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A one-step synthesis towards new ligands based on aryl-functionalised thiazolo[5,4-*d*]thiazole chromophores

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ABSTRACT

A general synthesis of disubstituted thiazolo[5,4-*d*]thiazoles was achieved by condensing two equivalents of an aryl aldehyde with dithiooxamide in nitrobenzene at 130 °C for 24 h. The method is tolerant to a range of aromatic aldehydes including derivatives of pyridine, quinoline, mono- and dihydroxybenzene. An X-ray crystal structure of 2,5-bis(2-hydroxy-3,5-di-*tert*-butylphenyl)thiazolo[5,4-*d*]thiazole was obtained confirming the proposed formulation, together with supporting spectroscopic data that suggests that for the 2-hydroxyphenyl derivatives intramolecular hydrogen bonding exists in both solution and solid states.

Thiazolo[5,4-*d*]thiazoles are an important class of bicyclic aromatic molecule comprising two fused thiazole rings (Fig. 1).[1] Initially, these compounds were explored for their potential biological activity,[1b] but recent effort has focused on their inclusion in materials for applications such as semi-conducting polymers,[2] field-effect transistors[3] and optical devices (including electroluminescence and photovoltaics).[4] Thiazolothiazoles have actually been known for over a century: in 1891, Ephraim first reported the condensation of dithiooxamide (also often referred to as rubeanic acid) with benzaldehyde.[5] The product was obtained using excess benzaldehyde as the solvent under reflux, however, the precise identity of the product was mis-assigned, only to be fully characterised in subsequent studies by Johnson et al.[6] From a synthetic perspective the reported requirement of using the aldehyde as the solvent has obvious limitations: firstly, the aldehyde must be liquid at the required temperature to affect cyclisation, and secondly, the large excess of aldehyde implies cost limitations and restriction to simpler substrates. More recently reported syntheses have utilised solvents with higher boiling points,[7] but still reported a need for excess aldehyde to facilitate thiazolothiazole formation. The synthesis of thiazolothiazoles is not confined to the condensation of dithiooxamide: Seybold et al.[8] reported the synthesis of a di(acetylamino)thiazolothiazole from a functionalised thiazole precursor. This synthesis provides an alternative route to functionalised thiazolothiazoles with the advantages of lower reaction temperatures (albeit with relatively poor overall yields) and possible routes towards asymmetric thiazolothiazoles, something that was not possible with the aforementioned dithiooxamide condensation.

Our interest in this area stems from the ongoing development of new chromophoric-ligand scaffolds for supramolecular metallo-architectures, which have demonstrated potential applications ranging from biological sensors to photovoltaic devices. Contextually, thiazolothiazoles represent a fascinating and hitherto untapped class of ligand, with only a handful of reports relating to their coordination chemistry.[7a,9] In this paper we present a general synthetic route (Scheme 1) towards potential new ligands via the syntheses of di-substituted thiazolothiazoles from dithiooxamide and stoichiometric quantities of an appropriate aldehyde. Firstly,the protocol is tolerant to a variety of aryl aldehydic substrates and should ultimately lead to the ability to tune the electronic, steric and donor properties of these comparatively rare heterocyclic species. Secondly, preliminary studies demonstrate that an unsymmetrical species can be isolated, wherein two different aldehydes are utilised in the reaction mixture.

The 2,5-disubstituted thiazolo[5,4-*d*]thiazoles **1**–**7** (Fig. 2) were synthesised according to the general procedure shown in Scheme 1, whereby 2 equiv of the aldehyde were stirred with dithiooxamide in nitrobenzene at 130 °C (for compound **8**, better results were ob-

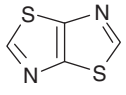

Figure 1. Thiazolo[5,4-*d*]thiazole.

Scheme 1. General route to the symmetrical thiazolo[5,4-*d*]thiazoles. Typical conditions: $PhNO_2$, 130 °C, 24 h.

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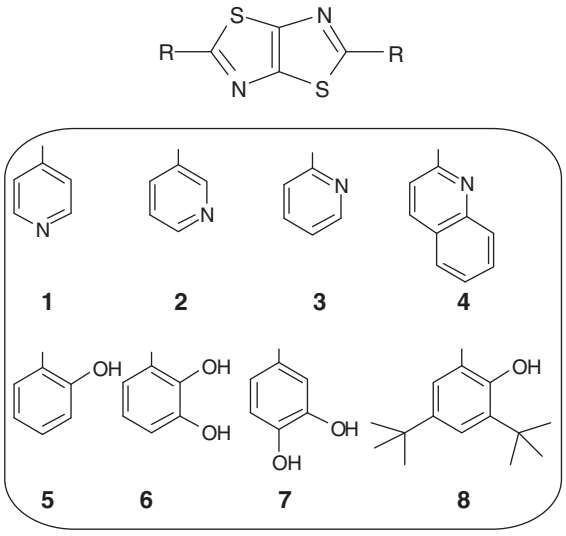


