New synthesis of isothiazoles from primary enamines

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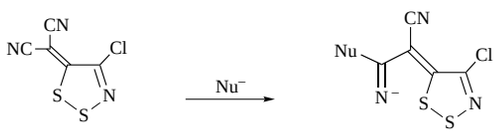
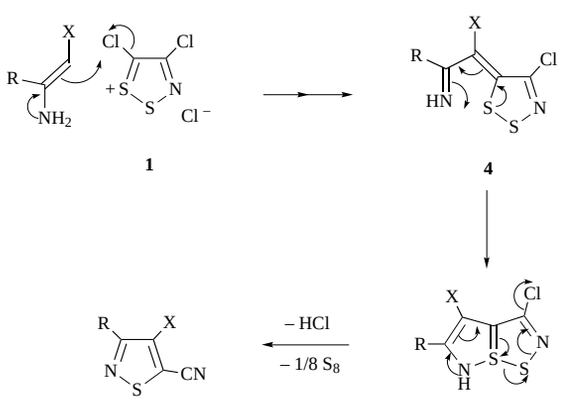
Methyl 3-aminocrotonate 7 reacts with 4,5-dichloro-1,2,3-dithiazolium chloride 1 at room temperature to give methyl 5-cyano-3-methylisothiazole-4-carboxylate 9 in high yield (78%) (Schemes 1 and 2). This reaction is formally related to Woodward's synthesis of methyl 3-methylisothiazole-4-carboxylate 24 from the same enamine and thiophosgene (Scheme 7). 3-Aminocrotononitrile 10 is similarly converted into 4,5-dicyano-3-methylisothiazole 12 but the yield is much reduced (to 40%) since the reaction is more complex (Scheme 3) giving 2,3,5-tricyano-4,6-dimethylpyridine 14 (20%), in a new pyridine ring construction, and three other minor products. All the products can be accounted for by reasonable mechanisms (Schemes 4, 5 and 6). One of the minor products, ketone 13, has been synthesized from the enolate anion 21 and the reagent 1, and the analogous ketones 23 have been readily prepared in high yield from the active methylene compounds 22 and reagent 1.

We have shown that 4,5-dichloro-1,2,3-dithiazolium chloride **1** reacts with malononitrile to give the dicyanomethylenedithiazole **2**. Nucleophiles add to **2** and induce cyclisation onto



2 **3**

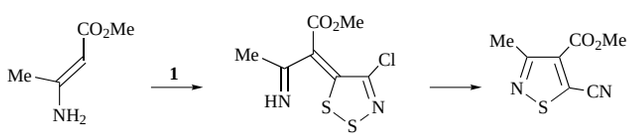
the dithiazole ring to provide a new route to isothiazoles, presumably *via* the intermediate **3**.[1] It seemed possible that primary enamines could react with **1** to give an adduct **4**, very similar to the proposed intermediate **3**, which could similarly give isothiazoles **6**, by collapsing to the hypervalent sulfur species **5** followed by elimination of hydrogen chloride and sulfur (Scheme 1). This could provide a one-step route to 5-cyanoisothiazoles **6** with a useful range of 3- and 4-substituents.



1 **4** **5** **6**

Scheme 1

We therefore treated methyl 3-aminocrotonate **7** with the salt **1** (1 equiv.) in dichloromethane at room temperature, after which pyridine was added to the reaction mixture, in the standard way.[2] This gave methyl 5-cyano-3-methylisothiazole-4-carboxylate **9** cleanly and in good yield (78%) (Scheme 2); the



