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The reaction of 4,5-dichloro-1,2,3-dithiazolium chloride with DMSO: an improved synthesis of 4-chloro-1,2,3-dithiazol-5*H*-one

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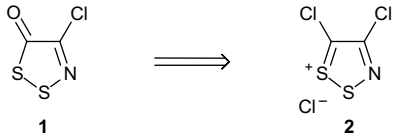
ABSTRACT

4,5-Dichloro-1,2,3-dithiazolium chloride **2** (Appel salt) reacts with either DMSO, diphenylsulfoxide **11** or methylphenylsulfoxide **12** to give 4-chloro-5*H*-1,2,3-dithiazol-5-one **1** in excellent yields. The use of catalytic amounts of DMSO (1 mol %) in MeCN in the presence of water (1 equiv) transforms Appel salt **2** into dithiazolone **1** in near quantitative yields (92%). Rational mechanisms are proposed to explain the catalytic nature of these reactions.

1. Introduction

4-Chloro-1,2,3-dithiazol-5*H*-one **1** has good antimicrobial activity,[1] and reacts with 1° and 2° alkylamines to afford *N*-alkyl- and *N*,*N*-dialkylcyanothioformamides.[2] Furthermore dithiazolone **1** was a good α-thiocyanating agent for α,β-unsaturated β-amino esters,[3] and a useful reagent for the synthesis of symmetrical *N*,*N*′-dialkylureas.[4]



1 **2**

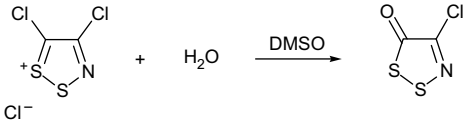
Dithiazolone **1** can be prepared by reacting 4,5-dichloro-1,2,3-dithiazolium chloride **2** (Appel salt)[5] with either $NaNO_3$ in DCM at ca. 39 °C for 16 h,[5] or with *ortho*-trimethylsilylbenzamidoxime and pyridine in DCM at ca. 20 °C for 34 h[6] which give the dithiazolone **1** in 73 and 70% yields respectively. The chemistry of Appel salt **2**, an important reagent for the preparation of neutral 1,2,3-dithiazoles, has been reviewed.[2,7] While Appel salt **2** condenses with either active methylenes, 1° anilines or H_2S to afford 4-chloro-5*H*-1,2,3-dithiazolylidenes, dithiazolimines or dithiazole-5-thione respectively in good yields, treating Appel salt **2** with water surprisingly does not give a good recovery of the expected 4-chloro-1,2,3-dithiazol-5*H*-one **1**.

During ongoing studies of the chemistry of Appel salt **2** we discovered a new rapid and near quantitative synthesis of dithiazol-5-one **1** which required water and catalytic quantities of DMSO. An account of our findings is outlined below.

2. Reactions of dimethylsulfoxide (DMSO) with Appel salt 2

The reaction of Appel salt **2** with DMSO (1 equiv) in dry DCM at ca. 20 °C gave the dithiazolone **1** rapidly (3–4 h) in high yield (83%). The reaction worked equally well in dry or wet DCM, however, in dry MeCN or THF the consumption of Appel salt **2** was faster, 1.5 and 1 h respectively. What was more suprising was that the conversion of Appel salt **2** into dithiazolone **1** could be achieved with only

Table 1
Reaction of Appel salt **2** with dry DMSO and water (0–1 equiv), in dry solvent at 20 °C, protected with a $CaCl_2$ drying tube



