1] Bromination of thiazole has been reported to give low yields.[2,3] It has been shown that the 5-bromo derivative separates as its protonated tribromide during the reaction thus impeding further bromination.[4] However, yields can be improved considerably by using *two* equivalents of bromine. Electrophilic attack at the 4-position of thiazoles requires harsh conditions and occurs only if C-5 is blocked.[1] Electrophilic substitution at C-2 has been reported only for nitration and mercuration under forcing conditions and with protection of C-4 and C-5.[1] Regioselective introduction of halogen at C-4 and C-2 must therefore be brought about by hydroxy group–halogen exchange using not always readily available precursors, or through diazotation of 2-aminothiazoles.

In nucleophilic substitution reactions the 2-position is usually the most reactive.[5] The 5-position is less reactive while nucleophilic attack at C-4 requires the presence of strongly electron-attracting substituents at C-5.[6]

In thiazoles the 2-position has been deprotonated and the corresponding anion reacted with electrophiles like alkyl iodides, aldehydes, acyl chlorides, and chloro(trimethyl)silane.[7,8] Recently, the 5-position has been deprotonated with butyllithium and the anion formed reacted with formylating agents[9] or amides.[10] The 4-position has only been metalated by metal–halogen exchange of 4-bromothiazoles which so far have not proved readily accessible.[10] The 2-position has also been metalated by metal–halogen exchange.[10]

Owing to these limitations effective methods for the regioselective introduction of substituents into the 5- and particularly into the 4-position of thiazoles are of great interest. Therefore, the reactivity of thiazole *N*-oxides towards electrophiles has now been investigated.

Thiazole 3-oxides (**2**) have been prepared by oxidation of the corresponding thiazoles (**1**) using peracetic acid,[11] *m*-chloroperbenzoic acid,[12] permaleic acid,[13] or trifluoroperacetic acid[14] (Scheme 1). Yields range from 4 to 40 %, the more basic thiazoles producing higher yields. A few thiazole 3-oxides have been prepared by cyclization of thiocyanomethylketoximes[12] or *o*-nitro thiol esters.[15] That oxidation of thiazoles leads to *N*- and not to *S*-oxides has

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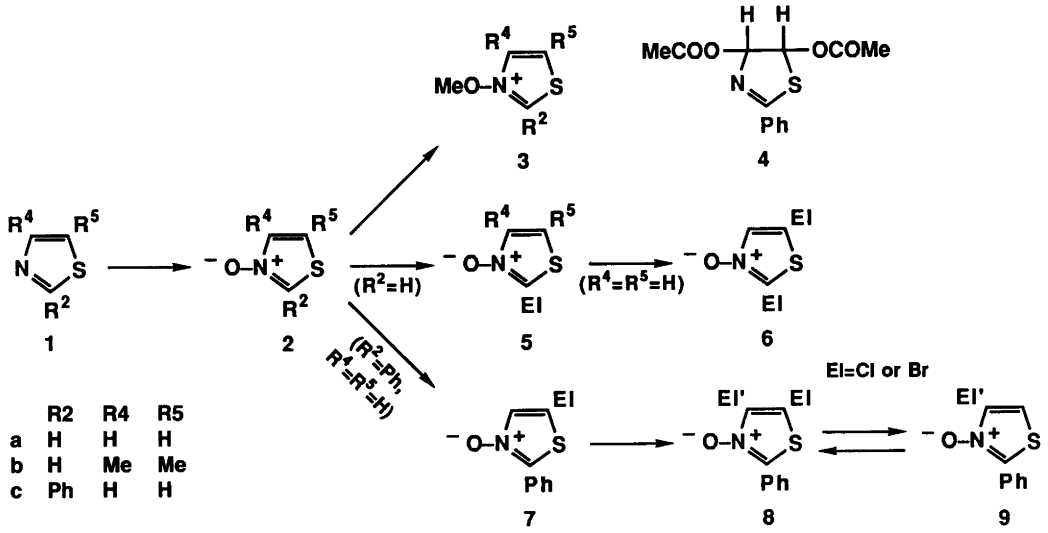
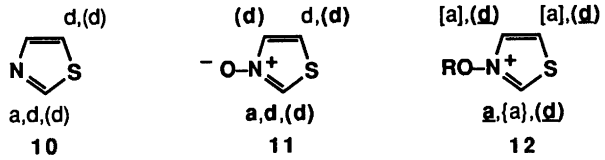


Scheme 1.



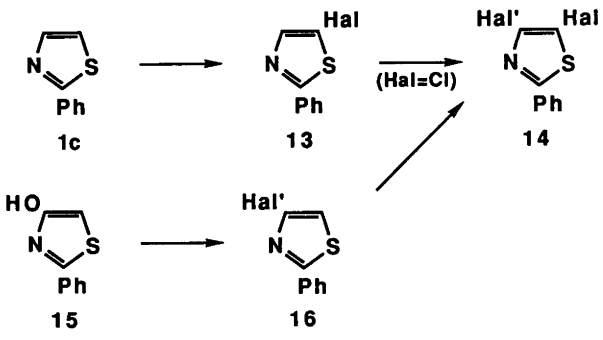
Scheme 2. a,d, acceptor or donor center as the result of π-electron delocalization; (d), donor center created after deprotonation; [a], acceptor center in 1,3 or 1,5 nucleophilic substitution reactions; {a}, acceptor center in nucleophilic addition–elimination reaction. Order of acceptor or donor potential: ***a*** > **a** > a and ***d*** > **d** > d.

been shown by an X-ray analysis on 4-carboxamido-2-β-D-ribofuranosylthiazole 3-oxide[16] and by the fact that the same product is obtained by oxidation and cyclization.[12] Little chemistry has been performed on thiazole 3-oxides. 2-Unsubstituted thiazole 3-oxides (**2**; R^2=H) have been reported to be unstable.[17] 2-Aryl-substituted thiazole 3-oxides (**2**; R^2=Ar) react with acetic anhydride to produce 2-aryl-4,5-diacetoxy-Δ^2-thiazolines[13] (**4**) and with aryliso-cyanates to give 5-mercaptoimidazoles.[18] A donor–acceptor analysis (Scheme 2) indicates that *N*-oxidation leads to enhancement of the donor and acceptor properties of the 2-position. In addition, the acidity of all ring protons should be enhanced. Activation of the *N*-oxide (**11**) by *O*-alkylation or *O*-acylation further enhances the acceptor character at C-2 and ring proton acidity while ordinary donor properties caused by π-electron delocalization vanish (see **12**). In addition, the 4- and 5-positions of *O*-alkyl- and *O*-acylthiazolium salts (**12**) are potential acceptor centres in 1,3 and 1,5 substitution reactions. In these, nucleophilic attack at C-4 or C-5 takes place with simultaneous cleavage of the weak nitrogen–oxygen bond, alkoxide or acylate ions serving as leaving groups.

We have studied the halogenation of thiazoles and the reactivity of thiazole 3-oxides using thiazole (**1a**), 4,5-dimethylthiazole (**1b**), and 2-phenylthiazole (**1c**), as well as their *N*-oxides (**2a–c**) as model compounds.

Results and discussion

Our attempts to chlorinate 4,5-dimethylthiazole (**1b**) and 2-phenylthiazole (**1c**) with chlorine at 20 °C gave unchanged starting material. However, at reflux temperature sulfuryl chloride chlorinated 2-phenylthiazole (**1c**) sequentially at the 5- and then at the 4-position (Scheme 3). 5-Chloro-2-phenylthiazole (**13**; Hal=Cl) and 4,5-dichloro-2-phenylthiazole (**14**; Hal=Hal′=Cl) could both be obtained in high yields. With bromine in chloroform 2-phenylthiazole (**1c**) gave 5-bromo-2-phenylthiazole (**13**; Hal=Br) in excellent yield. However, attempts to introduce a second bromine into this compound failed. 4-Chloro-2-phenylthiazole (**16**; Hal′=Cl) was obtained by treatment of 2-phenylthiazol-4-one (**15**) with phosphorus oxychloride in the presence of pyridinium chloride.



Scheme 3.

