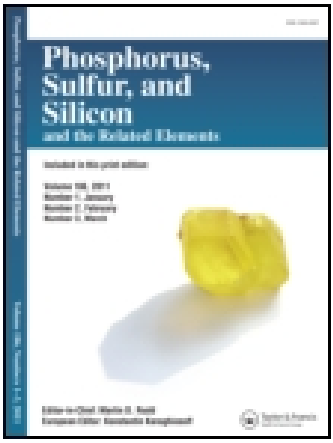

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3-Hydroxythiazole and 1-Hydroxyimidazole as Products of a Mutual Ring Closure Reaction: Extension to Selenium Derivatives

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3-Hydroxythiazole and 1-Hydroxyimidazole as Products of a Mutual Ring Closure Reaction: Extension to Selenium Derivatives

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*A thiazole derivative can be easily prepared, e.g., from an α-thiocyanatoketone and a nitrogen nucleophile. In this work, α-bromopropiophenone was chosen as a starting compound. Since the carbonyl group facilitates nucleophilic substitution, bromine can be simply replaced with the thiocyanato group. The following reaction with hydroxylamine hydrochloride provides an intermediate, which undergoes a ring closure reaction. Finally, 3-hydroxy-5-methyl-4-phenylthiazol-2(3H)-iminium chloride **4a** or 1-hydroxy-4-methyl-5-phenyl-1,3-dihydro-2H-imidazole-2-thione **5a** arises depending on the presence of a base. In the next part, this interesting phenomenon was successfully investigated on selenium derivatives as well. All prepared substances have not been described in the literature yet.*

Keywords Cyclization; imidazole; selenium; thiazole

INTRODUCTION

A thiazole derivative can be easily prepared, e.g., from an α-thiocyanatoketone and a nitrogen nucleophile. However, a compound containing both nitrogen atoms in the ring arises under certain conditions.

In 1956, Bayer and Ruhlig[1] investigated a series of transformations of α-thiocyanatoketones by various nitrogen nucleophiles. First, they studied a reaction of thiocyanatoacetone with hydrazine hydrate under acid catalysis. This reaction provided different products depending on

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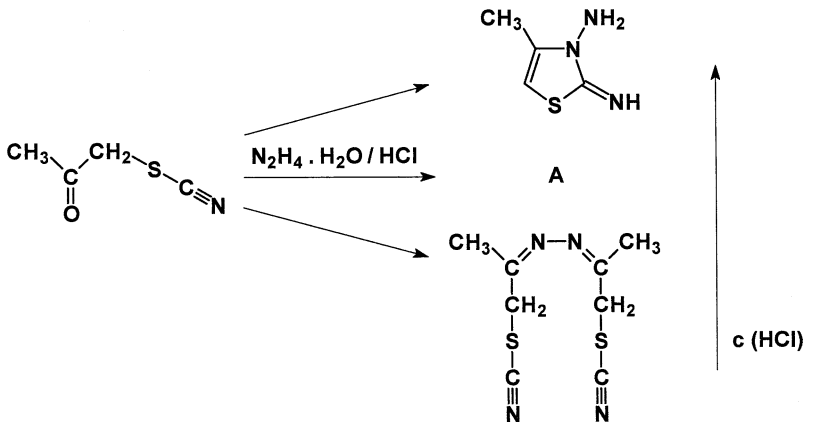


SCHEME 1 The reaction of thiocyanatoacetone with hydrazine hydrate provided various products depending on the concentration of hydrochloric acid.

the acid concentration. When the acid concentration was 0.02 mol/L, thiocyanatoacetonazine was isolated; a further addition of hydrochloric acid led to the formation of an insoluble amorphous product *A*, structure of which was not defined. Finally, 3-amino-2-imino-4-methyl-2,3-dihydrothiazole was obtained; the reactants were used in the 1:1:1 ratio in this case (Scheme 1). When the concentration of hydrochloric acid raised over 3 mol/L, no reaction was observed.

