

Article

## The Reaction of 4,5-Dichloro-1,2,3-dithiazolium Chloride with Sulfinimides: A New Synthesis of *N*-Aryl-1,2,3-dithiazolamines

Andreas S. Kalogirou and Panayiotis A. Koutentis \*

Department of Chemistry, University of Cyprus, P.O. Box 20537, 1678 Nicosia, Cyprus;  
E-mail: andreas\_ch05@hotmail.com (A-S.K.)

\* Author to whom correspondence should be addressed; E-mail: koutenti@ucy.ac.cy;  
Tel.: +35722892783; Fax: +35722892809

Received: 26 May 2009; in revised form: 10 June 2009 / Accepted: 12 June 2009 /

Published: 2 July 2009

---

**Abstract:** *N*-Aryl-*S,S*-dimethylsulfinimides **3** (Ar = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>), **4** (Ar = Ph) and **5** (Ar = 4-Tol) react with Appel salt **1** to give the corresponding *N*-aryl-(4-chloro-5*H*-1,2,3-dithiazolylidene)benzenamines **8** (Ar = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>), **9** (Ar = Ph) and **10** (Ar = 4-Tol) in 84, 94 and 87% yields, respectively. The reaction proceeds in the absence of base and a proposed reaction mechanism is given.

**Keywords:** dithiazole; dithiazolimine; sulfinimide; sulfilimine; heteroarene; appel salt

---

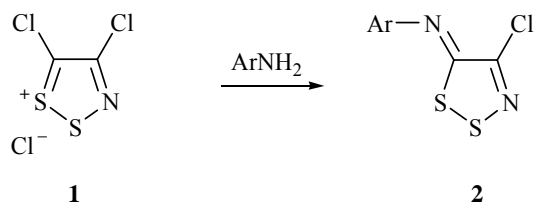
### 1. Introduction

*N*-Aryl-1,2,3-dithiazol-5*H*-imines show interesting antitumour [1], antibacterial [2-4], antifungal [5-7], and herbicidal [8] activities. The biological activity could be due to the 1,2,3-dithiazole ring, which acts as a powerful inhibitor of several enzymes that are structurally related to serine proteases [9]. Furthermore *N*-aryldithiazolamines are useful precursors to other heterocycles through ANRORC [10-11] style ring transformations. For example the thermolysis of *N*-aryldithiazolamines can afford benzothiazoles [12,13], benzimidazoles [14], thiazolopyridines [15] and benzoxazines [16].

Most primary arylamines react readily with 4,5-dichloro-1,2,3-dithiazolium chloride **1** (Appel salt) [9,17-19] to give, after treatment with tertiary amine base (2 equiv.), the corresponding *N*-aryl-4-chloro-5*H*-1,2,3-dithiazolamines **2** in good to excellent yields [20,21] (Scheme 1). In some cases, such

as with arylamides [22], heteroarylamines [21,23] or alkylamines [20,21], the reactions are low yielding or complex. As such this simple condensation reaction has room for improvement.

**Scheme 1.** The classical reaction of anilines with Appel salt **1** to afford dithiazolimines **2**.

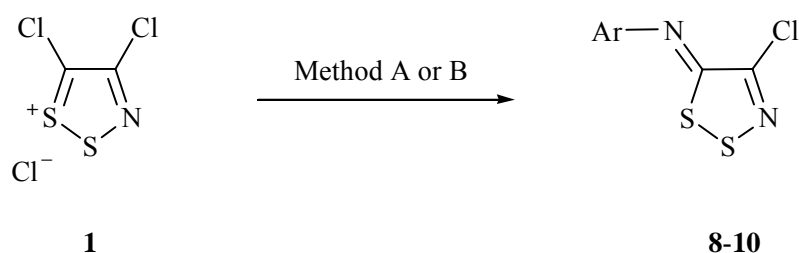


Sulfimides act as transfer reagents in the form of an “activated amine”. For example sulfimides react with nitrile oxides to afford 1*H*-1,2,4-triazole 2-oxides [24], and react with alkoxychromium (Fischer) carbenes to form imidates [25]. In view of their use as *N*-transfer reagents to electrophiles, we examined an alternative route to *N*-aryl-1,2,3-dithiazolimines by reacting *N*-aryl-*S,S*-dimethylsulfimides with Appel salt **1**.