4-Bromo-2-phenylthiazole (**16**; Hal′=Br) was obtained similarly. The 4-halo-substituted thiazoles (**16**; Hal′=Cl or Br) could be chlorinated with sulfuryl chloride or brominated with bromine at C-5 to give the dihalothiazoles (**14**). In this way chlorine and bromine could be introduced at the 4- and 5-positions in all possible combinations. Halogen attack at the phenyl group was never observed.

Thiazole (**1a**), 4,5-dimethylthiazole (**1b**) and 2-phenylthiazole (**1c**) were oxidized by *m*-chloroperbenzoic acid to their *N*-oxides (**2a–c**) in 52, 42, and 37% yield, respectively. Neither 4-chloro-2-phenylthiazole (**16**; Hal′=Cl) nor 5-chloro-2-phenylthiazole (**13**; Hal=Cl) could be *N*-oxidized, even using dimethyldioxirane[19,20] as the oxidant. In contrast to previous reports,[17] we found that thiazole *N*-oxides are stable for months when stored cool and dry. In 4,5-dimethylthiazole 3-oxide (**2b**) the 2-position is expected to be activated towards electrophiles owing to delocalization of the negative charge at the oxygen atom. Such activation was observed when *N*-chloro- or *N*-bromosuccinimide was used as electrophile converting compound **2b** into its 2-halo-substituted derivatives (**5b**; El=Cl or Br). In contrast, chlorine and bromine left compound **2c** unchanged.

In 2-phenylthiazole 3-oxide (**2c**) the positive charge in the ring is expected to reduce the reactivity of the 4- and 5-position towards electrophiles. Accordingly the *N*-oxide **2c** was not halogenated by bromine in contrast with the parent thiazole.

As predicted, *N*-oxidation leads to enhanced acidity of the thiazole ring protons. Deprotonation gave rise to anions which reacted with a series of electrophiles to give substituted thiazole *N*-oxides. In these, the activating *N*-oxygen could be removed under mild conditions. This sequence is useful for the regioselective introduction of substituents in the thiazole nucleus. Thus, H-2 of 4,5-dimethylthiazole 3-oxide (**2b**) is readily abstracted using sodium hydride as the base. The anion generated reacts with dimethyl disulfide to give 2-mercapto-4,5-dimethylthiazole 3-oxide (**5b**; El=SH). It is likely that (**5b**; El=SH) is formed through methylthiolation to give 2-methylthio-4,5-dimethylthiazole 3-oxide (**5b**; El=SMe) and methylthiolate ions. These then dealkylate (**5b**; El=SMe) to give the isolated mercapto compound.

The 2-position is by far the most acidic position and it may be possible to introduce substituents selectively in this position. In an attempt to investigate the regioselectivity thiazole 3-oxide **2a** was treated with 1 equiv. of sodium hydride and excess 2,2-dimethylpropanal. This afforded 2,5-bis(1-hydroxy-2,2-dimethylpropyl)thiazole (**6**; El=CHOHBu^t) as the sole product. The reason for the lack of monoselectivity may be that the initial product, the mono (1-hydroxy-2,2-dimethylpropyl)thiazole, is formed as its alkoxide serving as a base for removal of a second ring proton. The selectivity between the 2 and the 5 position was not studied further, since many substituents can be introduced selectively at the 2-position by using thiazoles[8] or thiazolium salts as the starting materials.[21]

In thiazole *N*-oxides, the 5-position is more acidic than the 4-position as demonstrated by the regioselective introduction of a series of substituents at C-5 of 2-phenylthiazole 3-oxide (**2c**). Thus, **2c**, after deprotonation with sodium hydride in *N,N*-dimethylformamide, reacted with paraformaldehyde and 2,2-dimethylpropanal to give the 5-hydroxymethyl and 5-(1-hydroxy-2,2-dimethylpropyl) derivatives (**7**; El=CH_2OH) and (**7**; El=CHOHBu^t), respectively in good yields. A similar reaction takes place with 2,2-dimethylpropanoyl chloride to give the 5-(2,2-dimethylpropanoyl) substituted thiazole *N*-oxide (**7**; El=COBu^t). Acetyl chloride failed to react under similar conditions probably because the strong base deprotonates its methyl group. In these cases further attack at the 4-position was not observed. However, when dimethyl disulfide is used as an electrophile the initially formed 5-methylthio-substituted thiazole *N*-oxide (**7**; El=SMe) reacts further at C-4 producing the 4,5-bismethylthio compound (**8**; El′=SMe). In order to avoid dealkylation or methylthiolation at the 5-methylthio group the reaction must be performed in neat dimethyl disulfide. When hexachloroethane or tetrabromomethane are employed as electrophiles, the first halogen introduced at C-5 of **2c** seems to enhance the acidity of the adjacent H-4. Hence, the 5-chloro- and bromo-substituted thiazole *N*-oxides (**7**; El=Cl or Br) could only be isolated in low yields even when the halogenation agent is present in deficient amounts. On the other hand, the dichloro- and dibromothiazole *N*-oxides (**8**; El=El′=Cl) and (**8**; El=El′=Br) were attained in high yields. The dibromo compound **8**; El=El′=Br can be dehalogenated selectively and stepwise, first at C-5 to give the 4-bromothiazole *N*-oxide (**9**; El′=Br), then at C-4 to give the unsubstituted *N*-oxide (**2c**). Moreover, the dichlorothiazole *N*-oxide (**8**; El=El′=Cl) can be dehalogenated at C-5 with production of (**9**; El′=Cl), although in moderate yield. The 4-halothiazole *N*-oxides (**9**; El′=Cl or Br) can be chlorinated or brominated at C-5. In this way, chlorine and bromine can be introduced at the 4- and 5-positions of the thiazole *N*-oxide **2c** in all possible combinations.

Thiazole *N*-oxides are easily deoxygenated[22] by phosphorus trichloride in chloroform at 70 °C to give the parent thiazole in excellent yield. In this way, thiazole 3-oxides with almost any substitution pattern can be converted into the corresponding thiazoles.

The thiazole *N*-oxides **2a–c** are readily alkylated by trimethyloxonium tetrafluoroborate to give the 3-methoxythiazolium salts **3a–c**. When treated with nucleophiles such as cyanide or azide ion or with dimethylamine, demethylation takes place with regeneration of the *N*-oxides. Only when **3b** was treated with dimethylamine did the reaction also give rise to a minute amount of the 2-dimethylaminothiazole (**1**; R^2=NMe_2, R^4=R^5=Me). Methoxide ion demethoxylates **3b** probably through deprotonation followed by deformylation, a reaction also observed for *N*-methoxypyridinium salts.[23]

The thiazole *N*-oxides **2a–c** reacted with acylating agents

such as phosphorus oxychloride and acetyl chloride at elevated temperatures. When treated with phosphorus oxychloride thiazole 3-oxide (**2a**) produced a 8.0:3.5:1.0 mixture of 2-chlorothiazole (**19**), 4-chlorothiazole (**23**) and 5-chlorothiazole (**21**). Most probably, *O*-phosphorylation to give **17**; Ac=$POCl_2$ is followed by addition of the liberated chloride ions. Attack at C-2 is followed by elimination of acid, while attack at C-4 or C-5 takes place with simultaneous elimination of phosphate (Scheme 4). 2-Phenylthiazole *N*-oxide (**2c**) also reacts with low regioselectivity to produce the 4- and 5-chlorothiazoles **1**; R=Ph, R^4=Cl, R^5=H and **1**; R=Ph, R^4=H, R^5=Cl in almost equal amounts. In contrast, acetyl chloride reacts selectively with the 2-phenylthiazole *N*-oxide (**2b**) to afford the 5-chlorothiazole (**1**; R=Ph, R^4=H, R^5=Cl) as the sole product. The expected 5-acetoxythiazole (**1**; R=Ph, R^4=H, R^5=OCOMe) was not detected. The 4,5-dimethyl substituted thiazole *N*-oxide **2c** reacts with acetyl chloride to give 2-chloro-4,5-dimethylthiazole (**1**; R^2=Cl, R^4=R^5=Me) as the main product. In addition minor amounts of a 1:8 mixture of 4-chloromethyl-5-methyl- and 5-chloromethyl-4-methylthiazole (**1**; R^2=H, R^4=CH_2Cl, R^5=Me and **1**; R^2=H, R^4=Me, R^5=CH_2Cl) are formed. Again, no acetoxy-substituted products were observed.

