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Ring transformation of (4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitriles to 3-haloisothiazole-5-carbonitriles†

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Ring transformation of readily prepared (4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitriles afford 3-haloisothiazole-5-carbonitriles in good to excellent yields. The transformation can be mediated using HBr (g), HCl (g) or $BnEt_3NCl$. Mechanisms for the transformations are discussed, together with rationalizations for the formation of side products. Furthermore, single crystal X-ray structures are provided for (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile and (*E*)-2-bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile confirming the stereochemistry of the exocyclic ethene bond.

1. Introduction

Isothiazoles find uses as pharmaceuticals, agrochemicals, stabilizers, dyes as well as electronic materials and their synthesis, chemistry and applications have been extensively reviewed.[1] Commercial isothiazoles include methylchloroisothiazolone (MCIT), a major component of the Kathon preservatives, the antibacterial sulfa drug sulfasomizole and the fungicide isotianil (Stout®) which is particularly effective against rice blast (Fig. 1).

Recent developments in pharmacologically interesting monocyclic isothiazoles include the selective Checkpoint kinase 2 inhibitor 3-hydroxyisothiazole-4-amidine **1**, which is useful as a radiation protection agent in anticancer radiotherapy,[2] while other isothiazoles inhibit tyrosine,[3] MEK-1 and MEK-2,[4] and p38α MAP kinases.[5] Some isothiazole-4-carboxamides behave as prodrugs for the treatment of cancerous and noncancerous hyperproliferative disorders,[6] while 3-methylsulfanyl-5-phenylisothiazole-4-carbonitrile (**2**) displayed antiviral activity against polio,[7] and 3-benzyloxyisothiazole-4/5-carboxylic acids (**3a** and **3b**) exerted moderate activity to protect C8166 cells from HIV-1 infection.[8] The 3,4-diarylisothiazole-5-amide **4** (ref. 9) acts as selective negative allosteric modulators (NAMs) for metabotropic glutamate receptor 5 (mGlu5) related to the treatment of chronic pain conditions, while the 5-pyrazolyl-isothiazole-3-carboxamide **5** (ref. 10) inhibits 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) for the treatment of metabolic syndrome and related disorders, which includes disorders such as type 2 diabetes, obesity and CNS disorders such as early dementia (Fig. 2).

Furthermore, interest in isothiazoles as agrochemicals continues with recent patents on antibacterial/antifungal,[11] insecticidal,[11c,12] herbicidal,[13] and plant growth regulator behavior.[14] Isothiazoles have also recently been studies as azo dyes,[15] or as dyes with high dichroism for display devices.[16]

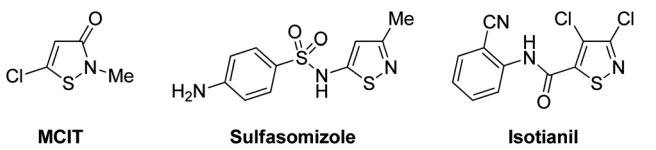

Fig. 1 Commercially important isothiazoles.

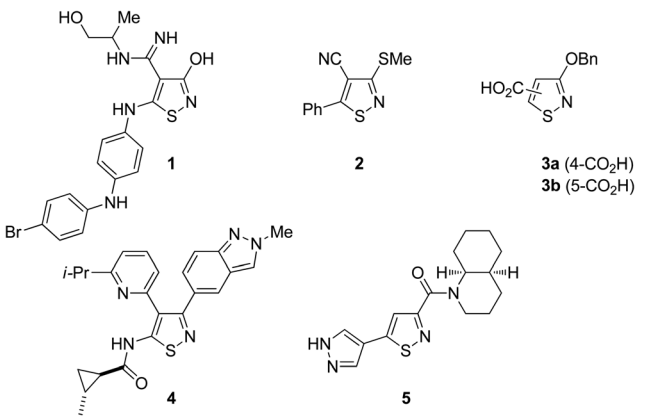

Fig. 2 Chemical structures of selected biologically active isothiazoles.

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† Electronic supplementary information (ESI) available: Copies of 1D ^1H and ^{13}C NMR spectra of all new compounds. Mass spectra for all mixtures and structure elucidation discussion for compound **27b**. CCDC 963573 and 963574. See DOI: 10.1039/c3ra47261b

Most routes to isothiazoles involve construction of the ring with the desired carbon substituents in place, as such the routes are often product specific.[1e] The availability of haloisothiazoles combined with modern transition metal-catalyzed C–C bond forming reactions enables useful nonproduct specific routes to alkyl-,[17] alkenyl-,[18] alkynyl-,[18a,b,19] aryl-,[17,18b,20] and hetaryl-substituted[17b,18b,20] isothiazoles. Furthermore, palladium catalyzed direct C–H arylation and hetarylation has recently been demonstrated on C-5 unsubstituted 3-bromoisothiazole-4-carbonitrile.[21]

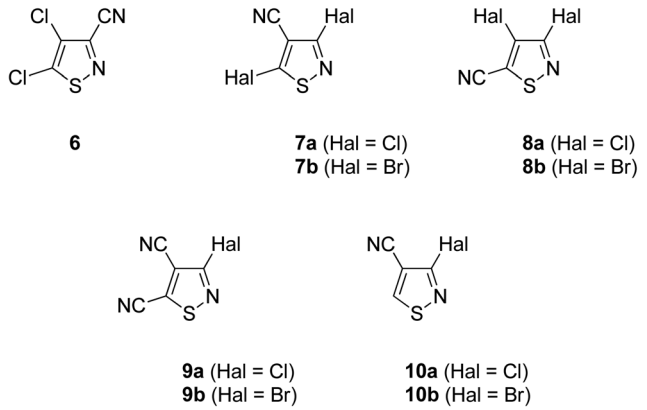


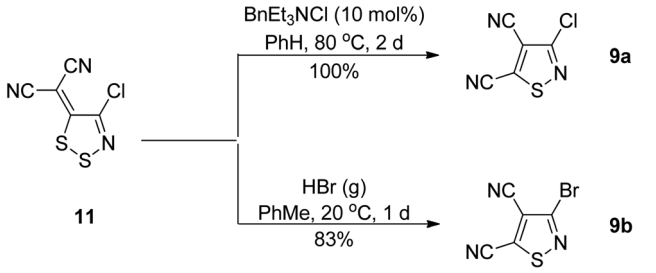
Fig. 3 Chemical structures of common haloisothiazolecarbonitriles.

Haloisothiazolecarbonitriles are a particularly useful class of compounds (Fig. 3). Nitriles can readily be transformed into a wide range of useful functional groups,[22] and activate arenes towards nucleophilic aromatic substitution, furthermore, nitriles can *ortho* direct transition metal catalysed reactions *via* coordination with the metal catalyst.[23]

Interestingly, while all three dichloroisothiazolecarbonitriles **6**,[24] **7a** (ref. 25) and **8a** (ref. 26) are known, their chemistry up until recently was limited to nucleophilic aromatic substitution of the halogen,[24,25,27] functional group transformations of the nitrile[24,25,28] and alkylation of the ring nitrogen.[29] We recently demonstrated the broader potential of these haloisothiazolecarbonitrile building blocks by carrying out a wide range of C5-regioselective transition metal catalysed reactions on 3,5-dichloro- and 3,5-dibromoisothiazole-4-carbonitriles (**7a** and **7b**, respectively)[17b,18b] and also a C-5 regioselective protodehalogenation to give the 3-chloro- and 3-bromoisothiazole-4-carbonitriles **10a** and **10b**, respectively.[30]

The methods for synthesizing isothiazolecarbonitriles such as **7a** (ref. 25) and **8a** (ref. 26, 28 and 31) often involve hazardous chemicals such as chlorine gas (TOXIC),[25,26,28,31] sodium cyanide (TOXIC),[26,28] carbon disulfide (HIGHLY FLAMMABLE)[26,28,32] or disulfur dichloride (SMELLY).[31] In the case of 3,4-dibromoisothiazole-5-carbonitrile (**8b**),[33] the need for low temperatures (−50 °C) and exotic reaction solvents such as liquid sulfur dioxide can limit the practical availability of these useful isothiazoles.

In light of this, there is a need to develop new routes to these and other potentially useful haloisothiazolecarbonitriles. A surprisingly efficient route to difficult to access cyano substituted heterocycles involves the thermal or addition of nucleophile-ring opening-ring closure (ANRORC)[34] ring transformation of carefully designed 4-chloro-5*H*-1,2,3-dithiazoles.[35]



Scheme 1 Preparation of 3-chloro- and 3-bromoisothiazole-4,5-dicarbonitriles **9a** and **9b**.

In particular *N*-substituted 1,2,3-dithiazolimines have been converted *via* thermolysis to benzothiazoles,[36] benzimidazoles,[37] thiazolopyridines[38] and benzoxazines.[39] While isothiazoles,[40] thiazoles,[41] 1,3,4-thiadiazoles[41] and heteroazine fused thiazoles,[38b] have been prepared using ANRORC type transformations.[38a] Neutral 1,2,3-dithiazolimines have also been used to prepare acyclic functionalities such as isothiocyanates[42] and thiocyanoformamides.[43]

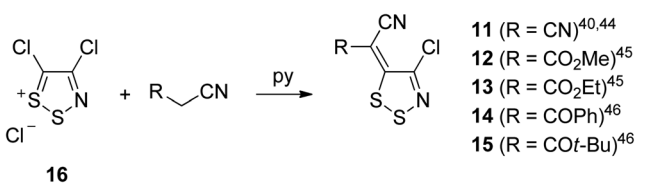
Particularly interesting was the reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)malononitrile (**11**)[40,44] with either catalytic chloride, or anhydrous HBr to give in high yield 3-chloro- or 3-bromoisothiazole-4,5-dicarbonitriles **9a** (ref. 40*a*) and **9b**,[40b] respectively (Scheme 1).

Below we describe our efforts to generalize this (dithiazolylidene)acetonitrile to isothiazole transformation and indicate several notable limitations.

2. Results and discussion

2.1. Synthesis of (dithiazolylidene)acetonitriles

The number of (dithiazolylidene)acetonitriles reported in the literature is currently very limited. The (dithiazolylidene)-malononitrile **11**,[40,44] the methyl and ethyl (dithiazolylidene)-2-cyanoacetates **12** and **13** (ref. 45*a*) and the dithiazole ketones (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4,4-dimethyl-3-oxopentanenitrile (**14**) and (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-3-oxo-3-phenylpropanenitrile (**15**)[46] have all been prepared in moderate to good yields by condensing active methylenes with 4,5-dichloro-1,2,3-dithiazolium chloride (**16**)[45] (Appel salt), followed by the addition of pyridine (2 equiv.) (Scheme 2).