2 **1**

2 (mmol)	Solvent (mL)	DMSO (equiv)	H_2O (equiv)	Time (h)	Yield of **1**[a] (%)
0.96	DCM (10)	1	0	4	83
0.96	MeCN (10)	1	0	1.5	83
0.96	THF (10)	1	0	1	83
2.40	DCM (25)	1	0	3.5	77
2.40	DCM (25)	0.5	1	3	84
2.40	DCM (25)	0.1	1	3	86
2.40	DCM (25)	0.01	1	4.5	88
2.40	DCM (25)	0	1	8.5	59[b]
2.40	MeCN (25)	0.01	1	1	86
2.40	MeCN (25)	0	1	6	54[b]
2.40	THF (25)	0.01	1	2	44
2.40	THF (25)	0	1	2.5	19[b]
82.60	MeCN (200)	0.01	1	2	91[c]
82.60	MeCN (200)	0.001	1	6	77[c]

[a] Isolated by chromatography unless otherwise stated.
[b] Sulfur, dithiazolethione **3** and the thiazolone **4** byproducts observed.
[c] Isolated by distillation (92 °C, 23 mbar).

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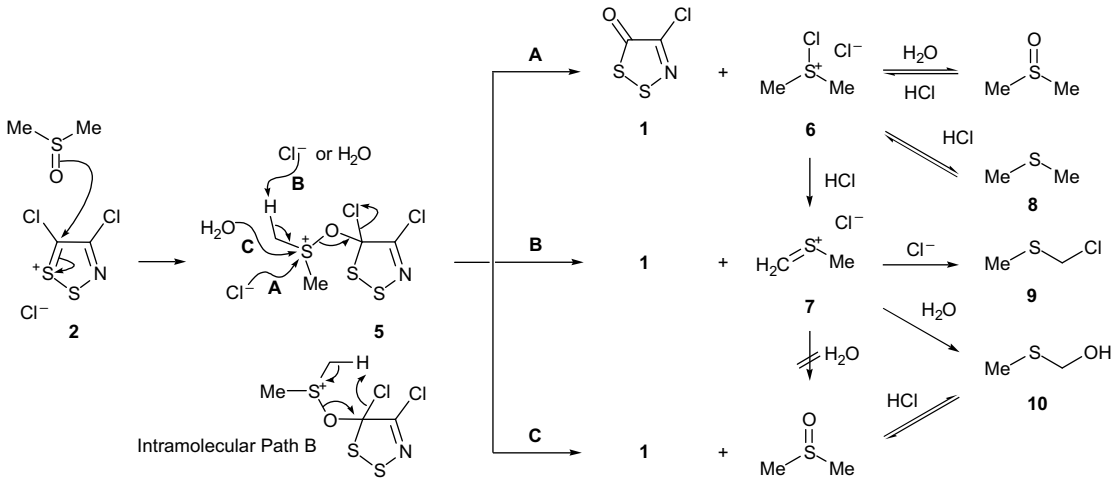
catalytic quantities of DMSO, when water (1 equiv) was added to the reaction mixture (Table 1).

When only 1 mol % of DMSO was used the reaction in THF gave a complex mixture and dithiazolone **1** in moderate yield (44%). Repeating the reactions in either DCM, MeCN or THF in the absence of DMSO (0 mol %) also led to low recoveries of dithiazolone **1** and complex reaction mixtures from which 4-chloro-1,2,3-dithiazole-5*H*-thione **3** and the thiazol-5-one **4** could be identified by TLC. Since the use of MeCN rapidly provided good yields of dithiazolone **1**, the reaction was scaled up. As such reacting a suspension of Appel salt **2** (82.60 mmol) in dry MeCN with DMSO (1 mol %) and water (1 equiv) gave rapidly (2 h) dithiazolone **1**, isolated by distillation (bp 92 °C at 23 mbar) directly from the reaction mixture, in very high yield (91%). At this scale reducing the amount of DMSO to 0.1 mol % led to a longer reaction time (6 h) and lower yield of dithiazolone **1** (77%) although still higher than the reaction performed in the absence of DMSO (0 mol %) (54%) which was complex (by TLC).

A reaction mechanism that supported the catalytic behaviour of DMSO was proposed and some preliminary studies helped identify some important byproducts. The nucleophilic oxygen of the DMSO[8] can attack the highly electrophilic dithiazolium C-5 position to afford a new oxosulfonium dithiazole intermediate **5**, from which a number of possible senarios can be postulated (Scheme 1).