NMR characteristics. *N*-Oxidation of thiazoles causes characteristic changes of ^1H and ^{13}C NMR parameters. On *N*-oxidation the chemical shift of H-2 and H-4 increases ca. 0.3 ppm and 0–0.2 ppm, respectively, while that of H-5 decreases 0–0.2 ppm. $J_{H\text{-}4,H\text{-}5}$ increases ca. 0.8 Hz (see Table 2). The 2′-protons of 2-phenylthiazole 3-oxides exhibit a chemical shift 0.3 ppm higher than the analogous protons of the parent 2-phenylthiazoles. In 2-phenylthiazoles the chemical shift difference between C-3′ and C-2′ is ca. 3 ppm indicating that the two aromatic rings are not coplanar.[24] Accordingly, no change is observed in this parameter upon *N*-oxidation. The chemical shift of C-2 and C-4 decreases ca. 25 ppm and 4–12 ppm upon *N*-oxidation (see Table 4). The chemical shift of C-5 decreases 2–4 ppm when unsubstituted or substituted with halogen. When substituted with a methylthio group the chemical shift of C-5 increases by ca. 9 ppm.

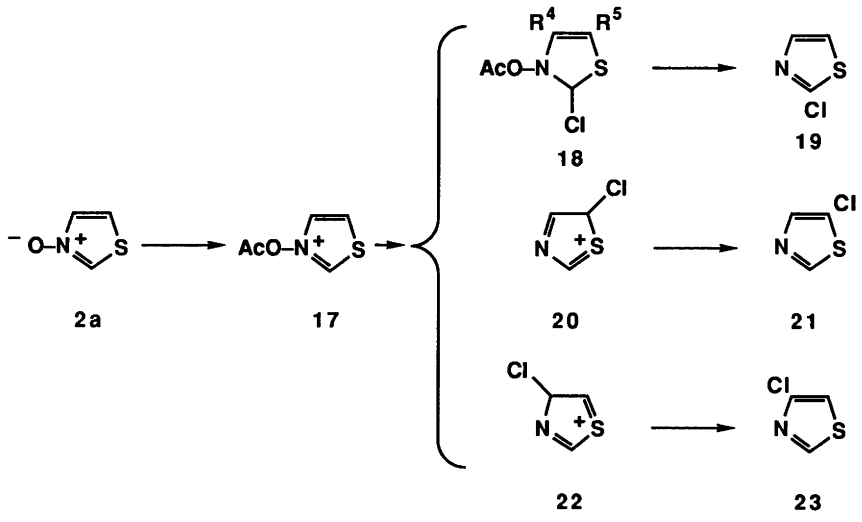
N-oxidation leads to an increase of $J_{C\text{-}2,H\text{-}2}$ by 2–6 Hz, of $J_{C\text{-}4,H\text{-}4}$ by 14–16 Hz, and of $J_{C\text{-}5,H\text{-}5}$ by 10–12 Hz.

Conclusions

Using a combination of halogenation and replacement of hydroxy groups with halogen, chlorine and bromine have been introduced selectively at the 4 and 5-positions giving access to 2-phenylthiazole with all possible combinations of one or two chlorine or bromine substituents. These halo-substituted thiazoles are of great utility e.g. in halogen–metal exchange reactions.

Peracid oxidation procedures of thiazoles itself and two representative derivatives have been developed to produce the corresponding *N*-oxides in fair yields which increase with the basicity of the thiazole. The thiazole *N*-oxides can be *O*-methylated in almost quantitative yield with trimethyloxonium tetrafluoroborate and they can be *O*-acylated with acetyl chloride or *O*-phosphorylated by phosphorus oxychloride.

The observed reactivity of the thiazole *N*-oxides **11** and the *N*-methoxy- or *N*-acyloxy-thiazolium salts **12** is in accord with a donor–acceptor analysis of these species. Thus, the 2-position is more reactive towards electrophilic substitution in the thiazole *N*-oxides **11** than in the parent thiazoles **10** while the 4 and 5-positions are not. In addition, the ring-protons are more acidic in the thiazole *N*-oxides **11**. All ring positions of the *N*-acetyloxythiazolium salts (**12**; R=MeCO) exhibit enhanced acceptor properties in 1,3 or 1,5 nucleophilic substitution reactions in which chloride or acetate ion serve as the nucleophile.



Scheme 4.

Table 1. ^{1}H NMR data of thiazoles (**1**) in $CDCl_3$ with tetramethylsilane as an internal standard.

Compound **1**			Chemical shift (ppm)		
R^2	R^4	R^5	$\delta_{H\text{-}4}$	$\delta_{H\text{-}5}$	δ_{Ph}
Ph[a]	H	H	7.85	7.30	2 H 7.96; 3 H 7.42
Ph	Cl	H		7.08	2 H 7.94; 3 H 7.47
Ph	Br	H		7.20	2 H 7.92; 3 H 7.44
Ph	Cl	Cl			2 H 7.82; 3 H 7.44
Ph	Cl	Br			2 H 7.83; 3 H 7.66
Ph	Br	Cl			2 H 7.83; 3 H 7.45
Ph	Br	Br			2 H 7.85; 3 H 7.44
Ph	H	Cl	7.64		2 H 7.85; 3 H 7.45
Ph	H	Br	7.73		2 H 7.86; 3 H 7.44

[a] $J_{H\text{-}4,H\text{-}5}$ = 3.2 Hz.

Deprotonation of the thiazole *N*-oxides **11** can be followed by addition of electrophiles. This allows selective introduction of carbon, halogen and sulfur substituents in the thiazole-ring in good to excellent yields. In these reactions the reactivity of the ring positions decreases in the order 2 > 5 > 4, deprotonation of the 4 position requiring C-5 to possess an electron-attracting substituent.

Experimental

Dichloromethane was dried over sodium hydride. Acetonitrile,[25] methanol,[26] and *N,N*-dimethylformamide (DMF)[27] were dried as described in the references. Liquid electrophiles were distilled before use; solid ones were

Table 2. ^{1}H NMR data of thiazole 3-oxides (**2**) in $CDCl_3$ with tetramethylsilane as an internal standard, unless otherwise stated.

Compound **2**			Chemical shift (ppm)				
R^2	R^4	R^5	$\delta_{H\text{-}2}$	$\delta_{H\text{-}4}$	$\delta_{H\text{-}5}$	δ_{Ph}	δ_{CH_3}, δ_{CH_2} or δ_{CH}
Ph	Cl	H			7.28	2 H 8.22; 3 H 7.47	
Ph	Br	H			7.40	2 H 8.35; 3 H 7.49	
Ph	Cl	Cl				2 H 8.26; 3 H 7.49	
Ph	Br	Br				2 H 8.27; 3 H 7.49	
Ph	SCH_3	SCH_3				2 H 8.30; 3 H 7.47	CH_3 2.57, 2.60
CH_3[29]	CH_3	H			6.87		CH_3 2.60, 2.39
Br	CH_3[a]	CH_3					CH_3 2.39, 2.26
Cl	CH_3[b]	CH_3					CH_3 2.38, 2.32
Ph	H	Cl		7.64		2 H 7.85; 3 H 7.45	
Ph	H	Br		7.73		2 H 7.86; 3 H 7.44	
Ph	H	SCH_3		7.60		2 H 8.25; 3 H 7.50	CH_3 2.57
Ph	H	CH_2OH		7.75		2 H 8.22; 3 H 7.55	CH_2 4.76
SH	CH_3[c]	CH_3					CH_3 2.23, 2.27; SH 9.50
Ph	H	C(=O)Bu^t		8.40		2 H 8.37; 3 H 7.57	CH_3 1.41
Ph[d]	H[e]	CH(OH)Bu^t		7.72		2 H 8.26; 3 H 7.52	CH 4.63; CH_3 1.02
CH(OH)Bu^t[g]	H[f]	CH(OH)Bu^t		7.54			CH 5.02, 4.57; CH_3 1.02, 0.97
H[g,h]	H[i]	H	8.98	7.89	7.90		
H	CH_3	CH_3	8.17				CH_3 2.38, 2.29
H[g]	CH_3[j]	CH_3	8.49				CH_3 2.18, 2.34

[a] $J_{4\text{-}CH_3,5\text{-}CH_3}$ = 0.8 Hz. [b] $J_{4\text{-}CH_3,5\text{-}CH_3}$ = 0.85 Hz. [c] $J_{4\text{-}CH_3,5\text{-}CH_3}$ = 0.9 Hz. [d] In CD_3OD with tetramethylsilane as internal standard. [e] $J_{H\text{-}4,5\text{-}CH_3}$ = 0.8 Hz. [f] $J_{H\text{-}4,5\text{-}CH_3}$ = 0.85 Hz. [g] In D_2O with dioxane (δ = 3.70) as internal standard. [h] $J_{H\text{-}2,H\text{-}4}$ = 2.05 Hz, $J_{H\text{-}2,H\text{-}5}$ = 0.65 Hz. [i] $J_{H\text{-}4,H\text{-}5}$ = 3.85 Hz. [j] $J_{4\text{-}CH_3,5\text{-}CH_3}$ = 0.8 Hz.

