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Ring transformations of 2-hydroxy-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)arenes

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Dedicated to the memory of Professor Alan R. Katritzky who sadly passed away on the 10th Feb. 2014

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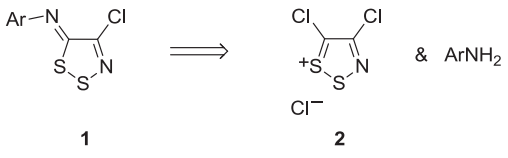
A B S T R A C T

The cyclisation reactions of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene-amino)phenol (**5a**), 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol (**5b**) and 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol (**5c**) are investigated. Thermolysis in hot PhCl (132 °C) or under solvent free conditions at ca. 200 °C gave benzo[*d*]oxazole-2-carbonitrile (**4a**), oxazolo[5,4-*b*]pyridine-2-carbonitrile (**4b**) and oxazolo[4,5-*b*]pyridine-2-carbonitrile (**4c**) in high yields, while treatment with either NaH in dry THF at 66 °C or with *i*-Pr_2NEt in DCM at 20 °C gave benzo[*b*][1,2,3]dithiazolo[5,4-*e*][1,4]oxazine (**6a**), [1,2,3]dithiazolo[5,4-*e*]pyrido[2,3-*b*][1,4]oxazine (**6b**) and oxazolo[4,5-*b*]pyridine (**4c**), respectively. The transformation of benzoxazine **6a** and the pyridoxazine **6b** into the corresponding oxazoles **4a** and **4b** was also investigated, and tentative mechanistic pathways for these transformations are proposed.

1. Introduction

(4-Chloro-1,2,3-dithiazol-5*H*-ylideneamino)(het)arenes **1**, can be readily prepared in good to excellent yields[1–3] from the reaction of a primary (het)arylamine with 4,5-dichloro-1,2,3-dithiazolium chloride **2** (Appel salt)[1] followed by treatment with a tertiary amine base (2 equiv) (Scheme 1). They can also be formed from the reaction of *N*-aryl-*S*,*S*-dimethylsulfimides,[4] *N*-aryl-1,1,1-trimethyl-*N*-(trimethylsilyl) silanamines,[1] or tetrazoles[5] with Appel salt **2**.



Scheme 1. Synthesis of (dithiazolylideneamino)arenes **1** from Appel salt **2**.

Early reports on the biological activity of [(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)amino]arenes showed that some 1,2,3-dithiazoles have antifungal[6] and herbicidal[7] activities, while more recently, interesting antitumour,[8] antibacterial[9] activities and inactivation of the glutamine/amino acid transporter ASCT2[10] have been demonstrated. Furthermore, benzo and heteroazine fused 1,2,3-dithiazoles are of interest to the material sciences.[11]

In addition, (4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)arenes are useful precursors to other heterocycles through *A*ddition of the *N*ucleophile, *R*ing *O*pening, and *R*ing *C*losure (ANRORC)[12] style ring transformations.[13] For example, thiazoles,[14] 1,3,4-thiadiazoles[14] and heteroazine fused thiazoles[15] have been prepared via ANRORC type transformations,[16] while the thermolysis of (1,2,3-dithiazolylideneamino)arenes can afford (het)areno fused thiazoles,[15–17] 1,2,4,-dithiazines,[18] imidazoles[19] oxazoles[17c,20] and oxazines.[21] Moreover, 1,2,3-dithiazolylideneamines have also been used to prepare acyclic functionalities such as isothiocyanates[22] and thiocyanoformamides.[2,23]

Several examples of (4-chloro-5*H*-1,2,3-dithiazol-5-ylidene amino)arene ring transformations involve a nucleophilic *ortho* substituent on the arene. Where the *ortho* substituent is a primary, secondary[19,24] or even a tertiary amine,[25] thermolysis affords the analogous imidazole-2-carbonitriles **3**, and when the *ortho* substituent is a hydroxyl group the analogous benzo[*d*]oxazole-2-carbonitrile (**4a**) forms (Scheme 2).[17a,20] Surprisingly, in the latter case, treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino) phenol (**5a**) with NaH in dry THF gave benzo[*b*][1,2,3]dithiazolo [5,4-*e*][1,4]oxazine (**6a**) (Scheme 2).[17a]

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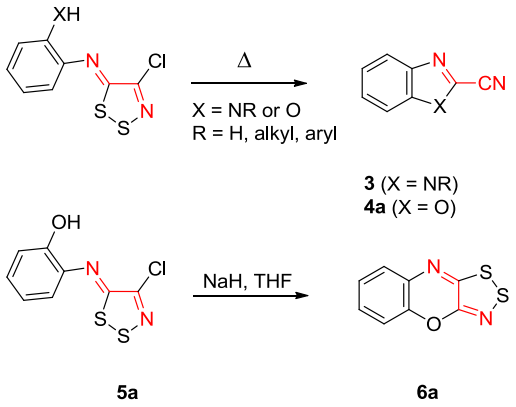


Scheme 2. Ring transformations of (dithiazolylideneamino)arenes bearing a nucleophilic *ortho* substituent on the arene.

