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Classical heterocycles with surprising properties: the 4-hydroxy-1,3-thiazoles

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ABSTRACT

4-Hydroxy-1,3-thiazoles 1, being 'classical' heterocycles, revealed unexpected physicochemical properties. The compounds show pH-sensible fluorescence, which can be employed for the generation of white emission light. NMR data and quantum chemical results provide a better insight into the keto-enol-tautomerism and the nature of the chromophoric system.

4-Hydroxy-1,3-thiazoles **1** are well known for a long time.[1] They have been found, for example as active inhibitors of 5-lipoxygenase[2] and CDK5.[3] However, their structure–property relationship has not been completely understood up until now, and there exists some confusion concerning the tautomerism. In addition, not enough is yet known about their UV/vis and fluorescence data. We have been working for quite a long time on the syntheses and applications of derivatives of type **1**. Following the classical Hantzsch synthesis[4] and, alternatively, another one starting from nitriles and thiolactic acid,[2,5] a series of 4-hydroxythiazoles was synthesized. Recently, highly fluorescent 2-pyridyl substituted 4-hydroxy-thiazoles and related systems have been reported.[6] New unexpected findings have been made with regard to chemical as well as physicochemical properties, however without explanation of these observations.

As depicted in (Scheme 1), 4-hydroxy-1,3-thiazoles **1** can generally exist in two tautomeric forms, the aromatic enol form (**A**) and the keto form (**B**).[1] The question of keto or enolic form has always been a point of interest not only for oxygen in 4, but also in position 2.[7] Usually, polar solvents favour form **A** and nonpolar solvents form **B**. Using NMR measurements in DMSO for derivative **1a** and similar compounds, only the enolic form **A** can be detected. Unfortunately, **1a** and other compounds with R^1 = aryl are nearly insoluble in $CDCl_3$ and no spectra could be recorded in this solvent. Spectral data of **1c** were only obtained by NMR. In these spectra, both forms were detected in equilibrium (ratio enol/keto ~ 1:1.5). The compounds **3**–**5** were synthesized in order to investigate the tautomerism in detail (Scheme 2).[8]

Based on NMR data, other authors have reported that derivative **2** only exists in the enol form.[2] Measurements carried out in our group revealed that **3** predominantly exists in the keto form, whereas **4** and **5** display phenolic OH groups. In addition, the X-ray structure[†] of **4** revealed the presence of (form) **A** even in the crystalline state. This is shown in Figure 1.[†] The bond length C_2O_1 (1.342 Å) clearly underlines that a typical hydroxy group is present in the molecule. The phenyl moiety is twisted around the C3–C4 axis by about 2.9° and the phenyl moiety around the C1–C11 axis by about 44.6°. Furthermore, the benzyl moiety is twisted (114°) out of the plane of the central thiazol ring. Thus, according to our findings, we can complement Barrett's statement[9] '... unlike most

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[†] *Crystal structure determination*: The intensity data for the compounds were collected on a Nonius KappaCCD diffractometer using graphitemonochromatic Mo-Kα radiation. Data were corrected for Lorentz and polarization effects but not for absorption effects.[17,18] The structures were solved by direct methods (SHELXS[19]) and refined by full-matrix least squares techniques against F_o^2 (SHELXL-97[19]). All hydrogen atoms were located by difference Fourier synthesis and refined isotropically. All non-hydrogen atoms were refined anisotropically.[19] XP (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representations. *Crystal data for* **4**: $C_{16}H_{13}NOS$, M_r = 267.33 g mol^{-1}, colourless prism, size 0.05 × 0.05 × 0.04 mm^3, monoclinic, space group $P21/c$, a = 5.3336(2), b = 25.0882(9), c = 9.8391(5) Å, β = 94.111(3)°, V = 1313.2(1) Å^3, T = −140 °C, Z = 4, ρ_{calcd} = 1.352 g cm^{-3}, μ(Mo-K$_\alpha$) = 2.36 cm^{-1}, F(0 0 0) = 560, 7754 reflections in h(−6/6), k(−28/32), l(−12/10), measured in the range 2.64° ⩽ Θ ⩽27.48°, completeness Θ_{max} = 99.6%, 2991 independent reflections, R_{int} = 0.0596, 1881 reflections with $F_o > 4\sigma(F_o)$, 224 parameters, 0 restraints, R_1^{obs} = 0.0453, wR_2^{obs} = 0.0896, R_1^{all} = 0.1013, wR_2^{all} = 0.1055, GOOF = 0.961, largest difference peak and hole: 0.283/−0.290 e Å^{-3}.