Table 3. ^{1}H NMR data of 3-methoxythiazolium tetrafluoroborates (**3**) in $CDCl_3$ with tetramethylsilane as an internal standard, unless otherwise stated.

Compound **3**			Chemical shift (ppm)				
R^2	R^4	R^5	$\delta_{H\text{-}2}$	$\delta_{H\text{-}4}$	$\delta_{H\text{-}5}$	δ_{Ph}	δ_{CH_3}, δ_{CH_2} or δ_{CH}
H[a,b]	H[c]	H	10.17	8.51	8.22		CH_3: 4.40
Ph	H[d]	H		8.50	8.27	2 H: 7.85 1 H: 7.79 2 H: 7.69	CH_3: 4.25
H	CH_3[e]	CH_3	9.89				OCH_3: 4.42 CCH_3: 2.55, 2.47

[a] In D_2O with dioxane (δ = 3.70) as internal standard. [b] $J_{H\text{-}2,H\text{-}4}$ = 2.6 Hz, $J_{H\text{-}2,H\text{-}5}$ = 1.85 Hz. [c] $J_{H\text{-}4,H\text{-}5}$ = 4.0 Hz. [d] $J_{H\text{-}4,H\text{-}5}$ = 4.5 Hz. [e] $J_{4\text{-}CH_3,5\text{-}CH_3}$ = 0.8 Hz.

Table 4. ^{13}C NMR data of thiazoles (**1**) in $CDCl_3$ with the solvent signal ($\delta = 76.90$) as an internal standard, unless otherwise stated.

Compound **1**			Chemical shift (ppm)			
R^2	R^4	R^5	δ_{C-2} ($\delta_{C-1'}$)	δ_{C-4} ($\delta_{C-2'}$)	δ_{C-5} ($\delta_{C-3'}$)	δ_{CH_3} δ_{CH_2} ($\delta_{C-4'}$)
Ph	H	H	168.3 (133.5)	143.6[b] (126.5)	118.8[c] (128.9)	(129.9)
Ph	Cl	H	168.0 (132.6)	140.0 (126.2)	113.0[d] (129.0)	(130.7)
Ph	Br	H	169.0 (132.4)	126.0 (126.2)	116.5 (128.9)	(130.6)
Ph	Cl	Cl	164.2 (132.2)	138.0 (125.8)	119.6 (129.0)	(131.0)
Ph	Cl	Br	167.4 (132.2)	140.9 (125.9)	108.8 (129.1)	(131.1)
Ph	Br	Cl	165.9 (132.2)	126.2 (126.0)	122.6 (129.1)	(131.0)
Ph	Br	Br	168.8 (132.2)	129.4 (126.0)	106.8 (129.1)	(131.1)
Ph	SMe	SMe	168.3 (133.1)	153.7 (126.2)	123.8 (128.9)	CH_3: 20.7, 16.4 (130.4)
Ph	H	Cl	166.9 (133.2)	141.6[e] (126.2)	126.3 (129.1)	(130.4)
Ph	H	Br	169.6 (133.1)	144.8 (126.2)	108.5 (129.1)	(130.4)
H	Me	Me	148.2[f]	148.3[g]	125.5[h]	4-CH_3: 14.0 5-CH_3: 10.6
H[a]	CH_2Cl	CH_3	156.2	141.8	137.6	5-CH_3: 11.4 CH_2: 35.4
H[a]	CH_2OH	CH_3	155.7[i]	143.4[j]	136.0[k]	5-CH_3: 11.4 CH_2: 54.8

[a]As the hydrochloride in D_2O solution with dioxane ($\delta = 67.40$) as an internal standard. [b]$J_{C-4,H-4}$ = 184 Hz, $J_{C-4,H-5}$ = 6.4 Hz. [c]$J_{C-5,H-5}$ = 187 Hz, $J_{C-5,H-4}$ = 15.7 Hz. [d]$J_{C-5,H-5}$ = 194.5 Hz. [e]$J_{C-4,H-4}$ = 191 Hz. [f]$J_{C-2,H-2}$ = 210.5 Hz, $J_{C-2,5-CH_3} < 0.3$ Hz. [g]$J_{C-4,4-CH_3}$ = 6.6 Hz, $J_{C-4,5-CH_3}$ = 4.3 Hz, $J_{C-4,H-2}$ = 3.3 Hz. [h]$J_{C-5,5-CH_3}$ = 6.7 Hz, $J_{C-5,4-CH_3}$ = 4,5 Hz, $J_{C-5,H-2}$ = 1.4 Hz. [i]$J_{C-2,H-2}$ = 216.8 Hz. [j]$J_{C-4,4-CH_3}$ = 7.8 Hz. [k]$J_{C-5,H-2}$ = 3.6 Hz, $J_{C-5,4-CH_3}$ = 3.6 Hz, $J_{C-5,5-CH_3}$ = 7.1 Hz.

dried over phosphorus pentaoxide. Filtration through silica gel was performed using silica gel Merck 60 (70–230 mesh). All new compounds were colourless, unless otherwise stated. The purity of all compounds were confirmed using melting points, ^1H and ^{13}C NMR spectra recorded at 200 and 50.32 MHz, respectively, on a Bruker AC-200 instrument. NMR data of all new compounds are given in Tables 1–6.

Thiazoles. Thiazole[28] (**1a**) and 4,5-dimethylthiazole[29] (**1b**) were prepared using reported procedures. 2-Phenylthiazole (**1c**) was obtained by a modification of the described method[30] as follows. Acetic anhydride (40 ml) and toluene (20 ml) were added to a mixture of chloroacetaldehyde monohydrate (30 g)* and thiobenzamide (32 g). Heating with stirring gave rise to a violent reaction, which was controlled by use of an efficient double reflux condenser. When the reaction had ceased the mixture was stirred with heating to reflux for 10 min. Removal of the toluene and excess of chloroacetaldehyde *in vacuo,* addition of water (120 ml) and addition of 1 M aqueous sodium hydroxide until pH ca. 8 followed by extraction with dichloromethane (5×20 ml), drying ($MgSO_4$), removal of the dichloromethane, and distillation gave 28 g (79 %) of 2-phenylthiazole (**1c**), b.p. 80 °C / 0.3 mmHg. (Reported b.p. 135–138 °C / 18 mmHg,[30] 147–151 °C / 21 mmHg[31]).

* Aqueous chloroacetaldehyde (40 %) and calcium chloride (0.35 g per ml) were stirred with cooling in an ice bath for 1 h. The lower layer consisting of chloroacetaldehyde monohydrate was then isolated.

Table 5. ^{13}C NMR data of thiazole 3-oxides (**2**) in $CDCl_3$ with the solvent signal ($\delta = 76.90$) as an internal standard, unless otherwise stated.