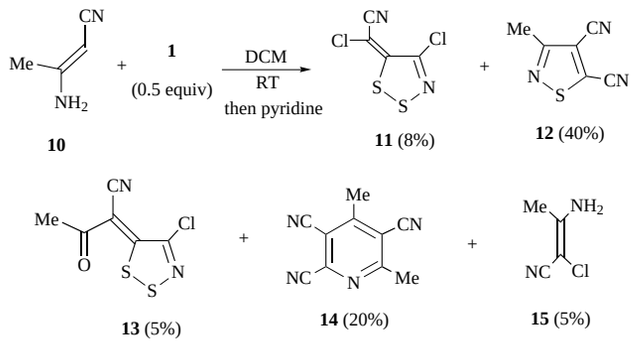
7 **8** **9**

Scheme 2

structure of **9** was based on analogy with the earlier work[2] and confirmed by analysis and spectroscopy. It was probably formed by the above mechanism (Schemes 1 and 2) with the intermediate **8** spontaneously forming the aromatic product **9**, hydrogen chloride and sulfur. Sulfur was presumably not extruded as (high energy) sulfur atoms but as S_8, formed in a sequence of biomolecular sulfur transfer reactions,[3] possibly involving the nitrile sulfide derivative of the nitrile **9**. Elemental sulfur was detected as a product in this reaction.

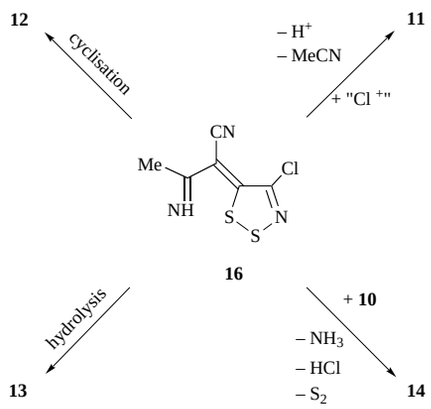
Transformation of the presumed intermediate **8** into the isothiazole **9** is a variant of the Boulton–Katritzky rearrangement in which a three-atom side chain on a five-membered heterocyclic ring attacks and opens the ring to form a new five-membered heterocycle.[4] The normal central, pivotal nitrogen atom in the Boulton–Katritzky rearrangement is here replaced by sulfur and a ring S–S bond is cleaved. One or two such rearrangements are known for 1,2,4-dithiazoles and 1,2-dithioles,[4] but not (apart from our previous work[2]) for 1,2,3-dithiazoles. The spontaneous conversion of **8** into **9** occurs under unusually mild conditions; presumably the ready cleavage of the S–S bond, the aromaticity of the isothiazole ring, and the accompanying formation of a cyano group all contribute to this. Reaction of an enamino nitrile, 3-aminocrotononitrile **10**, with the salt **1** under the standard conditions was more complex, giving up to five products in all. Trial experiments showed that these were formed in highest total yield (78%) with a two-fold excess of enamine **10** over the salt **1**. The five products, **11**–**15**, were separated by flash chromatography on silica in the yields shown in Scheme 3, in the order of elution from the column. Their structures are based upon analysis and spectroscopy and, for **13**, an independent synthesis (below).

The major product in the reaction of the enamino nitrile **10** with **1** was the dicyanoisothiazole **12** (40%), exactly analogous to the formation of **9** from **7** (Scheme 2); this was presumably formed by the general mechanism of Scheme 1 by spontaneous



Scheme 3

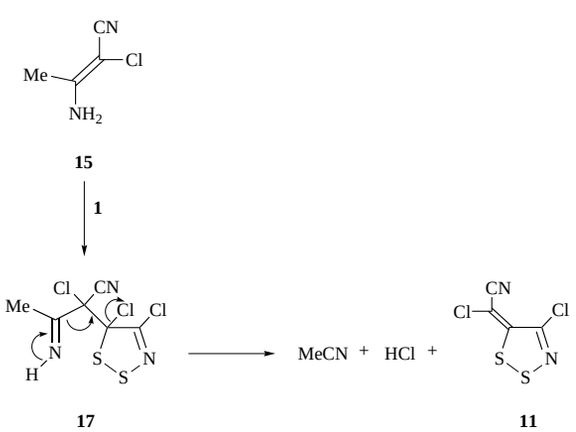
cyclisation of the initial intermediate **16**. Good evidence for this intermediate is provided by the isolation of a small amount of its hydrolysis product, the ketone **13**, after chromatography (Scheme 4). Another possible decomposition pathway open to