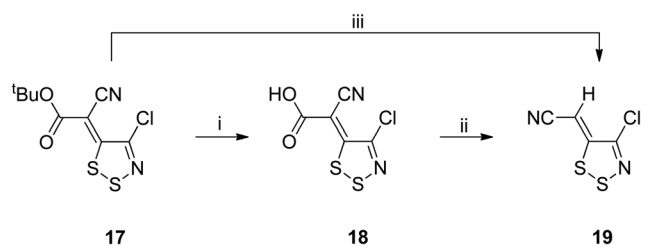


Scheme 2 Route to known (dithiazolylidene)acetonitriles **11**–**15**.

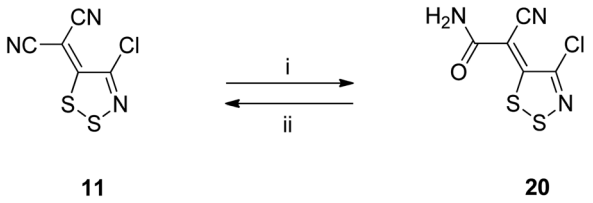
The isolation of these neutral dithiazoles on a gram scale typically involved at least one chromatographic step, however, by modifying the work-up procedures we were able to avoid chromatography. As such, the esters **12** and **13** and the ketones **14** and **15** could be isolated in multigram quantities (10 g) without the need for chromatography by following a wash sequence [acetone (2×), H_2O (1×) and MeOH (1×)]. Furthermore, the available range of (dithiazolylidene)acetonitriles was enlarged by preparing unsubstituted and halo-substituted acetonitrile analogs. The shortest route to these was considered to be *via* the hydrolysis and (halo)decarboxylation of the available methyl and ethyl esters. However, alkali hydrolysis of the esters **12** and **13** led only to decomposition of both starting dithiazoles; a strong odor of H_2S indicated reductive/hydrolytic ring cleavage. Attempted demethylation of the methyl ester using either BBr_3 in DCM (ref. 47) or NaI, TMSCl in MeCN (ref. 48) gave only recovered starting material. Nevertheless, the methyl and ethyl (dithiazolylidene)-2-cyanoacetates **12** and **13** were stable to acid (HCl 37% or TFA neat). In light of this, we prepared (*Z*)-*tert*-butyl 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetate (**17**) from *t*-butyl 2-cyanoacetate and Appel salt **16** in a chromatography free multigram (10 g) scale in 48% yield. *t*-Butyl esters are typically expected to be acid labile[49] and not surprisingly, treating the *t*-butyl (dithiazolylidene)cyanoacetate **17** with c. H_2SO_4 at *ca.* 0 °C for 5 min gave the desired (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetic acid (**18**) in 93% yield. This could then be protodecarboxylated in PhCl with TsOH·H_2O (10 mol%) heated at *ca.* 132 °C for 4 h to give (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**19**) in 87% yield. The two steps could also be performed in one pot to give the desired (dithiazolylidene)acetonitrile **19** in 94% together with a small quantity of the carboxylic acid **18** (6%) (Scheme 3).

Furthermore, the selective hydration of one cyano-group of the (dithiazolylidene)malononitrile **11** using c. H_2SO_4 at *ca.* 20 °C for 15 min gave (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetamide (**20**) in 100% yield. Attempts to independently prepare the latter from Appel salt **16** and cyanoacetamide gave a complex reaction mixture that was not resolved. Interestingly, the cyanoacetamide **20** could be dehydrated back to the malononitrile **11** on treatment with neat $POCl_3$ at *ca.* 110 °C for 4 h in 90% yield (Scheme 4).

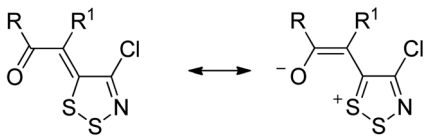
The stereochemistry of dithiazolylidenes bearing exocyclic alkenes with carbonyl functional groups has been studied by



Scheme 3 *Reagents and conditions*: (i) c. H_2SO_4, *ca.* 20 °C, 5 min, 93%; (ii) TsOH (10 mol%), PhCl, 132 °C, 4 h, 87%; (iii) TsOH (10 mol%), PhCl, 132 °C, 4 h, 94%.



Scheme 4 *Reagents and conditions*: (i) c. H_2SO_4, *ca.* 20 °C, 15 min, 100%; (ii) $POCl_3$, *ca.* 110 °C, 4 h, 90%.



Scheme 5 Resonance structures of dithiazolylidenes supporting β-carbonyl groups.

Kim *et al.*,[50] and shows the most electron rich carbonyl group to be *syn* to the dithiazole ring sulfur S-1, owing to stabilized charge separated resonance forms or "non-bonding" interactions between the carbonyl oxygen and the dithiazole (Scheme 5).

In the absence of such stabilizing interaction the stereochemistry of the new (dithiazolylidene)acetonitrile **19** was less predictable. ^{1}H NMR spectroscopy of the (dithiazolylidene)-acetonitrile **19** gave a single peak at δ_H 5.81 ppm and ^{13}C NMR spectroscopy gave four carbon signals in the range of δ_C 158.2–83.2 ppm indicating the existence of a single isomer on the NMR time scale. The stereochemistry of the (dithiazolylidene)-acetonitrile **19** was eventually determined by single crystal X-ray crystallography (Fig. 4), which showed the nitrile group to be *syn* to the ring sulfur S-1 (*i.e.*, the thermodynamically more stable stereoisomer).

Presumably, the exocyclic ethene has some single bond character owing to electron release from the dithiazole sulfur atoms towards the nitrile that could allow, under the reaction

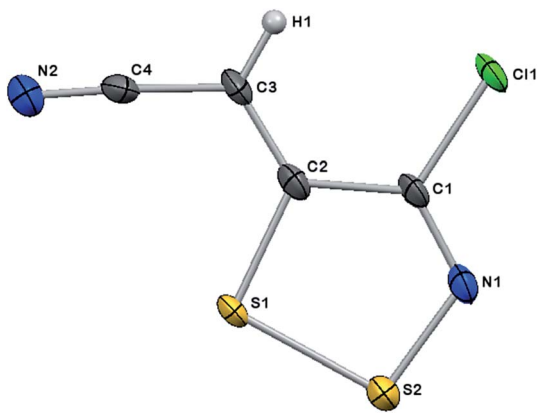


Fig. 4 Ellipsoid (probability level of 50%) representation of the crystal structure of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**19**) with crystallographic atom labelling.

Scheme 6 Resonance structures supporting rotation around the exocyclic ethane bond.

conditions, a degree of rotation and attainment of the thermodynamically most stable stereoisomer (Scheme 6).

^{13}C NMR data tentatively supports some delocalization extending between the dithiazole ring and the nitrile group since the data for the exocyclic double bond was δ_C 158.2 (*C*CHC≡N) and 83.2 ppm (*C*C≡N) indicating a relatively polarized double bond. Nevertheless, an analysis of the bond lengths obtained from the single crystal X-ray structure showed that the C(2)–C(3) and C(1)–N(1) bonds [1.344(5) and 1.277(5) Å, respectively] had pronounced double bond character (typical C=C and C=N bond lengths are 1.34 Å and 1.29 Å, respectively) while the C(1)–C(2) and C(3)–C(4) bonds [1.456(5) and 1.413(5) Å, respectively] were shorter than a typical single C–C bond (1.54 Å) and closer to the bond length associated with an aromatic C–C bond (1.40 Å). The C(2)–S(1) bond (1.729 Å) are midway between a typical C–S single (1.82 Å) and C=S double (1.60 Å) bond. While this data is somewhat contradictory, it is worthy of note that single crystal X-ray data provides bond lengths and angles for the molecule in the solid state and this may not reflect accurately the situation of the compound in solution.

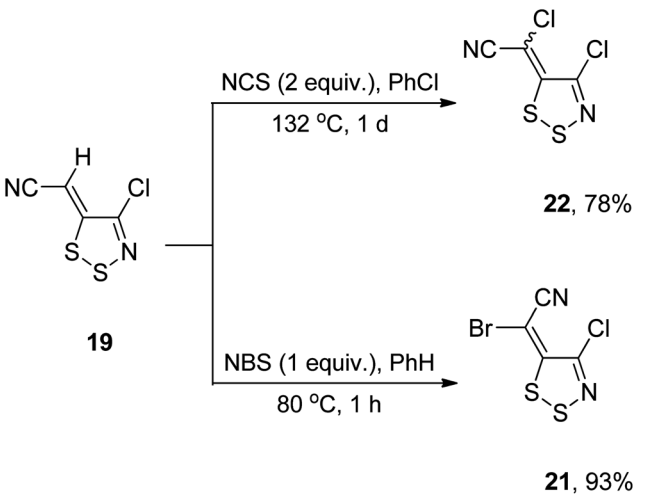
Having successfully prepared the (dithiazolylidene)acetonitrile **19**, the synthesis of the halogenated derivatives was pursued. Treatment of the ylidene **19** with *N*-bromosuccinimide (1 equiv.) in PhH heated at reflux, gave (*E*)-2-bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**21**) in 93% yield while the chlorination reaction needed more vigorous conditions. As such, treating the ylidene **19** with *N*-chlorosuccinimide (2 equiv.) in PhCl heated at reflux, gave 2-chloro-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**22**) in 78% yield (Scheme 7). Attempts to prepare the 2-iodo(dithiazolylidene)acetonitrile from dithiazolylidene **19** and *N*-iodosuccinimide led only to the recovery of unreacted starting dithiazole **19**.

Owing to the difficulty of obtaining single crystals of the chloro(dithiazolylidene)acetonitrile **22** the stereochemistry of the exocyclic C=C bond could not be verified. Single crystal X-ray crystallography of the bromo(dithiazolylidene)acetonitrile **21**, however, indicated the nitrile group to be *anti* to the ring sulfur S-1 (Fig. 5). This orientation presumably avoided the steric clash between the bromo and the C-4 chlorine substituents.

The stereochemical information deduced from the substituted (dithiazolylidene)acetonitriles **17**, **19** and **21** supported that the stereochemistry of the exocyclic C=C bond can change. The dithiazole ester **17** has an *anti* orientation with respect to the nitrile group and the ring sulfur atom S-1, however, decarboxylation to afford the (dithiazolylidene)acetonitrile **19** leads to *syn* stereochemistry, while subsequent bromination switches the stereochemistry back to *anti* (Scheme 8).

2.2. Reactions with HBr (g) and HCl (g)

Having access to a number of (dithiazolylidene)acetonitriles, we then investigated their transformations into isothiazoles. The (dithiazolylidene)acetonitriles were treated with either HBr (g) or HCl (g) to investigate their transformation into 3-bromo- or 3-chloroisothiazole-5-carbonitriles, respectively (Table 1). Initially, two different reaction set ups were used: the first involved briefly (30 s) purging a stirred solution of the dithiazole with gaseous HBr or HCl and then leaving the reaction to stir at



Scheme 7 Preparation of 2-bromo and 2-chloro(dithiazolylidene) acentonitriles **21** and **22**.