The latter cyclisation is analogous to the base (NaH or *i*-Pr_2NEt in THF or K_2CO_3 in MeCN) catalysed cyclisation of 2-(4-chloro-3*H*-1,2-dithiol-3-ylideneamino)phenols **7**, prepared from 3,4,5-trichloro-1,2-dithiolium chloride (**8**) (Boberg salt)[26] and 2-aminophenols, to give 1,2-dithiolo[4,3-*b*][1,4]benzoxazines **9**, in moderate yields (39–45%) (Scheme 3).[27]

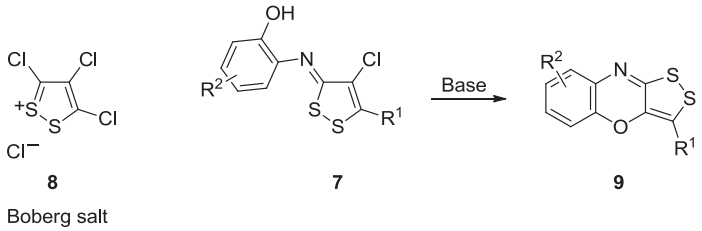
via an ANRORC style mechanism where the amine attacks the ring sulfur to generate a disulfide intermediate that then recyclises. Kim et al. has reported several examples of ANRORC style indirect displacement of the Cl by amines.[28,29]

In light of our access to 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene amino)phenol (**5a**), 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneam ino)pyridin-2-ol (**5b**) and 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol (**5c**) and our on-going interest in the chemistry of Appel salt **2** we probed this chemistry further. Our aims were to identify additional examples and to improve the reaction conditions leading to the fused oxazines, to determine the influence of additional ring nitrogens, and to propose mechanistic pathways for the products formed.

2. Results and discussion

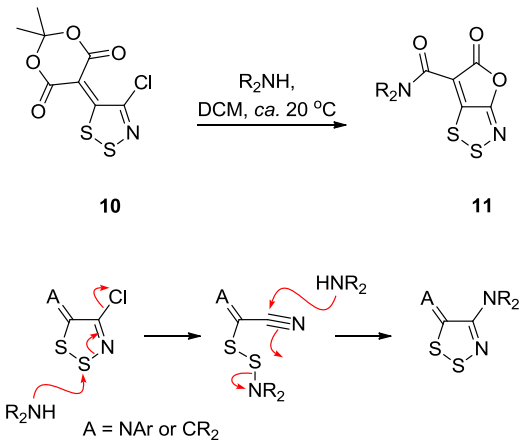
2.1. Synthesis of fused oxazoles and oxazines

2.1.1. Synthesis of dithiazolimine starting materials. 2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol (**5a**), 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol (**5b**) and 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol (**5c**) were prepared from Appel salt **2** and the corresponding *ortho* hydroxy amino arenes **12** (Scheme 5).



Scheme 3. Cyclisation of 2-(4-chloro-3*H*-1,2-dithiol-3-ylideneamino)phenols **7**.

Direct displacement of the dithiazoles C4 chlorine atom has proved to be difficult,[17a] and the intramolecular cyclisation of the (dithiazolylideneamino)phenol **5a** to afford the benzoxazine **6a** is a very rare example of a cyclisation onto the dithiazole C4 position that maintains the integrity of the dithiazole ring. The only other known example is the reaction of 5-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**10**) with secondary alkylamines to yield 6-carbamoyl-5-oxo-5*H*-furo[2,3-*d*][1,2,3]dithiazoles (**11**) (Scheme 4).[28] However, this cyclisation proceeds



Scheme 4. Example of intramolecular cyclisation onto the dithiazole C4 position that maintains the integrity of the dithiazole ring, and the proposed mechanism for the ANRORC mediated indirect displacement of the C4 chlorine by amine.

Interestingly, the pyridin-3-ol **5c** was obtained only in 11% yield, and was accompanied by several deeply coloured side products. Two of these were isolable and tentatively assigned as (*Z*)-4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-[(*Z*)-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)amino]pyridin-3(4*H*)-one (**13**) (2%) and (*Z*)-2-amino-6-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3(6*H*)-one (**14**) (4%), respectively, and were a reminder that electron rich arenes can react directly via the ring carbon in an enolic[30] or enaminic[17e,18] manner.

Compound **13** was obtained as blue dust, mp 288–289 °C (from DCE). Elemental analysis and LR (EI) mass spectrometry supported the molecular formula $C_9H_2Cl_2N_4OS_4$; a clear two chlorine isotope pattern was observed for the parent ion [*m*/*z* 384 (M^++4, 2%), 382 (M^++2, 4), 380 (M^+, 8)]. UV/vis spectroscopy showed a λ_{max} of 614 nm (log ε 3.52) that suggested the compound had extended conjugation. ^{1}H NMR spectroscopy showed two doublets at 9.23 and 8.08 ppm with *J* values of 6.0 and 5.5 Hz, respectively. The small *J* values observed in the ^{1}H NMR data supported a 5,6-unsubstituted pyridine since $^1J_{H4H5}$ couplings are typically larger than $^1J_{H5H6}$ couplings (7–9 vs 4–6 Hz).[31] ^{13}C NMR spectroscopy, revealed the presence of nine carbon resonances of which seven were quaternaries and two secondaries. Based on these data a bis-dithiazole structure was proposed for compound **13**, however, a number of geometric isomers are possible. Of these, the *Z*,*Z* isomer has two favourable non-bonding interactions: the first interaction between the S1 sulfur atom of the dithiazolylidene and the oxygen atom of the carbonyl group, and the second between the S1 sulfur atom of the other dithiazolimine and the pyridone nitrogen atom. The non-bonding interaction between the S1 sulfur