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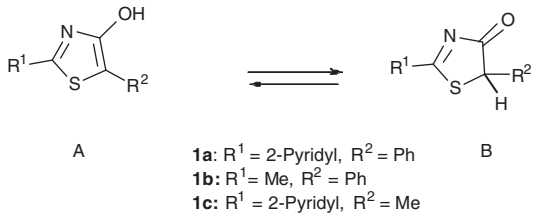
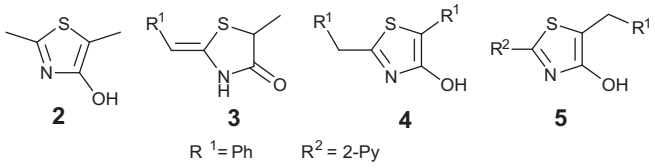


Scheme 1. Equilibrium between enol and keto form of 4-hydroxythiazoles.



Scheme 2. Thiazoles for the determination of the keto-enol-tautomerism.

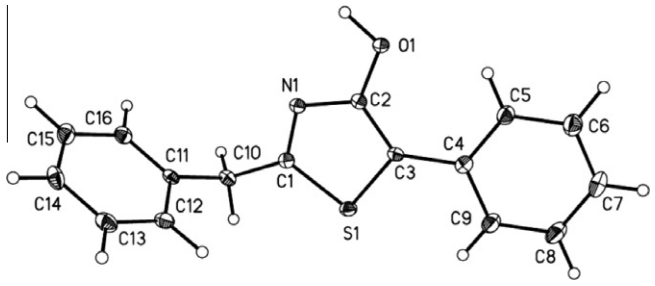


Figure 1. ORTEP plot (50% probability ellipsoids) of the solid state molecular structure (X-ray crystal structure analysis) of derivative **4**, selected bond lengths in Å: C1–S1, 1.709; C1–N1, 1.316; C2–O1, 1.342; C2–C3, 1.380; C3–C4, 1.467; C1–C10, 1.491; C10–C11, 1.517.

4-hydroxythiazoles, which adopt keto-form, 2-methyl-5-phenyl-thiazolin-4-one exists as the enol'. Apparently introduction of at least one aromatic substituent in the 2 or 5 position gives rise to the enol form. Calculations (DFT-B3LYP 6-311G+(2d,p) for **1b** in both $CHCl_3$ and DMSO showed that the 4-hydroxythiazole tautomer is predicted to be preferred over the thiazol-4(5*H*) one. In gas phase calculations, the enol form is lower in energy, probably reflecting the aromatic character of the 4-hydroxythiazole structure. These results are in excellent agreement with those previously reported for derivatives of luciferine.[7]

In the neutral state, **1a** is featured by a relatively strong fluorescence in THF at λ_{max} = 450 nm with a quantum yield of 87%. Upon deprotonation of **1a** with strong bases such as KOH or NaH, a drastic change in colour takes place in combination with a bathochromic shift of fluorescence (λ_{max} = 590 nm). The resulting deep red colour of **1a**′ along with the strong fluorescence (**1a**′: Φ_{fl} = 0.4 in THF) are quite unexpected for such a small molecule. The last mentioned resonance formula **1a**″ may suggest the appearance of the bathochromic shift. In the case of **1c** ($R^2 = CH_3$),[5] the colour of the deprotonated **1c**′ is orange and is deep blue in the case of **1d.**[6] The deep blue colour is due to the more extended electron delocalisation including the nitro group.[10] The acidochromic derivatives of type **1** are very sensitive even towards traces of bases showing a large difference between the neutral and deprotonated form in their emission spectra. Biological assays frequently use substrates which develop a colour or become fluorescent upon reaction with the enzyme. The enzymatic (esterases) cleavage of esters derived

Figure 2. Varying fluorescence of **1a** (excitation: 366 nm diode array) from left to right: solution in DMSO, addition of KOH solution, deprotonated form, addition of MeI and after completed reaction.