Scheme 4

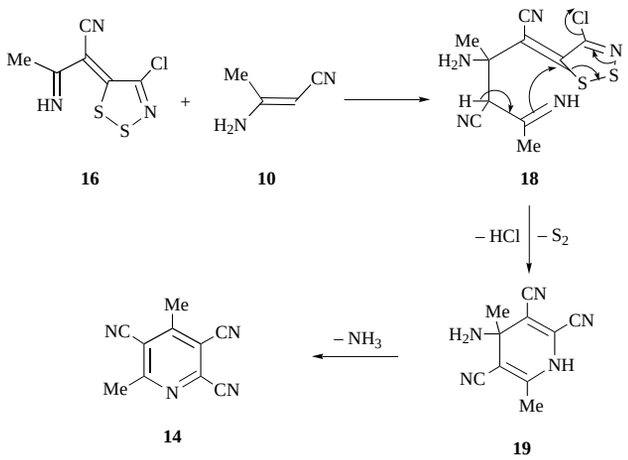
16 is the elimination of acetonitrile and (possibly concomitant) chlorination to give the chlorocyanomethylene compound **11** which was also isolated in low yield. Another minor product was compound **15**, probably formed by chlorination of the starting enamine **10**. It thus appears that the reagent **1** can in some circumstances act as a chlorinating agent converting the enamine **10** into the enamine **15**, analogous to the chlorination of enamines by *N*-chlorosuccinimide.[5]

The new enamine **15** formed in the reaction could also react with the salt **1**, just like the enamine **10**, to give the intermediate **17** which could fragment as shown (Scheme 5) to give the last of



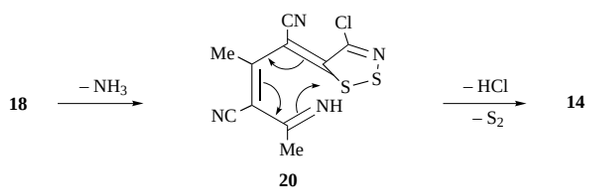
Scheme 5

the minor products **11**. The remaining product of the reaction in Scheme 3, and the second most abundant, was 2,3,5-tricyano-4,6-dimethylpyridine **14** (20%). We propose that this is formed by nucleophilic addition of a second mole of the enamine **10**, present in excess, to the imine group of the initial product **16** to give the adduct **18**. This adduct is now well set up to cyclise to the dihydropyridine **19** and hence to **14** and ammonia (Scheme 6). We have observed other examples of such



Scheme 6

attack at C-5 of the dithiazole ring with the elimination of S_2 and HCl.[2] It is also possible that loss of ammonia from **18** could occur first to give the 'push pull' stabilised imino diene **20**, followed by electrocyclisation (arrows in **20**) and elimination

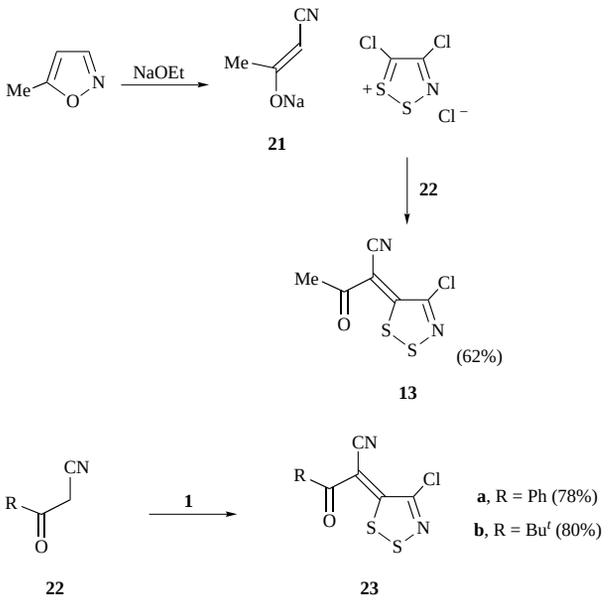


as before to give **14**. This new synthesis of the pyridine ring system could well be general and is worthy of further investigation.