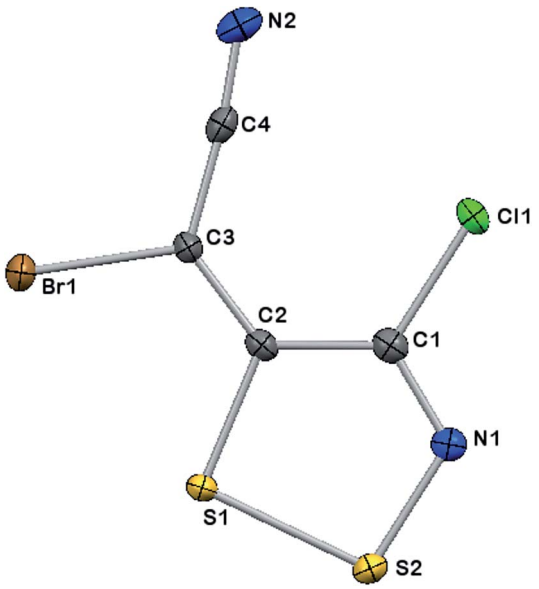
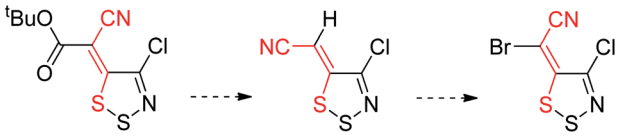


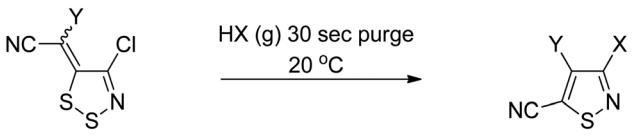
Fig. 5 Ellipsoid (probability level of 50%) representation of the crystal structure of (*E*)-2-bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene) acetonitrile (**21**) with crystallographic atom labelling.



17, *anti* **19**, *syn* **21**, *anti*

Scheme 8 Stereochemical changes on transforming dithiazole **17** into **21**.

Table 1 Reaction of (dithiazolylidene)acetonitriles with HCl (g) or HBr (g) in either Et_2O or THF at *ca.* 20 °C to give 3-chloro or 3-bromo-isothiazole-5-carbonitriles, respectively



11-13,19,21,22 **8,9,24-26**

Entry	Dithiazole	Y	X	Solvent	Time	Yield (%)
1	**19**	H	Br	Et_2O	10 min	**24b** (82)
2	**19**	H	Br	THF	5 min	**24b** (97)
3	**19**	H	Cl	Et_2O	48 h	**24a** (59)
4	**19**	H	Cl	THF	3 h	**24a** (84)
5	**21**	Br	Br	Et_2O	10 min	**8b** (83)
6	**21**	Br	Br	THF	5 min	**8b** (18) + **24b** (50)
7	**21**	Br	Cl	Et_2O	24 h	Mix[a] + **24a** (34)
8	**21**	Br	Cl	THF	5 h	Mix[a] + **24a** (68)
9	**22**	Cl	Br	Et_2O	10 min	Mix[b]
10	**22**	Cl	Br	THF	10 min	Mix[c] + **24b** (15)
11	**22**	Cl	Cl	Et_2O	48 h	**8a** (64)
12	**22**	Cl	Cl	THF	24 h	**8a** (45)
13	**12**	CO_2Me	Br	Et_2O	5 h	**25b** (78)
14	**12**	CO_2Me	Br	THF	24 h	**25b** (71)
15	**12**	CO_2Me	Cl	Et_2O	24 h	nr[d]
16	**12**	CO_2Me	Cl	THF	18 h	nr[d]
17	**13**	CO_2Et	Br	Et_2O	2 h	**26b** (87)
18	**13**	CO_2Et	Br	THF	48 h	**26b** (65)
19	**13**	CO_2Et	Cl	Et_2O	24 h	nr[d]
20	**13**	CO_2Et	Cl	THF	18 h	nr[d]
21	**11**	CN	Br	Et_2O	1 h	**9b** (65)
22	**11**	CN	Br	THF	5 min	**9b** (96)
23	**11**	CN	Cl	Et_2O	72 h	**9a** (50)
24	**11**	CN	Cl	THF	20 h	**9a** (55)

[a] Inseparable mixture of 3,4-dichloroisothiazole-5-carbonitrile (**8a**), 3,4-dibromoisothiazole-5-carbonitrile (**8b**), 3-bromo-4-chloroisothiazole-5-carbonitrile (**27b**) and an **unknown** compound (by ^{13}C NMR). [b] Inseparable mixture of 3,4-dibromoisothiazole-5-carbonitrile (**8b**) and 3-bromo-4-chloroisothiazole-5-carbonitrile (**27b**) (**8b** : **27b** = 1 : 3 by NMR). [c] Inseparable mixture of 3,4-dibromoisothiazole-5-carbonitrile (**8b**) and 3-bromo-4-chloroisothiazole-5-carbonitrile (**27b**) (**8b** : **27b** = 1 : 9 by NMR). [d] nr = no reaction, recovered starting dithiazoles (>82%).

ca. 20 °C, while the second involved stirring a solution of the dithiazolylidene under an atmosphere of HBr (g) or HCl (g). While both sets of conditions led, in most cases, to the conversion of the dithiazolylidenes into the desired isothiazoles and some elemental sulfur, the procedure involving the purge gave higher yields. Furthermore, the choice of solvent was critical; presumably this was attributed to solubility issues, both of the anhydrous hydrogen halides and of the starting dithiazolylidenes.

Early investigations on the conversion of the (dithiazolylidene)malononitrile **11** into 3-chloro- or 3-bromoisothiazole-4,5-dicarbonitrile (**9a**)[40a] and (**9b**),[40b] using HCl (g) or HBr (g), respectively determined that while DCM and aromatic solvents such as PhH, PhMe, xylene and PhCl were suitable for use with HBr (g) these solvents were not suitable with the use of HCl (g).[38a,40b] The reported solubilities of the two gases in organic solvents show that in general HBr is more soluble than HCl and solubilities are much greater in ether solvents.[51] As such, we pursued the use of ethers as solvents for performing this transformation.

Furthermore, the use of dry solvents and glassware improved the product yields, which was not altogether surprising, since the nitrile substituent at the isothiazole C-5 position was highly electrophilic and susceptible to hydration.[52] In particular, performing the reaction of the (dithiazolylidene)malononitrile **11** with HBr (g) in wet toluene led to isolation of 3-bromoisothiazole-4,5-dicarbonitrile (**9b**) and 3-bromo-4-cyanoisothiazole-5-carboxamide (**23**) in 39 and 35% yields, respectively indicating partial hydration of the isothiazole **9b** under the reaction conditions. The carboxamide **23** could be also synthesised independently from reaction of the dicyanoisothiazole **9b** with NaOH in dioxane is 90% yield.

In most cases, the reactions carried out in THF led to faster consumption of the starting (dithiazolylidene)acetonitriles, the notable exceptions were the reactions of the methyl and ethyl (dithiazolylidene)-2-cyanoacetates **12** and **13** with HBr (g) which required more time in THF than in Et_2O, and in these cases (entries 13, 14, 17 and 18), the yields of isothiazoles were higher in the reactions with the shortest reaction times. Furthermore, in nearly all cases, shorter reaction times correlated with higher isothiazole yields and the use of THF as solvent. The exception to this was the reaction of the 2-chloro(dithiazolylidene)acetonitrile **22** with HCl (g) which consistently gave a higher yield of 3,4-dichloroisothiazole-5-carbonitrile (**8a**) in Et_2O than in THF (64 *vs.* 45%) despite a significantly longer reaction time (48 *vs.* 24 h) (entries 11 and 12). In several cases, the ring transformation proceeded in excellent and synthetically useful yields: the unsubstituted (dithiazolylidene)acetonitrile **19** with HCl (g) or HBr (g) gave the corresponding 3-chloro- and 3-bromoisothiazole-5-carbonitriles **24a** (84%) and **24b** (97%), respectively (entries 4 and 2), the 2-bromo(dithiazolylidene)acetonitrile **21** with HBr (g) in Et_2O gave 3,4-dibromoisothiazole-5-carbonitrile (**8b**) in 83% yield (entry 5), while the methyl and ethyl 3-bromo-5-cyanoisothiazole-4-carboxylates **25b** and **26b** could be isolated from THF in 78 and 87% yields, respectively (entries 13 and 17) and 3-bromoisothiazole-4,5-dicarbonitrile **9b** in 96% yield (entry 22). Although not shown in Table 1, we were surprised to see no reaction of the dithiazole ketones **14** and **15**, the (dithiazolylidene)cyanoacetic acid **18** or the

(dithiazolylidene)cyanoacetamide **20** with either HBr (g) or HCl (g) in either Et_2O or THF; in all cases the starting dithiazoles were recovered in over 80% yields from these reactions.

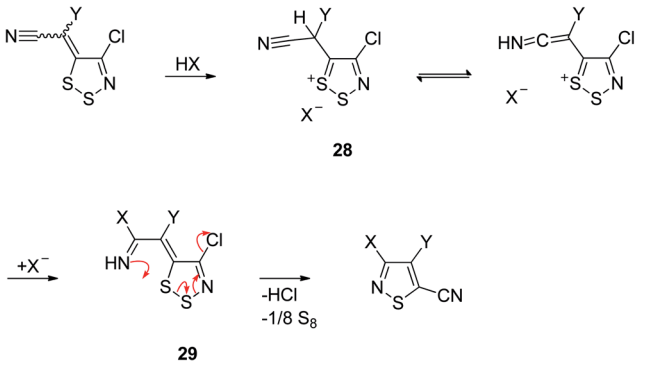
Nevertheless, the reactions that led to mixtures of isothiazoles were also informative: the reaction of the 2-bromo(dithiazolylidene)acetonitrile **21** with HBr (g) in THF led to a separable mixture of the desired 3,4-dibromoisothiazole-5-carbonitrile (**8b**) (18%) and also the protodehalogenated 3-bromoisothiazole-5-carbonitrile (**24b**) (50%) (entry 6). The reaction of the 2-bromo(dithiazolylidene)acetonitrile **21** with HCl (g) in both Et_2O and THF (entries 7 and 8, respectively) gave as major product 3-chloroisothiazole-5-carbonitrile (**24a**) together with an inseparable mixture of 3,4-dichloroisothiazole-5-carbonitrile (**8a**), 3,4-dibromoisothiazole-5-carbonitrile (**8b**), 3-bromo-4-chloroisothiazole-5-carbonitrile (**27b**) and an **unknown** product, as judged by ^{13}C NMR spectroscopy and mass spectrometry (see ESI†).