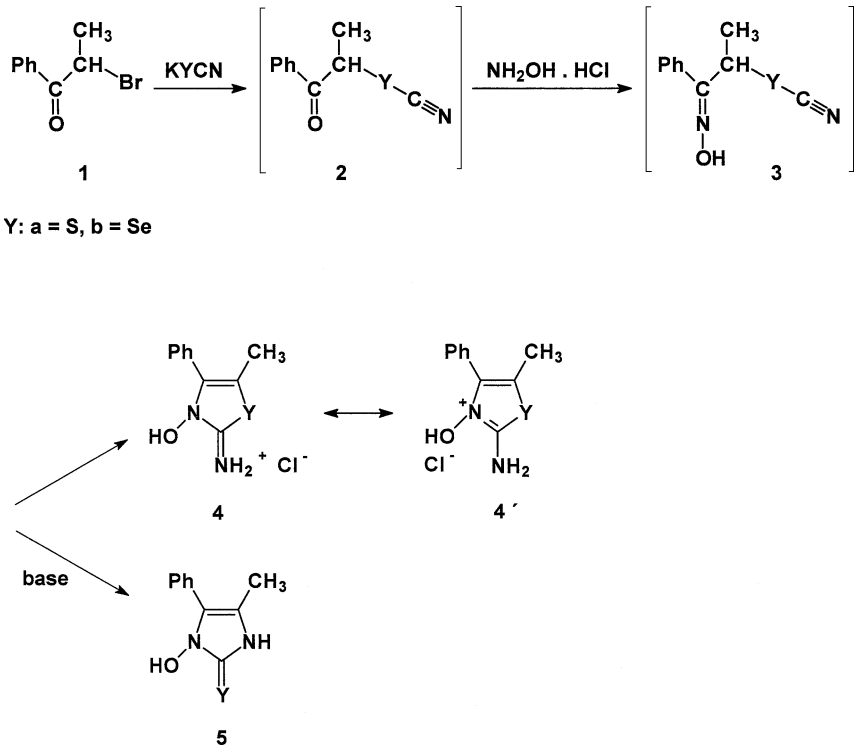
A reaction of phenacylthiocyanate with hydrazine dihydrochloride[1] did not afford any corresponding thiazole derivative. In addition, a reaction with phenyl hydrazine or 1,1-diphenylhydrazine provided only phenyl hydrazone or diphenyl hydrazone.

On the other hand, the transformations using thiourea and aniline[1] proceeded in the desired way and (4-phenylthiazolyl-2-)isothiourea and 2-imino-4-methyl-3-phenyl-2,3-dihydrothiazole, respectively, were obtained.

In the case of hydroxylamine hydrochloride application, the reactants were converted into 2-imino-3-hydroxy-2,3-dihydrothiazoles. The authors have carried out this reaction with thiocyanatoacetone, phenacylthiocyanate, and 3-thiocyanatobutan-2-one; all the products were stable only as hydrochlorides.[1]

RESULTS AND DISCUSSION

In our work, we have chosen α-bromopropiophenone **1** as a starting compound. Since the carbonyl group facilitates nucleophilic substitution of bromine, thiocyanato group introduction is simply feasible



SCHEME 2 The reaction of α-bromopropiophenone **1** with potassium thiocyanate or selenocyanate and hydroxylamine hydrochloride proceeds *via* intermediates **2** and **3** and provides various products depending on the presence of a base.

and results in a substrate on which this transformation has not been examined yet. Therefore, we have carried out a reaction of α-bromopropiophenone **1** with potassium thiocyanate in the first step. α-Thiocyanatopropiophenone **2a** was obtained and, together with hydroxylamine hydrochloride, *in situ* subjected to reflux according to the original procedure[1] (Scheme 2).

Indeed, 3-hydroxy-5-methyl-4-phenylthiazol-2(3*H*)-iminium chloride **4a** was isolated. Its structure was confirmed by the X-ray analysis.* Additionally, it was shown that the iminium form **4** (C2-N3 bond

*CCDC 242563 contains the supplementary crystallographic data for this article. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK.

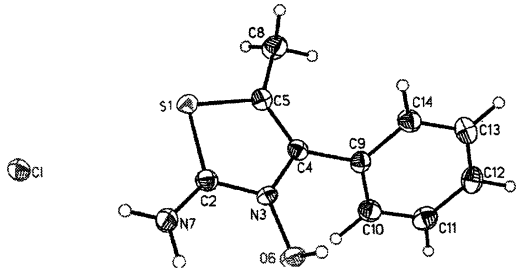


FIGURE 1 A successful monocrystal preparation enabled X-ray analysis of 3-hydroxy-5-methyl-4-phenylthiazol-2(3*H*)-iminium chloride **4a**. Crystallographic data for **4a**: $C_{10}H_{11}ClN_2OS$, M = 242.72, monoclinic crystal system, S. G. P-2(1)/c, a = 9.5303(10) Å, b = 13.7937(12) Å, c = 8.9540(10) Å, $\alpha = 90^\circ$, $\beta = 106.433(11)^\circ$, $\gamma = 90^\circ$, V = 1129.0(2) Å^3, Z = 4, $D_{calc} = 1.428$ Mg/m^3. Number of collected/independent reflections was 4778/1909; $R_{int} = 0.0344$. The final R indices [$1 > 2\sigma(1)$]: R1 = 0.0315, wR2 = 0.0985, the largest diff. peak and hole were 0.315 and −0.312 e/Å^3.

length = 1,332(2) Å, C2-N7 = 1,317(3) Å) is preferred over the form **4′** (Figure 1).