Compound **2**			Chemical shift (ppm)			
R^2	R^4	R^5	$\delta_{C\text{-}2}$ ($\delta_{C\text{-}1'}$)	$\delta_{C\text{-}4}$ ($\delta_{C\text{-}2'}$)	$\delta_{C\text{-}5}$ ($\delta_{C\text{-}3'}$)	δ_{CH_3} δ_{CH_2} ($\delta_{C\text{-}4'}$)
Ph	H	H	143.6 (127.7)	139.4[a] (126.8)	115.0[b] (128.8)	(130.5)
Ph	Cl	H	143.0 (127.8)	135.5 (126.6)	109.6 (129.0)	(131.1)
Ph	Br	H	142.7 (127.7)	124.1 (126.5)	112.9 (128.8)	(130.9)
Ph	Br	Cl	143.4 (127.1)	124.5 (126.7)	120.8 (129.1)	(131.3)
Ph	Br	Br	143.8 (127.4)	127.5 (126.7)	104.0 (129.1)	(131.3)
Ph	Cl	Cl	141.1 (127.1)	133.9 (126.7)	117.7 (129.1)	(131.3)
Ph	Cl	Br	143.9 (127.2)	136.3 (126.7)	101.0 (129.2)	(131.4)
Ph	H	SMe	144.7 (127.6)	138.7 (126.8)	129.8 (128.9)	CH_3: 20.1 (130.6)
Ph	SMe	SMe	142.2 (128.1)	141.2 (126.7)	132.9 (128.9)	CH_3: 16.3, 18.1 (130.4)
Me[29]	Me	H	142.9[c]	145.2[c]	108.6	CH_3: 13.3, 13.4
Br	Me	Me	113.1	141.3	125.6	CH_3: 11.5, 13.3
Cl	Me	Me	127.8	141.1	122.2	CH_3: 11.4, 13.1
Ph	H	Br	145.3 (127.2)	139.9 (126.8)	105.1 (129.0)	(131.0)
Ph	H	CH_2OH	147.9 (128.6)	139.4 (128.7)	135.4 (130.2)	CH_2: 57.6 (132.3)
SH	Me	Me	167.7	132.1	115.6	CH_3: 11.0, 11.8
Ph[d]	H	CH(OH)Bu^t	147.8 (128.7)	135.8 (128.7)	141.4 (130.2)	CH_3: 26.1 CH: 76.1 C: 31.7 (132.3)
Ph	H	C(=O)Bu^t	– (127.9)	140.9 (127.7)	130.9 (129.1)	CH_3: 44.4 C=O: 196.5 C: 27.5 (131.9)
CH(OH)Bu^t[d]	H	CH(OH)Bu^t	155.5	142.1	133.2	2-CH_3: 26.0 2-CH: 76.0 2-C: 38.2 5-CH_3: 26.0 5-CH: 74.3 5-C: 36.5
H	H	H	139.7[e]	136.3[f]	123.2[g]	
H	Me	Me	127.4[h]	141.6	125.7	CH_3: 10.6, 13.3
H	Me	Me	126.8[i]	140.8[j]	125.5[k]	4-CH_3: 12.9 5-CH_3: 10.1

[a] $J_{C\text{-}4,H\text{-}4} = 199.3$ Hz, $J_{C\text{-}4,H\text{-}5} = 9.6$ Hz. [b] $J_{C\text{-}5,H\text{-}5} = 197.4$ Hz, $J_{C\text{-}5,H\text{-}4} = 6.4$ Hz. [c] $\delta_{C\text{-}2}$ and $\delta_{C\text{-}4}$ may be interchanged. [d] In CD_3OD with the solvent signal ($\delta = 47.07$) as an internal standard. [e] $J_{C\text{-}2,H\text{-}2} = 215.5$ Hz. [f] $J_{C\text{-}4,H\text{-}4} = 201.2$ Hz. [g] $J_{C\text{-}5,H\text{-}5} = 201.1$ Hz. [h] $J_{C\text{-}2,H\text{-}2} = 212.6$ Hz. [i] $J_{C\text{-}2,H\text{-}2} = 212.6$ Hz. [j] $J_{C\text{-}4,4\text{-}CH_3} = 6.5$ Hz, $J_{C\text{-}4,5\text{-}CH_3} = 4.6$ Hz, $J_{C\text{-}4,H\text{-}2} = 5.9$ Hz. [k] $J_{C\text{-}5,5\text{-}CH_3} = 6.9$ Hz, $J_{C\text{-}5,4\text{-}CH_3} = 4.4$ Hz, $J_{C\text{-}5,H\text{-}2} = 4.3$ Hz.

Table 6. ^{13}C NMR data of 3-methoxythiazolium tetrafluoroborates (**3**).

Compound **3**			Chemical shift (ppm)			
R^2	R^4	R^5	$\delta_{C\text{-}2}$ ($\delta_{C\text{-}1'}$)	$\delta_{C\text{-}4}$ ($\delta_{C\text{-}2'}$)	$\delta_{C\text{-}5}$ ($\delta_{C\text{-}3'}$)	δ_{CH_3} ($\delta_{C\text{-}4'}$)
H[a]	H	H	151.8[b]	133.6[b]	126.2[b]	OCH_3: 70.4
Ph[c]	H	H	163.8	134.2	122.5	OCH_3: 68.8
			(122.1)	(129.6)	(129.0)	(133.3)
H[c]	Me	Me	146.2	138.8	132.6	OCH_3: 68.9
						CCH_3: 11.4, 8.8

[a] In D_2O with dioxane ($\delta = 67.4$) as internal standard. [b] $J_{C\text{-}4,H\text{-}4}$ = 197.8 Hz, $J_{C\text{-}5,H\text{-}5}$ = 206.6 Hz, $J_{C\text{-}4,H\text{-}5}$ = 7.6 Hz, $J_{C\text{-}5,H\text{-}4}$ = 9.1 Hz. The 2-proton exchanges so rapidly, that coupling is not observed. [c] In $CDCl_3$ with tetramethylsilane as internal standard.

2-Phenyl-4-halothiazoles. (a) 2-Phenylthiazol-4-one[32] (**15**, 5.90 g), pyridinium hydrochloride (8.1 g), phosphoric acid (crystalline H_3PO_4, 2.8 g), and phosphorus oxychloride (25 ml) were stirred and heated to 100 °C for 6 h. Excess phosphorus oxychloride was removed *in vacuo*. Toluene (30 ml) was added and removed *in vacuo*. Satd. aqueous sodium hydrogencarbonate (250 ml) and ethyl acetate (100 ml) were added. Extraction with a further 3×100 ml of ethyl acetate, drying, removal of the solvents, and ball-tube distillation (160 °C / 0.2 mmHg) afforded 4.68 g (72 %) of 4-chloro-2-phenylthiazole (**16**; Hal′=Cl), m.p. 63.5–64 °C. Anal. C_9H_6ClNS: C, H, Cl, N.

(b) Similarly, 2-phenylthiazol-4-one[32] (**15**, 1.03 g), pyridinium hydrobromide (2.0 g), and phosphorus oxybromide (22 g) were stirred at 110 °C for 20 h. Removal of the phosphorus oxybromide using ball-tube distillation (120 °C / 0.5 mmHg) gave a residue which was stirred with 1 M sodium hydroxide (50 ml) and ethyl acetate (100 ml) for 15 min. Extraction with a further 2×50 ml of ethyl acetate, drying, removal of the solvents, dissolution in ether, filtration through activated carbon, and removal of the ether gave 1.20 g of a 5.7:1 mixture of 4-bromo-2-phenylthiazole (**16**; Hal=Br) and 4,5-dibromo-2-phenylthiazole (**14**; Hal=Hal′=Br) (^1H NMR). Preparative TLC [ethyl acetate–hexane (1:10)] gave 0.16 g of 4,5-dibromo-2-phenylthiazole (**14**; Hal=Hal′=Br) ($R_f = 0.71$), m.p. 75–76 °C and 0.90 g (64 %) of 4-bromo-2-phenylthiazole (**16**; Hal=Br) ($R_f = 0.55$), m.p. 77–78 °C [ethanol–water (4:1)]. Anal. C_9H_6BrNS: C, H, Br, N.

Halogenation of 2-phenylthiazole. (a) To a solution of 2-phenylthiazole (**1c**) (1.00 g) in chloroform (5.0 ml) was added a solution of sulfuryl chloride (1.25 ml) in chloroform (5 ml). Reflux for 1 h, removal of sulfuryl chloride and chloroform followed by ball-tube distillation gave 0.81 g (67 %) of 5-chloro-2-phenylthiazole (**13**; Hal=Cl), m.p. 20–30 °C. Recrystallization from 50 % ethanol gave m.p. 48–49 °C. Anal. C_9H_9ClNS: C, H, Cl, N.

