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The reaction of 4,5-dichloro-1,2,3-dithiazolium chloride with dimethylsulfonium dicyanomethylide: an improved synthesis of (4-chloro-1,2,3-dithiazolylidene)malononitrile

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ABSTRACT

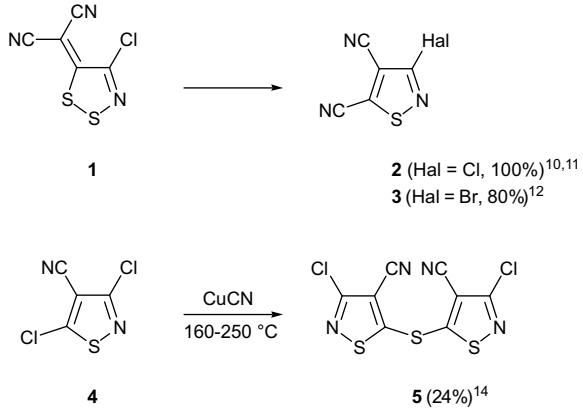
4,5-Dichloro-1,2,3-dithiazolium chloride **6** (Appel salt) reacts with dimethylsulfonium dicyanomethylide **11** to give 5-(4-chloro-1,2,3-dithiazolylidene)malononitrile **1** and a mixture of *E*/*Z* isomers of 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3-chloro-2-(methylthio)acrylonitrile **13**. The reaction of 4-chloro-5*H*-1,2,3-dithiazole-5-thione **10** with dimethylsulfonium dicyanomethylide **11** gives (dithiazolylidene)malononitrile **1** in 92% yield. All new compounds are fully characterised and rational mechanisms are proposed for the formation of all key compounds.

1. Introduction

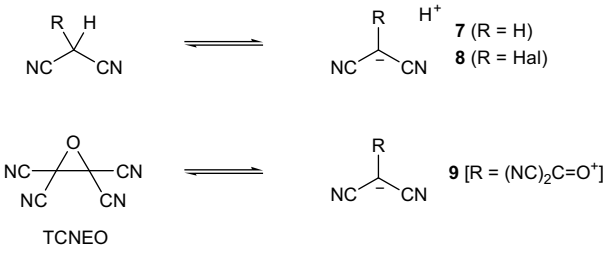
1,2,3-Dithiazoles have uses in both biological and material sciences. *N*-aryldithiazolimines show interesting antitumour,[1] antibacterial,[2] antifungal,[3] and herbicidal[4] activities. A search for organic conductors based on neutral radicals has led to the preparation of two 1,2,3-dithiazolyl radicals[5] and also a tetrathiadiazafulvalene analogue[6] has been prepared and studied.

Our interest in 4-chloro-5*H*-1,2,3-dithiazoles focuses on their ANRORC[7] style ring transformations into otherwise difficult to access heteroarenes.[8,9] An example of which was the high yielding formation of 3-chloro- and 3-bromoisothiazole-4,5-dicarbonitriles **2** (100%)[10,11] and **3** (80%)[12] prepared by treating the (dithiazolylidene)malononitrile **1** with either catalytic chloride, or anhydrous HBr respectively. These isothiazoles were useful for the preparation of novel potent biocides.[13] Earlier attempts to prepare 3-chloroisothiazole-4,5-dicarbonitrile **2** from 3,5-dichloroisothiazole-4-carbonitrile **4** by direct displacement of halide using cyanide failed and gave instead 5,5′-thiobis(3-chloroisothiazole-4-carbonitrile) **5**.[14] Interestingly the (dithiazolylidene)malononitrile **1** was also a precursor to two examples of the rare 3*H*-pyrrole system.[15]

This high yielding dithiazole into isothiazole transformation was marred by the low yielding (30–40%) synthesis of the (dithiazolylidene)malononitrile **1** from malononitrile and 4,5-dichloro-1,2,3-dithiazolium chloride **6** (Appel salt)[16] in the presence of 3° amine base.[10] Several methods were developed to improve the yield of ylidene **1**: The first method involved the use of tetracyanoethylene oxide (TCNEO) which reacted via its ring



opened form,[10,11] and the second method used halo substitutued malononitriles.[12] Both methods gave improved yields (60–70%) of the desired dithiazolylidene **1**, but TCNEO was expensive, and halomalononitriles were lachrymators and disproportioned at elevated temperatures.[12]