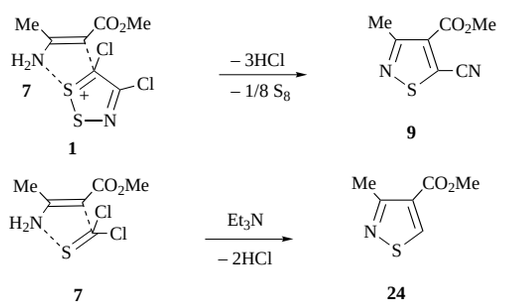
Thus, of the five products shown in Scheme 3, one results from chlorination of the starting enamine **10**, present in excess, and the remainder, **11**–**14** (combined yield 73%), can all be readily derived from the initial product **16** of nucleophilic attack of the enamine on the dithiazolium salt **1** (Scheme 4). In general agreement with this, when the reaction was run with equimolar amounts of **10** and **1** the enamine chlorination product **15** and the pyridine **14**, requiring 2 mol equiv. of enamine per mole equiv. of **1**, were not isolated; the isothiazole **12** was again the major product (43%).

It occurred to us that the enolate anion **21** of the ketone corresponding to the enamine **10** could react similarly with the salt **1** to give the dithiazolo ketone **13** directly and in high yield; this ketone should be more stable than its imine **16** with fewer decomposition pathways available to it. The required salt **21** is readily generated from 5-methylisoxazole and sodium ethoxide, and when the salt **1** was added to this in dichloromethane, the dithiazolo ketone **13**, identical with that isolated from the enamine reaction, was indeed produced in good yield (62%). This last reaction was then extended to two other 3-keto nitriles, benzoylacetonitrile **22a** and pivaloylacetonitrile **22b**. Both condensed readily with **1** in dichloromethane at room temperature to give the analogous dithiazolo ketones **23a** (78%) and **23b** (80%) in high yield.

The conversion of the enamines **7** and **10** by the reagent **1** into 5-cyanoisothiazoles **9** and **12** is a new, very short and simple synthesis of isothiazoles from readily available materials. It is a [3+2] atom construction of the ring with the enamine providing $N–C_3–C_4$ and the reagent **1** providing $S–C_5–CN$ (Scheme 7). This is very reminiscent of Woodward's remarkable



construction of the isothiazole ring at the beginning of his brilliant synthesis of colchicine.[6] His synthesis combined the enamine **7** with thiophosgene in a similarly spontaneous process to give the isothiazole **24** lacking the 5-cyano group of our product **9**. The formal similarity between the two reactions is shown in Scheme 7.

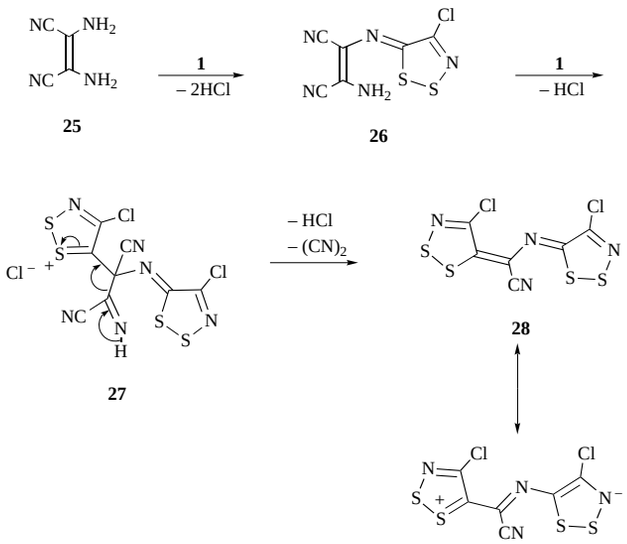


Scheme 7

We have seen in this paper that primary enamines react with 4,5-dichloro-1,2,3-dithiazolium chloride **1** exclusively through carbon, whilst primary aromatic amines react with it exclusively through nitrogen,[2] much as would be expected. An interesting intermediate case is provided by diaminomaleonitrile (DAMN) **25** which, though formally a bis(enamino nitrile), is known to react with electrophiles through the amino nitrogen.[7] We therefore treated DAMN with the reagent **1** (1 equiv.) in dichloromethane at room temperature in the standard manner. The clean product, formed in good yield, was orange in colour like the normal arylimino products, and its spectroscopic properties showed it to be the imine **26** (68%). Thus DAMN has reacted as an amine rather than an enamine.