(b) Similarly, a mixture of 4-chloro-2-phenylthiazole (**16**; Hal′=Cl) (1.49 g) and sulfuryl chloride (1.56 ml) in chloroform (10 ml) was refluxed for 3 h. Removal of sulfuryl chloride and chloroform followed by ball-tube distillation gave 1.56 g (90 %) of 4,5-dichloro-2-phenylthiazole (**14**; Hal=Hal′=Cl),[33] m.p. 41–45 °C. Recrystallization from 90 % ethanol gave m.p. 53–54 °C. Anal. $C_9H_5Cl_2NS$: C, H, Cl, N.

(c) Similarly, a mixture of 4-bromo-2-phenylthiazole (**16**; Hal′=Br) (150 mg) and sulfuryl chloride (0.130 ml) in chloroform (1.0 ml) was refluxed for 2 h. Removal of sulfuryl chloride and chloroform gave 157 mg (91 %) of 4-bromo-5-chloro-2-phenylthiazole (**14**; Hal=Cl, Hal′=Br), m.p. 48–65 °C. Recrystallization from 50 % ethanol gave m.p. 55–56 °C. Anal. $C_9H_5BrClNS$: C, H, Br, Cl, N.

(d) To a solution of 2-phenylthiazole (**1c**) (0.94 g) in chloroform (5.0 ml) was added a solution of bromine (0.60 ml) in chloroform (5 ml). Stirring for 20 h, removal of bromine and chloroform, addition of 2 M sodium hydroxide (5 ml) followed by extraction with 4×5 ml dichloromethane, drying, and removal of the dichloromethane gave a 1:2 mixture of 2-phenylthiazole and 5-bromo-2-phenylthiazole. Preparative TLC [ethyl acetate–hexane (1:10)] gave 198 mg (21 %) of 2-phenylthiazole (**1c**) ($R_f = 0.33$) and 0.87 g (62 %) of 5-bromo-2-phenylthiazole (**13**; Hal=Br) ($R_f = 0.50$), m.p. 79–80 °C. Reported[3] m.p. 81 °C.

(e) Similarly, bromine (0.050 ml) was added to a solution of 4-bromo-2-phenylthiazole (**16**; Hal′=Br) (48.2 mg) in chloroform (2.0 ml). Stirring for 6 h, addition of 1 M sodium hydroxide (5 ml), extraction with 3×4 ml of dichloromethane, drying, and removal of the dichloromethane gave 92 mg (99 %) 4,5-dibromo-2-phenylthiazole (**14**; Hal=Hal′=Br), m.p. 75–76 °C (90 % ethanol), [reported[3] m.p. 94–94.5 °C (hexane)] Anal. $C_9H_5Br_2NS$: C, H, Br, N.

(f) Similarly, bromine (0.50 ml) was added to a solution of 4-chloro-2-phenylthiazole (**16**; Hal′=Cl) (0.88 g) in chloroform (10 ml). Stirring for 2 h, addition of 2 M sodium hydroxide (10 ml), extraction with 4×5 ml of dichloromethane, addition of sodium sulfite (0.5 g), drying, filtration, and removal of the dichloromethane followed by ball-tube distillation (180 °C / 0.8 mmHg) gave 1.16 g (94 %) of 5-bromo-4-chloro-2-phenylthiazole (**14**; Hal=Br, Hal′=Cl), m.p. 89–90 °C [ethanol–water (3:1)]. Anal. $C_9H_5BrClNS$: C, H, Br, Cl, N.

Thiazole 3-oxides. (a) Thiazole (**1a**) (1.50 g) was added to a solution of *m*-chloroperbenzoic acid (90 %, 4.42 g) in ethyl acetate (25 ml). After 18 h water (25 ml) and ether (25 ml) were added and the organic phase was extracted with water (2×15 ml). The combined aqueous phases were evaporated to dryness *in vacuo* at max. 40 °C to yield 1.00 g (63 %) of crude thiazole 3-oxide (**2a**). Extraction with 20 ml of ethyl acetate–methanol (1:1), filtration through a column with silica gel (10 g) washing with a further 150 ml of ethyl acetate to remove minor impurities, elution with 150 ml of ethyl acetate–methanol (1:1), and evaporation to dryness gave 0.83 g (52 %) of thiazole 3-oxide (**2a**) as a light yellow glass which solidified on standing. The compound was identified through its *O*-methylated derivative, see below.

(b) 4,5-Dimethylthiazole (**1b**) (11.0 g) was added to a solution of *m*-chloroperbenzoic acid (90 %, 24.3 g) in ethyl acetate (150 ml). Stirring at ambient temperature for 16 h (a rise in temperature was observed after 30 min), addition of potassium fluoride (8.7 g), evaporation *in vacuo* (bath temperature below 40 °C), addition of dichloromethane (150 ml), filtration, washing with further dichloromethane (2×25 ml), removal of the dichloromethane, dissolution in ethyl acetate (50 ml), filtration through silica gel, elution with a further 300 ml of ethyl acetate, and removal of the ethyl acetate gave 10 g of *m*-chlorobenzoic acid together with unchanged starting material. Subsequent elution with 300 ml ethyl acetate–methanol (1:1) and removal of the solvents gave a brown oil which crystallised upon addition of ether (150 ml) to produce 4.6 g (37 %) of 4,5-dimethylthiazole 3-oxide (**2b**), m.p. 116–117 °C [ethyl acetate–hexane (1:2)]. Anal. C_5H_7NOS: C, H, N.

(c) To 2-phenylthiazole (**1c**) (2.50 g) was added an ice-cold solution of *m*-chloroperbenzoic acid (90 %, 5.01 g) in ethyl acetate (15 ml). Stirring at 20 °C for 4 days, addition of dichloromethane (50 ml), washing with 1 M sodium hydroxide (2×25 ml), extraction of the aqueous solution with chloroform (5×20 ml), combination of the organic solutions, drying ($MgSO_4$), evaporation to dryness, extraction with ethyl acetate (10 ml), filtration through silica gel (4 g, column diameter 2 cm), elution with further 50 ml of ethyl acetate and removal of the ethyl acetate gave 1.40 g (56 %) of unchanged starting material. Subsequent elution with ethyl acetate–methanol (1:1) (100 ml), evaporation to dryness, addition of water (10 ml), filtration through activated carbon, removal of the water, and drying over P_2O_5, or by addition of toluene (100 ml), followed by removal of the toluene, gave 1.14 g (42 %) of 2-phenylthiazole 3-oxide (**2c**), m.p. 82–84 °C (toluene). Anal. C_9H_7NOS: C, H, N.

O-Methylation. (a) Thiazole 3-oxide (**2a**) (0.13 g), trimethyloxonium tetrafluoroborate (0.40 g), and nitromethane (2 ml) were stirred for 18 h. Addition of methanol (4 ml), stirring for further 30 min, removal of the solvents, dissolution in water (5 ml), filtration through activated carbon, removal of the water, and two precipitations from methanol–ether gave 0.22 g (88 %) of 3-methoxythiazolium tetrafluoroborate (**3a**; X=BF_4) as a brown oil. A 0.25 M solution of sodium tetraphenylborate in water (8 ml) was added to a solution of 3-methoxythiazolium tetrafluoroborate (**3a**; X=BF_4) (0.10 g) in water (5 ml). Filtration, washing with water (3×5 ml) gave 204 mg (94 %) of 3-methoxythiazolium tetraphenylborate (**3a**; X=BPh_4) m.p. 156–158 °C (acetone). Anal. $C_{28}H_{26}BNOS$: C, H, N, S.

(b) 4,5-Dimethylthiazole 3-oxide (**2b**) (1.00 g), trimethyloxonium tetrafluoroborate (1.80 g) and dichloromethane (15 ml) were stirred for 24 h. Addition of methanol (5 ml), stirring for 10 min, removal of the solvents, and precipitation (methanol–ether) gave 1.50 g (88 %) of 3-methoxy-4,5-dimethylthiazolium tetrafluoroborate (**3b**; X=BF_4) m.p. 91–93 °C (ethanol). Anal. $C_6H_{10}BF_4NOS$: C, H, N, S.

(c) 2-Phenylthiazole 3-oxide (**2c**) (0.56 g), trimethyloxonium tetrafluoroborate (0.98 g), and dichloromethane (15 ml) were stirred for 100 min. Methanol (10 ml) was added and the mixture stirred for further 10 min. Removal of the solvents and recrystallization (methanol–ether) gave 0.90 g (99 %) of 3-methoxy-2-phenylthiazolium tetrafluoroborate (**3c**; X=BF_4), m.p. 145–146 °C. Anal. $C_{10}H_{10}BF_4NOS$: C, H, N, S.

