A novel heterocyclic atom exchange reaction with Lawesson's reagent: a one-pot synthesis of dithiomaltol

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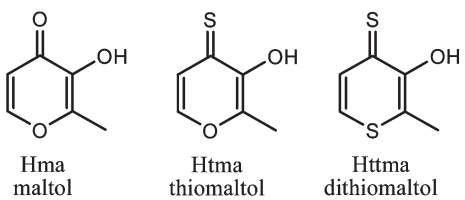
A one-pot reaction of maltol with Lawesson's reagent generates dithiomaltol, a thiopyran-4-thione, *via* an unusual heterocyclic atom exchange (HCAE) reaction; only pyrones with proton or aliphatic substituents undergo the HCAE substitution.

Maltol (Scheme 1) is a condensed sugar by-product, most readily recognized as the smell of cotton candy (a.k.a. candy floss or fairy floss).[1] It also functions as an excellent metal ion chelator, one of a family of α-hydroxy ketones that have been studied over the past two decades for their potential applications in the treatment of Alzheimer's, anemia, cancer, use in radio-pharmaceuticals, and an oxo-vanadium derivative that is in clinical trials.[2–6] Structurally-related compounds such as deferiprone and kojic acid have been used in chelation treatments for the iron-overload disease hemochromatosis.[7]

Several groups have been investigating the modulation of these activities by replacing the oxy-functionalities with sulfur.[8–13] The simplest analogue, thiomaltol, or 3-hydroxy-2-methyl-4-thiopyrone (Htma), was first synthesized in 1969[14] and used for the extraction and determination of a variety of cationic metals.[15–19] Most recently, thiomaltol and related ligands have been re-investigated for their biological activity, as metalloprotein protease inhibitors and as pro-oxidant cancer drugs.[8,12,13,20–23]

Thiomaltol and related species may be obtained directly from the parent α-hydroxy ketone by reaction with thionating agents like P_4S_{10} or Lawesson's reagent (LR). In one such reaction with excess LR, we observed a product resulting from an apparent second substitution of sulfur for oxygen in maltol by LR, route A in Scheme 2. To our surprise, the second substitution is of the heterocyclic ring oxygen, not the α-hydroxyl group. We have subsequently developed a single step synthesis for this new compound, 3-hydroxy-2-methyl-4*H*-thiopyran-4-thione (dithiomaltol or Httma), which has been characterized by a variety of methods.†



Scheme 1

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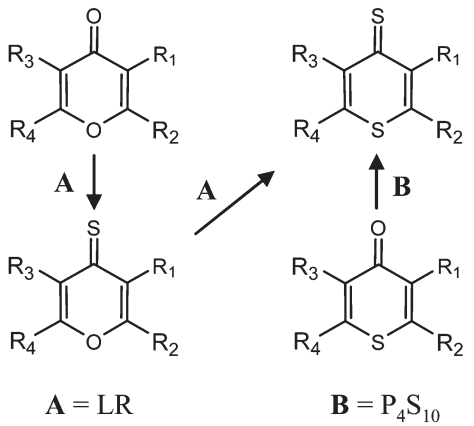


Scheme 2

The ^{1}H NMR resonances of the ring protons (R_3 and R_4) allow the direct distinction of the various maltol-derived products due to the sequential downfield shifts that these protons undergo upon sulfur substitution. Fig. 1 shows their comparative spectra in $CDCl_3$; for maltol, two doublets appear at δ 6.45 and 7.73, for thiomaltol, the signals are at δ 7.33 and 7.59, and for dithiomaltol, the resonances are at δ 7.52 and 8.16. This downfield shift in the ring protons for thiopyranthiones is known in the literature.[24] Similar, but smaller downfield shifts are also observed for the methyl group.

The mass spectra also verified that a second S for O substitution had occurred, but could not identify the position of substitution. Substitution of the ring position was confirmed by a crystallographic analysis of the complex [($Tp^{Ph,Me}$)Zn(dithiomaltolato)] ($Tp^{Ph,Me}$ = hydrotris(3-phenyl-5-methylpyrazolyl)borate), shown

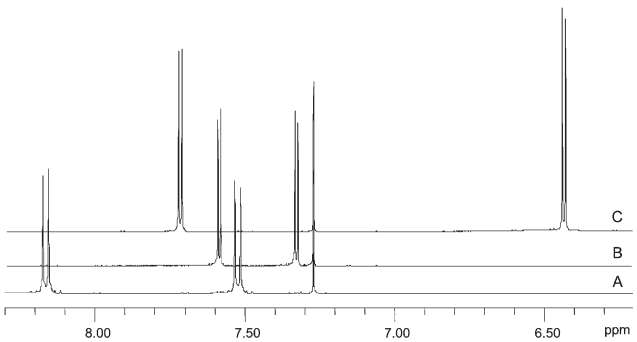


Fig. 1 ^{1}H NMR spectra of (A) dithiomaltol, (B) thiomaltol and (C) maltol.