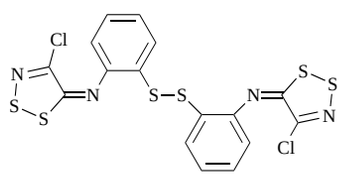
When DAMN was treated similarly but with 2 equiv. of the reagent **1** a small amount of the imine **26** was again formed but the main product was now a deep purple, high melting solid. This compound had only one cyano group but two chlorine atoms, with molecular formula $C_6Cl_2N_4S_4$ from the accurate mass measurements, and was assigned structure **28**. This is in accord with all its properties, and its deep colour can be explained by the highly delocalised structure, as shown in Scheme 8. It thus appears that the initial product **26** has reacted with **1**, not *via* nitrogen to give a symmetrical bis(imine), but as an enamino nitrile to give the 1:2 adduct **27** which loses hydrogen chloride and cyanogen to give the observed product **28** (39%).

We noted above that in the conversion of the enamine **10** into



Scheme 8

the enamine **15**, the salt **1** appeared to be acting as a chlorinating agent. Another example of this was observed in its reaction with 2-aminobenzenethiol. Whilst 2-aminophenol gave the normal iminodithiazole derivative in almost quantitative yield,[2] 2-aminobenzenethiol gave the dimeric product, the disulfide **29**



(64%) rapidly and exclusively. Thus, in addition to forming the iminodithiazole the salt **1** appears to have oxidised the arenethiol to the symmetrical disulfide.

Experimental

For general experimental details and the preparation of reagent **1**, see our related papers.[2]

Methyl 5-cyano-3-methylisothiazole-4-carboxylate 9

A mixture of methyl 3-methylcrotonate **7** (0.34 g, 3 mmol) and the chloride **1** (0.63 g, 3 mmol) in dichloromethane (25 ml) was stirred at room temperature for 1 h after which pyridine (0.49 ml, 6 mmol) was added to it. The mixture was stirred for a further 30 min. The product was separated by flash chromatography on silica gel eluting with dichloromethane–light petroleum (1:3) to give the *title compound* (0.43 g, 78%) as colourless crystals from dichloromethane–light petroleum, mp 55–56 °C (Found: C, 46.4; H, 3.3; N, 15.2. $C_7H_6N_2O_2S$ requires C, 46.2; H, 3.3; N, 15.4%); ν_{max}(Nujol)/cm^{-1} 2230s (CN), 1710s (C=O), 1200w; δ_H(270 MHz, $CDCl_3$) 3.95 (3H, s, CO_2Me) and 2.75 (3H, s, Me); δ_C(63 MHz, $CDCl_3$) 168.9, 160.4, 138.5, 132.9, 109.8 (CN), 52.8 (O–CH_3) and 19.8 (CH_3); *m*/*z* (EI) 182 (M^+, 62%) and 151 (M^+ − OMe, 12).

Reaction of 4,5-dichloro-1,2,3-dithiazolium chloride 1 with 3-aminocrotononitrile 10

(i) A mixture of 3-aminocrotononitrile **10** (0.34 g, 4 mmol) and the chloride **1** (0.42 g, 2 mmol) in dichloromethane (30 ml) was stirred at room temperature for 1 h after which pyridine (0.32 ml, 4 mmol) was added to it. The mixture was stirred for a further 30 min after which the products were separated by flash chromatography on silica gel eluting with dichloromethane–light petroleum (1:5) to give: 4-*chloro*-5-(*chlorocyanomethyl*-