Reaction of thiazole 3-oxides with acylating agents. (a) Thiazole 3-oxide (**2a**) (0.100 g) was suspended in nitromethane (0.50 ml) and phosphorus oxychloride (0.50 ml) was added. After being stirred at 60 °C for 1 h in a screw-cap sealed vessel the solution contained a 8.0:3.5:1.0 mixture of 2-chlorothiazole (**19**),[34] 4-chlorothiazole (**23**)[35] and 5-chlorothiazole (**21**)[35] (^{1}H NMR, the compounds were identified through their chemical shifts and characteristic coupling constants: $J_{H\text{-}4,H\text{-}5} = 4.3$ Hz, $J_{H\text{-}2,H\text{-}5} = 2.0$ Hz and $J_{H\text{-}2,H\text{-}4} = 0.8$ Hz, respectively). Owing to the volatility of the chlorothiazoles their isolation was not attempted.

(b) Acetyl chloride (2 ml) was added in one portion to 4,5-dimethylthiazole 3-oxide (**2b**) (0.25 g). Stirring for 6 h followed by removal of the acetyl chloride gave an oil which contained a 25:10:1 mixture of 2-chloro-4,5-dimethylthiazole (**1**; R^2=Cl, R^4=R^5=Me),[36] 4-chloromethyl-5-methylthiazole (**1**; R^2=H, R^4=CH_2Cl, R^5=Me), and 5-chloromethyl-4-methylthiazole (**1**; R^2=H, R^4=Me, R^5=CH_2Cl)[37] (^{1}H NMR). Ball-tube distillation produced 70 mg (24 %) of 2-chloro-4,5-dimethylthiazole (**1**; R^2=Cl, R^4=R^5=Me), (b.p. ca. 100 °C / 6 mmHg, reported[34] 104–106 °C / 58 mmHg). Anal. C_5H_6ClNS: C, H, Cl, N. Further distillation gave 28 mg (10 %) 4-chloromethyl-5-methylthiazole hydrochloride (**1**; R^2=H, R^4=CH_2Cl, R^5=Me, HCl), [subl. 120 °C, m.p. 152–153 °C (sealed tube)]. Anal. $C_5H_7Cl_2NS$: C, H, Cl, N.

Halogenation of 4,5-dimethylthiazole 3-oxide. (a) 4,5-Dimethylthiazole 3-oxide (**2b**, 43 mg) and *N*-bromosuccinimide (59 mg) in acetonitrile (1.0 ml) were stirred for 18 h at 20 °C. Removal of the acetonitrile, addition of chloroform (1 ml), filtration and preparative TLC [ethyl acetate–methanol (4:1)] gave 58 mg (85 %) of 2-bromo-4,5-dimethylthiazole 3-oxide (**5b**; El=Br) ($R_f = 0.47$) as light yellow

crystals, m.p. 104 °C (decomp). The compound was unstable and had to be stored in the refrigerator. Anal. C_5H_6BrNOS: C, H, Br, N, S.

(b) A mixture of 4,5-dimethylthiazole 3-oxide (**2b**, 80 mg), *N*-chlorosuccinimide (100 mg), benzoyl peroxide (2.5 mg), chloroform (0.50 ml), and tetrachloromethane (0.50 ml) were stirred for 6 h at 20 °C. Filtration and preparative TLC [ethyl acetate–methanol (4:1)] gave 50 mg (49 %) of 2-chloro-4,5-dimethylthiazole 3-oxide (**5b**; El=Cl) ($R_f = 0.41$) as light yellow crystals m.p. ca. 15 °C [ethyl acetate–hexane (1:4)]. The compound was unstable and had to be stored in the refrigerator. Owing to the hygroscopic nature of the product and its rapid decomposition, a correct elemental analysis could not be obtained.

Deprotonation followed by reaction with electrophiles. Unless otherwise stated, reactions were performed with exclusion of moisture by mixing the thiazole 3-oxide (0.5 mmol) and a 60 % suspension of sodium hydride in mineral oil in a screw-cap vessel.[36] A magnetic stirring bar and the electrophile, if solid, were added and the vessel closed with a rubber septum. Liquid electrophiles and solvents were added within 1 min with cooling in a dry-ice–acetone bath by means of syringe techniques. The mixture was stirred while being allowed to warm to 20 °C and then stirred for the time indicated below. After reaction, quenching was effected by addition of dichloromethane (4 ml) and water (1 ml). Reaction conditions and work-up conditions are given below.

(a) Thiazole 3-oxide (**2a**, 50 mg) was dried at 25 °C at 10^{-5} mmHg for 24 h in a screw-cap vessel. Sodium hydride suspension (27 mg) was added. Cooling to 0 °C, addition of DMF (1.0 ml) and 2,2-dimethylpropanal (0.110 ml), stirring at 0 °C for 3 h and standing at 5 °C for 3 days, quenching, extraction with chloroform (3×4 ml), removal of the chloroform, and washing with hexane (2×3 ml) yielded 110 mg (80 %) of crude 2,5-bis(1-hydroxy-2,2-dimethylpropyl)thiazole 3-oxide (**6**; El=CHOHBu^t), m.p. 183–186 °C, as a mixture of the four stereoisomers in equal amounts. Preparative TLC [ethyl acetate–methanol (4:1)] gave 45 mg (33 %) of one racemate (**6**; El=CHOHBu^t) ($R_f = 0.65$), m.p. 201–202 °C. Anal. $C_{13}H_{23}NO_3S$: C, H, N. The second racemate (**6**; El=CHOHBu^t) R_f = 0.51, m.p. 197–198 °C was isolated in 40 mg (29 %) yield. The configuration of the two racemates was not determined.

(b) 2-Phenylthiazole 3-oxide (**2c**, 124 mg), sodium hydride suspension (34 mg), paraformaldehyde (121 mg), and DMF (2.0 ml) were mixed. Stirring at 20 °C for 3 h, quenching by addition of 20 ml dichloromethane and 20 ml 4 M hydrochloric acid, extraction of the organic solution with 4 M hydrochloric acid (3×10 ml), neutralization of the combined aqueous solutions with 33 % sodium hydroxide, removal of the water, extraction with boiling ethyl acetate (5×20 ml), and removal of ethyl acetate gave 132 mg (90 %) of light yellow 5-hydroxymethyl-2-phenylthiazole 3-oxide (**7**; El=CH_2OH), m.p. 166 °C (2-propanol). Anal. $C_{10}H_9NO_2S$: C, H, N.

(c) 2-Phenylthiazole 3-oxide (**2c**, 108 mg), sodium hydride suspension (37 mg), 2,2-dimethylpropanal (0.20 ml) and DMF (1.0 ml) were stirred at 20 °C for 18 h. Dichloromethane (4.0 ml) and 0.10 M sodium hydroxide (2.0 ml) were then added. The organic product was isolated and methanol added until all the precipitate had dissolved. Drying, removal of the solvents *in vacuo*, washing with ether (4×5 ml), and removal of the ether gave 142 mg (89 %) of 5-(1-hydroxy-2,2-dimethylpropyl)-2-phenylthiazole 3-oxide (**7**; El=CHOHBu^t), m.p. 212–213 °C [2-propanol–water (20:1)]. Anal. $C_{14}H_{17}NO_2S$: C, H, N, S. The compound is hygroscopic and forms a monohydrate. Dissolution in methanol and addition of 2 M hydrochloric acid gave the hydrochloride of **7**; El=CHOHBu^t as a monohydrate, m.p. 191–192 °C. Anal. $C_{14}H_{20}ClNO_3S$: C, H, Cl, N, S.

(d) 2-Phenylthiazole 3-oxide (**2c**, 97 mg), sodium hydride suspension (50 mg), 2,2-dimethylpropanoyl chloride (0.20 ml) and DMF (1.0 ml) were stirred at 20 °C for 18 h. Quenching, addition of 33 % aqueous sodium hydroxide until pH ca. 10, extraction with dichloromethane (4×4 ml), drying, removal of the dichloromethane, and preparative TLC [ethyl acetate–methanol (8:1)] gave 30 mg (21 %) of 5-(2,2-dimethyl-1-oxopropyl)-2-phenylthiazole 3-oxide (**7**; El=COBu^t) as yellow, fluorescent needles, ($R_f = 0.73$), m.p. 151–154 °C [ethyl acetate–hexane (1:4)] Anal. $C_{14}H_{15}NO_2S$: C, H, N.