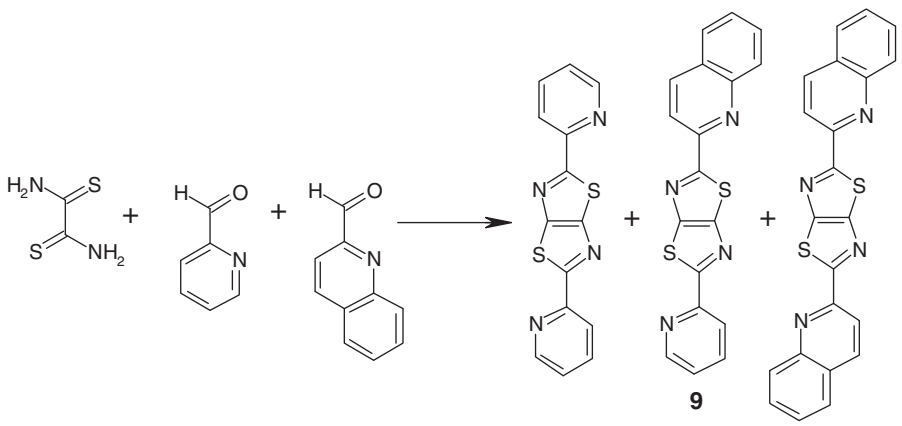
Figure 2. The various symmetrical aryl-derived thiazolo[5,4-*d*]thiazoles used in this study.

tained using DMF at 153 °C) for 24 h.[10] All reactions were performed under a dinitrogen atmosphere to avoid oxidation of starting materials. The reaction mixture was then cooled and diethyl ether was added resulting in precipitation of the desired product [if required further purification could be undertaken using column chromatography (silica gel; 99:1 CH_2Cl_2/MeOH)]. Compound **8** was intentionally exceptional in this regard, since the *tert*-butyl groups impart much greater solubility to the product. However, an initial crop of crystalline material was obtained upon cooling the reaction mixture and further product was isolated via recrystallisation; layering hexane upon a concentrated DMSO solution resulted in the production of additional crystals, which were filtered and dried. Compounds **1**–**8** were obtained in moderate-to-good yields (30–80%). As a demonstration of the utility of this synthetic approach, it is important to note that compound **3**, 2,5-di(2-pyridyl)thiazolo[5,4-*d*]thiazole, has been previously reported[9] to be obtained in a 19% yield, using 2-pyridinecarboxaldehyde as solvent. The methodology reported herein, dramatically improves this yield to 60%, whilst only requiring stoichiometric aldehyde. Generally, with the exception of compound **8**, the new compounds possessed relatively poor solubility in common organic solvents. However, all compounds were characterised by ^{1}H NMR and where solubility allowed, ^{13}C{^{1}H} NMR spectroscopy. LR and HRMS, IR and UV–vis spectra were also obtained.

In the context of designing ditopic ligand architectures with tunable electronic properties, the isolation of unsymmetrical thiazolo[5,4-*d*]thiazoles would be attractive from a coordination chemistry as well as a chromophoric perspective. Preliminary studies (Scheme 2) into the synthesis of unsymmetrical hetero-substituted thiazolo[5,4-*d*]thiazoles were undertaken using two aldehydes which were assumed to possess similar reactivity (2-pyridinecarboxaldehyde and 2-quinolinecarboxaldehyde). Thin layer chromatographic analysis (silica gel; 99:1 CH_2Cl_2/MeOH) of the reaction mixture revealed the presence of three species: two R_f values consistent with compounds **3** and **4** and a new species with an R_f value intermediate between the two. Following chromatographic purification of the crude reaction mixture (i.e., removal of compounds **3** and **4**) the new brown band (overall yield 13%; statistical yield 26%) was characterised as compound **9**, hetero-substituted, unsymmetrical 2-(2-pyridyl)-5-(2-quinolyl)thiazolo[5,4-*d*]thiazole.