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This problem was readdressed by considering the common features of the above three syntheses of the dithiazolylidene **1**. An analysis of the reagents showed the common denominator to be the availability of an anionic methylene coupled with a good electrofuge [**7** R=H^+, **8** R=Hal^+, **9** R=$(NC)_2C{=}O$]. A review of the malononitrile literature[17] identified several reagents that met the above requirements, which included the diazonium,[18] *N*-pyridinium,[19] triphenylphosphonium[20] and dimethylsulfonium dicyanomethylides.[21] Interestingly diphenyldiazomethane was shown to react with 4-chloro-1,2,3-dithiazole-5-thione **10** to give (4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)diphenylmethane[10] but diazoalkanes are shock sensitive, while triphenylphosphonium would be expected to release the sulfur hungry triphenylphosphine which could degrade the 1,2,3-dithiazole.[9,15,22] Furthermore the *N*-pyridinium would release pyridine which reacts with Appel salt **6** to afford undesirably high recoveries of 4-chloro-5*H*-1,2,3-dithiazole-5-thione **10**.[23] As such the first two reagents were not investigated. A quick screening of both the pyridinium and the dimethylsulfonium dicyanomethylides showed that both reacted with Appel salt **6** to give the desired product but the reaction with the pyridinium was slow and relatively complex (by TLC), while that of the sulfonium was promising. As such a detailed investigation of the reaction of Appel salt **6** with dialkylsulfonium dicyanomethylides was initiated.

2. Reaction of dimethylsulfonium dicyanomethylide with Appel salt 6

There are several methods for preparing dimethylsulfonium dicyanomethylide **11** and in our hands the procedure involving the condensation of DMSO and malononitrile in the presence of thionyl chloride worked well.[21] Dicyanomethylide **11** was obtained as a highly crystalline material that could be stored without special precautions. Treatment of Appel salt **6** with dicyanomethylide **11** (1 equiv) in various solvents gave the desired dithiazolylidene **1** together with dithiazole-5-thione **10**, 4-chloro-5*H*-1,2,3-dithiazol-5-one **12** and a new product **13** (Table 1).

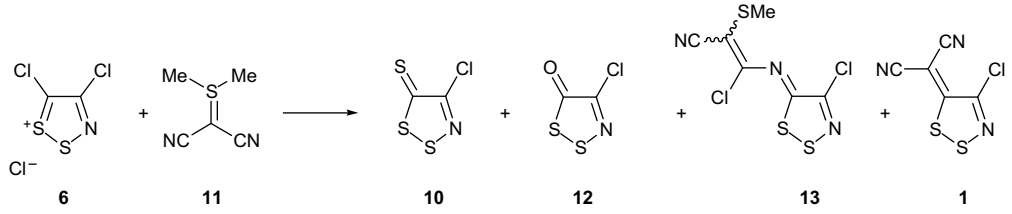
The product ratio was solvent and temperature dependant. In either MeCN or THF the reaction proceeded rapidly to completion (as judged by consumption of Appel salt **6**), and gave good yields (60–70%) of the desired ylidene **1**; highest yields (68–70%) were obtained at ca. 20 °C and the use of excess of dicyanomethylide **11** (1.5 equiv) only marginally improved the yield of ylidene **1** (71–72%). Interestingly the yield of the byproduct **13** was not affected in either of MeCN or THF at elevated temperatures. However, in the chlorinated solvents, DCM, $CHCl_3$ and 1,2-DCE, the yield of the byproduct **13** increased (46%) with higher reaction temperature. The use of a non chlorinated solvent such as benzene at reflux did not increase the yield of the byproduct **13**.

