# Synthesis of 1,3,4-thiadiazolines from 1,2-dithiole-3-thiones

**Vladimir A. Ogurtsov,[a] Oleg A. Rakitin,*[a] Charles W. Rees*[b] and Alexey A. Smolentsev[a]**

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 095 135 5328; e-mail: orakitin@ioc.ac.ru*

[b] *Department of Chemistry, Imperial College of Science, Technology and Medicine, London, UK SW7 2AZ. E-mail: c.rees@imperial.ac.uk*

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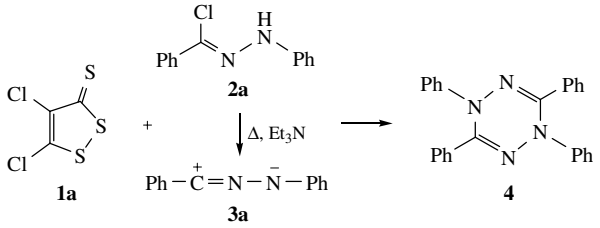
**The thiocarbonyl group of 4,5-dichloro-1,2-dithiole-3-thione reacts as a 1,3-dipolarophile towards diaryl nitrile imines by 1,3-dipolar cycloaddition followed by opening of the dithiole ring with loss of sulfur to give 5-methylene-1,3,4-thiadiazolines; this reaction together with nucleophilic displacement (before or after cycloaddition) of the selectively reactive 5-chlorine atom provides a rapid access to stable 5-methylene-1,3,4-thiadiazolines.**

1,3,4-Thiadiazoles and thiadiazolines are of great pharmaceutical and industrial importance.[1] Technological uses include dyes, optically active liquid crystals and photographic materials; large numbers have been patented as herbicides, insecticides, fungicides, bactericides, and anthelmintics, and in medicine derivatives were found to have antihypertensive, anticonvulsive and other activities.[1,2]

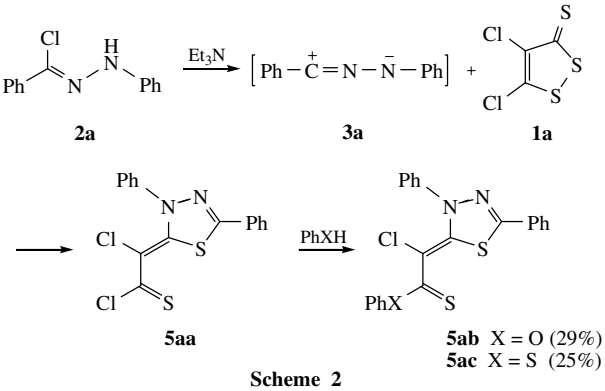
Many methods are available for the synthesis of these compounds, and 1,3-dipolar cycloaddition showed early promise.[1] Such a reaction was the addition of nitrile imines, from the corresponding hydrazonyl chlorides to the C=S group of thioamides and thioketones,[1] and these included two isolated reactions between nitrile imines and 1,2-dithiole-3-thiones.[3,4] Recently, we found that this reaction can be extended to fused 1,2-dithiole-3-thiones such as bis[1,2]dithiolo[1,4]thiazines.[5]

4,5-Dichloro-1,2-dithiole-3-thione **1a** is readily available and has useful functionality and reactivity;[6] it seemed to us that if **1a** reacted similarly with nitrile imines it could provide a ready route to a range of unusual 1,3,4-thiadiazolines suitable for biological testing and further elaboration. However, the addition of diphenyl nitrile imine **3a** to **1a** gives unstable products, which could not be isolated from the reaction mixture. The only substance obtained, in boiling benzene, was dihydrotetrazine **4**, the known product of dimerization of **3a** (Scheme 1).