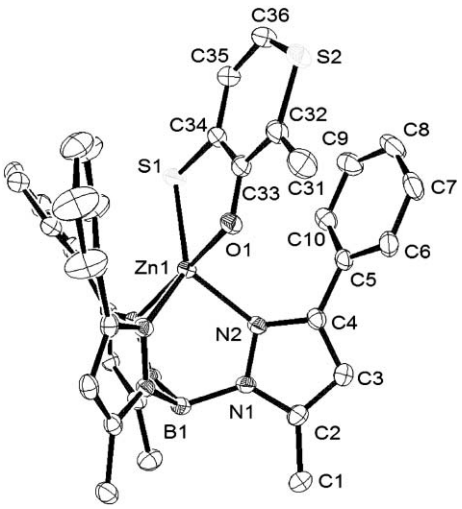
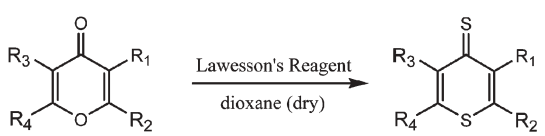


Fig. 2 Structural diagram of [($Tp^{Ph,Me}$)Zn(dithiomaltolato)] with a partial atom numbering scheme; hydrogen atoms and solvent have been omitted for clarity.

in Fig. 2.‡ The $Tp^{Ph,Me}$ framework has previously been used as a model for the active site of matrix metalloproteinases (MMP) and in the development of chelating inhibitors for these enzymes, similar in structure to dithiomaltol.[8,20–23]

In our hands, dithiomaltol is not observable in the reaction of maltol with P_4S_{10}, but adding a two-fold excess of LR to maltol cleanly generates the product in good yield. We were intrigued with the heterocyclic atom exchange reaction, which is unprecedented in the literature of thiopyrones. Previously thiopyran-4-thiones have been synthesized *via* thiopyrone intermediates, obtained by the cyclization of unsaturated ketones and subsequent thionation of the ketone, arrow B in Scheme 2.[25] However, thiopyran-4-thiones with hydryl or methyl substituents are air sensitive, and the subsequent anaerobic thionations have been reported using P_4S_{10}. With the use of LR, a one pot synthesis directly yields the thiopyran-4-thione from the parent pyrone, isolable by bench-top chromatography. It is unclear at this point what structural features of dithiomaltol lead to its enhanced stability under aerobic conditions.

To probe this unique substitution, other pyrones were reacted with excess LR and their products analyzed. The structural variations and outcomes of these experiments are outlined in Scheme 3 and Table 1, while Scheme 4 illustrates the specific substrates used. A distinct structural dependence was observed, in that only those pyrones with proton or aliphatic substituents underwent the second substitution to yield thiopyranthione derivatives. Pyrones with an arene group (*e.g.*, hydroxyflavanone, xanthone, and chromone, Scheme 4) were not converted to their corresponding thiopyranthione analogues. The structural selectivity of this heterocyclic ring atom exchange suggests that the reaction is initiated by a Michael addition at the 2-position of the

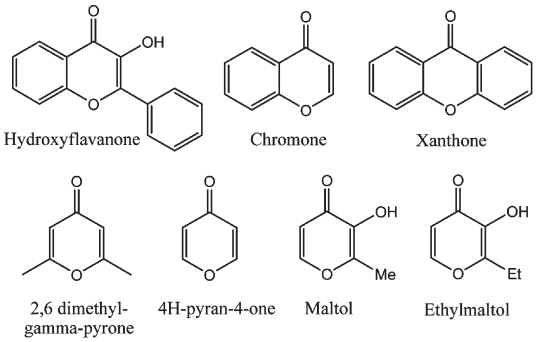


Scheme 3

Table 1 Pyrones investigated for potential HCAE

Substrate	R_1	R_2	R_3	R_4	Thiopyranthione[a]
Maltol, Hma	OH	Me	H	H	Isolated
Ethylmaltol, Hema	OH	Et	H	H	Isolated
Hydroxyflavanone	OH	Ring	Ring	Ring	Not observed
Xanthone	Ring	Ring	Ring	Ring	Not observed
Chromone	H	H	Ring	Ring	Not observed
4*H*-Pyran-4-one	H	H	H	H	Observed
2,6 Dimethyl-γ-pyrone	H	Me	Me	H	Observed

[a] Isolated indicates characterization by ESI-MS, ^{1}H NMR and elemental analysis (EA) within 0.3%. Observed indicates ESI-MS and ^{1}H NMR characterization only.



Scheme 4

pyrone ring, and which most likely proceeds by ring opening and closing steps. For the arene substituted species, such an initial addition would be disfavored by the loss of aromaticity in the intermediate.