The new product **13** [mp 136–138 °C (cyclohexane)], which was deep orange red in colour [λ_{max} (DCM) 473 nm (log ϵ 3.32)] suggesting conjugation and possibly an intact dithiazole ring, gave a correct microanalysis for the formula $C_6H_3Cl_2N_3S_2$ and LREI mass spectrometry gave a molecular parent ion of *m*/*z* 283 Da (70%) with an isotope pattern indicative of two chlorine atoms. ^{1}H NMR spectroscopy indicated the presence of two singlet resonances (δ_H 2.61 and 2.57 ppm) that were probably SMe in origin and ^{13}C NMR spectroscopy showed what looked like two sets of 6 carbon resonances. It was evident from the data that the isolated material was in fact two isomers in nearly equal proportions as judged by the SMe intergrations in the ^{1}H NMR spectroscopy. Unfortunatley chromatographic resolution of the isomers was not possible in our laboratory. The spectroscopic data was similar to the *N*-(1,2-dihaloethene) substituted dithiazolimines isolated as byproducts from the reactions of both TCNEO[11] and halomalononitriles[12] with Appel salt **6**. However, there was one significant difference; one halide had been replaced by an SMe group.

The mechanistic rationale for the formation of both the dithiazolylidene **1** (Scheme 1) and the dithiazolimines **13** (Scheme 2) was similar to that proposed in the earlier TCNEO and halomalononitrile studies. The notable difference was the demethylation of the dimethylsulfonium that led to the formation of the methylsulfides **13**.

The resonance forms that describe dimethylsulfonium dicyanomethylide **11** support electron density at the methylene carbon and at the nitrile nitrogen. The dimethylsulfonium dicyanomethylide **11** can attack Appel salt **6** at the highly electrophilic C-5 position to give, after elimination of chloride, a new dithiazolium intermediate **14** (Scheme 1). The cationic dimethylsulfonium can

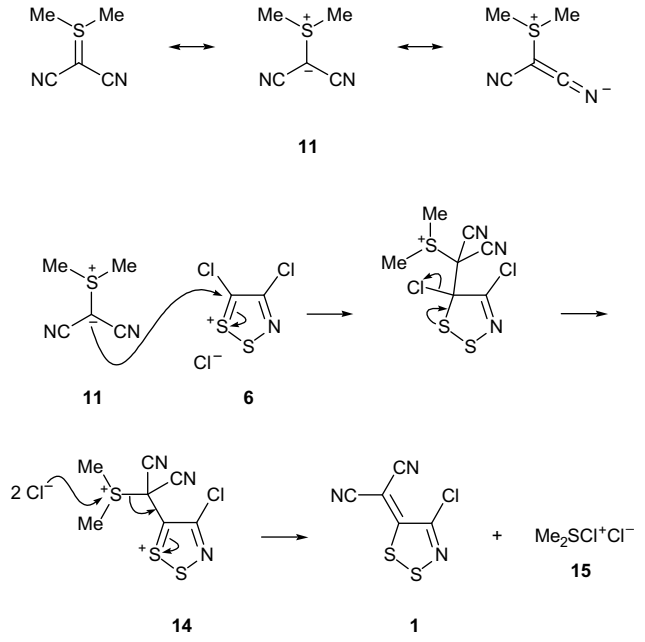
Table 1
Reaction of Appel salt **6** (0.48 mmol) with dimethylsulfonium dicyanomethylide **11** (1 equiv), protected from moisture with a $CaCl_2$ drying tube