Scheme 1.

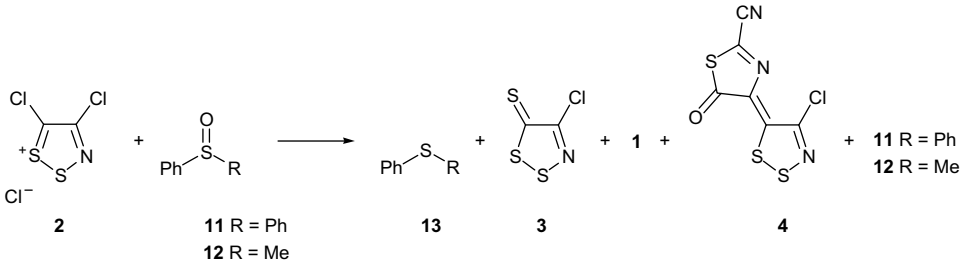
In scenario A, chloride attacks the oxosulfonium intermediate **5** at sulfur[9,10] to eliminate dithiazolone **1** and chlorodimethylsulfonium chloride **6**. In scenario B, water or chloride deprotonates the α-proton from the oxosulfonium intermediate **5** to release dithiazolone **1** and also methyl(methylene)sulfonium chloride **7**. Finaly in scenario C water could directly attack the sulfonium intermediate **5** to release dithiazolone **1** and regenerate DMSO. Scenario B could also proceed via an intramolecular pathway that may be favoured. Interestingly in the presence of HCl and/or water the chemistry of DMSO, chlorodimethylsulfonium chloride **6** and methyl(methylene)sulfonium chloride **7** became more complex. In the presence of HCl, DMSO can convert to the chlorodimethylsulfonium chloride **6**, which can hydrolyse back to DMSO in the presence of water,[11] or eliminate HCl to form methyl(methylene)sulfonium chloride **7**.[12] Methyl(methylene)sulfonium chloride **7** reportedly reacts with water to afford methylthiomethanol **10** and not DMSO while reaction with chloride gave (chloromethyl)(methyl)sulfane **9** and not chlorodimethylsulfonium chloride **6**.[9] Furthermore methylthiomethanol **10** in the presence of HCl was in equilibrium with DMSO.[13] Lastly chlorodimethylsulfonium chloride **6** can suffer chloride assisted Pummerer rearrangement of the unstable chlorodimethylsulfonium chloride **6**.[15] The identity of the species displaying δ_C 38.2 and δ_H 2.87 ppm resonances was more tentative, and the NMR resonances closely matched those reported for hydroxyldimethylsulfonium chloride (δ_C 37.2 and δ_H 2.87 ppm).[15] When the NMR study was repeated using $CDCl_3$ instead of DCM-d_2 a new resonance was observed in both the ^{13}C and ^1H NMR spectra which was tentatively assigned to dimethylsulfide **8** (δ_C 37.2 and δ_H 2.87 ppm). These peaks were avoided when the $CDCl_3$ was passed through a column of basic alumina prior to its use indicating possibly that HCl was responsible for reductive dechlorination of the intermediate chlorodimethylsulfonium chloride **6**. None of these species were actually isolated and these assignments remain tentative.