The reaction of 2-chloro(dithiazolylidene)acetonitrile **22** with HBr (g) in either Et_2O or THF (entries 9 and 10), led to inseparable mixtures of 3,4-dibromo- and 3-bromo-4-chloroisothizole-5-carbonitriles **8b** and **27b** in a 1 : 3 ratio when the reaction was performed in Et_2O. The reaction in THF gave 3-bromoisothizole-5-carbonitrile (**24b**) along with an inseparable mixture of 3,4-dibromo- and 3-bromo-4-chloroisothizole-5-carbonitriles **8b** and **27b** in a 1 : 9 ratio. The identity of the products from these inseparable mixtures (entries 7–10) were tentatively deduced by NMR and MS while the ratios were crudely deduced from ^{13}C NMR spectroscopy by increasing the relaxation time ($D1 = 6$ s) and integrating the fully relaxed signals. The identity of isothiazole **27b** was based on a fragmentation analysis of a low resolution electron impact GC-MS of the mixture from entry 9 (see ESI†) and its presence in other mixtures was supported by ^{13}C NMR spectroscopy. The reactions above (entries 6–10) indicate that both protodehalogenation and halogen scrambling can occur.

2.3. Mechanistic rationale

Tentatively, we propose that initially the dithiazolylidenes protonate to give the dithiazoliums **28**, thus allowing free rotation around the exocyclic ylidene. The ^{13}C NMR data suggests considerable electron density is concentrated at the alkene terminus [δ_C *C*-5 155.1–158.2 and $C(CN)_2$ 74.6–90.5 ppm] assisted by the electron release of the dithiazole ring sulfurs. The dithiazolium salt is presumably in equilibrium with its ketenimine prototautomer which can trap the halide to give the neutral imine **29**. Subsequent intramolecular cyclisation onto the dithiazole S-1 ring sulfur is followed by a concomitant ring cleavage and loss of HCl and elemental sulfur presumably *via* a sulfur chain extension mechanism.[53] The reaction is potentially thermo-dynamically driven owing to the formation of a new stable nitrile bond (Scheme 9).

Tentatively, the side reactions that were observed with the 2-halo(dithiazolylidene)acetonitriles **21** (Hal = Br) and **22** (Hal = Cl), which included protodehalogenation (Table 1, entries 6–8 and 10) at the isothiazole C-4 position or halogen exchange (Table 1, entries 7–10), support this mechanism. It was clear,



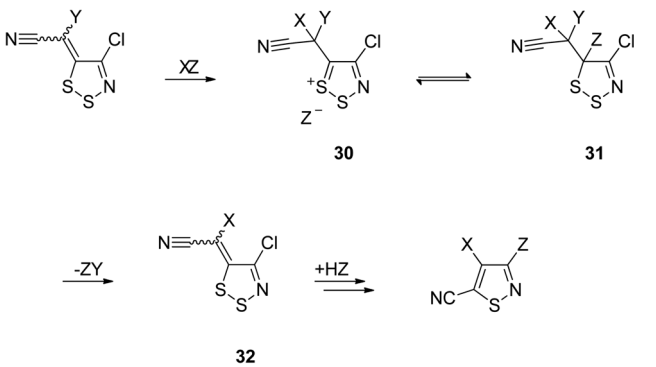
Scheme 9 General mechanism for the ring transformation of dithiazoles to give isothiazoles.

however, that these reactions were occurring prior to the formation of the isothiazoles since the 3,4-dihaloisothiazole-5-carbonitriles **8a** (Hal = Cl) and **8b** (Hal = Br) were stable to either HCl (g) or HBr (g), in dry THF at *ca.* 20 °C for 20 h. As such, we propose that the dithiazolylidenes capture not only protons but also electrophilic halogen, particularly bromine, at the terminus of the exocyclic alkene to give either species such as the dithiazolium **30** which can either equilibrate to its neutral form **31** and loose ZY to afford a new dithiazolylidene **32** (Scheme 10).

The elimination of ZY could be assisted by electron release from the ring sulfurs or by X-philic[54] attack by an external halide (*e.g.*, Z). Since bromine substituents are more prone to X-philic attack than chlorine substituents[54] then this could explain why protodebromination was more prevalent than protodechlorination. Furthermore, worthy of note was that HBr in the presence of light or oxygen can oxidize to Br_2,[55] while HCl under similar conditions was considerably more stable leading to more protodehalogenation than halogen exchange than HBr (Scheme 10).

2.4. Reactions with chloride

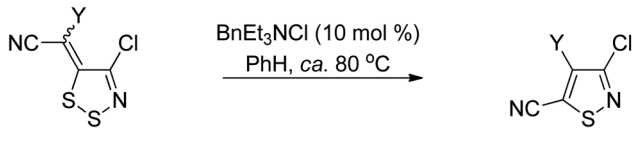
The (dithiazolylidene)acetonitrile to 3-haloisothiazole-5-carbonitrile conversion can also be triggered with catalytic



Scheme 10 Y = H or Hal, X = Z = Hal or X = H, Z = Hal.

chloride,[40a] as such we investigated the transformation further by treating all the new (dithiazolyliedene)acetonitriles with $BnEt_3NCl$ (10 mol%) in dry benzene, heated to reflux; analogous conditions to those reported for the quantitative conversion of the (dithiazolylidene)malononitrile **11** to 3-chloroisothiazole-4,5-dicarbonitrile (**9a**).[40a] Reaction of the ethyl (dithiazolylidene)cyanoacetate **13** pleasingly gave ethyl 3-chloro-5-cyanoisothiazole-4-carboxylate (**26a**) in 67% yield, however, the methyl (dithiazolylidene)cyanoacetate **12** reacted more slowly and gave only a trace of what appeared to be isothiazole **25a**. Tentatively, we believe this difference in reactivity was attributed to possible demethylation of the ester by chloride under the reaction conditions and subsequent degradation of the carboxylic acid formed. Unfortunately, treating the available (dithiazolylidene)cyanoacetic acid **18** with $BnEt_3NCl$ (10 mol%) in PhH heated at reflux led to a complex reaction mixture from which the protodecarboxylated dithiazole **19** could be observed (by TLC). Reactions of the 2-unsubstituted, 2-bromo- and 2-chloro-(dithiazolylidene)acetonitriles **19**, **21** and **22** gave a complex mixture of products. From the 2-unsubstituted (dithiazolylidene)acetonitrile **19** only a trace of 3-chloroisothiazole-5-carbonitrile (**24a**) was isolated, while reaction of the 2-chloro(dithiazolylidene)acetonitrile **22** fortunately gave 3,4-dichloroisothiazole-5-carbonitrile (**8b**) in a useful 63% yield. The 2-bromo(dithiazolylidene)acetonitrile **21**, however, gave a mixture of 3,4-dichloro- and 3-bromo-4-chloroisothiazole-5-carbonitriles **8a** and **27b** in a 1 : 2 ratio as judged by integration of ^{13}C NMR spectra obtained with a long *D*1 relaxation time (6 s) (Table 2). The ketones **14**, **15** and the carboxamide **20** were unreactive to the reaction conditions.

Table 2 Reaction of (dithiazolydene)acetoniriles with $BnEt_3NCl$ (10 mol%) in dry PhH heated at *ca.* 80 °C to give 3-chloroisothiazole-5-carbonitriles



11-13,19,21,22 **8a,9a,26a**

Entry	Dithiazole	Y	Time (h)	Yield (%)
1	**19**	H	0.5	[a]
2	**21**	Br	7	[b]
3	**22**	Cl	7	**8a** (63)
4	**12**	CO_2Me	72	[c]
5	**13**	CO_2Et	48	**26a** (67)
6	**11**	CN	48	**9a** (100)

[a] Complex reaction mixture with only a trace of 3-chloroisothiazole-5-carbonitrile (**24a**) by TLC. [b] Inseparable mixture of 3,4-dichloroisothizole-5-carbonitrile (**8a**) and 3-bromo-4-chloroisothiazole-5-carbonitrile (**27b**) (**8a** : **27b** = 1 : 2 by NMR). [c] Degradation, only intractable baseline on TLC.

3. Conclusions

The ring transformation of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitriles into 3-haloisothiazole-5-carbonitriles using HBr (g) or HCl (g) successfully led to the preparation of useful isothiazoles: 3-bromo- and 3-chloroisothiazole-5-carbonitriles were prepared in 97 and 84% yields, respectively, 3,4-dibromoisothiazole-5-carbonitrile in 83% yield, methyl and ethyl 3-bromo-5-cyanoisothiazole-4-carboxalates in 78 and 87% yields, respectively and 3-bromoisothiazole-4,5-dicarbonitrile in 96% yield. Side reactions that lead to protodehalogenation or halogen scrambling have been observed and partially rationalized. The complementary ring transformation using catalytic $BnEt_3NCl$ (10 mol%) was also extended to provide 3,4-dichloroisothiazole-5-carbonitrile and ethyl 3-chloro-5-cyanoisothiazole-4-carboxylates in moderately good yields 63 and 67%, respectively.

4. Experimental

4.1. General procedures

Anhydrous Na_2SO_4 was used for drying organic extracts and all volatiles were removed under reduced pressure. All reaction mixtures and column eluents were monitored by TLC using commercial glass backed thin layer chromatography (TLC) plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. The technique of dry flash chromatography was used throughout for all non-TLC scale chromatographic separations using Merck Silica Gel 60 (less than 0.063 mm). Melting points were determined using a PolyTherm-A, Wagner & Munz, Koefler – Hotstage Microscope apparatus or were determined using a TA Instruments DSC Q1000 with samples hermetically sealed in aluminium pans under an argon atmosphere; using heating rates of 5 °C min^{-1} (DSC mp listed by *onset* and *peak* values). Solvents used for recrystallization are indicated after the melting point. UV spectra were obtained using a Perkin-Elmer Lambda-25 UV/vis spectrophotometer and inflections are identified by the abbreviation "inf". IR spectra were recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer with Pike *Miracle* Ge ATR accessory and strong, medium and weak peaks are represented by s, m and w respectively. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 machine (at 500 and 125 MHz, respectively). Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. ^{13}C NMR multiplicity assignments were determined using APT or DEPT NMR experiments. Low resolution (EI) mass spectra were recorded on a Shimadzu Q2010 GCMS with direct inlet probe or on a Micromass AutoSpec machine at 70 eV, while ESI-APCI+ mass spectra were recorded on a Model 6110 Quadrupole MSD, Agilent Technologies. 2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene) malononitrile (**11**)[44] and 4,5-dichloro-1,2,3-dithiazolium chloride (**16**)[45] were prepared according to literature procedures.