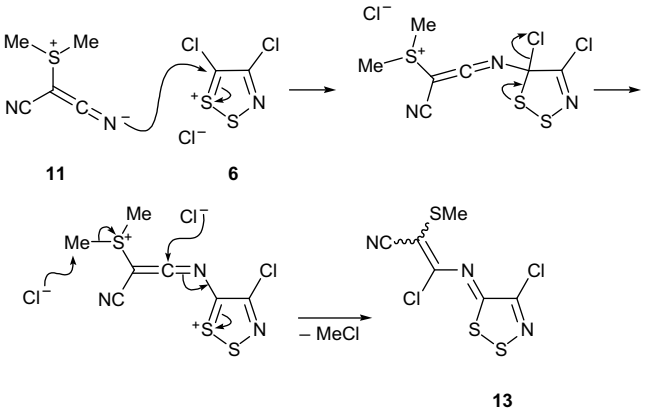
6 **11** **10** **12** **13** **1**

Solvent (6 mL)	Temp (°C)	Time (h)	Yield %			
			10	**12**	**13**	**1**
MeCN	0	4.0	7	22	1	60
MeCN	20	3.0	8	10	3	68
MeCN[a]	20	5.0	2	11	4	71
MeCN	82	0.3	12	13	4	62
THF	20	2.5	3	4	6	70
THF[a]	20	5.5	2	10	6	72
THF	66	2.5	8	8	6	66
PhH	81	3.0	9	10	16	45
DCM	20	5.5	3	15	15	29
DCM[a]	20	13.5	4	15	17	31
DCM	39	3.5	6	9	46	32
$CHCl_3$	61	2.5	3	10	46	31
1,2-DCE[b]	84	1.0	6	15	29	30

[a] Dimethylsulfonium dicyanomethylide **11** (1.5 equiv).
[b] DCE = dichloroethane.



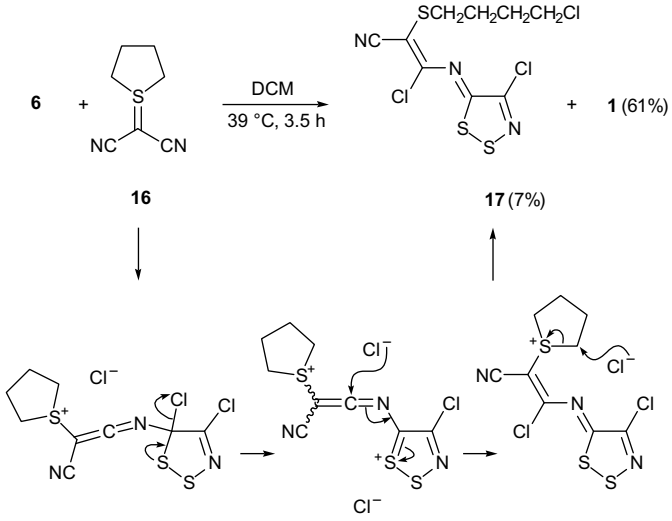
Scheme 1.



Scheme 2.

depart assisted by chloride or an equivalent species. The proposed chlorodimethylsulfonium chloride **15** byproduct was a well known species and under the reaction conditions can convert into a number of alternative species including DMSO on hydrolysis[24] or dimethylsulfide[25] on reductive dechlorination. The isolation of 4-chloro-5*H*-1,2,3-dithiazol-5-one **12** could be due to the reaction of Appel salt **6** and moisture or traces of DMSO.

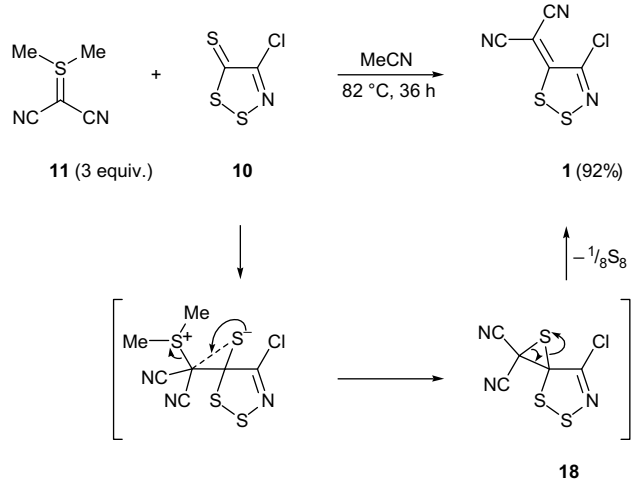
Chloride, which was in abundance, can demethylate dimethylsulfoniums,[26] and was the most likely demethylating agent. To support the role of chloride in the dimethylation, a tethered dialkylsulfonium analogue, tetramethylenesulfonium dicyanomethylide **16**[21] was prepared and reacted with Appel salt **6** in DCM at ca. 39 °C; conditions that led to good yields of the dithiazolimines **13** with dimethylsulfonium dicyanomethylide **11**. Suprisingly even in DCM at ca. 39 °C this reaction gave a good yield of the dithiazolylidene **1** (61%) and only a low yield of the desired dithiazolimine **17** (7%). Nevertheless, the dithiazolimine **17** derived from the monodealkylated sulfonium showed incorporation of chloride, supporting the proposed chloride mediated demethylations. Nucleophilic ring openings of tetramethylenesulfoniums are known.[27] Interestingly in this case only one dithiazolimine isomer was obtained and this was informative. The dithiazolimine **17** was presumed to be the anti isomer owing to the greater steric bulk of the tetramethylenesulfonium which would prefer to be away from the ethene chlorine. This implied the dealkylation step occurred after the geometry of the ethene bond was fixed (Scheme 3).