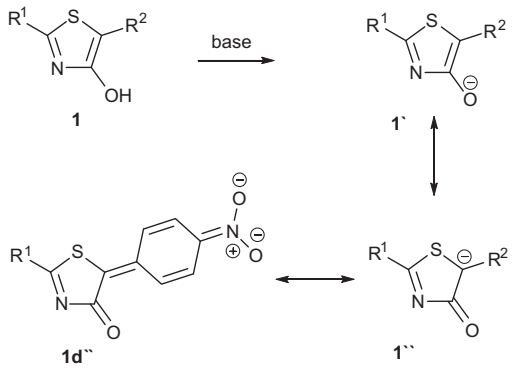
from 4-hydroxythiazoles should result in a strong red fluorescence which can be quantified. We are, therefore, actually developing new fluorescence based triggerable systems for biochemical analysis.

Surprisingly, in DMSO solution of **1a** (excitation at 360 nm), white fluorescence is observed (Fig. 2). This phenomena is due to the coexistence of protonated and deprotonated species. Pure DMSO, therefore is basic enough to partly deprotonate **1a**. The result of which is the superposition of both emission bands resulting in the white fluorescence. The occurrence of white fluorescence is quite remarkable for such simple systems and makes them interesting for applications, such as OLEDS (Scheme 3).[11]

The emission wavelengths can be additionally varied by the substituent R^1 and R^2. In the case of **1e**, R^1 is the electron deficient pyrazine whereas R^2 is the relatively electron rich 4-methoxyphenyl. The structure formed along this way causes a bathochromic shift of the emission in the case of the hydroxy form and a hypsochromic shift with deprotonation compared to **1a**. As described earlier,[5,6] deprotonated thiazoles **1** can easily react with alkyl and benzyl halides to produce highly fluorescent ethers. Deprotonation and alkylation can be realized as a one-pot reaction. The resulting colours are visualized in Figure 2.

To compare the effect of different substituents at the same position, derivatives **1f** (NO_2 is a strong acceptor) and **1g** (NMe_2 is a strong donor) were synthesized. Whereas **1f** displays only weak fluorescence, **1g** is strongly fluorescent with a bathochromic shift of emission wavelength by 34 nm whereas the emission of the deprotonated species is unchanged.

Deprotonated **1h**′ shows a deep blue colour (DMSO: λ_{ex} = 593 nm, log ε = 3.7). These spectroscopic findings are quite surprising, because in the series of conventional phenols such a



Scheme 3. Deprotonation of 1 (Table 1) and extended charge delocalization for 1d″ (R^2 = 4-NO_2Ph).

Table 1
Spectral data of the studied 4-hydroxy-thiazole-based chromophores and fluorophores measured in DMSO

1	R^1	R^2	Excitation λ_{max} (log) of **1** (nm)	Excitation λ_{max} (log) of **1′** (nm)	Emission λ_{max} (log) of **1**, **1′** (nm)
1a[5]	2-Py	Ph	381 (4.2)	506 (4.2)	450, 590
1b[5]	3-Py	Ph	384 (3.9)	499 (3.8)	474, 622
1c[5]	2-Py	Me	351 (3.5)	474 (3.5)	442, 602
1d[6]	3-Py	4-NO_2Ph	410 (4.4)	588 (4.6).	430
1e[6]	Pyrazine	4-MeOPh	411 (3.7)	556 (4.2)	520
1f	2-(4-NO_2)Py	Me	346 (4.0)	462 (3.6)	441, 582
1g	2-(4-NMe_2)Py	Me	347 (4.1)	470 (3.3)	475, 580
1h	4-NO_2Ph	Me	400 (4.1)	593 (3.7)	Not detected
1i	3-NO_2Ph	Me	347 (4.0)	462 (3.6)	Not detected

