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The degradation of 4,5-dichloro-1,2,3-dithiazolium chloride in wet solvents

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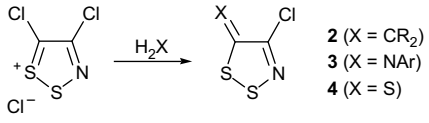
ABSTRACT

4,5-Dichloro-1,2,3-dithiazolium chloride **1** (Appel salt) reacts in wet DCM, THF or MeCN to give elemental sulfur, dithiazole-5-thione **4**, dithiazol-5-one **5** and thiazol-5-one **6**. Furthermore the reaction of 2-phenylthiazol-5(4*H*)-one **12** with Appel salt **1** at ca. 20 °C gives 4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-phenylthiazol-5(4*H*)-one **13** (26%) while at ca. 82 °C a new product 2,2′-diphenyl-4,4′-bithiazol-ylidene-5,5′-dione **14** (36%) is additionally isolated. Finally, 4,4′-bithiazolylidene-5,5′-dione **14** is prepared directly by treating 2-phenylthiazol-5(4*H*)-one **12** with *N*-chlorosuccinimide. All new compounds are fully characterised and rational mechanisms are proposed for the formation of all key compounds.

1. Introduction

4,5-Dichloro-1,2,3-dithiazolium chloride **1** (Appel salt), readily prepared from chloroacetonitrile and disulfur dichloride,[1,2] is an important reagent for the preparation of neutral 1,2,3-dithiazoles.[1,3–5] Appel salt **1** condenses with either active methylenes, 1° anilines or H_2S to afford 4-chloro-5*H*-1,2,3-dithiazolylidenes **2**, dithiazolimines **3** or dithiazolethione **4** respectively in good yields. The chemistry of Appel salt **1** and related 1,2,3-dithiazoles has been reviewed.[6]



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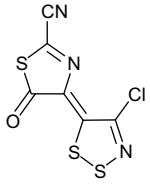
1,2,3-Dithiazoles have uses in both biological and material sciences: *N*-aryldithiazolimines show interesting antitumour,[5] antibacterial,[7] antifungal,[8] and herbicidal[9] activities. A search for organic conductors based on neutral radicals has led to the preparation of two 1,2,3-dithiazolyl radicals[10] and also a tetrathiadiazafulvalene analogue[11] has been prepared and studied.

Often the desired neutral dithiazoles are isolated in good to excellent yields, however, the reactions mixtures normally contain minor impurities, often unreported, which include elemental sulfur, dithiazolethione **4**, and the dithiazolone **5**. In one case Rees and Sivadasan reported the isolation of the structurally unusual, maroon coloured thiazol-5-one **6** from the reaction mixture of Appel salt **1** and aminotetrazole.[12] The structure was solved by single crystal X-ray crystallography but little was reported regarding the compound's origin.



6

We have observed the formation of this thiazol-5-one **6** in several unrelated Appel salt reactions, in particular when the reactions proceeded slowly. This suggested that thiazol-5-one **6** was a degradation product of Appel salt alone and prompted an investigation studying the behaviour of Appel salt in a range of solvents.

2. Formation of the thiazol-5-one 6 from Appel salt 1

Stirring a suspension of Appel salt **1** in either DCM, THF and MeCN gave a good recovery of thiazol-5-one **6** while solvents such as benzene, diethyl ether, MeOH or DMF gave little or no trace of the compound. The behaviour of Appel salt **1** in DCM, THF and MeCN was studied more closely (Table 1).

The study indicated that some water (moisture) was necessary for complete consumption of Appel salt **1**. Protecting the reaction mixture from atmospheric moisture by introducing a drying tube containing anhydrous $CaCl_2$ led to incomplete consumption of Appel salt **1**; after 24 h stirring ca. 50% of the Appel salt **1** was recovered from the reaction mixture by filtration. This implied that

