A Novel and Convenient Approach to 2-Unsubstituted Imidazolium and Thiazolium Salts

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Abstract: The selective reductive cleavage of highly functionalized 5-(*tert*-butylamino)-2-(phenylthio)thiazolium chlorides and mesoionic 2-(phenylthio)thiazolium-5-thiolates has been effected efficiently at room temperature using an excess of PhSH in the presence of Et_3N to give the corresponding 2-unsubstituted imidazolium and thiazolium-5-thiolates. The $NaBH_4$ reduction of 2-(methylthio)imidazolium chlorides and the H_2O_2 treatment of a thiazoline-2-thione are also reported.

Key words: thiazoles, imidazoles, mesoionic compounds, reduction

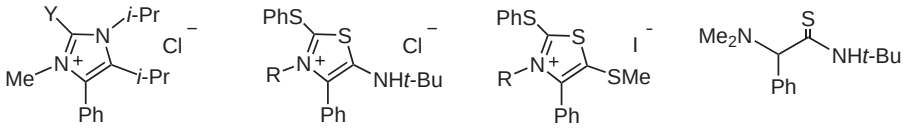
Thiazolium cations, which are active moieties of thiamine (vitamin B_1), have attracted great interest in recent years from both chemical and biological viewpoints. Especially, the reactivities of the C-2 acidic proton and the nucleophilic carbene character of intermediates formed by this proton abstraction have been discussed for a long time.[1] Conjugated bases are now recognized to be of particular importance for access to dimeric 2,2′-bithiazolinylidenes (dithiadiazafulvalenes)[1–3] which are excellent π-donor organic materials. Deprotonation of 2-unsubstituted imidazolium salts has also received considerable attention on account of the possible isolation of corresponding bases.[4] Such carbenoid species appear to be more reluctant to produce 2,2′-biimidazolinylidenes (tetraazafulvalenes).[2]

We previously developed one-pot preparations of highly substituted imidazolium[5] and thiazolium[6,7] halides like **1**–**3** (Figure 1). Considering the remarkable ease with which our reactions occur, it appeared attractive to examine the possibilities of generating 2-unsubstituted imidazolium and thiazolium salts by the reductive cleavage of these 2-(methylthio) and 2-(phenylthio) derivatives. The results of such investigation are described in the present paper.

$NaBH_4$ treatment in EtOH solution of thiazolium cations possessing a piperidino or a thio group at the 2-position produced either the 2-piperidino-2,3-dihydrothiazoles[8] or the 2-unsubstituted thiazolidines.[7,9] An attempt to remove the phenylthio substituent of **2a** (R = Me) under identical conditions resulted in the ring-opening of the reduced thiazolium salt via the α-aminothioamide **4**. In contrast to these observations, $NaBH_4$ induced a selective cleavage of the C–S bond of the 2-(methylthio)imidazolium chloride **1** to afford the expected salt **5** in moderate yield.[10]

The literature reports that reaction of thiazoline-2-thiones with H_2O_2 causes the formation of reduced thiazolium hydrogensulfates. To achieve the anion interchange, a barium halide[11] or a strong protonic acid[3] was included in the reaction mixture. Conversion of the 2-(phenylthio)thiazolium iodide **3a** (R = Me) to the thiazoline-2-thione **6** was carried out in the presence of sodium hydrosulfide, by analogy with the procedure employed in the related selenone series[12] (Scheme 1). However, the H_2O_2 sequence was found to be unsatisfactory in the case of **6** owing to a ready oxidation of the anticipated 5-(methylthio)thiazolium salt **7**. A longer reaction time (6 h) promoted the complete formation of the sulfoxide derivative **8**.[13]

A new method is based on our recent discovery[14] that the reaction of the 2-(phenylthio)thiazolium salt **2a** with $PhSH/Et_3N$ promotes the formation of the imidazolium-4-thiolate **9a** which is then quantitatively converted into the methiodide **10a**. Such a result was rationalized assuming a Dimroth type rearrangement with a subsequent reduction of the transient mesoionic imidazole **11a** (Scheme 2).