Yellow needle-like single crystals of compound 2,5-di(2-hydroxy-3,5-di-*tert*-butylphenyl)thiazolo[5,4-*d*]thiazole (**8**) were obtained from the crude reaction mixture. The parameters associated with the data collection[11] are collated in Table 1. The obtained pictorial representation of the structure is shown in Figure 3 and reveals the expected formulation of the new compound. The molecule adopts a distorted planar conformation, with the phenol group and azole nitrogen functionalities *syn* to each other. The planarity is supported by the presence of two intramolecular H-bonding interactions between the azole nitrogens and phenol protons with d(N···H) at just 1.855 Å and therefore, typical of a strong interaction. The key bond-lengths and angles are collected in the Supplementary data, Table S1; the parameters associated with the thiazolo[5,4-*d*]thiazole core correlate very well with those obtained from 2,5-di(2-pyridyl)thiazolo[5,4-*d*]thiazole.[9]

Mass spectra generally showed the parent ion $\{M\}^+$ of each ligand as well as occasionally showing (usually in EI mode) characteristic fragmentation due to the cleavage of the C–C bond joining the central thiazolothiazole moiety with the appended aromatic unit. More usefully, ^{1}H NMR spectroscopy was used to confirm the proposed formation of the products, in each case displaying aromatic resonances, which were slightly shielded in comparison to the relevant aldehyde starting materials as well as the obvious absence of the downfield aldehyde proton. With reference to the spectra of the relevant homo-substituted species **3** and **4**, the ^{1}H NMR spectrum of **9** revealed that the chemical shifts of the quinoline proton resonances matched very closely to those of compound **4** suggesting a very similar electronic environment. In contrast, although possessing comparable chemical shifts, the pyridyl resonances were much broader than in **3** and indicative of rotameric



Scheme 2. Synthetic route to compound **9**. Typical conditions: $PhNO_2$, 130 °C, 24 h.

Table 1
Parameters associated with the single crystal diffraction data collection for 2,5-di(2-hydroxy-3,5-di-*tert*-butylphenyl)thiazolo[5,4-*d*]thiazole, **8**

Formula	$C_{32}H_{42}N_2O_2S_2$
Molecular weight	550.8
Wavelength (Å)	0.71073
Temperature (K)	150
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	
a	5.9428(3) Å
b	9.7978(4) Å
c	13.5783(5) Å
α	75.466(2)°
β	85.973(2)°
γ	80.694(2)°
Volume (Å^3)	754.88(6)
Z	1
Density (calculated)	1.212
F(0 0 0)	296
Crystal size	0.45 × 0.10 × 0.04 mm^3
Absorption coefficient	0.207 mm^{-1}
Range for data collection	3.48–27.50°
All reflections collected	4735
Independent reflections	3399
Observed reflections	2562
Goodness-of-fit	1.068
Final R indices [I >2σ(*I*)]	R1 = 0.0591, wR2 = 0.1321
R indices (all data)	R1 = 0.0867, wR2 = 0.1482

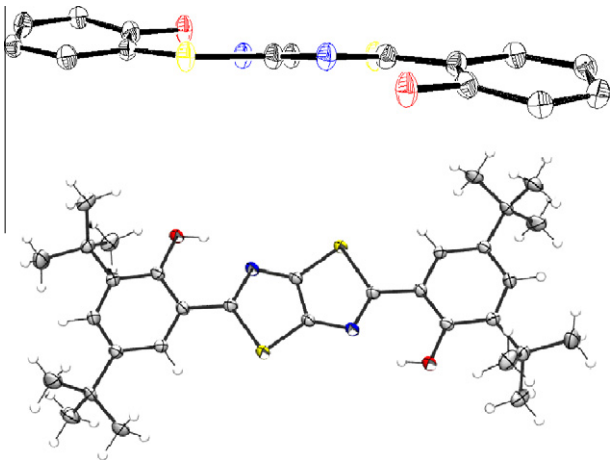


Figure 3. X-ray crystal structure of compound **8**. Top: side view with *t*-Bu groups and H atoms removed for clarity.

behaviour about the C–C bond adjoining the thioazole and pyridyl rings.

The ^{1}H NMR spectra of the 2-hydroxyphenyl-substituted compounds (**5**, **6** and **8**) displayed proton resonances indicative of inequivalent terminal 2-hydroxyphenyl rings. The number of resonances and range of chemical shifts are suggestive of an intramolecular interaction between one of the phenol groups and the azole nitrogen, thus inducing a loss of symmetry about the C_2 axis of the molecule (Fig. 4). For example, the ^{1}H NMR spectrum of compound **6**, 2,5-di(2,3-dihydroxyphenyl)thiazolo[5,4-*d*]thiazole, showed that there are four unique O*H* resonances between

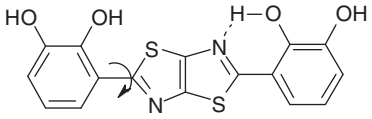


Figure 4. Suggested mode of solution state intramolecular hydrogen bonding for **6**.