Scheme 3.

3. Reaction of dimethylsulfonium dicyanomethylide 11 with dithiazole-5-thione 10

In an attempt to improve the product yields, the reactivity of the dithiazolimines **13**, dithiazolethione **10** and dithiazolone **12** with the dimethylsulfonium dicyanomethylide **11** was investigated. Heating the respective dithiazoles with the dicyanomethylide **11** in MeCN at ca. 82 °C indicated that the dithiazolimines **13** and the dithiazolone **12** were stable to the reagent. The dithiazolethione **10**, however, gave traces of the dithiazolylidene **1** (by TLC). This result was comparable to the earlier studies of TCNEO[10] and dibromomalononitrile[11] with dithiazolethione **10** which also gave dithiazolylidene **1** in good yields (>70%). The reaction was partially optimised with respect to dithiazolethione **10** and a portionwise addition of dicyanomethylide **11** (3 equiv) to a hot MeCN solution of dithiazolethione **10** gave after 36 h at ca. 82 °C the dithiazolylidene **1** in 92% yield. A tentative mechanism involved nucleophilic attack at the dithiazolethione C-5 carbon followed by immediate ring closure to the spirocyclic thiirane **18** that thermally loses sulfur to give the dithiazolylidene **1** (Scheme 4). While the correct



Scheme 4.

stoichiometry for elemental sulfur was isolated from the reaction mixture, it was not possible to explain the need for the excess (3 equiv) of reagent **11**. The possibility that dimethylsulfonium dicyanomethylide **11** decomposed to form tetracyanoethylene (TCNE) was investigated, but all our efforts to identify TCNE in the reaction mixture failed.[28]

4. Conclusion

The reaction of Appel salt **6** and dithiazole-5-thione **10** with dimethylsulfonium dicyanomethylide **11** gave the desired (dithiazolylidene)malononitrile **1** in 70 and 92% yields respectively. Furthermore the reaction with Appel salt **6** was accompanied by the unusual and mechanistically interesting dithiazolimines **13**.

5. Experimental

5.1. General

Solvents DCM, MeCN, THF and PhH were freshly distilled from CaH_2 under argon. $CHCl_3$ and 1,2-dichloroethane (DCE) were dried by passing through a column of dry neutral alumina. DMSO was dried with neutral alumina, refluxed with CaH_2 and then redistilled under vacuum and stored over 4 Å molecular sieves under argon. Reactions were protected from atmospheric moisture by $CaCl_2$ drying tubes. 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. Decomposition points (decomp.) and mp >250 °C 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. 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 a 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 300 machine (at 300 and 75 MHz, respectively). Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. Low resolution (EI) mass spectra were recorded on a Shimadzu Q2010 GCMS with direct inlet probe. 4,5-Dichloro-1,2,3-dithiazolium chloride **6**,[16] 4-chloro-5*H*-1,2,3-dithiazole-5-thione **10**,[16] dimethylsulfonium dicyanomethylide **11**,[21] and tetramethylenesulfonium dicyanomethylide **16**,[21] were prepared according to literature procedures.