ene)-1,2,3-*dithiazole* **11** (35 mg, 8%) as a pale yellow solid from dichloromethane–light petroleum, mp 166–168 °C (Found: C, 22.7; N, 13.2. $C_4Cl_2N_2S_2$ requires C, 22.7; N, 13.3%); ν_{max}(Nujol)/cm^{-1} 2925w, 2205s (CN), 1704s, 1525 and 1200s; δ_C(63 MHz, $CDCl_3$) 155.1 (Het), 139.3 (Het), 113.1 (CN) and 90.5; *m*/*z* (EI) 210 (M^+, 100%), 175 ($M^+ - Cl$, 13), 149 ($M^+ - ClCN$, 37), 105 ($M^+ - ClCNS$, 21), 79 (13), 70 (23) and 64 (S_2^+, 32); 4,5-*dicyano*-3-*methylisothiazole* **12** (120 mg, 40%) as colourless crystals from dichloromethane–light petroleum, mp 69–70 °C (Found: C, 48.2; H, 1.9; N, 28.1. $C_6H_3N_3S$ requires C, 48.3; H, 2.0; N, 28.2%); ν_{max}(CCl_4)/cm^{-1} 2930w, 2235s (CN), 1525w and 1420s; δ_H(270 MHz, $CDCl_3$) 2.76 (s); *m*/*z* (EI) 149 (M^+, 100%), 122 ($M^+ - HCN$, 18) and 108 ($M^+ - NHCN$, 18); 5-(*acetylcyanomethylene*)-4-*chloro*-1,2,3-*dithiazole* **13** (22 mg, 5%) as a golden yellow solid from dichloromethane–light petroleum, mp 180–181 °C (Found: C, 32.9; H, 1.4; N, 12.6. $C_6H_3ClN_2OS_2$ requires C, 32.9; H, 1.4; N, 12.8%); ν_{max}(CCl_4)/cm^{-1} 2930s, 2200s (CN), 1620s (C=O), 1460s, 1380w, 1280w, 1220s, 1080w and 875w; δ_H(270 MHz, $CDCl_3$) 2.52 (s); δ_C(63 MHz, $CDCl_3$) 189.1 (CO), 164.2 (Het), 145.7 (Het), 116.9 (CN), 98.5 and 25.4 (Me); *m*/*z* (EI) 218 (M^+, 30%), 183 ($M^+ - Cl$, 17), 114 (2) and 43 (CH_3CO^+); 2,3,5-*tricyano*-4,6-*dimethylpyridine* **14** (73 mg, 20%) as colourless needles, mp 132–133 °C (Found: C, 65.9; H, 3.3; N, 30.5. $C_{10}H_6N_4$ requires C, 65.9; H, 3.3; N, 30.8%); ν_{max}(CCl_4)/cm^{-1} 2380s, 2220s (CN), 1570w, 1440w, 1410w and 1040w; δ_H(270 MHz, $CDCl_3$) 2.9 (s) and 2.85 (s); δ_C(63 MHz, $CDCl_3$) 166.4, 156.3, 137.4, 113.9, 113.5, 113.21, 113.20, 111.8, 24.4 (Me) and 20.2 (Me); *m*/*z* (EI) 182 (M^+, 14%), 142 (3), 141 ($M^+ - CH_3CN$, 4) and 90 (4); 3-*amino*-2-*chlorocrotononitrile* **15** (12 mg, 5%) as colourless needles, mp 120–121 °C (Found: C, 41.6; H, 4.1; N, 23.8. $C_4H_5ClN_2$ requires C, 41.2; H, 4.3; N, 24.0%); δ_C(63 MHz, $CDCl_3$) 153.5, 117.9 (CN), 72.5 and 18.8 (Me); *m*/*z* (EI) 116 (M^+, 70%), 101 (13), 88 (6), 79 (4) and 75 ($M^+ - CH_3CN$, 63).

(ii) A mixture of 3-aminocrotononitrile **10** (0.17 g, 2 mmol) and the chloride **1** (0.42 g, 2 mmol) in DCM (10 ml) was stirred at ambient temperature for 0.5 h after which pyridine (0.32 ml, 4 mmol) was added to it. The mixture was stirred for a further 2 h, and then separated by flash chromatography on silica gel with dichloromethane–light petroleum to give: 4-chloro-1,2,3-dithiazole-5-thione (72 mg, 21%); the dithiazole **11** (35 mg, 8%), mp 166–168 °C, identical with that described above, and 4,5-dicyano-3-methylisothiazole **12** (130 mg, 43%), mp 69–70 °C, identical with that described above.