In conclusion, the one-pot synthesis gives direct access to the family of thiopyrone compounds *via* an unusual heterocyclic atom exchange, unique to Lawesson's reagent. Through the use of this transformation, new biologically-active compounds may be obtained, potentially allowing significant tuning of their chelating ability. With dithiomaltol in hand, several metal complexes have been obtained in a similar fashion to their thiomaltol analogues,[8–10] and have been reported elsewhere.[12]

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Notes and references

† **General procedures**: All other solvents used were reagent grade; 1,4-dioxane was dried-over and distilled-from calcium hydride. All chemicals were purchased from Aldrich. Where anaerobic techniques were required, a glove box and standard Schlenk techniques were used. ^{1}H and ^{13}C NMR spectra were recorded on either Nicolet Omega 500 or GN 500 spectrometers at ambient temperatures, with chemical shifts (δ) measured in ppm relative to the specified solvent. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA.

Synthesis of 3-hydroxy-2-methyl-4*H*-thiopyran-4-thione (Httma) dithiomaltol: Maltol, 3-hydroxy-2-methyl-4*H*-pyrone (2.501 g, 19.8 mmol), Lawesson's reagent (8.421 g, 20.8 mmol) and 25 mL of dry 1,4-dioxane were combined in a dry box. The solution turned from lime green to orange after 2–3 min stirring. As the solution was brought to reflux it turned a

dark reddish-brown color and eventually black. After refluxing for ~1 h, the solution was filtered while it was still hot, the dark brown solid collected by the filter washed twice with pentane and the filtrate run on silica; the first yellow band was collected and evaporated to yield 1.218 g (39%) of a brown solid. ^{1}H NMR (499.93 MHz, $CDCl_3$): δ 2.49 (s, 3 H, –CH_3), 7.52 (d, 1 H, –CH–, J = 9.6 Hz), 8.16 (d, 1 H, –CH–, J = 9.6 Hz) and 9.33 (s, 1 H, –OH). ^{13}C NMR (125.70 MHz, C_6D_6): δ 17.80, 123.29, 129.11, 139.09, 158.37 and 184.91. Electrospray MS: 159 ([M + H]$^+$). Anal. calc. for $C_6H_6S_2O$: C, 45.45; S, 40.52; H, 3.82. Found: C, 45.53; S, 40.53; H, 3.95%.

Synthesis of dithio pyrone analogs: 0.5 g samples of each substrate were added to solutions of toluene and dioxane containing a 2-fold excess of Lawesson's reagent. Solutions were refluxed for 1 h and monitored by TLC, ESI-MS and ^{1}H NMR. For each substrate, the first thionation was completed readily; the second conversion was observed and the product isolated for ethylmaltol. For 4*H*-pyran-4-one and 2,6 dimethyl-γ-pyrone, the products were observed but not isolated. For hydroxyflavanone, xanthone and chromone no evidence of the second conversion was observed.

‡ **Synthesis of [(Tp^{Ph,Me})Zn(dithiomaltolato)]**: In a 50 mL round-bottomed flask, [(Tp^{Ph,Me})ZnOH] (50 mg, 0.09 mmol) was added to 10 mL of CH_2Cl_2. To this solution was added 1.0 equiv. of dithiomaltol (10.3 mg, 0.09 mmol) dissolved in 20 mL of MeOH. The mixture was stirred at room temperature overnight under a nitrogen atmosphere. After stirring, the solution was evaporated to dryness on a rotary evaporator to give a yellow solid. The solid was dissolved in the minimum amount of benzene (~3 mL), filtered to remove any insoluble material, and the filtrate recrystallized by diffusion of the solution with pentane. Yield: 89%

X-ray crystallographic analysis of [(Tp^{Ph,Me})Zn(dimaltolato)]: Yellow thin plates were grown out of a solution of the complex in benzene diffused with pentane. A single crystal suitable for X-ray diffraction structural determination was mounted on a quartz capillary by using Paratone oil and cooled in a nitrogen stream on the diffractometer. Data was collected on a Bruker AXS diffractometer equipped with area detectors. Peak integrations were performed using the Siemens SAINT software package. Absorption corrections were applied using the program SADABS. Space group determination was performed by the program XPREP. The structure was solved by direct methods and refined with the SHELXTL software package. All hydrogen atoms were fixed at calculated positions with isotropic thermal parameters, and all non-hydrogen atoms refined anisotropically. The hydrogen atom on the boron atom was found in the difference map and its position refined. The compound co-crystallized with one equivalent of benzene per complex.

Data for [(Tp^{Ph,Me})Zn(dithiomaltolato)]: $C_{42}H_{39}BN_6OS_2Zn$, M = 784.09, orthorhombic, space group *Pbca*, a = 21.3832(18), b = 14.9241(13), c = 24.177(2), V = 7715.5(12) Å, T = 100(2) K, Z = 8, μ = 0.787, 8784 independent reflections, R_{int} = 0.0497, R_1 = 0.0383, wR_2 = 0.0913 (for $I > 2\sigma(I)$). CCDC 281752. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b511966a

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