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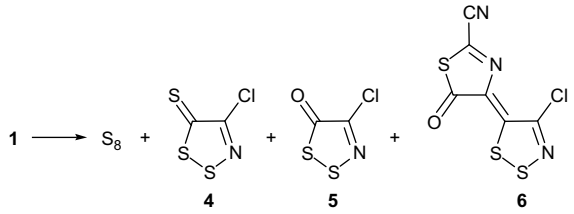
Table 1
Reaction of Appel salt **1** (0.48 mmol) in various solvents (10 mL), at ca. 20 °C



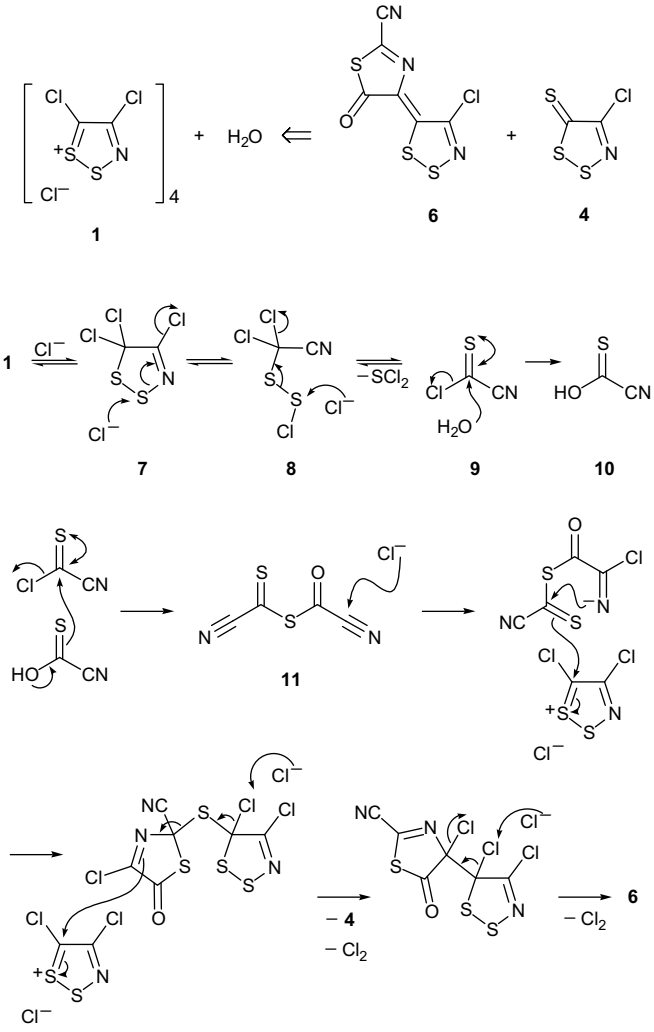
Solvent	Time (h)	Yields[b] (%)				
		1	S_8	**4**	**5**	**6**
DCM	24	0	7	14	31	24
DCM[a]	24	52	7	15	46	21
DCM[a]	6	48	5	7	32	24
DCM[a,c]	24	0	2	8	39	5
THF	1.5	0	6	8	17	23
THF	24	0	13	8	28	25
THF[a,c]	2	0	2	6	12	13
MeCN	3	0	2	17	35	12
MeCN	24	0	3	12	35	15
MeCN[a,c]	4.5	0	1	15	53	13
MeCN[a,d]	1	0	3	10	32	Traces

[a] With $CaCl_2$ drying tube.
[b] Based on recovered starting material.
[c] 1 equiv of water added.
[d] 10 equiv of water added.

water was needed for the reaction to take place, however, the addition of excess water to the reaction mixture led to a reduced yield of the thiazol-5-one **6**. Of the three solvents examined DCM and THF were superior to MeCN and gave yields as high as 25% (yields are based on 4 equiv of Appel salt **1** for each thiazol-5-one **6**, see Scheme 1) while the latter solvent gave at best yields of 15%. Furthermore the consumption of Appel salt **1** proceeded faster in THF. Allowing the reaction mixture to stir for longer did not alter the yield of the thiazol-5-one **6** although the yield of dithiazolone **5** did improve in some cases. The addition (1 equiv) of a variety of additives (S_8, Bu_4NCl, DMF, dithiazolone **5**, dithiazolethione **4**) in all cases led to a reduced yield of thiazol-5-one **6** and so little additional information could be obtained from these studies.