1: Y = SMe **2** **3** **4**

5: Y = H

Figure 1

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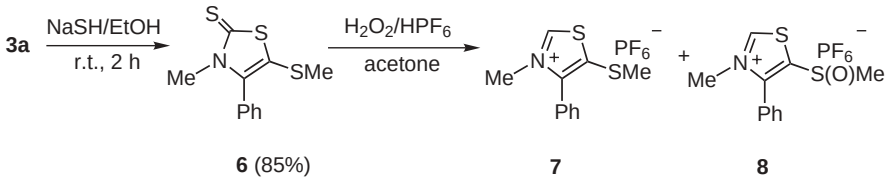
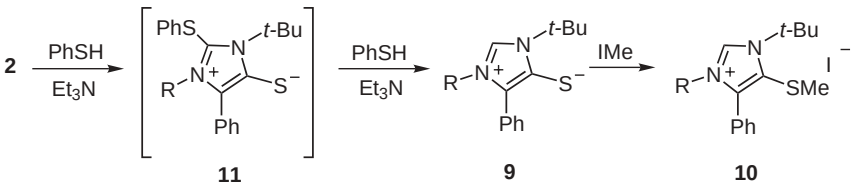


6 (85%) **7** **8**

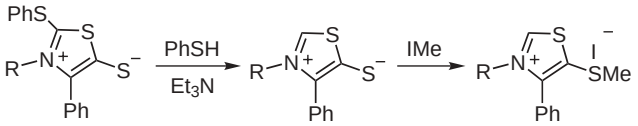
Scheme 1



11 **9** **10**

Scheme 2 **a**: R = Me, **b**: R = Et, **c**: R = CH2Ph, **d**: R = 4-$MeOC_6H_4$ **e**: R = 2,6-$Me_2C_6H_3$

The development of this simple and mild reduction process provides further examples of 2-unsubstituted imidazolium-4-thiolates **9**. In support of the proposal displayed in Scheme 2, we also describe additional data based on the action of PhSH/Et_3N on the thiazolium-5-thiolates **12**[7] (Scheme 3) that are structurally analogous to intermediates **11**.



12a–d **13a–d** **14a–d**

Scheme 3 **a**: R = Me, **b**: R = Et, **c**: R = CH2Ph, **d**: R = 4-$MeOC_6H_4$

Our results are summarized in the Table 1. Reductions were typically carried out at room temperature in anhydrous THF or $CHCl_3$ containing a large excess of benzenethiol and Et_3N. It was thus possible to isolate in moderate to high yields a series of mesoionic imidazoles **9** and thiazoles **13** of very poor solubility in common organic solvents, which nevertheless displayed an excellent reactivity towards electrophilic compounds as CH_3I. All the products were characterized by satisfactory elemental analyses and usual spectroscopic methods.[15]

Large amounts of diphenyl disulfide were also recovered as well as the *N*-*tert*-butyl-2-phenyl-2-oxo-thioacetamide[16] in the case of starting material **2**. Omission of Et_3N from the PhSH treament of **12a** resulted in the complete recovery of starting thiazole.

On account of its operational ease, it was reasonable to expect that a similar process could occur with *N*,*N*′-bridged bis(thiazolium) salts to furnish the corresponding 2, 2′-unsubstituted bis(imidazolium) species. The reaction has been performed as represented in Scheme 4 by the conversion of the *N*, *N*′-polymethylene dication **15** to the bisimidazole **16** in 53% yield.[17]

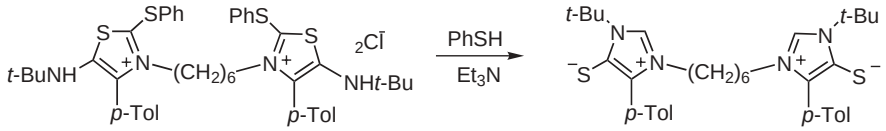
Table 1 2-Unsubstituted Imidazolium and Thiazolium-Thiolates According to Schemes 2 and 3