8.75 and 10.44 ppm. The broadened downfield resonances are more characteristic of non-H-bonded hydroxy protons, correlating with those obtained for compound **7** where no intramolecularly H-bonded conformations are possible, but the sharper upfield resonance at 8.75 ppm can be attributed to an H-bonded (and thus more shielded) hydroxy proton. Analogous intramolecular H-bonding interactions have been well documented in systems based upon, for example, 2-(2′-hydroxyphenyl)pyridine.[12] More specifically, the behaviour of the very closely related species 2-(2′-hydroxyphenyl)thiazole has been studied from a theoretical perspective[13] revealing that, in the ground state, the normal form (phenol *syn* to N) is energetically favoured over either the rotameric (phenol *syn* to S) or tautomeric forms. Further, the calculations show that the thiazole differs significantly from the related oxazole and imidazole analogues, with significant single bond character between the phenol and azole ring. Additional evidence of this intramolecular interaction was also provided by the ^{13}C{^{1}H} NMR spectrum of compound **8**, which showed sixteen unique aromatic carbon resonances, again indicative of inequivalence and a loss of symmetry across the thiazolo[5,4-*d*]thiazole core. Therefore, whilst the solid-state structure revealed a double and thus symmetrical intramolecular H-bonding interaction, the subsequent NMR spectroscopic characterisation of the 2-hydroxyphenyl derivatives suggests that, on average, one hydroxyl group participates in H-bonding to the N-azole ring in solution (Fig. 4).

The UV–vis absorption properties of compounds **1**–**9** were assessed in aerated MeCN solution (10^{-4} M). Each chromophore absorbs in the long-wavelength UV region with a weaker absorption tailing into the visible region. In each case this band is assigned to a π–π^* transition. With reference to previous studies into related systems,[14] although n–π^* transitions cannot be ruled out as a component of the absorptions, the magnitude of the recorded extinction coefficients ($\varepsilon > 2 \times 10^4$ M^{-1} cm^{-1}) would seem to preclude their observation. The precise positioning of the longest wavelength absorption was subtly modulated by the nature of the terminating aryl units. For example, 2,5-di(2-quinolyl)thiazolo[5,4-*d*]thiazole (**4**) absorbed at a lower energy compared to the related pyridyl analogues (**1**–**3**), suggesting that good electronic communication occurs across the fused bicyclic core. The hetero-substituted species **9** possessed λ_{max} = 373 nm, which is intermediate between **3** and **4** and therefore, consistent with the proposed structure. In the cases of the hydroxyphenyl derivatives (**5**–**8**) the variation in absorption maxima was far less-pronounced, each absorbing with a λ_{max} at *ca.* 360 nm.

In summary, this Letter discusses a general method for synthesising 2,5-disubstituted thiazolo[5,4-*d*]thiazole derivatives together with supporting spectroscopic and structural data. Future work will focus upon the exploitation of these functionalised heterocycles, including their incorporation into metallo-containing arrays as well as fully elucidating their electronic characteristics and photophysical behaviour, with particular focus upon the excited state proton-coupled electron transfer phenomena of the 2-hydroxyphenyl (**5**, **6** and **8**) derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.172.

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10. *A representative synthesis of compound* **(7)***:* 2,5-bis(3,4-dihydroxyphenyl)thiazolo[5,4-*d*]thiazole. The title compound was prepared by adding dithiooxamide (250 mg, 2.0 mmol) and 3,4-dihydroxybenzaldehyde (575 mg, 4.0 mmol) to nitrobenzene (10 mL). The reaction mixture was heated at 130 °C for 24 h under a dinitrogen atmosphere. Following cooling to room temperature, Et_2O (50 mL) was added and the resultant precipitate was filtered and dried in vacuo to give **7** as a dark brown solid. Yield = 586 mg (79%). ^{1}H NMR (250 MHz; DMSO-d_6): δ_H 9.73 (2H, br s, O*H*), 9.52 (2H, br s, O*H*), 7.41 (2H, d, $^3J_{HH}$ = 2.3 Hz, ArH), 7.32 (2H, dd, J_{HH} = 8.5 Hz and 2.3 Hz, ArH), 6.88 (2H, d, $^3J_{HH}$ = 8.4 Hz, ArH) ppm. ^{13}C{^{1}H} NMR (62.5 MHz; DMSO-d_6): δ_C 168.24, 148.82, 148.62, 145.87, 124.79, 118.17, 116.17, 112.93 ppm. LRMS (EI) found m/z = 358.0; calculated 358.4 for {M}$^+$. HRMS (EI): found 358.0081; cal 358.0082 for $C_{16}H_{10}N_2O_4S_2$. IR (solid): ν_{max} 3213, 1596, 1173, 1024, 788 cm^{-1}. UV–vis (CH_3CN): λ_{max} (M^{-1} cm^{-1}) 274 (93000), 356 (24000) nm.
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