5-(Acetylcyanomethylene)-4-chloro-1,2,3-dithiazole 13

To a suspension of the chloride **1** (1.0 g, 4.8 mmol) in dichloromethane (40 ml) was added the sodium salt **21** (0.5 g, 4.8 mmol). The mixture was stirred at room temperature for 2 h after which pyridine (0.77 ml, 9.6 mmol) was added to it. The mixture was stirred for a further 1 h after which the product was separated by flash chromatography on silica gel eluting with dichloromethane–light petroleum to give 5-(acetylcyanomethylene)-4-chloro-1,2,3-dithiazole **13** (0.63 g, 60%) as a golden yellow solid from dichloromethane–light petroleum, mp 180–181 °C, identical with that described above.

5-(Benzoylcyanomethylene)-4-chloro-1,2,3-dithiazole 23a

To a suspension of the chloride **1** (0.62 g, 3 mmol) in dichloromethane (25 ml) was added benzoylacetonitrile **22a** (0.44 g, 3 mmol). The mixture was stirred at room temperature for 1 h after which pyridine (0.48 ml, 6 mmol) was added to it. The mixture was stirred for a further 30 min after which the product was separated by flash chromatography on silica gel eluting with dichloromethane–light petroleum (1:2) to give the *title compound* **23a** (0.66 g, 78%) as orange crystals, mp 244–245 °C (Found: C, 46.8; H, 1.7; N, 9.8. $C_{11}H_5ClN_2OS_2$ requires C, 47.1; H, 1.8; N, 9.9%); ν_{max}(Nujol)/cm^{-1} 2250s (CN), 1600 (C=O), 1380w, 1300w and 800w; δ_H(270 MHz, $CDCl_3$) 8.01–7.97 (2H, m, *o*–H) and 7.65–7.49 (3H, m, *m* and *p*–H); δ_C(63 MHz, $CDCl_3$) 187.7 (CO), 163.3, 146.5, 134.7, 132.8, 129.1, 128.6, 115.7 (CN) and 98.1; *m*/*z* (EI) 280 (M^+, 22%), 245 (68), 105 ($PhCO^+$, 100) and 77 (Ph, 71).

5-(Cyanotrimethylacetylmethylene)-4-chloro-1,2,3-dithiazole 23b

To a suspension of the chloride **1** (0.62 g, 3 mmol) in dichloromethane (25 ml) was added pivaloylacetonitrile **22b** (0.38 g, 3 mmol). The mixture was stirred at room temperature for 1 h after which pyridine (0.48 ml, 6 mmol) was added to it. The mixture was stirred for a further 30 min after which the product was separated by flash chromatography on silica gel eluting with dichloromethane–light petroleum (1:1) to give the *title compound* **23b** (0.63 g, 80%) as orange crystals from dichloromethane–light petroleum, mp 190–191 °C (Found: C, 41.4; H, 3.3; N, 10.5. $C_9H_9ClN_2OS_2$ requires C, 41.5; H, 3.5; N, 10.7%); ν_{max}(Nujol)/cm^{-1} 2200s (CN), 1580s (C=O), 1100w, 980w, 950m and 900; δ_H(270 MHz, $CDCl_3$) 1.5 (s, Me_3C); δ_C(63 MHz, $CDCl_3$) 199.1 (CO), 163.1, 145.8, 115.8 (CN), 97.4, 42.9 and 26.9; *m*/*z* (EI) 260 (M^+, 16%), 204 (8), 176 (9), 162 (4), 57 (100) and 41 (27).