5.2. Reaction of Appel salt 6 with dimethylsulfonium dicyanomethylide 11: typical procedure (see Table 1)

To a stirred solution of 4,5-dichloro-1,2,3-dithiazolium chloride **6** (100 mg, 0.48 mmol) in dry MeCN (6 mL) at ca. 20 °C, dimethylsulfonium dicyanomethylide **11** (60.5 mg, 0.48 mmol) was added in one portion. After 3 h no 4,5-dichloro-1,2,3-dithiazolium chloride **6** remained and the reaction mixture was adsorbed on silica. Chromatography (hexane–DCM, 8:1) gave 4-chloro-5*H*-1,2,3-dithiazole-5-thione **10** (2.8 mg, 7%) as red needles, mp 75–76 °C (lit.[16] 78–79 °C) (from pentane); identical with an authentic sample and further elution (hexane–DCM, 2:1) gave 4-chloro-5*H*-1,2,3-dithiazol-5-one **12** (15.4 mg, 21%) as pale yellow plates, mp 35–36 °C (lit.[16] 39 °C) (from pentane) identical with an authentic sample. Further elution (hexane–DCM, 1:1) gave an inseparable mixture of *E*/*Z* isomers (1:1 by ^1H NMR) of 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3-chloro-2-(methylthio)acrylonitriles **13a** and **b** (4.1 mg, 3%) as red needles, mp 136–138 °C (from cyclohexane) (Found: C, 25.4; H, 1.1; N, 14.8. $C_6H_3Cl_2N_3S_3$ requires C, 25.4; H, 1.1; N, 14.6%); λ_{max} (DCM)/nm 230 (log ϵ 2.99), 263 inf (2.85), 302 (2.73), 373 inf (2.82), 422 inf (3.19), 452 (3.34), 473 inf (3.32), 508 inf (3.10); ν_{max}/cm^{-1} 2928w, 2211s (C≡N), 2195s (C≡N), 1545s, 1514m, 1462s, 1427w, 1321m, 1211m, 1200m, 1144m, 1130m, 1103m, 1088w, 980m, 964w, 874s, 839w, 808s, 766w and 708s; δ_H (300 MHz; $CDCl_3$) 2.61 (s, SCH_3) and 2.57 (s, SCH_3); δ_C (75 MHz; $CDCl_3$) 158.1 (*C*-5), 154.3 (*C*-5), 150.1 (*C*-4), 150.0 (*C*-4), 140.5 (N–*C*═), 140.5 (*C*═CCN), 134.8 (*C*═CCN), 114.3 (*C*≡N), 112.8 (*C*≡N), 109.6 (*C*–C≡N), 108.2 (*C*–C≡N), 17.2 (S*C*H$_3$), 16.8 (S*C*H$_3$); δ_C (75 MHz; DEPT-135; $CDCl_3$) 17.2 (S*C*H$_3$), 16.8 (S*C*H$_3$); *m*/*z* (EI) 287 (M^++4, 14%), 285 (M^++2, 55), 283 (M^+, 70), 270 (6), 268 (6), 250 (M^+−HS, 27), 252 (18), 248 (M^+−Cl, 12), 238 (15), 236 (M^+−CH_3S, 15), 207 (26), 209 (13), 201 (25), 175 (21), 151 (41), 111 (14), 99 (43), 70 (C_2NS^+, 100), 64 (S_2^+, 69), 58 (13). A final elution (DCM) gave 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)malononitrile **1** (64.8 mg, 67%) as orange crystals, mp 178–179 °C (lit.[10] 181–182 °C) (from cyclohexane) identical with an authentic sample.