Nevertheless, a close structural analysis of the product revealed the carbon skeleton of at least three Appel salt molecules. In the absence of any other reagent or incorporation of solvent molecule (except H_2O) in the structure, it can only be surmised that the thiazol-5-one **6** was formed only from Appel salt **1** in wet solvent. A tentative proposed mechanism involved a total of four equivalents of Appel salt **1** (Scheme 1).

While Appel salt **1** is normally represented in its ionic form it could be considered to be in equilibrium with the covalent 4,5,5-trichloro-1,2,3-dithiazole **7**, and it is worthy of note that 4-chloro-5,5-difluoro-1,2,3-dithiazole is a distillable oil.[1] Owing to the reduced aromaticity of the 4,5,5-trichloro-1,2,3-dithiazole **7** the S–N bond could be sufficiently weak to cleave in the presence of nucleophilic chloride to afford the thiosulfenyl chloride **8**. This cleavage could also be thermodynamically driven by the release of a new nitrile triple bond. Similar chloride mediated S–S bond cleavage of the thiosulfenyl chloride **8** can lead to the formation of chlorothioformyl cyanide **9**.[13] This unusual small molecule can surprisingly be prepared by pyrolysing trichloroacetonitrile in the presence of elemental sulfur, and was reportedly stable at room temperature; however, except for its polymerisation on cooling, nothing has been reported regarding its chemistry.[13] It would not be unreasonable to assume that this species, being highly electrophilic, could react with any moisture in the reaction mixture to afford cyanomethanethioic *O*-acid **10** which could go on to react via the thione with an additional equivalent of chlorothioformyl cyanide **9**

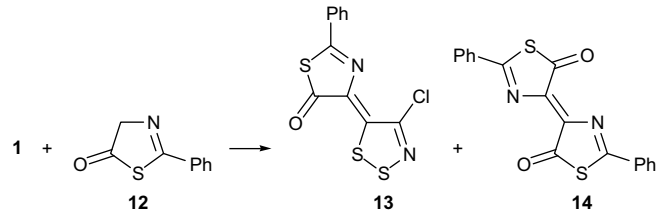


Scheme 1.

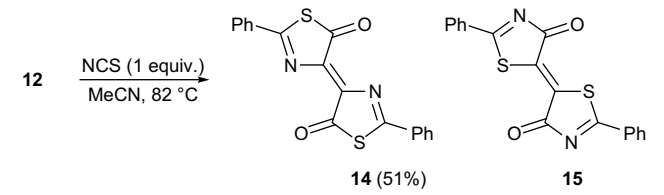
to give the (cyanothioformyl)(cyanoformyl)sulfane **11**. Chloride, which can add to activated nitrile bonds,[14] could attack the cyanoformyl nitrile triggering an intramolecular cyclisation. This chloride induced cyclisation of the (cyanothioformyl)(cyanoformyl)sulfane **11** can give 4-chloro-2-cyanothiazol-5(*H*)-one but this would require the release of elemental sulfur, substantial quantities of which were not isolated from the reaction mixture. To account for the poor recovery of elemental sulfur an additional equivalent of Appel salt **1** was envoked to simultaneously assist this cyclisation step and 'mop up' the sulfur. This additional equivalent of Appel salt **1** can then be released as dithiazolethione **4** and finally after elimination of molecular chlorine afford the observed thiazol-5-one **6**.

Verifying this proposed mechanism, by preparing the chlorothioformyl cyanides **9** was not within the capabilities of our laboratory owing to the molecules precarious synthesis.[13] Furthermore it should be noted that the introduction of the necessary oxygen atom could occur at different stages of the reaction mechanism. Nevertheless, an analogue of the thiazol-5-one **6** was prepared from the readily prepared 2-phenylthiazol-5(4*H*)-one **12**, which on treatment with Appel salt **1** gave the maroon-red 4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-phenylthiazol-5(4*H*)-one **13** (26%) together with traces of other products. At higher reaction temperatures (ca. 82 °C) the yield of thiazol-5-one **13** decreased (17%) and the bright orange coloured 2,2′-diphenyl-4,4′-bithiazolylidene-5,5′-dione **14** was additionally isolated in moderate yield (36%). The formation of 4,4′-bithiazolylidene **14** in the reaction mixture

required oxidation. A pure solution of thiazol-5-one **12** in MeCN at ca. 82 °C open to the atmosphere gave no formation of the dimer **14**. This indicated that Appel salt **1** or one of its decomposition products acted as an oxidizing agent.