In an attempt to identify the formation of any byproducts, the reaction between Appel salt **2** (0.036 mmol) and dry DMSO (2.6 μL, 1 equiv) was repeated in DCM-d_2 (0.75 mL) in an NMR tube. Initially ^{13}C NMR (75 MHz) spectroscopy showed the presence of the dithiazolone **1** C-5 and C-4 carbon resonances at 183.3 and 146.95 ppm respectively together with three additional resonances at 52.7, 38.2 and 15.3 ppm. DEPT-180 ^{13}C NMR studies supported the resonance at 52.7 ppm to be a CH_2 while those at 38.2 and 15.3 were both CH_3 resonances. ^1H NMR spectroscopy showed three single resonances at 4.75, 2.87 and 2.29 ppm. After 24 h only the dithiazolone C-5 and C-4 and the 52.7 and 15.3 ppm resonances remained in the ^{13}C spectra while only the 4.75 and 2.29 ppm resonances, integrating 2:3, were visible in the ^1H NMR spectra. These figures corresponded closely to the reported ^{13}C and ^1H NMR resonances for (chloromethyl)(methyl)sulfane **9** (δ_C 52.0, 15.0 and δ_H 4.65, 2.25 ppm),[15] strongly supporting the transformation of DMSO into this molecule on treatment with Appel salt **1** under anhydrous conditions. DMSO can be transformed into (chloromethyl)(methyl)sulfane **9** on treatment with either acid chlorides, chloroiminium salts or chlorine,[15] and the mechanism involved

In dry MeCN the reaction of Appel salt **2** with either diphenyl or methylphenylsulfoxide **11** or **12** (1 equiv) gave dithiazolone **1** in 69 and 84% respectively together with a moderate recovery of the

Examining the reaction of Appel salt **2** with diphenylsulfoxide **11** and methylphenylsulfoxide **12** respectively was also instructive (Table 2).

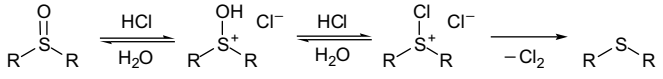
Table 2
Reaction of Appel salt **2** (2.40 mmol) with sulfoxides **11** or **12**, in dry MeCN (25 mL) with water (0–1 equiv) at ca. 20 °C



PhSO·R (equiv)	H_2O (equiv)	Time (h)	**13**	**3**	Yields (%) **1**	**4**	**11** or **12**
11 (1)	0	1	52	0	69	2	**11** (48)
11 (1)	1	1	11	0	76	2	**11** (88)
11 (0.10)	1	2	99	4	70	8	(0)
11 (0.01)	1	6	98	13	59	7	(0)
12 (1)	0	1	—[a]	0	84	Traces	**12** (22)
12 (1)	1	1	—[a]	0	84	1	**12** (91)
12 (0.1)	1	2	—[a]	0	81	3	**12** (71)
12 (0.01)	1	4	—[a]	4	74	6	(0)
— (0)	1	7	—	13	55	6	—

[a] Unresolved and unidentified mixture of organic sulfides.

respective starting sulfoxides **11** (48%) and **12** (22%). Under these conditions the reaction with diphenylsulfoxide **11** also gave diphenylsulfide **13** (R=Ph) (52%), while that with methylphenylsulfoxide **12** gave a mixture of unidentified sulfides. The reduction of sulfoxides into sulfides can occur in the presence of chloride, via the chlorosulfonium species[14] and in the absence of sufficient water in the reaction mixture these chlorosulfonium species cannot hydrolyse back to the starting sulfoxides (Scheme 2). Adding water (1 equiv) to both of these reactions gave higher yields of diphenyl and methylphenylsulfoxides **11** (88%) and **12** (91%) respectively.



Scheme 2.