The reaction of α-thiocyanatopropiophenone **2a** with hydroxylamine hydrochloride proceeds presumably *via* an intermediate **3a**, which undergoes a ring closure reaction. We have found that this cyclization provides a different product **5a** under the presence of a base (Scheme 2). Its structure was determined as 1-hydroxy-4-methyl-5-phenyl-1,3-dihydro-2 *H*-imidazole-2-thione **5a**.

We have carried out this reaction in ethanol/water mixture using sodium carbonate. The 2:1 ratio proved to be very convenient in respect to the solubility of all reaction components. Moreover, the whole procedure could be performed in one step without separation of potassium bromide. However, the solid obtained after a partial evaporation of the solvent had to be subjected to an extraction in dichloromethane.

In the next part, we have investigated such a mutual ring closure reaction on selenium derivatives. 3-Hydroxy-5-methyl-4-phenylselenazol-2(3 *H*)-iminium chloride **4b** was prepared in the same way as the thioanalogue using potassium selenocyanate. The procedure leading to 1-hydroxy-4-methyl-5-phenyl-1,3-dihydro-2*H*-imidazole-2-selenone **5b** was modified; we have replaced the mixture of solvents with ethanol under ultrasound activation. Unfortunately, both cyclization reactions were accompanied by an efficient elimination process of elementary selenium. The identity of degradation products was not examined.

In conclusion, we have studied the mutual ring closure reaction of the intermediate arising from the reaction of α-thiocyanatopropiophenone **2a** with hydroxylamine hydrochloride. Depending on the presence of sodium carbonate, the thiazole derivative **4a** or the imidazole derivative **5a** was obtained. This interesting phenomenon was successfully investigated on selenium analogues as well.

While the procedure leading to product **4** was known,[1] we have developed other methods leading to the product **5**. All prepared substances have not been described in the literature yet.

We currently study the transformations of the imidazole derivatives, in respect to their possible applications in the field of ligand chemistry.

EXPERIMENTAL

IR spectra were recorded on an ATI Mattson Genesis spectrometer, NMR spectra at 200 MHz on a Varian Inova spectrometer (**4a** and **5a**) and at 300 MHz on a Bruker Avance 300 spectrometer (**4b** and **5b**). Melting points were determined on a Kofler hot stage and are uncorrected. Reaction courses were monitored by thin-layer chromatography on Silufol UV 254 in diethyl ether. X-ray intensity data were collected at 120(2) K on a KUMA KM-4 kappa four-circle diffractometer with MoK\a radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods (SHELXS-97) and refined by weighted full-matrix least-squares on F^2 (SHELXL-97). All nonhydrogens were refined anisotropically; hydrogens were localized from difference Fourier map and refined isotropically.

3-Hydroxy-5-methyl-4-phenylthiazol-2(3H)-iminium Chloride 4a

A mixture of α-bromopropiophenone (4.26 g, 18.8 mmol) and potassium thiocyanate (2.14 g, 22.1 mmol) in ethanol (10 mL) was stirred at the room temperature for 4 h. Precipitated potassium bromide was filtered off and washed with ethanol. Hydroxylamine hydrochloride (1.54 g, 22.1 mmol) was added to the filtrate and this mixture was refluxed for 20 h. After cooling, colorless crystals were separated and washed with ethanol. Yield 70%, m.p. 194–196°C. ^{1}H NMR (DMSO-d_6): 2.19 (s, 3H, CH_3); 7.48–7.59 (m, 5H, C_6H_5); 9.63 (s, 2H, NH_2); 13.01 (s, br, 1H, OH). ^{13}C NMR (DMSO-d_6): 12.30 (CH_3); 111.59 (5-C); 126.66 (1-C C_6H_5); 128.65 (2,6-C C_6H_5); 129.81 (4-C C_6H_5); 130.46 (3,5-C C_6H_5); 134.20 (4-C); 161.09 (2-C). $\tilde{\nu}$ (KBr): 3230 (OH), 3181, 3071, 2728, 2669, 2586, 1632 (C=N), 1618, 1567, 1489, 1441, 1213.