4.2. Preparation of dithiazolylidenes

4.2.1. (*Z*)-*tert*-Butyl 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetate (17). To a stirred suspension of

4,5-dichloro-1,2,3-dithiazolium chloride (**16**) (20.85 g, 100 mmol) in DCM (160 mL) was added *tert*-butyl 2-cyanoacetate (14.12 g, 100 mmol) and the reaction mixture was stirred at *ca.* 20 °C for 4 h. Pyridine (16.16 mL, 200 mmol) was then added and the reaction mixture was stirred for another 2 h. The solvent was then evaporated and acetone (20 mL) was added to form a suspension which was filtered and washed with H_2O (2 × 20 mL) and MeOH (20 mL) and then dried (Na_2SO_4) to afford the *title compound* **17** (13.28 g, 48%) as yellow plates, (DSC) mp onset: 164.5 °C, peak max: 173.4 °C, decomp. onset: 178.9 °C, peak max: 180.6 °C (from cyclohexane); R_f 0.54 (*n*-hexane–DCM, 1 : 1); (found: C, 39.07; H, 3.36; N, 10.29. $C_9H_9ClN_2O_2S_2$ requires C, 39.06; H, 3.28; N, 10.12%); λ_{max} (DCM)/nm 414 inf (log ε 3.15), 432 (3.21), 454 inf (3.01); ν_{max}/cm^{-1} 3003w, 2990w and 2941w (CH_3), 2208m (C≡N), 1648s (C=O), 1479m, 1473m, 1456w, 1449w, 1391w, 1375w, 1370w, 1307s, 1257m, 1228m, 1154s, 1110m, 964w, 950w, 880m, 844m, 835s, 792m, 769m; δ_H (500 MHz; $CDCl_3$) 1.59 [9H, s, C(CH_3)$_3$]; δ_C (125 MHz; $CDCl_3$) 166.6 (s), 161.9 (s), 144.4 (s), 113.4 (s), 92.8 (s), 84.9 (s), 28.0 (q); *m*/*z* (EI) 278 (M^+ + 2, 8%), 276 (M^+, 21), 222 (40), 220 (92), 203 (21), 185 (83), 114 (7), 110 (6), 99 (7), 82 (10), 64 (15), 57 (100).

4.2.2. (*Z*)-2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetic acid (18). To a sample of (*Z*)-*tert*-butyl 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetate (**17**) (100 mg, 0.361 mmol) was added conc. H_2SO_4 (3 mL) at *ca.* 0 °C and the reaction mixture was stirred at this temperature until no starting material remained (TLC, 5 min). The mixture was poured onto ice and the yellow precipitate that formed was isolated by filtration to give the *title compound* **18** (41 mg, 52%). The filtrate was extracted with EtOAc (3 × 10 mL) and the organic phase was then dried (Na_2SO_4) and evaporated to afford a further quantity of the title compound **18** (32 mg, 41%, total yield 93%) as yellow-orange cubes, mp 151–152 °C (from PhCl); R_f 0.35 (*n*-hexane–DCM, 1 : 1); (found: C, 27.19; H, 0.51; N, 12.87. $C_5HClN_2O_2S_2$ requires C, 27.22; H, 0.46; N, 12.70%); λ_{max} (EtOH)/nm 416 inf (log ε 3.09), 430 (3.13), 447 inf (3.99); ν_{max}/cm^{-1} 3038w, 2942w, 2825w, 2657w, 2531w, 2224m (C≡N), 1643m (C=O), 1467m, 1442w, 1414s, 1270s, 1229s, 1180w, 1126w, 1112m, 1037w, 1009w, 958w, 945w, 876s, 827s, 772w, 767w, 731s; δ_C (125 MHz; DMSO-d_6) 168.7 (s), 163.9 (s), 142.9 (s), 114.9 (s), 88.6 (s); *m*/*z* (EI) 222 (M^+ + 2, 12%), 220 (M^+, 29), 187 (9), 185 (100), 178 (3), 176 (7), 115 (12), 93 (22), 82 (25), 77 (23), 70 (22), 64 (38), 56 (7).

4.2.3. (*Z*)-2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (19)

4.2.3.1. Method 1, via decarboxylation of (Z)-2-(4-chloro-5H-1,2,3-dithiazol-5-ylidene)-2-cyanoacetic acid (18). To a stirred solution of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetic acid (**18**) (400 mg, 1.81 mmol) in PhCl (20 mL) at *ca.* 20 °C, TsOH·H_2O (9.5 mg, 10 mol%) was added and the reaction was heated to *ca.* 132 °C. The mixture was kept at *ca.* 132 °C until no starting material remained (TLC) and then allowed to cool to *ca.* 20 °C. The mixture was then adsorbed onto silica and chromatography (*n*-hexane–DCM, 6 : 4) gave (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**19**) (348 mg, 87%) as yellow needles, mp 113–114 °C (from cyclohexane); R_f 0.43 (*n*-hexane–DCM, 6 : 4); (found: C, 27.29; H, 0.52; N, 15.82. $C_4HClN_2S_2$ requires C, 27.20; H, 0.57; N, 15.86%); λ_{max} (DCM)/nm 304 (log ε 2.31), 389 (3.07); ν_{max}/cm^{-1} 3077w and 3035w (CH), 2205s (C≡N), 1534s, 1505w, 1497w, 1367w, 1280w, 1262w, 1177s, 882s, 874m, 794, 749m; δ_H (500 MHz; $CDCl_3$) 5.82 (1H, s, C*H*); δ_C (125 MHz; $CDCl_3$) 158.2 (s), 144.0 (s), 117.8 (s), 83.3 (d); *m*/*z* (EI) 178 (M^+ + 2, 43%), 176 (M^+, 100), 141 (5), 115 (60), 105 (6), 102 (4), 95 (15), 93 (38), 88 (10), 83 (34), 76 (9), 70 (21), 64 (40), 57 (8), 51 (10).

4.2.3.2. Method 2, via one-pot saponification–proto-decarboxylation of (Z)-tert-butyl 2-(4-chloro-5H-1,2,3-dithiazol-5-ylidene)-2-cyanoacetate (17). To a stirred solution of (*Z*)-*tert*-butyl 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetate (**17**) (500 mg, 1.81 mmol) in PhCl (20 mL) at *ca.* 20 °C, TsOH·H_2O (9.5 mg, 10 mol%) was added and the reaction was heated to *ca.* 132 °C. During the heating a yellow-orange precipitate was formed which was later dissolved. The mixture was kept at *ca.* 132 °C until no starting material remained (TLC) and allowed to cool to *ca.* 20 °C. Filtration and wash (DCM) gave (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetic acid (**18**) (24 mg, 6%) as yellow-orange cubes, mp 151–152 °C (from PhCl); R_f 0.35 (*n*-hexane–DCM, 1 : 1); identical to that described above. The filtrate was adsorbed onto silica and chromatography (*n*-hexane–DCM, 6 : 4) gave (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**19**) (300 mg, 94%) as yellow needles, mp 113–114 °C (from cyclohexane); R_f 0.43 (*n*-hexane–DCM, 6 : 4); identical to that described above.

4.2.4. (*E*)-2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetamide (20). To 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene) malononitrile (**11**) (100 mg, 0.496 mmol) was added conc. H_2SO_4 (4 mL) and the reaction mixture was stirred at *ca.* 20 °C until no starting material remained (TLC). The mixture was poured onto ice and extracted with Et_2O (3 × 20 mL). The organic layer was dried (Na_2SO_4) and evaporated to afford the *title compound* **20** (109 mg, 100%) as yellow needles, (DSC) mp onset: 213.8 °C, peak max: 223.4 °C, decomp. onset: 230.8 °C, peak max: 231.8 °C (from PhH); R_f 0.78 (*t*-BuOMe); (found: C, 27.46; H, 0.87; N, 19.21. $C_5H_2ClN_3OS_2$ requires C, 27.34; H, 0.92; N, 19.13%); λ_{max} (DCM)/nm 207 (log ε 3.10), 217 inf (3.00), 241 inf (2.60), 258 inf (2.51), 276 inf (2.30), 414 inf (3.00), 430 (3.07), 443 inf (2.95); ν_{max}/cm^{-1} 3408br, 3329br, 3265br and 3206br (NH), 2195m (C≡N), 1667s (C=O), 1599m, 1470m, 1458m, 1391m, 1233s, 1111s, 1049w, 879s, 825s, 764s; δ_H (500 MHz; DMSO-d_6) 7.97 (1H, s, NH_2), 7.57 (1H, s, NH_2); δ_C (125 MHz; DMSO-d_6) 166.5 (s), 160.8 (s), 142.3 (s), 115.3 (s), 90.4 (s); *m*/*z* (EI) 219 (M^+, 19%), 203 (3), 184 (100), 176 (5), 149 (3), 115 (12), 93 (8), 82 (14), 77 (22), 70 (12), 64 (20).

4.2.5. Conversion of (*E*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetamide (20) to 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)malononitrile (11). To (*E*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetamide (**20**) (44 mg, 0.20 mmol) was added $POCl_3$ (1 mL) and the mixture heated to *ca.* 110 °C. The reaction mixture was kept at *ca.* 110 °C until no starting material remained (TLC, 4 h), then allowed to cool to *ca.* 20 °C and the volatiles evaporated *in vacuo*. The mixture was then adsorbed into silica and chromatography (DCM) of the residue gave 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)malononitrile (**11**) (36 mg, 90%) as orange crystals, mp 178–179 °C (ref. 40*a*, 181–182 °C) (from cyclohexane); R_f 0.37 (DCM); ν_{max}/cm^{-1} 2219s and

2189w (C≡N), 1457s, 1249w, 1142m, 941m, 891m, 810m, 722w; δ_C (125 MHz; $CDCl_3$) 167.3 (s), 143.2 (s), 115.6 (s), 110.4 (s), 67.3 (s); identical to an authentic sample.[40a]

4.2.6. (*Z*)-2-Bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-acetonitrile (21). To a stirred solution of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**19**) (300 mg, 1.70 mmol) in PhH (15 mL) at *ca.* 20 °C, *N*-bromosuccinimide (302.6 mg, 1.70 mmol) was added and the reaction was heated to *ca.* 80 °C. The mixture was kept at *ca.* 80 °C until no starting material remained (TLC), then allowed to cool to *ca.* 20 °C and adsorbed on silica. Chromatography (*n*-hexane–DCM, 6 : 4) gave the *title compound* **21** (404 mg, 93%) as yellow needles, mp 176–177 °C (from cyclohexane); R_f 0.47 (*n*-hexane–DCM, 1 : 1); (found: C, 19.03; N, 10.94. $C_4BrClN_2S_2$ requires C, 18.80; N, 10.96%); λ_{max} (DCM)/nm 256 (log ε 2.69), 291 (2.09), 400 (3.11); ν_{max}/cm^{-1} 2192s (C≡N), 1513s, 1486w, 1195s, 1156w, 1057w, 1021w, 894s, 845m, 811w, 770s; δ_C (125 MHz; $CDCl_3$) 157.6 (s), 138.8 (s), 113.8 (s), 74.6 (s); *m*/*z* (EI) 258 (M^+ + 2, 49%), 257 (M^+ + 1, 11), 256 (M^+, 100), 254 (98), 221 (2), 195 (18), 193 (17), 177 (29), 175 (71), 163 (6), 161 (6), 114 (35), 93 (11), 82 (12), 70 (8), 64 (7).