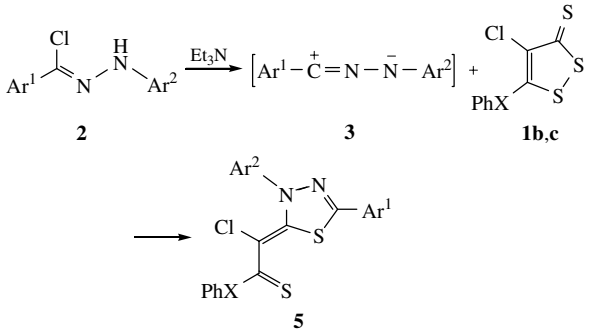
**Scheme 1**

It seems likely that the expected 1:1 adduct **5aa** was formed by 1,3-dipolar cycloaddition followed by loss of sulfur[5] but, as an aliphatic thioacyl chloride,[7] it was too unstable to be readily isolated. If so, it might be intercepted by nucleophiles at the thioacyl group to give more stable thiocarboxylic acid derivatives.[8] Indeed, the reaction of **1a** and **2a** with triethylamine in benzene at room temperature followed by addition of phenol or thiophenol led to thiadiazolines **5**, X = O and S, though in low yields (Scheme 2).



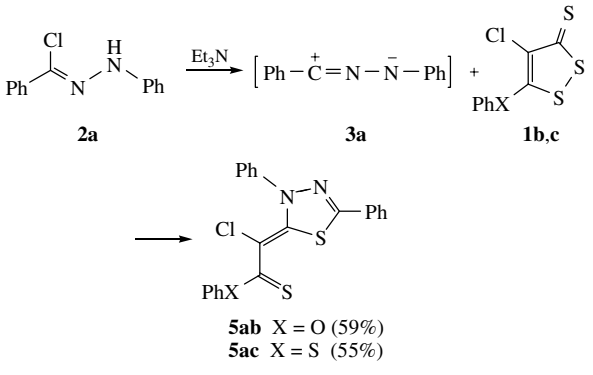
**Scheme 2**

**Table 1** Yields of 1,3,4-thiadiazoles **5** in the reaction of substituted 4-chloro-1,2-dithiole-3-thiones **1b**,**c** with various diaryl nitrile imines.



| **2** $Ar^1$, $Ar^2$ | **1b** X = O | **1c** X = S |
|---|---|---|
| **a** $Ar^1 = Ar^2 = Ph$ | **5ab** 59% | **5ac** 55% |
| **b** $Ar^1$ = 4-$NO_2C_6H_4$, $Ar^2 = Ph$ | **5bb** 65% | **5bc** 62% |
| **c** $Ar^1 = Ph$, $Ar^2$ = 4-$NO_2C_6H_4$ | **5cb** 59% | **5cc** 57% |
| **d** $Ar^1$ = 4-$MeC_6H_4$, $Ar^2 = Ph$ | **5db** 61% | **5dc** 59% |

Alternatively, the reactive 5-chlorine in **1a** could first be displaced by the nucleophile to give stable products (**1b**,**c**), which underwent cycloaddition with diphenyl nitrile imine **3a** to give thiadiazolines **5** in much better yields (Scheme 3).† The ejected sulfur could be isolated by column chromatography in an almost quantitative yield.



**Scheme 3**

To confirm the stability of 1,3,4-thiadiazolines and to broaden the scope of this reaction, we also investigated the reactions of 5-phenoxy- **1b** and 5-phenylthio-1,2-dithiole-3-thione **1c** with substituted nitrile imines **3** (Table 1). In all cases, 1,3,4-thiadiazolines **5** were obtained under the same conditions as for **5ab**,**ac** in comparable yields (55–65%) (Table 1) and were stable to column chromatography and in storage at room temperature.

Thus, nucleophilic displacement of the reactive 5-chlorine in 4,5-dichloro-1,2-dithiole-3-thione **1** and cycloaddition of diaryl nitrile imines provides a short and ready access to 5-methylene-1,3,4-thiadiazolines capable of further elaboration.

† *General procedure for the preparation of* **5**. Triethylamine (1.7 mmol) was added to a stirred solution of *N*-aryl-α-chloroarylhydrazone **2** (1.5 mmol) in benzene (15 ml). Then, a solution of 5-substituted 4-chloro-1,2-dithiole-3-thiones **1a–c** (1 mmol) in benzene (10 ml) was added dropwise, and stirring was continued for 1 h. Triethylamine hydrochloride was filtered off, the filtrate was evaporated under reduced pressure, and final products and sulfur were separated by column chromatography (Silica gel Merck 60).