1-Hydroxy-4-methyl-5-phenyl-1,3-dihydro-2H-imidazole-2-thione 5a

α-Bromopropiophenone (1.00 g, 4.4 mmol) and ammonium thiocyanate (1.10 g, 14.3 mmol) were dissolved in ethanol/water (2:1). The reaction mixture was stirred at the room temperature until no more α-bromopropiophenone could be detected (TLC). After that, sodium carbonate (1.40 g, 13.2 mmol) and hydroxylamine hydrochloride (0.90 g, 13.2 mmol) were added and the stirring continued until only one compound was present (TLC). The solvent was partially evaporated; a solid was filtered off and subjected to an extraction by dichloromethane. The solution was dried and evaporated and a crystalline product was obtained. Yield 33%, m.p. 211–213°C. ^{1}H NMR (DMSO-d_6): 2.24 (s, 3H, CH_3); 7.30–7.52 (m, 5H, C_6H_5). ^{13}C NMR (DMSO-d_6): 8.66 (CH_3); 119.56 (5-C); 121.29 (4-C); 126.11 (2,6-C C_6H_5); 127.16 (4-C C_6H_5); 128.74 (3,5-C C_6H_5); 128.89 (1-C C_6H_5); 156.34 (2-C). $\tilde{\nu}$ (KBr): 3133 (NH), 3091, 2941, 2809 (CH_3), 1633 (C=N), 1443, 1404, 1269.

3-Hydroxy-5-methyl-4-phenylselenazol-2(3H)-iminium Chloride 4b

A solution of α-bromopropiophenone (2.00 g, 8.8 mmol) and potassium selenocyanate (1.52 g, 10.6 mmol) in ethanol (30 mL) was stirred at the room temperature. Precipitated potassium bromide was filtered off and washed with ethanol; hydroxylamine hydrochloride (0.73 g, 10.6 mmol) was added to the filtrate. The reaction then proceeded under reflux; a selenium exclusion accompanied by a color change was observed. After filtration, the solvent was partially evaporated; a crystalline product was filtered off and washed with ethanol. Yield 14%. ^{1}H NMR (MeOD): 2.31 (s, 3H, CH_3); 7.44–7.49 (m, 2H, C_6H_5); 7.52–7.56 (m, 3H, C_6H_5). ^{13}C NMR (MeOD): 14.37 (CH_3); 117.38 (5-C); 129.37 (1-C C_6H_5); 129.94 (2,6-C C_6H_5); 131.18 (4-C C_6H_5); 131.87 (3,5-C C_6H_5); 136.60 (4-C); 167.02 (2-C). $\tilde{\nu}$ (KBr): 3436 (OH), 3243 (NH), 3092, 2706, 2666, 1615, 1563, 1441, 1401, 1261.

1-Hydroxy-4-methyl-5-phenyl-1,3-dihydro-2H-imidazole-2-selenone 5b

Potassium selenocyanate (4.13 g, 28.6 mmol) was added to a solution of α-bromopropiophenone (2.00 g, 8.8 mmol) in ethanol (30 mL). The reaction mixture was stirred at the room temperature. Precipitated potassium bromide was filtered off and washed with ethanol. The filtrate together with hydroxylamine hydrochloride (1.84 g, 26.4 mmol)

and sodium carbonate (2.80 g, 26.4 mmol) was subjected to ultrasound. A selenium exclusion accompanied by a color change was observed. The solid was filtered off and the solution was treated with charcoal. The solvent was removed under reduced pressure and a residue crystallized by chloroform addition. According an infrared spectrum, remaining selenocyanate was present in the crystalline phase. A pure product was obtained by dissolving in acetone followed by addition of water. Acetone was then evaporated and the solid was filtered off and dried in vacuum. Yield 11%. ^{1}H NMR (MeOD): 2.19 (s, 3H, CH_3); 7.27–7.34 (m, 2H, C_6H_5); 7.36–7.43 (m, 3H, C_6H_5). ^{13}C NMR (MeOD): 10.40 (CH_3); 128.58 (2,6-C C_6H_5); 129.10 (4-C C_6H_5); 129.95 (1-C C_6H_5); 130.48 (3,5-C C_6H_5); 133.73 (4-C); 156.25 (5-C); 164.43 (2-C). $\tilde{\nu}$ (KBr): 3432 (OH), 3273 (NH), 2926, 2854 (CH_3), 1636 (C=N), 1419, 1293.

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[1] H. Beyer and G. Ruhlig, *Chem. Ber.*, **89,** 107 (1956).