5-(2-Amino-1,2-dicyanovinylimino)-4-chloro-1,2,3-dithiazole 26

To a suspension of diaminomaleonitrile **25** (0.32 g, 3 mmol) in dichloromethane (30 ml) was added the chloride **1** (0.63 g, 3 mmol). The mixture was stirred at room temperature for 6 h after which pyridine (0.46 ml, 6 mmol) was added to it. The mixture was stirred for a further 30 min after which the product was purified by flash chromatography on silica gel eluting with dichloromethane–light petroleum (1:1) to give the *title compound* **26** (0.49 g, 68%) as an orange solid from dichloromethane–light petroleum, mp 205–207 °C (Found: M^+, 242.9435. $C_6H_2ClN_5S_2$ requires M^+, 242.9456); ν_{max}(Nujol)/cm^{-1} 3460s (NH_2), 3320s, 2220s (CN), 2200s (CN), 1600s, 1580s, 1460s, 1380s, 1240w, 1200s, 1140s, 870s, 810s and 740s; δ_H(270 MHz, DMSO) 8.30 (2H, s, NH_2); δ_C(63 MHz, DMSO) 154.3 (Het), 147.4 (Het), 126.9, 114.4 (CN), 114.2 (CN) and 99.9; *m*/*z* (EI) 243 (M^+, 10%), 150 (12), 144 (26), 123 (7), 118 (5), 102 (3), 98 (5), 93 (5), 70 (15) and 64 (100).

2-Cyano-1,2-bis(4-chloro-5*H*-1,2,3-dithiazolylidene)-1-azaethane 28

To a suspension of diaminomaleonitrile **25** (0.32 g, 3 mmol) in dichloromethane (30 ml) was added the chloride **1** (1.25 g, 6 mmol). The mixture was stirred at room temperature for 24 h after which pyridine (0.97 ml, 12 mmol) was added to it. The mixture was stirred for a further 30 min after which the product was purified by flash chromatography on silica gel eluting with dichloromethane–light petroleum (1:3) to give the *title compound* **28** (0.38 g, 39%) as a deep purple solid from dichloromethane–light petroleum, mp 244–245 °C (Found: M^+, 325.8381. $C_6Cl_2N_4S_4$ requires M^+, 325.8383); ν_{max}(Nujol)/cm^{-1} 2203s (CN) and 1550w (imine); δ_C(63 MHz, DMSO) 157.2, 151.6, 147.6, 138.9, 111.7 (CN) and 105; *m*/*z* (EI) 326 (M^+, 21%), 277 (15), 233 ($M^+ - CClNS$, 10), 227 ($M^+ - CIS_2$, 12) and 201 ($M^+ - CClNS_2$, 10).

Bis[*o*-(4-chloro-1,2,3-dithiazol-5-ylideneamino)phenyl] disulfide 29

To a suspension of the chloride **1** (0.83 g, 4 mmol) in dichloromethane (40 ml) was added 2-aminobenzenethiol (0.43 ml, 4 mmol). The mixture was stirred at room temperature for 1 h after which pyridine (0.65 ml, 8 mmol) was added to it. The mixture was stirred for a further 30 min after which the product was separated by flash chromatography on silica gel eluting with dichloromethane–light petroleum (1:2) to give the *title compound* **29** (0.44 g, 64%) as yellow crystals from dichloromethane–light petroleum, mp 155–156 °C (Found: C, 36.5; H, 1.7; N, 10.5. $C_{16}H_8Cl_2N_4S_6$ requires C, 36.9; H, 1.5; N, 10.8%); ν_{max}(Nujol)/cm^{-1} 1590s, 1580m, 1570m, 1500m, 1460s, 1380s,

1300w, 1280w, 1220w, 1150s, 1130s, 1050s, 860s, 780s, 760s, 750s, 730w, 720w, 690s, 660 and 620w; δ_H(270 MHz, $CDCl_3$) 7.82–7.79 (2H, m, ArH), 7.71–7.69 (2H, m, ArH) and 7.36–7.14 (4H, m, ArH); δ_C(63 MHz, $CDCl_3$) 158.7, 147.7, 129.3, 127.6, 127.5, 127.1, 116.8 and 116.2; *m*/*z* (EI) 256 (2), 224 (7), 194 (3), 191 (25), 182 (2), 167 (3), 163 (2), 162 (9), 161 (10), 160 (100), 154 (4), 151 (4), 149 (3), 148 (7), 140 (4), 135 (3), 134 (5), 122 (4), 113 (3), 109 (2), 108 (30), 107 (2), 102 (7), 96 (10), 95 (2), 93 (3), 90 (5), 82 (9) and 64 (17).

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