All new compounds were characterised by elemental analysis, $^1$H NMR, IR and mass spectra and for some of them by HMRS.

**5ab**: yellow crystals, mp 181–182 °C. $^1$H NMR ($CDCl_3$) $\delta$: 7.10 (d, 2H, ArH, *J* 8.1 Hz), 7.28 (m, 1H, ArH), 7.50 (m, 10H, ArH), 7.87 (d, 2H, ArH, *J* 6.8 Hz). IR (KBr, $\nu$/cm$^{-1}$): 1592 (Ph), 1488, 1440, 1320, 1200, 1164, 1128, 920, 764. MS, *m*/*z* (%): 422 ($M^+$, 8), 329 (M – PhO, 72), 313 (M – PhS, 100). Found $M^+$, 422.0326; $C_{22}H_{15}ClN_2OS_2$ requires 422.0314. Found (%): C, 62.33; H, 3.68; N, 6.54. Calc. for $C_{22}H_{15}ClN_2OS_2$ (%): C, 62.48; H, 3.57; N, 6.62.

**5bb**: red crystals, mp 185–186 °C. $^1$H NMR ($CDCl_3$) $\delta$: 7.10 (m, 2H, ArH), 7.30 (m, 1H, ArH), 7.52 (m, 7H, ArH), 8.06 (d, 2H, ArH, *J* 6.9 Hz), 8.34 (d, 2H, ArH, *J* 8.6 Hz). IR (KBr, $\nu$/cm$^{-1}$): 3064 (C–H), 1616, 1588, 1536, 1520 ($NO_2$), 1488, 1444, 1344 ($NO_2$), 1316, 1196, 1176 (C=S), 920, 852, 760. MS, *m*/*z* (%): 467 ($M^+$, 7), 374 (M – PhO, 39), 358 (M – PhS, 100), 328 (M – PhS, NO, 85), 312 (M – PhS, $NO_2$, 30). Found $M^+$, 467.0174; $C_{22}H_{14}ClN_3O_3S_2$ requires 467.0165. Found (%): C, 56.23; H, 3.15; N, 8.56. Calc. for $C_{22}H_{14}ClN_3O_3S_2$ (%): C, 56.47; H, 3.02; N, 8.98.

**5cb**: bright yellow crystals, mp 187–189 °C. $^1$H NMR ($CDCl_3$) $\delta$: 7.12 (m, 2H, ArH), 7.30 (m, 1, ArH), 7.47 (m, 5H, ArH), 7.70 (m, 2H, ArH), 7.85 (m, 2H, ArH), 8.37 (m, 2H, ArH). $^{13}$C NMR ($CDCl_3$) $\delta$: 97.21, 128.52, 145.95, 146.81, 153.80, 154.74, 157.63, (7*sp*$^2$-tertiary C), 122.69, 124.18, 126.23, 126.38, 127.32, 129.37, 129.51, 131.80 (8C–H), 195.76 (C=S). IR (KBr, $\nu$/cm$^{-1}$): 1608, 1592, 1520 ($NO_2$), 1460, 1348 ($NO_2$), 1304, 1196, 1176 (C=S), 920, 760. MS, *m*/*z* (%): 467 ($M^+$, 7), 374 (M – PhO, 41), 358 (M – PhS, 100), 328 (M – PhS, NO, 98), 312 (M – PhS, $NO_2$, 43). Found $M^+$, 467.0171; $C_{22}H_{14}ClN_3O_3S_2$ requires 467.0165. Found (%): C, 55.94; H, 3.19; N, 8.89. Calc. for $C_{22}H_{14}ClN_3O_3S_2$ (%): C, 56.47; H, 3.02; N, 8.98.