When Appel salt **2** was treated with only catalytic quantities of either sulfoxide the reaction mixtures gave interesting results. The use of diphenylsulfoxide **11** (10 mol %) gave no recovery of sulfoxide, but afforded the diphenylsulfide **13** (R=Ph) in 98% and the dithiazolone **1** in 70% yield. The use of less diphenylsulfoxide **11** (1 mol %) gave yields of dithiazolone **1** (56%) and thiazol-5-one **4** (8%) similar to the control experiment which had only water (1 equiv) and no sulfoxide. By comparison the use of methylphenylsulfoxide (10 mol %) led to a good yield of dithiazolone **1** (80%) and a good recovery of methylphenylsulfoxide **12** (70%) indicating that the catalytic cycle was still active. With methylphenylsulfoxide **12** (1 mol %) no sulfoxide was recovered despite the reasonable recovery of dithiazolone **1** (70%). Since the formation of sulfides **13** in the reaction mixture can be considered byproducts originating from side reactions competing with the catalytic cycle, it can be deduced that the catalytic cycle involving the diphenylsulfoxide **11** was less efficient than that of the methylphenylsulfoxide **12** which inturn was less efficient than that of DMSO. Presumably the phenyl groups introduce steric crowding around the sulfur atom which favours the chloride promoted dechlorination of the chlorosulfonium to afford the sterically less demanding sulfide. Furthermore, the reaction of the diphenylsulfoxide **11** showed that the α-hydrogens in the methyl sulfoxides were not necessary for the reaction to occur.

3. Summary

A simple and convenient high yielding synthesis of 4-chloro-5*H*-1,2,3-dithiazol-5-one **1** has been achieved by treating 4,5-dichloro-1,2,3-dithiazolium chloride **2** with catalytic amounts of DMSO (1 mol %) in MeCN in the presence of water (1 equiv). Furthermore, a mechanistic study identified several byproducts originating from the DMSO and supported its catalytic role in the above transformation.

4. Experimental

4.1. General

Solvents DCM, MeCN and THF were freshly distilled from CaH_2 under argon. 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 Poly-Therm-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 **2**,[5] was prepared according to the literature procedure.

4.2. Reactions of Appel salt 2 with DMSO: typical procedure (see Table 1)

To a stirred solution of 4,5-dichloro-1,2,3-dithiazolium chloride **2** (500 mg, 2.40 mmol) in dry DCM (25 mL) at ca. 20 °C, H_2O (43 μL, 2.40 mmol) and then DMSO (1.7 μL, 2.40 mmol) were added. After 4.5 h no 4,5-dichloro-1,2,3-dithiazolium chloride **2** remained. The reaction mixture was adsorbed onto silica and chromatography (hexane–DCM, 2:1) gave 4-chloro-5*H*-1,2,3-dithiazol-5-one **1** (319.5 mg, 87%) as pale yellow plates, mp 35–36 °C (lit.,[5] 39 °C) (from pentane) identical to an authentic sample.

4.3. Reactions of Appel salt 2 with diphenyl or methylphenylsulfoxides 11 and 12: typical procedure (see Table 2)

To a stirred solution of 4,5-dichloro-1,2,3-dithiazolium chloride **2** (500 mg, 2.40 mmol) in dry MeCN (25 mL) at ca. 20 °C, H_2O (43 μL, 2.40 mmol) and then diphenylsulfoxide **11** (484.8 mg, 2.40 mmol) were added. After 1 h no 4,5-dichloro-1,2,3-dithiazolium chloride **2** remained. The reaction mixture was adsorbed onto silica and chromatography (hexane–DCM, 8:1) gave diphenylsulfide (49.1 mg, 11%) as an oil identical with an authentic sample, and further elution (hexane–DCM, 2:1) gave 4-chloro-5*H*-1,2,3-dithiazol-5-one **1** (319.5 mg, 87%) as pale yellow plates, mp 35–36 °C (lit.,[5] 39 °C) (from pentane) identical to that reported above. Further elution (hexane–DCM, 2:3) gave (4*E*)-4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4,5-dihydro-5-oxothiazole-2-carbonitrile **4** (3.1 mg, 2%) as dark red crystals, mp (DSC onset) 220 °C (decomp.) [lit.,[16] 252–254 °C (from cyclohexane)] identical to an authentic sample. A final elution (DCM–^{t}BuOMe, 4:1) gave recovered diphenylsulfoxide **11** (421.8 mg, 87%) as a colourless solid, mp 67–68 °C (lit.,[17] 70.5 °C) (hexane) identical to an authentic sample.

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