## 2. Results and Discussion

We were able to prepare five sulfimides according to literature procedures (**3**, R = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> [26]; **4**, R = Ph [26]; **5**, R = 4-Tol [26]; **6**, R = Pyrid-2-yl [27]; and **7**, R = Bz [26]). Disappointingly, treating Appel salt **1** with either the *N*-pyrid-2-yl or *N*-benzoyl sulfimides **6** and **7** (1 equiv.) in DCM (dry) at *ca.* 20 °C gave only complex reaction mixtures (by TLC) that were not investigated further. Nevertheless the three *N*-aryl-sulfimides **3-5** reacted rapidly with Appel salt **1** to give the anticipated *N*-aryl-(4-chloro-5*H*-1,2,3-dithiazol-5-imines) **8-10** in excellent yields (84, 94 and 87%, respectively), comparable to those obtained in our hands from the classical [21] condensation of Appel salt **1** with the corresponding aniline (1 equiv.) and pyridine (2 equiv.) (Table 1).

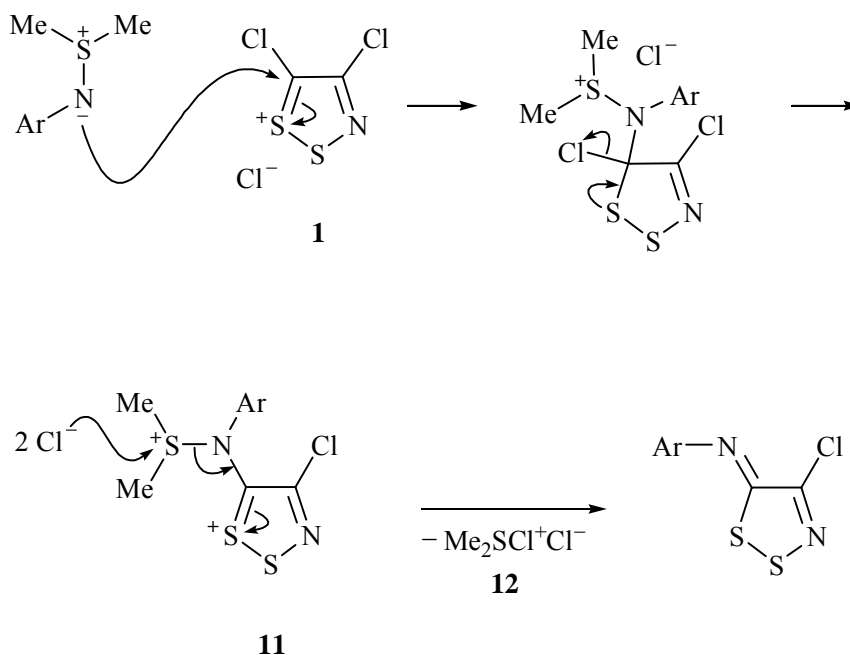
**Table 1.** Reaction of Appel salt **1** (0.96 mmol) with: sulfimides (Method A) and anilines (Method B), in dry DCM, at *ca.* 20 °C.



Method	Conditions (equiv.)	Yields (%)
<b>A</b>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> N=S(Me) <sub>2</sub> <b>3</b> (1), 2 h	<b>8</b> (84)
<b>B</b>	i) 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub> (1), 2.5 h, ii) C <sub>5</sub> H <sub>5</sub> N (2), 2 h	<b>8</b> (85), (lit. [21], 85)
<b>A</b>	PhN=S(Me) <sub>2</sub> <b>4</b> (1), 3 h	<b>9</b> (94)
<b>B</b>	i) PhNH <sub>2</sub> (1), 0.5 h, ii) C <sub>5</sub> H <sub>5</sub> N (2), 2 h	<b>9</b> (92), (lit. [21], 92)
<b>A</b>	4-MeC <sub>6</sub> H <sub>4</sub> N=S(Me) <sub>2</sub> <b>5</b> (1), 2.5 h	<b>10</b> (87)
<b>B</b>	i) 4-MeC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub> (1), 1 h, ii) C <sub>5</sub> H <sub>5</sub> N (2), 2 h	<b>10</b> (93), (lit. [21], 95)

Repeating the reaction of the *N*-(4-nitrophenyl)sulfimide **3** with Appel salt **1** in dry MeCN at *ca.* 20 °C gave marginally lower yields of the dithiazolimine **8** (79%). A tentative mechanism for these reactions is proposed (Scheme 2).

**Scheme 2.** Proposed reaction mechanism for the reaction of sulfimide with 4,5-dichloro-1,2,3-dithiazolium chloride **1**.



The *N*-aryl-*S,S*-dimethylsulfimide can attack Appel salt **1** at the highly electrophilic C-5 position to afford, after elimination of chloride, a new dithiazolium intermediate **11** (Scheme 2). The cationic dimethylsulfonium can depart assisted by chloride or an equivalent species. The proposed chlorodimethylsulfonium chloride **12** byproduct was a well known species and under the reaction conditions can convert into a number of alternative species including DMSO on hydrolysis [28] or dimethylsulfide [29,30] on reductive dechlorination.