While several 4,4′-bithiazolylidene-5,5′-diones have been reported[15] to our knowledge this 2,2′-diphenyl derivative **14** was new. Interestingly the isomeric 2,2′-diphenyl-5,5′-bithiazolylidene-4,4′-dione **15** was known[16] and its postulated formation via 5-chloro-2-phenylthiazol-4(5*H*)-one, suggested a possible independent synthesis. As such treatment of 2-phenylthiazol-5(4*H*)-one **12** with NCS (1 equiv) gave 4,4′-bithiazol-ylidene **14** in 51% yield.



3. Conclusion

Appel salt **1** degrades in wet solvents to give sulfur, dithiazolethione **4**, dithiazolone **5** and the unusal thiazol-5-one **6**. A tentative mechanism for the formation of the latter was proposed. Water thus complicates the formation and isolation of desired neutral 1,2,3-dithiazoles. The exclusion of moisture from the reaction solvent, or the atmosphere could lead to cleaner Appel salt reactions. Finally, the thiazol-5-one **13** was prepared by condensing 2-phenylthiazol-5-one **12** with Appel salt **1** which demonstrated a logical synthetic route to this unusual class of dithiazolylidenes.

4. Experimental

4.1. General

Solvents DCM, MeCN and THF were freshly distilled from CaH_2 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 **1**[1] and 2-phenylthiazol-5(4*H*)-one **12**[17] were prepared according to literature procedures.

4.2. Reactions of Appel salt 1 with various solvents: typical procedure (see Table 1)

To a stirred solution of THF (10 mL) at ca. 20 °C, 4,5-dichloro-1,2,3-dithiazolium chloride **1** (100 mg, 0.48 mmol) was added and the reaction was left open to an air atmosphere. After 1.5 h no 4,5-dichloro-1,2,3-dithiazolium chloride **1** remained. Chromatography (hexane) gave sulfur (1.5 mg, 5%) and further elution (hexane/DCM, 8:1) gave 4-chloro-5*H*-1,2,3-dithiazole-5-thione **4** (3.7 mg, 9%) as red needles, mp 75–76 °C (lit.,[1] 78–79 °C) (from pentane) identical to an authentic sample. Further elution (hexane/DCM, 2:1) gave 4-chloro-5*H*-1,2,3-dithiazol-5-one **5** (11.7 mg, 16%) as pale yellow plates, mp 35–36 °C (lit.,[1] 39 °C) (from pentane) identical with that reported. A final 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 **6** (7.2 mg, 23%) as dark red crystals, mp (DSC onset) 220 °C (decomp.) (lit.,[12] 252–254 °C) (from cyclohexane) identical with that reported.

4.3. (4*E*)-4-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-phenylthiazol-5(4*H*)-one 13