4.2.7. 2-Chloro-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-acetonitrile (22). To a stirred solution of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**19**) (300 mg, 1.70 mmol) in PhCl (15 mL) at *ca.* 20 °C, *N*-chlorosuccinimide (454 mg, 3.40 mmol) was added and the reaction was heated to *ca.* 132 °C. The mixture was kept at *ca.* 132 °C until no starting material remained (TLC), then allowed to cool to *ca.* 20 °C and adsorbed on silica. Chromatography (*n*-hexane–DCM 6 : 4) gave the title compound **22** (279.8 mg, 78%) as yellow needles, mp 164–165 °C (ref. 46, 166–168 °C) (from cyclohexane); R_f 0.47 (*n*-hexane–DCM, 1 : 1); (found: C, 22.83; N, 13.18. $C_4Cl_2N_2S_2$ requires C, 22.76; N, 13.27%); λ_{max} (DCM)/nm 255 (log ε 2.62), 293 (2.14), 396 (3.10); ν_{max}/cm^{-1} 2201s (C≡N), 1518s, 1488w, 1204s, 1164w, 1087w, 1074w, 1034w, 913w, 901m, 882w, 862m, 815w, 782s; δ_C (125 MHz; $CDCl_3$) 155.1 (s), 139.3 (s), 113.1 (s), 90.5 (s); *m*/*z* (EI) 214 (M^+ + 4, 17%), 212 (M^+ + 2, 71), 210 (M^+, 100), 177 (8), 175 (18), 151 (19), 149 (44), 117 (26), 114 (15), 105 (28), 93 (67), 82 (55), 79 (39), 76 (22), 70 (55), 64 (66).

4.3. Reactions of (dithiazolylidene)acetonitriles with HBr (g) or HCl (g)

4.3.1. 3,4-Dichloroisothiazole-5-carbonitrile (8a): typical procedure, Table 1, entry 11. A stirred solution of 2-chloro-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**22**) (212 mg, 1.00 mmol) in Et_2O (10 mL) at *ca.* 20 °C was purged with HCl (g) for 30 s. The mixture was stirred until the starting material was consumed (TLC). The reaction mixture was then adsorbed onto silica and chromatographed (*n*-hexane–DCM, 1 : 1) to give the title compound **8a** (115 mg, 64%) as colorless needles, mp (DSC) onset: 81.1 °C, peak max: 81.8 °C (from *n*-pentane/0 °C) (lref. 56, 83–84 °C from cyclohexane); R_f 0.68 (*n*-hexane–DCM, 1 : 1); ν_{max}/cm^{-1} 2236m (C≡N), 1495m, 1369m, 1348m, 1317s, 1298m, 1161m, 1126w, 1103w, 1059w, 1034w, 978w, 961m, 941w, 843m, 829m, 812s; δ_C (125 MHz; $CDCl_3$) 149.8 (s), 131.0 (s), 130.9 (s), 108.2 (s); identical to an authentic sample.

4.3.2. 3,4-Dibromoisothiazole-5-carbonitrile (8b), Table 1, entry 5. Similar treatment of (*Z*)-2-bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**21**) (254 mg, 1.00 mmol) in Et_2O (10 mL) with HBr (g) gave the title compound **8b** (222 mg, 83%) as colorless needles, mp (DSC) onset: 105.2 °C, peak max: 106.1 °C (from *n*-pentane/0 °C) (ref. 33*a*, 107–108 °C from EtOH–H_2O); R_f 0.56 (*n*-hexane–DCM, 7 : 3); ν_{max}/cm^{-1} 2230m (C≡N), 1476m, 1448w, 1357w, 1317w, 1283s, 1148m, 912m, 822w, 806w, 783m; δ_C (125 MHz; $CDCl_3$) 141.7 (s), 133.4 (s), 121.8 (s), 108.8 (s); *m*/*z* (EI) 270 (M^+ + 4, 49%), 268 (M^+ + 2, 100), 266 (M^+, 48), 189 (76), 187 (12), 163 (35), 161 (33), 137 (11), 113 (23), 111 (23), 108 (22), 82 (56); identical to an authentic sample.

4.3.3. 3-Chloroisothiazole-4,5-dicarbonitrile (9a); Table 1, entry 24. Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)malononitrile (**11**) (202 mg, 1.00 mmol) in THF (10 mL) with HCl (g) gave the title compound **9a** (94 mg, 55%) as colorless needles, mp (DSC) onset: 96.9 °C, peak max: 98.5 °C (from cyclohexane, ref. 40*a*, 98 °C); R_f 0.43 (*n*-hexane–DCM, 1 : 1); ν_{max}/cm^{-1} 2247m and 2239m (C≡N), 1510s, 1354s, 1196s, 1174s, 1146w, 1020m, 980w, 856m, 829m; δ_C (125 MHz; $CDCl_3$) 151.8 (s), 142.5 (s), 115.9 (s), 108.4 (s), 106.9 (s); identical to an authentic sample.

4.3.4. 3-Bromoisothiazole-4,5-dicarbonitrile (9b); Table 1, entry 22. Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)malononitrile (**11**) (202 mg, 1.00 mmol) in THF (10 mL) with HBr (g) gave the title compound **9b** (205 mg, 96%) as colorless needles, mp (DSC) onset: 138.6 °C, peak max: 139.6 °C (from cyclohexane, ref. 40*b*, 141 °C); R_f 0.43 (*n*-hexane–DCM, 1 : 1); ν_{max}/cm^{-1} 2245m and 2237m (C≡N), 1503s, 1379w, 1360w, 1342s, 1186m, 1167m, 1136w, 1007m, 978w, 843s, 800m; δ_C (125 MHz; $CDCl_3$) 142.4 (s), 139.8 (s), 119.3 (s), 109.0 (s), 106.7 (s); identical to an authentic sample.

4.3.5. 3-Chloroisothiazole-5-carbonitrile (24a), Table 1, entry 4. Similar treatment of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**11**) (177 mg, 1.00 mmol) in THF (10 mL) with HCl (g) gave the *title compound* **24a** (122 mg, 84%) as colorless needles, mp (DSC) onset: 65.2 °C, peak max: 66.3 °C (from *n*-pentane/0 °C); R_f 0.39 (*n*-hexane–DCM, 7 : 3); (found: C, 33.12; H, 0.64; N, 19.43. C_4HClN_2S requires C, 33.23; H, 0.70; N, 19.38%); λ_{max} (DCM)/nm 233 (log ε 3.04), 275 (3.00); ν_{max}/cm^{-1} 3109m (CH), 2234m (C≡N), 1495s, 1366m, 1337m, 1328m, 1310s, 1271m, 1159m, 1155m, 1126w, 1101w, 910s, 847s, 822m; δ_H (500 MHz; $CDCl_3$) 7.54 (1H, s, *H*-4); δ_C (125 MHz; $CDCl_3$) 150.5 (s), 135.6 (s), 130.4 (d), 109.5 (s); *m*/*z* (ESI-APCI+) 179 [(MH + MeOH + 2)$^+$, 36%], 177 [(MH + MeOH)$^+$, 100].

4.3.6. 3-Bromoisothiazole-5-carbonitrile (24b), Table 1, entry 2. Similar treatment of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**19**) (177 mg, 1.00 mmol) in THF (10 mL) with HBr (g) gave the *title compound* **24b** (183 mg, 97%) as colorless needles, mp (DSC) onset: 71.8 °C, peak max: 72.8 °C (from *n*-pentane/0 °C); R_f 0.59 (*n*-hexane–DCM, 1 : 1); (found: C, 25.46; H, 0.49; N, 14.94. C_4HBrN_2S requires C, 25.42; H, 0.53; N, 14.82%); λ_{max} (DCM)/nm 236 (2.89), 245 (2.88), 278 (3.22); ν_{max}/cm^{-1} 3109m (CH), 2230m (C≡N), 1487s, 1358m, 1300s, 1252w, 1150m, 1119w, 1099w, 881s, 845s, 808s; δ_H (500 MHz; $CDCl_3$) 7.61 (1H, s, *H*-4); δ_C (125 MHz; $CDCl_3$) 137.7 (s), 135.6 (s), 133.9

(d), 109.3 (s); *m*/*z* (EI) 190 (M^+ + 2, 100%), 188 (M^+, 87), 139 (14), 137 (13), 109 (57), 83 (45), 82 (40), 70 (56), 63 (7), 58 (27), 51 (30).

4.3.7. Methyl 3-bromo-5-cyanoisothiazole-4-carboxylate (25b); Table 1, entry 13. Similar treatment of (*Z*)-methyl 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetate (**12**) (235 mg, 1.00 mmol) in Et_2O (10 mL) with HBr (g) gave the *title compound* **25b** (193 mg, 78%) as colorless needles, mp (DSC) onset: 80.2 °C, peak max: 81.5 °C (from *n*-pentane/0 °C); R_f 0.45 (*n*-hexane–DCM, 1 : 1); (found: C, 29.30; H, 1.06; N, 10.98. $C_6H_3BrN_2O_2S$ requires C, 29.17; H, 1.22; N, 11.34%); λ_{max} (DCM)/nm 232 inf (log ε 2.77), 243 (2.81), 290 (2.89); ν_{max}/cm^{-1} 2955w, 2924w and 2855w (CH_3), 2235m (C≡N), 1732s (C═O), 1499m, 1441m, 1370m, 1344s, 1292w, 1219s, 1198m, 1153m, 1134s, 1009m, 993m, 925m, 854m, 810w, 781m, 773m; δ_H (500 MHz; $CDCl_3$) 4.03 (3H, s, OCH_3); δ_C (125 MHz; $CDCl_3$) 158.6 (s), 139.8 (s), 139.1 (s), 134.2 (s), 108.5 (s), 53.4 (q); *m*/*z* (EI) 248 (M^+ + 2, 29%), 246 (M^+, 27), 217 (100), 215 (97), 189 (4), 167 (59), 139 (5), 110 (30), 82 (39), 70 (29), 59 (20).

4.3.8. Ethyl 3-bromo-5-cyanoisothiazole-4-carboxylate (26b); Table 1, entry 17. Similar treatment of (*Z*)-ethyl 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetate (**13**) (249 mg, 1.00 mmol) in Et_2O (10 mL) with HBr (g) gave the *title compound* **26b** (227 mg, 87%) as colorless needles, mp (DSC) onset: 67.1 °C, peak max: 68.1 °C (from *n*-pentane/0 °C); R_f 0.32 (*n*-hexane–DCM, 1 : 1); (found: C, 32.26; H, 1.89; N, 10.64. $C_7H_5BrN_2O_2S$ requires C, 32.20; H, 1.93; N, 10.73%); λ_{max} (DCM)/nm 240 (log ε 3.07), 290 (3.13); ν_{max}/cm^{-1} 2999w, 2978w and 2936w (CH_2 and CH_3), 1728s (C═O), 1489s, 1467w, 1445w, 1400w, 1381s, 1341s, 1290w, 1225s, 1159m, 1142w, 1022s, 980w, 878m, 845w; δ_H (500 MHz; $CDCl_3$) 4.50 (2H, q, *J* 7.2, OCH_2), 1.46 (3H, t, *J* 7.3, CH_3); δ_C (125 MHz; $CDCl_3$) 158.1 (s), 139.6 (s), 139.1 (s), 134.3 (s), 108.5 (s), 63.1 (t), 13.9 (q); *m*/*z* (EI) 262 (M^+ + 2, 19%), 260 (M^+, 20), 234 (84), 232 (76), 217 (96), 215 (100), 190 (13), 188 (13), 181 (25), 113 (9), 110 (33), 109 (25), 108 (24), 82 (40), 77 (8), 70 (23).