It is worth noting however, that while the reaction of Appel salt **1** with *N*-aryl-*S,S*-dimethylsulfimides provides an alternative, mild and fast route to dithiazolimines in the absence of base, it has drawbacks owing to the limited availability of a wide range of sulfimide reagents [26,27,31].

### 3. Conclusions

*N*-Aryl-*S,S*-dimethylsulfimides **3** (Ar = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>), **4** (Ar = Ph) and **5** (Ar = 4-Tol) react with Appel salt **1** to give the corresponding *N*-aryl-(4-chloro-5*H*-1,2,3-dithiazolylidene)benzenamines **8** (Ar = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>), **9** (Ar = Ph) and **10** (Ar = 4-Tol) in 84, 94 and 87% yields, respectively. The reaction demonstrates an alternative and mild route to 1,2,3-dithiazolimines which does not require the addition of base (2 equiv.), but it is synthetically limited owing to the poor availability and stability of the required sulfimide reagents.

## 4. Experimental

### 4.1. General

Solvents DCM and MeCN were freshly distilled from CaH<sub>2</sub> under argon. Reactions were protected from atmospheric moisture by CaCl<sub>2</sub> drying tubes. Anhydrous Na<sub>2</sub>SO<sub>4</sub> 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<sub>254</sub>). 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, Koeffler-Hotstage Microscope apparatus. 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. <sup>1</sup>H- and <sup>13</sup>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** [20], *S,S*-dimethyl-*N*-(4-nitrophenyl)-sulfimide **3** [26], *S,S*-dimethyl-*N*-phenylsulfimide **4** [26], *S,S*-dimethyl-*N*-(4-tolyl)sulfimide **5** [26], *S,S*-dimethyl-*N*-(pyrid-2-yl)sulfimide **6** [27], and *N*-benzoyl-*S,S*-dimethylsulfimide **7** [26], were prepared according to literature procedures.

### 4.2. Reactions of Appel salt **1** with sulfimides: Typical procedure (see Table 1)

To a stirred solution of 4,5-dichloro-1,2,3-dithiazolium chloride **1** (100 mg, 0.48 mmol) in dry DCM (10 ml) at *ca.* 20 °C, *S,S*-dimethyl-*N*-(4-nitrophenyl)sulfimide **3** (95.5 mg, 0.48 mmol) was added in one portion. After 2 h no 4,5-dichloro-1,2,3-dithiazolium chloride remained. The reaction mixture was adsorbed onto silica and chromatography (hexane–DCM, 1 : 1) gave *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-nitrobenzenamine **8** (110.1 mg, 84%) as yellow needles, mp 161-162 °C (lit. [5], 160 °C) (from cyclohexane) identical with an authentic sample.

*N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)benzenamine **9**: Similarly treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **1** (100 mg, 0.48 mmol) with *S,S*-dimethyl-*N*-phenylsulfimide **4** (73.4 mg, 0.48 mmol) gave the title compound **9** (103.1 mg, 94%) as yellow needles, mp 61-62 °C (lit. [5], 63-65 °C) (from cyclohexane) identical with an authentic sample.

*N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-methylbenzenamine **10**: Similarly treatment of compound **1** (100 mg, 0.48 mmol) with *S,S*-dimethyl-*N*-(4-tolyl)sulfimide **5** (80.1 mg, 0.48 mmol) gave the title compound **9** (101.9 mg, 87%) as yellow needles, mp 64-65 °C (lit. [5], 66-67 °C) (from cyclohexane) identical with an authentic sample.

### 4.3. Reactions of Appel salt **1** with anilines: Typical procedure [21] (see Table 1)

To a stirred solution of 4-nitroaniline (66.2 mg, 0.48 mmol) in DCM (2 ml) at *ca.* 20 °C, 4,5-dichloro-1,2,3-dithiazolium chloride **1** (100 mg, 0.48 mmol) was added in one portion. After 2 h no Appel salt **1** remained and pyridine (80  $\mu$ l, 0.96 mmol) was added. The mixture was stirred for additional 2 h and then adsorbed onto silica. Chromatography (light petroleum–DCM, 1 : 1) gave *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-nitrobenzenamine **8** (110.1 mg, 84%) as yellow needles, mp 161–162 °C (lit. [5], 160 °C) (from cyclohexane) identical to an authentic sample.