5.3. Reaction of Appel salt 6 with tetramethylenesulfonium dicyanomethylide 16

To a stirred solution of 4,5-dichloro-1,2,3-dithiazolium chloride **6** (100 mg, 0.48 mmol) in dry DCM (6 mL) at ca. 20 °C, tetramethylenesulfonium dicyanomethylide **16** (73 mg, 0.48 mmol) was added in one portion and the mixture was heated to ca. 39 °C. After 3.5 h no 4,5-dichloro-1,2,3-dithiazolium chloride **6** remained and the reaction mixture was allowed to cool to ca. 20 °C and then adsorbed onto silica. Chromatography (hexane–DCM, 8:1) gave 4-chloro-5*H*-1,2,3-dithiazole-5-thione **10** (2.0 mg, 5%) as red needles, mp 75–76 °C (lit.[16] 78–79 °C) (from pentane) identical with that reported. Further elution (hexane–DCM, 2:1) gave 4-chloro-5*H*-1,2,3-dithiazol-5-one **12** (2.0 mg, 3%) as pale yellow plates, mp 35–36 °C (lit.[16] 39 °C) (from pentane) identical with an authentic sample. Further elution (hexane–DCM, 1:1) gave (2*Z*,3*Z*)-3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-2-(4-chlorobutylthio)-3-chloroacrylonitrile **17** (11 mg, 6%) as red needles, mp 93–94 °C (from cyclohexane); (Found: C, 29.9; H, 2.2; N, 11.7. $C_9H_8Cl_3N_3S_3$ requires C, 30.0; H, 2.2; N, 11.7%); λ_{max} (DCM)/nm 229 (log ϵ 2.95), 305 inf (2.82), 373 inf (2.80), 422 inf (3.27), 451 (3.40), 474 inf (3.36), 515 inf (3.01); ν_{max}/cm^{-1} 2961w, 2928w, 2868w, and 2847w (CH_2), 2208s (C≡N), 1557s, 1512m, 1477s, 1447m, 1431w, 1358w, 1308w, 1288w, 1250w, 1231w, 1215m, 1150m, 1092m, 989w, 887s, 839m, 804s and 745m; δ_H (300 MHz; $CDCl_3$) 3.58 (2H, t, *J* 6, ClCH_2), 3.10 (2H, t, *J* 6.6, SCH_2) and 1.97–1.88 (4H, m, CH_2CH_2); δ_C (75 MHz; $CDCl_3$) 155.0 (*C*-5), 150.1 (*C*-4), 142.2 (═*C*ClN), 113.1 (*C*≡N), 107.7 (*C*C≡N), 44.1 (*C*H_2Cl), 33.4 (S*C*H_2), 31.2 (*C*H_2) and 27.3 (*C*H_2); δ_C (75 MHz; DEPT-135; $CDCl_3$) 44.1 (*C*H_2Cl), 33.4 (S*C*H_2), 31.2 (*C*H_2) and 27.3 (*C*H_2); *m*/*z* (EI) 365 (M^++4, 2%), 363 (M^++2, 8), 361 (M^+, 22), 359 (19), 328 (5), 326 (M^+−Cl, 5), 227 (5), 207 (11), 201 (4), 172 (15), 170 (36), 163 (3), 149 (5), 137 (5), 117 (3), 102 (15), 99 (S_2Cl^+, 21), 93 (30), 91 ($C_4H_8Cl^+$, 75), 70 (C_2NS^+, 24), 64 (S_2^+, 32), 55 ($C_4H_7^+$, 100). A final elution (DCM) gave 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-malononitrile **1** (57.3 mg, 60%) as an orange solid, mp 178–179 °C (lit.[10] 181–182 °C) (from cyclohexane) identical with an authentic sample.

5.4. Reaction of 4-chloro-5*H*-1,2,3-dithiazole-5-thione 10 with dimethylsulfonium dicyanomethylide 11: typical procedure

To a stirred solution of 4-chloro-5*H*-1,2,3-dithiazole-5-thione **10** (81.4 mg, 0.48 mmol) in dry MeCN (6 mL), dimethylsulfonium dicyanomethylide **11** (60.5 mg, 0.48 mmol) was added in one portion and the reaction mixture was then heated to ca. 82 °C. After 12 h there was a further addition of dimethylsulfonium dicyanomethylide **11** (60.5 mg, 0.48 mmol) and after a further 12 h a final portion of dicyanomethylide **11** (60.5 mg, 0.48 mmol) was added. After a total of 36 h heating no dithiazolethione **10** remained (TLC) and the reaction mixture was allowed to cool to ca. 20 °C and adsorbed onto silica. Chromatography (hexane) gave sulfur (15.4 mg, 100%). Further elution (DCM) gave 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)malononitrile **1** (89.0 mg, 92%) as orange crystals, mp 178–179 °C (lit.[10] 181–182 °C) (from cyclohexane) identical with an authentic sample.

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