4.3.9. Reaction of (*Z*)-2-bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (21) with HBr in THF; Table 1, entry 6. Similar treatment of (*Z*)-2-bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**21**) (254 mg, 1.00 mmol) in THF (10 mL) with HBr (g) gave 3,4-dibromoisothiazole-5-carbonitrile (**8b**) (48 mg, 18%) as colorless needles, mp (DSC) onset: 105.2 °C, peak max: 106.1 °C (from *n*-pentane/0 °C); R_f 0.56 (*n*-hexane–DCM, 7 : 3), identical to that described above. Further elution (*n*-hexane–DCM, 1 : 1) gave 3-bromoisothiazole-5-carbonitrile (**24b**) (95 mg, 50%) as colorless needles, mp (DSC) onset: 71.8 °C, peak max: 72.8 °C (from *n*-pentane/0 °C); R_f 0.59 (*n*-hexane–DCM, 1 : 1), identical to that described above.

4.3.10. Reaction of (*Z*)-2-bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (21) with HCl in Et_2O; Table 1, entry 7. Similar treatment of (*Z*)-2-bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**21**) (254 mg, 1.00 mmol) in Et_2O (10 mL) with HCl (g) gave (by ^{13}C NMR) an inseparable mixture of 3,4-dichloroisothiazole-5-carbonitrile (**8a**), 3,4-dibromoisothiazole-5-carbonitrile (**8b**), 3-bromo-4-chloroisothiazole-5-carbonitrile (**27b**) and an **unknown** compound (11 mg) as a colorless solid (**8a : 8b : 27b : unknown** = 9 : 1 : 4 : 5 by ^{13}C NMR), mp 35–37 °C; R_f 0.45 (*n*-hexane–DCM, 7 : 3); ν_{max}/cm^{-1} 2234m (C≡N), 1493w, 1485w, 1367w, 1358w, 1348w, 1335w, 1317s, 1302s, 1288m, 1157m, 978w, 961m, 939m, 918w, 914w, 825m, 812m, 802m, 791m; δ_C (125 MHz; $CDCl_3$) (**8a**): 149.8 (s), 131.0 (s), 130.9 (s), 108.2 (s); (**8b**): 141.8 (s), 133.4 (s), 121.8 (s), 108.9 (s); (**27b**): 139.3 (s), 134.0 (s), 130.4 (s), 108.0 (s); (**unknown**): 152.0 (s), 133.8 (s), 118.2 (s), 109.0 (s); *m*/*z* (ESI-APCI+) 303 [**8b**, $(MH + MeOH + 4)^+$, 6%], 301 [**8b**, $(MH + MeOH + 2)^+$, 8], 299 [**8b**, $(MH + MeOH)^+$, 5], 259 [**27b**, $(MH + MeOH + 4)^+$, 13], 257 [**27b**, $(MH + MeOH + 2)^+$, 55], 255 [**27b**, $(MH + MeOH)^+$, 46], 215 [**8a**, $(MH + MeOH + 4)^+$, 25], 213 [**8a**, $(MH + MeOH + 2)^+$, 76], 211 [**8a**, $(MH + MeOH)^+$, 100]. Further elution (*n*-hexane–DCM, 7 : 3) gave 3-chloroisothiazole-5-carbonitrile (**24a**) (50 mg, 34%) as colorless needles mp (DSC) onset: 65.2 °C, peak max: 66.3 °C (from *n*-pentane/0 °C); R_f 0.39 (*n*-hexane–DCM, 7 : 3); δ_H (500 MHz; $CDCl_3$) 7.54 (1H, s, *H*-4); δ_C (125 MHz; $CDCl_3$) 150.5 (s), 135.6 (s), 130.4 (d), 109.5 (s); identical to that described above.

4.3.11. Reaction of (*Z*)-2-bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (21) with HCl in THF; Table 1, entry 8. Similar treatment of (*Z*)-2-bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**21**) (254 mg, 1.00 mmol) in THF (10 mL) with HCl (g) gave (by ^{13}C NMR) an inseparable mixture of 3,4-dichloroisothiazole-5-carbonitrile (**8a**), 3,4-dibromoisothiazole-5-carbonitrile (**8b**), 3-bromo-4-chloroisothiazole-5-carbonitrile (**27b**) and an **unknown** compound (20 mg) as a colorless solid (**8a : 8b : 27b : unknown** = 9 : 1 : 3 : 4 by ^{13}C NMR), mp 35–37 °C; R_f 0.45 (*n*-hexane–DCM, 7 : 3); ν_{max}/cm^{-1} 2234m (C≡N), 1493w, 1485w, 1368w, 1348w, 1335w, 1317s, 1302s, 1288m, 1157m, 978w, 961m, 939m, 918w, 914w, 841m, 825m, 812s, 804m, 791m; δ_C (125 MHz; $CDCl_3$) (**8a**): 149.8 (s), 131.0 (s), 130.9 (s), 108.2 (s); (**8b**): 141.8 (s), 133.4 (s), 121.8 (s), 108.9 (s); (**27b**): 139.3 (s), 134.0 (s), 130.4 (s), 108.0 (s); (**unknown**): 151.9 (s), 133.8 (s), 118.2 (s), 109.0 (s); *m*/*z* (ESI-APCI+) 303 [**8b**, $(MH + MeOH + 4)^+$, 6%], 301 [**8b**, $(MH + MeOH + 2)^+$, 8], 299 [**8b**, $(MH + MeOH)^+$, 5], 259 [**27b**, $(MH + MeOH + 4)^+$, 27], 257 [**27b**, $(MH + MeOH + 2)^+$, 65], 255 [**27b**, $(MH + MeOH)^+$, 51%], 215 [**8a**, $(MH + MeOH + 4)^+$, 18], 213 [**8a**, $(MH + MeOH + 2)^+$, 47], 211 [**8a**, $(MH + MeOH)^+$, 65]. Further elution (*n*-hexane–DCM, 7 : 3) gave 3-chloroisothiazole-5-carbonitrile (**24a**) (98 mg, 68%) as colorless needles mp (DSC) onset: 65.2 °C, peak max: 66.3 °C (from *n*-pentane/0 °C); R_f 0.39 (*n*-hexane–DCM, 7 : 3); δ_H (500 MHz; $CDCl_3$) 7.54 (1H, s, *H*-4); δ_C (125 MHz; $CDCl_3$) 150.5 (s), 135.6 (s), 130.4 (d), 109.5 (s); identical to that described above.

4.3.12. Reaction of 2-chloro-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (22) with HBr in Et_2O; Table 1, entry 9. Similar treatment of 2-chloro-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**22**) (210 mg, 1.00 mmol) in Et_2O (10 mL) with HBr (g) gave an inseparable mixture of 3,4-dibromoisothiazole-5-carbonitrile (**8b**) and 3-bromo-4-chloroisothiazole-5-carbonitrile (**27b**) (135 mg, **8b : 27b** = 1 : 3 by NMR); mp (DSC) onset: 89.9 °C, peak max: 92.5 °C (from *n*-pentane/0 °C); R_f 0.56 (*n*-hexane–DCM, 7 : 3); ν_{max}/cm^{-1} 2232m (C≡N), 1485m, 1356w, 1333w, 1298s, 1287s, 1155m, 1148m, 939s, 918m, 912m, 835w, 824m, 791m, 783w; δ_C (125 MHz; $CDCl_3$) *major* (**27b**): 139.3 (s), 134.0 (s), 130.4 (s), 108.0 (s), *minor* (**8b**): 141.7 (s), 133.4 (s), 121.8 (s), 108.8 (s); *m*/*z* (GCMS-EI) *major* (**27b**): 226 (M^+ + 4,

27%), 224 (M^+ + 2, 100), 222 (M^+, 70), 145 (10), 143 (28), 139 (13), 137 (12), 119 (36), 117 (95), 108 (24), 82 (40), *minor* (**8b**): 270 (M^+ + 4, 50%), 268 (M^+ + 2, 100), 266 (M^+, 49), 189 (12), 187 (11), 163 (37), 161 (42), 139 (12), 137 (13), 113 (26), 111 (27), 108 (28), 82 (59).

4.3.13. Reaction of 2-chloro-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (22) with HBr in THF; Table 1, entry 10. Similar treatment of 2-chloro-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**22**) (210 mg, 1.00 mmol) in THF (10 mL) with HBr (g) gave an inseparable mixture of 3,4-dibromoisothiazole-5-carbonitrile (**8b**) and 3-bromo-4-chloroisothiazole-5-carbonitrile (**27b**) (123 mg, **8b : 27b** = 1 : 9 by ^{13}C NMR); as a colorless solid; mp 88–89 °C; R_f 0.56 (*n*-hexane–DCM, 7 : 3); ν_{max}/cm^{-1} 2234s (C≡N), 1485w, 1358w, 1333w, 1298s, 1287m, 1155m, 939s, 914w, 835w, 824m, 791m; δ_C (125 MHz; $CDCl_3$) *major* (**27b**): 139.3 (s), 134.0 (s), 130.4 (s), 108.0 (s), *minor* (**8b**): 141.8 (s), 133.4 (s), 121.8 (s), 108.8 (s); *m*/*z* (ESI-APCI+) 303 [**8b**, $(MH + MeOH + 4)^+$, 9%], 301 [**8b**, $(MH + MeOH + 2)^+$, 12], 299 [**8b**, $(MH + MeOH)^+$, 10], 259 [**27b**, $(MH + MeOH + 4)^+$, 33], 257 [**27b**, $(MH + MeOH + 2)^+$, 100], 255 [**27b**, $(MH + MeOH)^+$, 72]. Further elution (*n*-hexane–DCM, 1 : 1) gave 3-bromoisothiazole-5-carbonitrile (**24b**) (29 mg, 15%) as colorless needles, mp (DSC) onset: 71.8 °C, peak max: 72.8 °C (from *n*-pentane/0 °C); R_f 0.59 (*n*-hexane–DCM, 1 : 1); identical to that described above.