*N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)benzenamine **9**: Similarly treatment of aniline (43.8  $\mu$ l, 0.48 mmol) with 4,5-dichloro-1,2,3-dithiazolium chloride **1** (100 mg, 0.48 mmol) gave the title compound **9** (100.9 mg, 92%) as yellow needles, mp 61–62 °C (lit. [5], 63–65 °C) (from cyclohexane) identical to an authentic sample.

*N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-methylbenzenamine **10**: Similarly treatment of 4-methylaniline (51.4 mg, 0.48 mmol) with 4,5-dichloro-1,2,3-dithiazolium chloride **1** (100 mg, 0.48 mmol) gave the title compound **10** (111.3 mg, 95%) as yellow needles, mp 64–65 °C (lit. [5], 66–67 °C) (from cyclohexane) identical to an authentic sample.

### Acknowledgements

The authors wish to thank the Cyprus Research Promotion Foundation [Grant No. NEAYPIOΔOMH/NEKYII/0308/02] and the following organisations in Cyprus for generous donations of chemicals and glassware: the State General Laboratory, the Agricultural Research Institute and the Ministry of Agriculture. Furthermore we thank the A.G. Leventis Foundation for helping to establish the NMR facility in the University of Cyprus.

### References and Notes

1. Konstantinova, L.S.; Bol'shakov, O.I.; Obruchnikova, N.V.; Laborie, H.; Tanga, A.; Sopéna, V.; Lanneluc, I.; Picot, L.; Sablé, S.; Thiéry, V.; Rakitin, O.A. One-pot Synthesis of 5-Phenylimino, 5-Thieno or 5-Oxo-1,2,3-dithiazoles and Evaluation of their Antimicrobial and Antitumor Activity. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 136–141.
2. Cottenceau, G.; Besson, T.; Gautier, V.; Rees, C.W.; Pons, A.M. Antibacterial Evaluation of Novel *N*-Arylimino-1,2,3-dithiazoles and *N*-Arylcyanothioformamides. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 529–532.
3. Thiery, V.; Rees, C.W.; Besson, T.; Cottenceau, G.; Pons, A.M. Antimicrobial Activity of Novel *N*-Quinolinylnyl and *N*-Naphthylimino-1,2,3-dithiazoles. *Eur. J. Med. Chem.* **1998**, *33*, 149–153.
4. Joseph, R.W.; Antes, D.L.; Osei-Gyimah, P. Antimicrobial Compounds with Quick Speed of Kill. *US Pat.* 5688744, 1997.
5. Moore, J.E. Certain 4-Halo-5-aryl-1,2,3-dithiazole Compounds and their Preparation. *US Pat.* 4059590, 1977.
6. Appel, R.; Janssen, H.; Haller, I.; Plempel, M. 1,2,3-Dithiazolderivate, Verfahren zu ihrer Herstellung Sowie ihre Verwendung als Arzneimittel. *DE Pat.* 2848221, 1980.