Substrate	Solvent	PhSH (and Et_3N) mol equiv	Time (h)[a]	Product/yield (%)[b]
2a	THF	3	23	**9a** (72)
2b	THF	4	28	**9b** (71)
2c	$CHCl_3$	4	28	**9c** (86)
2d	$CHCl_3$	4	28	**9d** (49)
2e	$CHCl_3$	4	28	**9e** (66)
12a	THF	3	24	**13a** (80)
12b	THF	4	48	**13b** (58)
12c	$CHCl_3$	3	28	**13c** (86)
12d	$CHCl_3$	3	48	**13d** (94)

[a] The reactions were run until starting compounds were completely transformed on the basis of ^1H NMR analyses.
[b] Yields refer to isolated pure mesoionic compounds.

Thiolate ions have already been shown to reduce a range of compounds.[18] In particular, the reduction of α-sulfenylated carbonyl derivatives[19] apparently involves direct nucleophilic attack by thiolates on the sulfur atom. A variety of studies have also suggested the occurrence of a single electron transfer pathway from thiolates to organic substrates.[20] We did not attempt here to distinguish between these two mechanisms.

In conclusion, the PhSH/Et_3N reduction of 2-(phenylthio)thiazolium derivatives provides an efficient synthetic route to 2-unsubstituted imidazolium and thiazolium salts. The need to use an excess of malodorous PhSH is widely compensated by the ready availability of starting



15 **16**

Scheme 4

materials and the simplicity of the process. Our approach avoids the classical quaternization of imidazoles and thiazoles, which sometimes requires prolonged reflux times[21] or drastic conditions.[22] Further use of salts **5**, **10** and **14** for the preparation of carbenes or dimers is under consideration.

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(10) **Experimental Procedure**: $NaBH_4$ (0.25 g, 6.6 mmol) was added portionwise over a period of 3 min to a solution of 1-methyl imidazolium chloride **1** (0.68 g, 2 mmol) in 95% EtOH (15 mL). After 45 min at r.t., the mixture was poured into 60 mL of water and washed with Et_2O. The aq phase was saturated with NaCl and extracted with CH_2Cl_2 (2 × 10 mL). The combined CH_2Cl_2 layers were dried over Na_2SO_4 and concentrated to dryness. Trituration of the residue with CH_2Cl_2–Et_2O gave a crystalline material (**5**, 0.28 g, 48%); mp 222 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.2 Hz, 6 H), 1.66 (d, *J* = 6.6 Hz, 6 H), 2.99 (m, 1 H), 3.82 (s, 3 H), 4.58 (d, *J* = 4 Hz, NH), 5.02 (m, 1 H), 7.50 (m, 5 H), 10.34 (s, 1 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 23.0, 23.1, 34.8 (3 × qd), 47.8, 48.6 (2 dm), 121.5 (m), 125.9, 129.3, 130.1, 130.5 (arom C), 131.7 (dm, ^1J = 215 Hz), 134.9 (m). MS (FAB): *m/z* $[M]^+$ calcd for $C_{16}H_{24}N_3$: 258.1970; found: 258.1955. Anal. Calcd for $C_{16}H_{24}ClN_3$: C, 65.40; H, 8.23; N, 14.30. Found C, 65.60; H, 8.28; N, 14.17.