bathochromic shift was not observed. Although the structures of derivatives **1i** and **1h** only differs in the position of the NO_2 group, deprotonation caused a considerably smaller bathochromic shift. EPR measurements of **1a′** and **1g′** (in THF) excluded any radical species that might be responsible for the generation of the deep colour of **1′**.

For a better understanding of properties and, in addition, for the large shifts upon deprotonation, quantum chemical calculations were performed. To reproduce organic spectral data extensive time-dependent density functional theory (TD-DFT) benchmark calculations were performed by Jacquemin et al.[13b] The results were strongly dependent on the functionals. Based on our previous study,[13a] the B3LYP functional was favored over other functionals using the 6+31G* basis set both in the calculation of spectral excitation and of optimized structures.[12]

The calculation of the deprotonated **1′** resulted in intense low-energy transitions corresponding to absorption wavelengths of about 600 nm in nonpolar solvents. However, the calculated absorption wavelengths are sensitive to the solvent polarity. TDDFT-B3LYP/6-31G* calculations using the Polarized Continuum Model (PCM) resulted in absorption maxima at about 550 nm, similar to that found experimentally. These absorption wavelengths of the anions are remarkably red-shifted relative to the protonated species. The anion of **1h**, for example was predicted to be shifted by 249 nm in DMSO compared with 193 nm found experimentally (cf. Table 1). The strong bathochromic shift is due to the replacement of the OH donor group of the neutral compound by the more strongly electron donating donor group O^- resulting from deprotonation. A significant charge transfer from O^- to the heterocyle takes place upon excitation. The electron density difference (EDD) map[14,15] of **1f** calculated by the ArgusLab program at the semiempirical INDO-CIS level revealed a typical CT chromophor with O^- as the donor and 4-nitrophenyl as the acceptor fragment.[14–16]

Supplementary data

Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-775070 for **4**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Email: deposit@ccdc.cam.ac.uk]. Supplementary data (selected experimental data for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.048.

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8. *General procedure for the synthesis of 4-hydroxythiazoles:* A mixture of the corresponding α-halogeno-ester (0.011 mol), thioamide (0.01 mol) and pyridine (0.8 g, 0.01 mol) was stirred under argon and slowly heated to 100–110 °C until the mixture solidified. After 3 h, ethanol was added (15 mL) and the mixture was stirred at room temperature for 30 min. After filtration the crude product was recrystallised from ethanol/DMF. Derivative **3** was recrystallised from ethanol/chloroform. The compounds were dried in vacuo and gave the analytical pure products.
   2-Benzyl-5-phenyl-1,3-thiazol-4-ol **4**: Colourless crystals; mp 190 °C; yield 1.90 g (71%). ^{1}H NMR (250 MHz; DMSO-d_6): δ = 4.19 (2H, s, CH_2), 7.13 (t, J = 7.3 Hz, 2H), 7.22–7.38 (m, 6H), 7.56–7.6 (m, 2H), 11.26 (s, 1H, OH). ^{13}C NMR (62.9 MHz; DMSO-d_6): δ = 39.4, 106.6, 126.0, 126.1, 127.4, 128.6, 128.7, 129.1, 132.5, 138.1, 157.7, 164.1. UV/vis (DMSO): λ_{max} (log ε) = 317 nm (4.1); deprotonated with KOH λ_{max} (log ε) = 342 nm (3.3). MS: m/z (%) = 267 (81, M^+), 150 (31), 121 (100), 91 (52). Microanalysis calcd for $C_{16}H_{13}NOS$ (267.35): C, 71.88; H, 4.90; N, 5.24; S, 11.99. Found: C, 71.72; H, 4.89; N, 5.10; S, 12.01.
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