**5db**: yellow crystals, mp 186–188 °C. $^1$H NMR ($CDCl_3$) $\delta$: 2.42 (s, 3H, Me), 7.12 (m, 2H, ArH), 7.29 (s, 2H, ArH), 7.51 (m, 8H, ArH), 7.74 (d, 2H, ArH, *J* 7.9 Hz). IR (KBr, $\nu$/cm$^{-1}$): 1592, 1492, 1448, 1360, 1324, 1200, 1164, 1132, 920, 760. MS, *m*/*z* (%): 436 ($M^+$, 10), 343 (M – PhO, 61), 327 (M – PhS, 100). Found $M^+$, 436.0466; $C_{23}H_{17}ClN_2OS_2$ requires 436.0471. Found (%): C, 63.22; H, 3.92; N, 6.41. Calc. for $C_{23}H_{17}ClN_2OS_2$ (%): C, 62.96; H, 4.00; N, 6.38.

**5ac**: dark red crystals, mp 197–200 °C. $^1$H NMR ($CDCl_3$) $\delta$: 7.48 (m, 13H, ArH), 7.82 (m, 2H, ArH). IR (KBr, $\nu$/cm$^{-1}$): 1592, 1488, 1440, 1404, 1276, 1148, 968, 768. MS, *m*/*z* (%): 438 ($M^+$, 5), 329 (M – PhS, 100). Found $M^+$, 438.0083; $C_{22}H_{15}ClN_2S_3$ requires 438.0086. Found (%): C, 59.58; H, 3.75; N, 6.14. Calc. for $C_{22}H_{15}ClN_2S_3$ (%): C, 60.19; H, 3.44; N, 6.38.

**5bc**: deep red crystals, mp 175–178 °C. $^1$H NMR ($CDCl_3$) $\delta$: 7.48 (m, 10H, ArH), 8.00 (d, 2H, ArH, *J* 8.8 Hz), 8.30 (d, 2H, ArH, *J* 8.8 Hz). IR (KBr, $\nu$/cm$^{-1}$): 1592, 1540, 1520 ($NO_2$), 1492, 1420, 1344 ($NO_2$), 1276, 976, 852. MS, *m*/*z* (%): 374 (M – PhS, 37), 328 (M – PhS, $NO_2$, 35). Found (%): C, 54.37; H, 2.83; N, 8.78. Calc. for $C_{22}H_{14}ClN_3O_2S_3$ (%): C, 54.59; H, 2.92; N, 8.68.

**5cc**: deep red crystals, mp 183–185 °C. $^1$H NMR ($CDCl_3$) $\delta$: 7.49 (m, 8H, ArH), 7.66 (m, 2H, ArH), 7.81 (m, 2H, ArH), 8.38 (m, 2H, ArH). IR (KBr, $\nu$/cm$^{-1}$): 1612, 1592, 1520 ($NO_2$), 1412, 1348 ($NO_2$), 1268, 1148, 1108, 972, 880. MS, *m*/*z* (%): 483 ($M^+$, 4), 374 (M – PhS, 13), 329 (59). Found (%): C, 54.34; H, 2.91; N, 8.55. Calc. for $C_{22}H_{14}ClN_3O_2S_3$ (%): C, 54.59; H, 2.92; N, 8.68.

**5dc**: orange crystals, mp 211–215 °C. $^1$H NMR ($CDCl_3$) $\delta$: 2.41 (s, 3H, Me), 7.25 (d, 2H, ArH, *J* 8.5 Hz), 7.51 (t, 10H, ArH, *J* 4.6 Hz), 7.70 (d, 2H, ArH, *J* 8.5 Hz). IR (KBr, $\nu$/cm$^{-1}$): 1704, 1592, 1416, 1288, 968, 876. MS, *m*/*z* (%): 452 ($M^+$, 9), 343 (M – PhS, 100). Found $M^+$, 452.0243; $C_{23}H_{17}ClN_2S_3$ requires 452.0242. Found (%): C, 60.75; H, 3.84; N, 5.90. Calc. for $C_{23}H_{17}ClN_2S_3$ (%): C, 60.98; H, 3.78; N, 6.18.

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