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(13) **Procedure for Preparation of Thiazolium Hexafluorophosphates 7 and 8**: To a solution of **6** (0.5 g, 2 mmol) in acetone (12 mL) were added HPF_6 (3 mmol, from 60% solution in water) and H_2O_2 (10 mmol, from 35% solution in water). The reaction medium was stirred at 0 °C for 30 min then at r.t. for 45 min and concentrated in vacuo. The residual syrup was triturated with Et_2O to afford a mixture of salts **7** and **8** as insoluble viscous oil.
NMR data for salt **7** (in admixture with **8**): ^{1}H NMR (200 MHz, $CDCl_3$): δ =2.47 (s, 3 H), 3.95 (s, 3 H), 7.50 (m, 5 H), 9.65 (s, 1 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.3 (q, ^1J = 143 Hz), 42.6 (qd, ^1J = 146 Hz, ^3J = 2 Hz), 125.9 (m), 130.0, 130.7, 132.0 138.0 (arom C), 147.5 (m), 158.0 (dq, ^1J = 216 Hz, ^3J = 4 Hz).
A similar treatment for 6 h gave a viscous oil insoluble in CH_2Cl_2. ^{1}H NMR spectroscopy analysis confirmed that the sulfoxide **8** was greatly preponderant (95%) in this final product; (0.54 g, 70% yield). ^{1}H NMR (500 MHz, D_2O): δ = 2.93 (s, 3 H), 3.94 (s, 3 H), 7.60 (m, 5 H), 10.26 (s, 1 H). ^{13}C NMR (125.8 MHz, D_2O): δ = 41.4 (q, ^1J = 142 Hz), 41.7 (qd, ^1J = 147 Hz, ^3J = 2.3 Hz), 123.7, 129.7, 129.9, 132.4 (arom C), 144.9, 148.5 (2 × m), 162.3 (dq, ^1J = 220 Hz, ^3J = 4.7 Hz). MS (EI): *m/z* $[M - HPF_6]^+$ calcd for $C_{11}H_{11}NOS_2$: 237.02821; found: 237.02835.

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(15) Due to its extremely unpleasant odour, manipulations of PhSH were carried out in a well-ventilated fume hood.
Typical Experimental Procedure for the Synthesis of Representative Examples 13a and 14a and Their Spectroscopic Data: PhSH (0.33 g, 3 mmol) and Et_3N (0.3 g, 3 mmol) were added to a solution of mesoionic heterocycle **3a** (0.32 g, 1 mmol) in anhyd THF (5 mL). A yellowish material precipitated slowly. The mixture was maintained at r.t. for 1 d. Thiazole **13a** was collected by filtration, washed with Et_2O, water and recrystallized from MeOH (0.17 g, 0.8 mmol); mp 228–230 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.74 (s, 3 H), 7.49 (m, 5 H), 8.15 (s, 1 H). MS (EI): *m/z* $[M]^+$ calcd for $C_{10}H_9NS_2$: 207.01764; found: 207.01791. Anal. Calcd C, 57.97; H, 4.35; N, 6.76; S, 30.92. Found C, 57.83; H, 4.35; N, 6.58; S, 31.31. The ^{13}C NMR spectrum could not be recorded because of the low solubility of **13a** in $CDCl_3$ and other usual solvents.
A suspension of **13a** in $CHCl_3$ was treated with 2 equiv of CH_3I at r.t. for 1 h. The resulting solution was concentrated in vacuo to give a greyish solid that was recrystallized from CH_2Cl_2–Et_2O (**14a**, 94% yield); mp 152–154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.53 (s, 3 H), 4.18 (s, 3 H), 7.60 (s, 5 H), 11.07 (s, 1 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.3 (q, ^1J = 143 Hz), 43.1 (qd, ^1J = 146 Hz, ^3J = 2.3 Hz), 125.6 (m), 129.5, 130.6, 131.4, 137.2 (arom C), 147.0 (m), 160.0 (dq, ^1J = 219 Hz, ^3J = 4.9 Hz). MS (EI): *m/z* $[M - CH_3I]^+$ calcd for $C_{10}H_9NS_2$: 207.01764; found: 207.01791. Anal.

Calcd for $C_{11}H_{12}INS_2$: C, 37.82; H, 3.44; N, 4.01; S, 18.34. Found C, 37.84; H, 3.46; N, 4.05; S, 18.67.

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(17) Compound **16**; amorphous semi-solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.97 (m, 2 H), 1.42 (m, 2 H), 1.98 (s, 9 H), 2.36 (s, 3 H), 3.81 (t, *J* = 7 Hz, 2 H), 7.22 (d, *J* = 8 Hz, 2 H), 7.38 (d, *J* = 8 Hz, 2 H), 7.76 (s, 1 H). MS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{47}N_4S_2$: 575.32422; found: 575.32410.

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