4.4. Preparation of 3-bromo-4-cyanoisothiazole-5-carboxamide (23)

4.4.1. 3-Bromo-4-cyanoisothiazole-5-carboxamide (23); method 1: reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene) malononitrile (11) with HBr in wet toluene. A stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)malononitrile (**11**) (202 mg, 1.00 mmol) in wet toluene (6 mL) at *ca.* 20 °C was purged with HBr (g) for 30 s. The mixture was stirred until the starting material was consumed (TLC). The reaction mixture was then adsorbed onto silica and chromatographed (*n*-hexane–DCM, 1 : 1) to give 3-bromoisothiazole-4,5-dicarbo-nitrile (**9b**) (83 mg, 39%), mp (DSC) onset: 138.6 °C, peak max: 139.6 °C (from cyclohexane, ref. 40*b*, 141 °C); R_f 0.43 (*n*-hexane–DCM, 1 : 1); identical to that described above. Further elution (Et_2O) gave the *title compound* **23** (82 mg, 35%) as colorless needles, mp (DSC) onset: 195.9 °C, peak max: 197.7 °C (PhH); R_f 0.48 (Et_2O); (found: C, 25.43; H, 0.82; N, 18.04. $C_5H_2BrN_3OS$ requires C, 25.88; H, 0.87; N, 18.11%); λ_{max} (DCM)/nm 241 (log ε 2.70), 288 (2.56); ν_{max}/cm^{-1} 3350br w, 3319m, 3262m and 3196m (NH), 2255m (C≡N), 1692s, 1626m, 1516m, 1399m, 1379m, 1327s, 1300m, 1124m, 1113m, 1005w, 847m, 794m, 774m; δ_H (500 MHz; acetone-d_6) 7.76 (2H, br s, NH_2); δ_C (125 MHz; acetone-d_6) 171.4 (s), 158.3 (s), 140.0 (s), 113.0 (s), 112.0 (s); *m*/*z* (EI) 233 (M^+ + 2, 35%), 231 (M^+, 34), 217 (41), 215 (42), 152 (100), 139 (5), 137 (5), 109 (34), 108 (34), 82 (64), 56 (7), 51 (17).

4.4.2. 3-Bromo-4-cyanoisothiazole-5-carboxamide (23); method 2: alkali hydration.[52c] of 3-bromoisothiazole-4,5-dicarbonitrile (9b) A stirred solution of 1 M NaOH (0.22 mL, 0.22 mmol) in dioxane (0.22 mL), cooled to *ca.* 0 °C was added 3-bromoisothiazole-4,5-dicarbonitrile (**9b**) (43 mg, 0.20 mmol). The reaction mixture was stirred at this temperature until the starting material was consumed (5 min) and then quenched with a sat. $NaHCO_3$ (5 mL) and extracted with DCM (3 × 10 mL), the organic layer was then dried (Na_2SO_4), filtered and evaporated to give the title product **23** (42 mg, 90%) as colorless needles, mp (DSC) onset: 195.9 °C, peak max: 197.7 °C (PhH); R_f 0.48 (Et_2O); δ_H (500 MHz; acetone-d_6) 7.76 (2H, br s, NH_2); δ_C (125 MHz; acetone-d_6) 171.4 (s), 158.3 (s), 140.0 (s), 113.0 (s), 112.0 (s); identical to that described above.

4.5. Reactions of (dithiazolylidene)acetonitriles with benzyltriethylammonium chloride

4.5.1. Reaction of (*Z*)-2-bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (21) with benzyltriethylammonium chloride; Table 2, entry 2 (typical procedure). To a stirred solution of (*Z*)-2-bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene) acetonitrile (**21**) (127 mg, 0.500 mmol) in dry benzene (5 mL) at *ca.* 20 °C was added $BnEt_3NCl$ (11 mg, 0.050 mmol) and the mixture heated to reflux until the starting material was consumed (TLC). The reaction mixture was then cooled to *ca.* 20 °C, adsorbed onto silica and chromatographed (*n*-hexane–DCM, 1 : 1) to give an inseparable mixture of tentatively 3,4-dichloroisothiazole-5-carbonitrile (**8a**) and 3-bromo-4-chloroisothiazole-5-carbonitrile (**27b**) (56 mg, **8a : 27b** = 1 : 3 by NMR) as a colorless solid, mp 80–82 °C; R_f 0.56 (*n*-hexane–DCM, 7 : 3); ν_{max}/cm^{-1} 2234m (C≡N), 1487w, 1368w, 1358w, 1348w, 1333w, 1319m, 1300s, 1288m, 1155m, 961m, 939m, 916w, 824m, 814m, 791m; δ_C (125 MHz; $CDCl_3$) *major* (**27b**): 139.3 (s), 133.9 (s), 130.4 (s), 108.0 (s), *minor* (**8a**): 149.7 (s), 130.90 (s), 130.86 (s), 108.2 (s); *m*/*z* (ESI-APCI+) 259 [**27b**, $(MH + MeOH + 4)^+$, 31%], 257 [**27b**, $(MH + MeOH + 2)^+$, 100], 255 [**27b**, $(MH + MeOH)^+$, 75], 215 [**8a**, $(MH + MeOH + 4)^+$, 13], 213 [**8a**, $(MH + MeOH + 2)^+$, 45], 211 [**8a**, $(MH + MeOH)^+$, 50].

4.5.2. 3,4-Dichloroisothiazole-5-carbonitrile (8a); Table 2, entry 3. Similar treatment of 2-chloro-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile (**22**) (106 mg, 0.500 mmol) in benzene (5 mL) with $BnEt_3NCl$ (11 mg, 0.050 mmol) on chromatography (*n*-hexane–DCM, 1 : 1) gave the title compound **8a** (57 mg, 63%) as colorless needles, mp (DSC) onset: 81.1 °C, peak max: 81.8 °C (from *n*-pentane/0 °C) (ref. 56, 83–84 °C from cyclohexane); R_f 0.68 (*n*-hexane–DCM, 1 : 1); δ_C (125 MHz; $CDCl_3$) 149.8 (s), 131.0 (s), 130.9 (s), 108.2 (s); identical to that reported above.

4.5.3. Ethyl 3-chloro-5-cyanoisothiazole-4-carboxylate (26a); Table 2, entry 5. Similar treatment of (*Z*)-ethyl 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetate (**13**) (124 mg, 0.500 mmol) in benzene (5 mL) with $BnEt_3NCl$ (11 mg, 0.050 mmol) on chromatography (*n*-hexane–DCM, 1 : 1) gave the *title compound* **26a** (73 mg, 67%) as colorless needles, mp (DSC) onset: 60.9 °C, peak max: 63.6 °C (from *n*-pentane/0 °C); R_f 0.55 (*n*-hexane–DCM, 1 : 1); (found: C, 38.75; H, 2.29; N, 12.96. $C_7H_5ClN_2O_2S$ requires C, 38.81; H, 2.33; N, 12.93%); λ_{max} (DCM)/nm 242 (log ε 2.57), 287 (2.68); ν_{max}/cm^{-1} 3001w, 2980w and 2963w (CH_2 and CH_3), 2237w (C≡N), 1730s (C=O), 1493s, 1466w, 1445w, 1404m, 1383s, 1348m, 1227s, 1211m, 1165m, 1150m, 1115m, 1024s, 989m, 887m, 852w, 839w, 796m, 783s; δ_H (500 MHz; $CDCl_3$) 4.48 (2H, q, *J* 7.2, CH_2), 1.45 (3H, t, *J* 7.1, CH_3);

δ_C (125 MHz; $CDCl_3$) 157.9 (s), 151.2 (s), 140.0 (s), 131.9 (s), 108.7 (s, *C*≡N), 63.0 (t), 13.85 (q); *m*/*z* (ESI-APCI+) 218.8 [$(MH + 2)^+$, 31%], 216.8 (MH^+, 100).

4.5.4. 3-Chloroisothiazole-4,5-dicarbonitrile (9a); Table 2, entry 6. Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)malononitrile (**11**) (101 mg, 0.500 mmol) in benzene (5 mL) with $BnEt_3NCl$ (11 mg, 0.050 mmol) on chromatography (*n*-hexane–DCM, 1 : 1) gave the title compound **9a** (85 mg, 100%) as colorless needles, mp (DSC) onset: 96.9 °C, peak max: 98.5 °C (from cyclohexane, ref. 40*a*, 98 °C); R_f 0.43 (*n*-hexane–DCM, 1 : 1); δ_C (125 MHz; $CDCl_3$) 151.8 (s), 142.5 (s), 115.9 (s), 108.4 (s), 106.9 (s); identical to that reported above.

4.6. X-ray crystallographic studies

Data were collected on an Oxford-Diffraction Supernova diffractometer, equipped with a CCD area detector utilizing Mo-Kα radiation ($\lambda = 0.71073$ Å). A suitable crystal was attached to glass fibers using paratone-N oil and transferred to a goniostat where they were cooled for data collection. Unit cell dimensions were determined and refined by using 6074 ($3.02 \leq \theta \leq 28.90°$) reflections. Empirical absorption corrections (multi-scan based on symmetry-related measurements) were applied using CrysAlis RED software.[57] The structure was solved by direct methods using SIR92 (ref. 58) and refined on F^2 using full-matrix least squares using SHELXL97.[59] Software packages used: CrysAlis CCD (ref. 57) for data collection, CrysAlis RED (ref. 57) for cell refinement and data reduction, WINGX for geometric calculations,[60] and DIAMOND[61] for molecular graphics. The non-H atoms were treated anisotropically. The hydrogen atom attached to C3 was located on a difference Fourier map.

Crystal refinement data for compound **19**:† $C_4HClN_2S_2$, $M = 176.64$, monoclinic, space group $P2_1/c$, $a = 8.1226(8)$, $b = 11.280(3)$, $c = 8.138(2)$ Å, $\beta = 108.04(2)°$, $V = 656.1(2)$ Å^3, $Z = 4$, $T = 100(2)$ K, $\rho_{calcd} = 1.788$ g cm^{-3}, $2\theta_{max} = 50$. Refinement of 86 parameters on 905 independent reflections out of 2781 measured reflections ($R_{int} = 0.0291$) led to $R_1 = 0.0527$ ($I > 2s(I)$), w$R_2 = 0.1555$ (all data), and $S = 1.045$ with the largest difference peak and hole of 0.706 and −0.803 e^{-3}, respectively.

Crystal refinement data for compound **21**:† $C_4BrClN_2S_2$, $M = 255.55$, orthorhombic, space group *Pnma*, $a = 7.517(2)$, $b = 6.7318(7)$, $c = 13.599(2)$ Å, $V = 743.6(2)$ Å^3, $Z = 4$, $T = 100(2)$ K, $\rho_{calcd} = 2.283$ g cm^{-3}, $2\theta_{max} = 50$. Refinement of 61 parameters on 588 independent reflections out of 2841 measured reflections ($R_{int} = 0.0333$) led to $R_1 = 0.0274$ ($I > 2s(I)$), w$R_2 = 0.0715$ (all data), and $S = 0.950$ with the largest difference peak and hole of 0.701 and −0.652 e^{-3}, respectively.

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