(e) 4,5-Dimethylthiazole 3-oxide (**2b**, 103 mg), sodium hydride suspension (49 mg), dimethyl disulfide (0.133 ml) and DMF (1.0 ml) were stirred at 20 °C for 48 h. Quenching, washing with dichloromethane (4×4 ml), acidification with 1 M hydrochloric acid (4 ml), and filtration yielded 80 mg (62 %) of 2-mercapto-4,5-dimethylthiazole 3-oxide (**5b**; El=SH), m.p. 85–86 °C. Extraction with dichloromethane gave a further 20 mg of (**5b**; El=SH), bringing the total yield to 78 %. (Found: C, 38.98; H, 4.91; N, 8.18. Calc. for $C_5H_7NOS_2$: C, 37.70; H, 4.38; N, 8.72 %).

(f) Similarly, 2-phenylthiazole 3-oxide (**2c**, 37 mg), sodium hydride suspension (16 mg), dimethyl disulfide (60 µl), and DMF (0.50 ml) were stirred at 20 °C for 4 h. quenching, additional extraction with 3×4 ml of dichloromethane, drying, removal of the dichloromethane, and preparative TLC (ethyl acetate) gave 39 mg (83 %) of light yellow, air-sensitive 5-methylthio-2-phenylthiazole 3-oxide (**7**; El=SMe), ($R_f = 0.25$), m.p. 87–88 °C (ether). Anal. $C_{10}H_9NOS_2$: C, H, N.

(g) In this way, 2-phenylthiazole 3-oxide (**2c**, 155 mg), sodium hydride suspension (114 mg), and dimethyl disulfide (1.0 ml) were stirred at 20 °C for 48 h. Quenching, additional extraction with dichloromethane (4×4 ml), drying, removal of the dichloromethane, and washing with heptane (3×0.5 ml) gave 200 mg (87 %) of light yellow, air-sensitive 4,5-bis(methylthio)-2-phenylthiazole 3-oxide (**8**; El=El′=SMe), m.p. 108–110 °C. Recrystallization [methanol–water (1:1)] gave m.p. 110 °C. Anal. $C_{11}H_{11}NOS_3$: C, H, N, S.

(h) Similarly, 2-phenylthiazole 3-oxide (**2c**, 70 mg),

sodium hydride suspension (38 mg), hexachloroethane (262 mg), and DMF (1.0 ml) were stirred at 20 °C for 72 h. Quenching, extraction with chloroform (4×4 ml), drying, removal of the solvents and preparative TLC (ethyl acetate) afforded 84 mg (86 %) of 4,5-dichloro-2-phenylthiazole 3-oxide (**8**; El=El′=Cl) ($R_f = 0.50$) m.p. 155 °C [methanol–water (1:1)]. Anal. $C_9H_5Cl_2NS$: C, H, Cl, N, S.

(i) Similarly, 2-phenylthiazole 3-oxide (**2c**, 108 mg), sodium hydride suspension (50 mg), tetrabromomethane (700 mg), and DMF (2 ml) were stirred at 20 °C for 15 min. Quenching, extraction with chloroform (4×20 ml), drying, removal of the solvents, and washing with acetonitrile (3×1 ml) yielded 160 mg of 4,5-dibromo-2-phenylthiazole 3-oxide (**8**; El=El′=Br), m.p. 179–181 °C (decomp.). Recrystallization from chloroform–acetonitrile gave m.p. 181.5–182.5 °C. Preparative TLC [ethyl acetate–hexane (2:1)] of the content of the acetonitrile solution gave a further 17 mg of **8**; El=El′=Br ($R_f = 0.72$), m.p. 181.5–182.5 °C, bringing the total yield to 177 mg (87 %). Anal. $C_9H_5Br_2NOS$: C, H, Br, N.

(j) 4-Chloro-2-phenylthiazole 3-oxide (**9**; El′=Cl, 13.0 mg), sodium hydride suspension (7.3 mg) tetrabromomethane (100 mg) and DMF (0.50 ml) were stirred at 20 °C for 15 h. Quenching, extraction with chloroform (4×4 ml), drying, removal of the solvents, and preparative TLC [ethyl acetate–hexane (1:2)] yielded 9.1 mg (52 %) of 5-bromo-4-chloro-2-phenylthiazole 3-oxide (**8**; El=Br, El′=Cl), m.p. 170–171 °C ($R_f = 0.62$). Anal. $C_9H_5BrClNOS$: C, H, Br, Cl, N.

(k) 4-Bromo-2-phenylthiazole 3-oxide (**9**; El′=Br, 46 mg), sodium hydride suspension (8.5 mg) and hexachloroethane (100 mg) were mixed and DMF (1 ml) was added over 5 min through a septum. Stirring for 16 h, quenching, extraction with dichloromethane (4×4 ml), removal of the solvents, washing with ether (2×10 ml) and hexane (2×10 ml) gave 52 mg (99 %) of 4-bromo-5-chloro-2-phenylthiazole 3-oxide (**8**; El=Cl, EL′=Br), m.p. 144–145 °C. Recrystallization from DMF–ether gave m.p. 144–145 °C. Anal. $C_9H_5BrClNS$: C, H, Br, Cl, N. The compound deteriorates slowly at room temperature.

Dehalogenation. (a) 4,5-Dibromo-2-phenylthiazole 3-oxide (**8**; El=El′=Br) (72 mg) anhydrous sodium sulfite (55 mg) water (1.0 ml) and methanol (1.0 ml) were stirred in a screw-cap vessel at 110 °C for 15 min. Cooling and extraction with dichloromethane (4×5 ml), drying, removal of the solvents, dissolution in ethyl acetate and filtration through activated carbon gave 48 mg (87 %) of 4-bromo-2-phenylthiazole 3-oxide (**9**; El=Br), m.p. 120 °C [ethyl acetate–hexane (1:2)]. Anal. C_9H_6BrNOS: C, H, Br, N, S.

(b) Similarly, 4,5-dichloro-2-phenylthiazole 3-oxide (**8**; El=El′=Cl, 103 mg), anhydrous sodium sulfite (127 mg), water (1.0 ml) and methanol (1.0 ml) were stirred in a screw-cap vessel at 110 °C for 2 h. Cooling and extraction with dichloromethane (4×5 ml), drying, removal of the solvents, and preparative TLC (ethyl acetate) gave 15.0 mg (18 %) of 4-chloro-2-phenylthiazole 3-oxide (**9**; El′=Cl) m.p. 130 °C (R_f = 0.43) [ethyl acetate–hexane (1:1)]. Anal. C_9H_6ClNOS: C, H, Cl, N.

Deoxygenation of thiazole 3-oxides. (a) To 2-phenylthiazole 3-oxide (**2c**, 71 mg) in chloroform (0.50 ml) was slowly added phosphorus trichloride (0.20 ml). Stirring at 70 °C for 70 min, removal of the solvents, addition of satd. aqueous sodium hydrogencarbonate (2 ml), extraction with dichloromethane (4×4 ml), drying, and evaporation of the dichloromethane yielded 64.4 mg (99 %) 2-phenylthiazole (**1c**) identical with an authentic specimen.

(b) To 4,5-bis(methylthio)-2-phenylthiazole 3-oxide (**8**; El=El′=SMe, 98 mg) in chloroform (0.50 ml) was slowly added phosphorus trichloride (0.20 ml). Stirring at 70 °C for 30 min, removal of the solvents, addition of satd. aqueous sodium hydrogencarbonate (2 ml), extraction with dichloromethane (4×4 ml), drying, evaporation of the dichloromethane, and preparative TLC [ethyl acetate–hexane (1:20)] gave 82 mg (87 %) of 4,5-bis(methylthio)-2-phenylthiazole (**1**; R^2=Ph, R^4=R^5=SMe) ($R_f = 0.41$) as a light yellow oil. Anal. $C_{11}H_{11}NS_3$: C, H, N.

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