7. Besson, T.; Rees, C.W.; Cottenceau, G.; Pons, A.M. Antimicrobial Evaluation of 3,1-Benzoxazin-4-ones, 3,1-Benzothiazin-4-ones, 4-Alkoxyquinazolin-2-carbonitriles and *N*-Arylimino-1,2,3-dithiazoles. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2343-2348.
8. Mayer, R.; Foerster, E.; Matauschek, B. Verfahren zur Herstellung von Aromatisch oder Heteroaromatisch Substituierten Cyanthioformamiden. *DD Pat.* 212387, 1984.
9. Konstantinova, L.S.; Rakitin, O.A. Synthesis and Properties of 1,2,3-Dithiazoles, *Russ. Chem. Rev.* **2008**, *77*, 521-546.
10. van der Plas, H.C. Chapter II S<sub>N</sub>(ANRORC) Reactions in Azines, Containing an "Outside" Leaving Group. *Adv. Heterocycl. Chem.* **1999**, *74*, 9-86.
11. van der Plas, H.C. Chapter III S<sub>N</sub>(ANRORC) Reactions in Azaheterocycles Containing an "Inside" Leaving Group. *Adv. Heterocycl. Chem.* **1999**, *74*, 87-151.
12. Rees, C.W. Polysulfur-nitrogen Heterocyclic Chemistry. *J. Heterocycl. Chem.* **1992**, *29*, 639-651.
13. Besson, T.; Dozias, M.J.; Guillard, J.; Rees, C.W. New Route to 2-Cyano-benzothiazoles via *N*-Arylimino-1,2,3-dithiazoles. *J. Chem. Soc. Perkin Trans. 1* **1998**, 3925-3926.
14. Rakitin, O.A.; Rees, C.W.; Vlasova, O.G. Direct Synthesis of 2-Cyano-benzimidazoles and the Generation of S<sub>2</sub>. *Tetrahedron Lett.* **1996**, *37*, 4589-4592.
15. Christoforou, I.C.; Koutentis, P.A.; Michaelidou, S.S. 1,2,3-Dithiazole Chemistry in Heterocyclic Synthesis. *Arkivoc* **2006**, *7*, 207-223.
16. Besson, T.; Guillaumet, G.; Lamazzi, C.; Rees, C.W. Synthesis of 3,1-Benzoxazines, 3,1-Benzothiazines and 3,1-Benzoxazepines via *N*-Arylimino-1,2,3-dithiazoles. *Synlett* **1997**, 704-706.
17. Rakitin, O.A. In *Comprehensive Heterocyclic Chemistry* 3rd ed. Zhdankin, V.V.; Katritzky, A.R.; Ramsden, C.A.; Scriven, E.F.V.; Taylor, R.J.K. Eds.; Elsevier: Oxford, UK, 2008; vol. 6, ch. 6.01, p. 1.
18. Kim, K. Synthesis and Reactions of 1,2,3-Dithiazoles. *J. Sulfur Chem.* **1998**, *21*, 147-207.
19. Kim, K. Recent Advances in 1,2,3-Dithiazole Chemistry. *Phosphorus Sulfur Silicon Relat. Elem.* **1997**, *120*, 229-244.
20. Appel, R.; Janssen, H.; Siray M.; Knoch, F. Synthese und Reaktionen des 4,5-Dichlor-1,2,3-dithiazolium-chlorids. *Chem. Ber.* **1985**, *118*, 1632-1643.
21. English, R.F.; Rakitin, O.A.; Rees, C.W.; Vlasova, O.G. Conversion of Imino-1,2,3-dithiazoles into 2-Cyanobenzothiazoles, Cyanoimidoyl Chlorides and Diatomic Sulfur. *J. Chem. Soc. Perkin Trans. 1* **1997**, 201-206.
22. English, R.F. Thesis, University of London, 1989.
23. Cuadro, A.M.; Alvarez-Buila, J. 4,5-Dichloro-1,2,3-dithiazolium Chloride (Appel's Salt): Reactions with *N*-Nucleophiles. *Tetrahedron* **1994**, *50*, 10037-10046.
24. Gilchrist, T.L.; Harris, C.J.; Hawkins, D.G.; Moody, C.J.; Rees, C.W. Synthesis of 1*H*-1,2,4-Triazole 2-Oxides and Annelated Derivatives. *J. Chem. Soc. Perkin Trans. 1* **1976**, 2166-2170.
25. Alcaide, B.; Casarrubios, L.; Domhiguez, G.; Sierra, M.A. Reaction of Chromium (Fischer) Carbenes and Sulfilimines. *J. Org. Chem.* **1993**, *58*, 3886-3894.
26. Sharma, A.K.; Ku, T.; Dawson, A.D.; Swern, D. Iminosulfuranes. XV. Dimethyl Sulfoxide-trifluoroacetic Anhydride. New and Efficient Reagent for the Preparation of Iminosulfuranes. *J. Org. Chem.* **1975**, *40*, 2758-2764.

27. Claus, P.K.; Rieder, W.; Hofbauer, P.; Vilsmaier, E. *N*-Aryl Sulfinimides. *Tetrahedron* **1975**, *31*, 505-510.
28. Warthmann, W.; Schmidt, A. Reaktionsprodukte aus Chlorsulfonium-Salzen und Alkoholen bzw. Wasser und deren IR-Spektren. *Chem. Ber.* **1975**, *108*, 520-527.
29. Chasar, D.W.; Pratt, T.M.; Shockcor, J.P. The Reaction of Anhydrous HCl/Chloroform with Diaryl Sulfoxides. *Phosphorus Sulfur Silicon Relat. Elem.* **1980**, *8*, 183-186.
30. Madesclaire, M. Reduction of Sulfoxides to Thioethers. *Tetrahedron* **1988**, *44*, 6537-6580.
31. Claus, P.; Vycudilik, W. Methylthiomethylierung von Aromatischen Aminen: *N*-Aryl-*S,S*-dimethylsulfinimide als Zwischenstufen. *Tetrahedron Lett.* **1968**, *9*, 3607-3610.

*Sample Availability:* Samples of the compounds are available from the corresponding author.

© 2009 by the authors; licensee Molecular Diversity Preservation International, Basel, Switzerland. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution license (<http://creativecommons.org/licenses/by/3.0/>).