To a stirred solution of 2-phenylthiazol-5(4*H*)-one **12** (17 mg, 0.10 mmol) in dry MeCN (2 mL) at ca. 20 °C, 4,5-dichloro-1,2,3-dithiazolium chloride **1** (20 mg, 0.10 mmol) was added in one portion. After 18 h no 4,5-dichloro-1,2,3-dithiazolium chloride **1** remained and pyridine (16 μL, 0.20 mmol) was added. The mixture was stirred for 2 h and then adsorbed onto silica. Chromatography (hexane/DCM, 1:1) gave the *title compound* **13** (8.4 mg, 26%) as dark red needles, 234–235 °C (from benzene); (Found: C, 42.3; H, 1.6; N, 8.9. $C_{11}H_5ClON_2S_3$ requires C, 42.2; H, 1.6; N, 9.0%); λ_{max} (DCM)/nm 230 (log ε 3.22), 298 inf (3.30), 307 (3.33), 361 (2.72), 385 inf (2.57), 487 inf (3.35), 512 (3.40), 551 inf (3.16); ν_{max}/cm^{-1} 1601s (C═N), 1582m, 1526s, 1485s, 1476m, 1447w, 1431s, 1315w, 1302w, 1283w, 1248s, 1238m, 1206w, 1150s, 1099w, 1076w, 1061w, 1028w, 1001w, 957s, 920w, 891s, 829s, 777w and 758s; δ_H (300 MHz; $CDCl_3$) 8.02–7.99 (2H, m, Ph *H*), and 7.53–7.46 (3H, m, Ph *H*); δ_C (75 MHz; $CDCl_3$) 189.45 (*C*═O), 155.8 (dithiazole *C*-5), 146.4, 146.2, 133.0, 131.7 (Ph *C*H), 129.3 (Ph *C*H) and 127.0 (Ph *C*H); δ_C (75 MHz; DEPT-135; $CDCl_3$) 131.7 (Ph *C*H), 129.3 (Ph *C*H) and 127.0 (Ph *C*H); *m*/*z* (EI) 314 (M^++2, 51%), 312 (M^+, 100), 277 (2), 153 (2), 121 ($C_7H_5S^+$, 73), 103 (1), 77 ($C_6H_5^+$, 11), 51 (2).

4.4. 2,2′-Diphenyl-4,4′-bithiazolylidene-5,5′-dione 14

To a stirred solution of 2-phenylthiazol-5(4*H*)-one **12** (17 mg, 0.10 mmol) in dry MeCN (2 mL), 4,5-dichloro-1,2,3-dithiazolium chloride **1** (20 mg, 0.10 mmol) was added in one portion and the mixture was heated at ca. 82 °C. After 0.5 h no 4,5-dichloro-1,2,3-dithiazolium chloride **1** remained. The mixture was adsorbed onto silica and chromatography (hexane/DCM, 1:1) gave (4*E*)-4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-phenylthiazol-5(4*H*)-one **13** (5.5 mg, 17%) as dark red needles, mp 234–235 °C (from benzene) identical with that described above. Further elution (hexane/DCM, 3:7) gave the *title compound* **14** (6.1 mg, 36%) as orange needles, mp (DSC onset) 290 °C (from 1,2-dichloroethane); (Found: C, 61.7; H, 2.8; N, 7.95. $C_{18}H_{10}N_2O_2S_3$ requires C, 61.7; H, 2.9; N,

8.0%); λ_{max} (DCM)/nm 230 (log ε 3.27), 267 inf (3.02), 304 (3.34), 314 inf (3.33), 349 (3.23), 452 inf (3.46), 479 (3.61), 507 inf (3.49); ν_{max}/cm^{-1} 1726m, 1701s (C=O), 1595m, 1504s, 1481s, 1447s, 1317m, 1283s, 1233w, 1194s, 1182m, 1161w, 1130w, 1099w, 1074w, 1051s, 1026s, 1001s, 955s, 922m, 845w, 804w, 762s and 704m; δ_H (300 MHz; CD_2Cl_2) 8.14–8.11 (4H, m, Ph *H*), 7.70–7.65 (2H, m, Ph *H*) and 7.61–7.55 (4H, m, Ph *H*); *m*/*z* (EI) 350 (M^+, 9%), 121 ($C_7H_5S^+$, 100), 77 ($C_6H_5^+$, 25), 69 (2), 51 (7).

4.5. Independent synthesis of 2,2′-diphenyl-4,4′-bithiazolylidene-5,5′-dione 14

To a stirred solution of 2-phenylthiazol-5(4*H*)-one **12** (20 mg, 0.11 mmol) in dry MeCN (1 mL), *N*-chlorosuccinimide (15.1 mg, 0.11 mmol) was added in one portion and the mixture was heated at ca. 82 °C for 3.5 h until no thiazolone **12** remained (TLC). The mixture was then allowed to cool to ca. 20 °C, adsorbed onto silica and chromatographed (hexane/DCM, 3:7) to afford the title compound **14** (9.9 mg, 51%) as orange needles, mp (DSC onset) 290 °C (from 1,2-dichloroethane) identical with that reported above.

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