Convenient Synthesis of Dithiooxamides from *N*-Arylimino-1,2,3-dithiazoles

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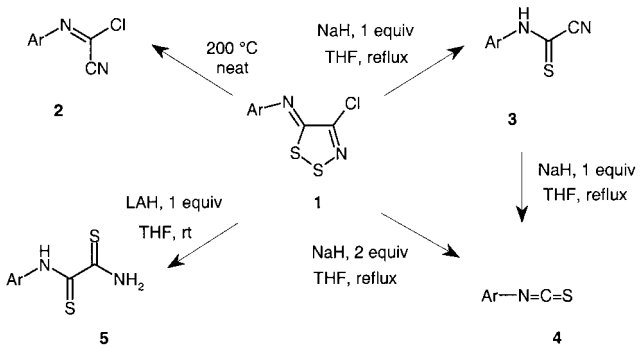
Abstract: Among several useful transformations of the readily available *N*-arylimino-1,2,3-dithiazoles **1** is their rapid conversion by lithium aluminum hydride into the rearranged *N*-aryldithiooxamides, $ArNHCSCSNH_2$, thus providing a two step synthesis of these unsymmetrical rubeanic acid derivatives from $ArNH_2$ (9 examples).

Key words: *N*-arylimino-1,2,3-dithiazoles, aryl isothiocyanates, cyanothioformamides, dithiooxamides, rubeanic acid

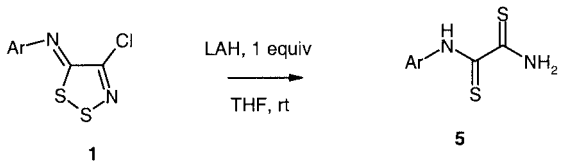
Primary aromatic amines are readily converted into the stable arylimino-1,2,3-dithiazoles (**1**) in high yield.[1] These derivatives are versatile synthetic intermediates, undergoing a variety of reactions initiated by nucleophilic attack at different sites on the dithiazole ring.[2] Some of these reactions transform the dithiazole ring only, whilst others involve cyclisation onto the adjacent aromatic ring. The former are shown in Scheme 1.



Scheme 1

Thermolysis of the imines **1** gave cyanoimidoyl chlorides **2** and disulfur, particularly when the *ortho*-positions of the aryl ring are substituted or when this ring has electron-withdrawing substituents.[3] Reduction of the imines **1** with one equivalent of sodium hydride[4] or of their hydrochloride salts with sodium cyanoborohydride[5] gave the cyanothioformanilides **3** which react further with sodium hydride, with elimination of cyanide, to give aryl isothiocyanates **4**.[4] Imines **1** were directly converted into **4** by treatment with two equivalents of sodium hydride in boiling THF overnight.[4] In an attempt to achieve this last reaction more quickly, we treated the imines with lithium aluminum hydride (LAH) and observed an entirely different, unexpected, reaction which resulted in the formation of *N*-aryldithiooxamides **5**. The reaction of iminodithiazoles **1** in anhydrous THF under argon with LAH (1 molar equiv) was rapid and exothermic to give the red or orange crystalline *N*-aryldithiooxamides **5** shown in the Table. Although the yields are only modest, the reaction provides an easy, general, two-step conversion of $ArNH_2 \rightarrow ArNHCSCSNH_2$. Sodium borohydride, sodium cyanoborohydride or sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) were less effective since they gave much less dithiooxamides **5** but afforded cyanothioformanilides **3** as the major product. Less than one molar equivalent of LAH resulted in lower yields of **5**. Yields were mostly in the 35–42% range, except where there was an *o*-chloro substituent (**5d**) or a *peri* ring nitrogen (**5h**).

Table Conversion of *N*-Aryliminodithiazoles **1** into *N*-Aryldithiooxamides **5**

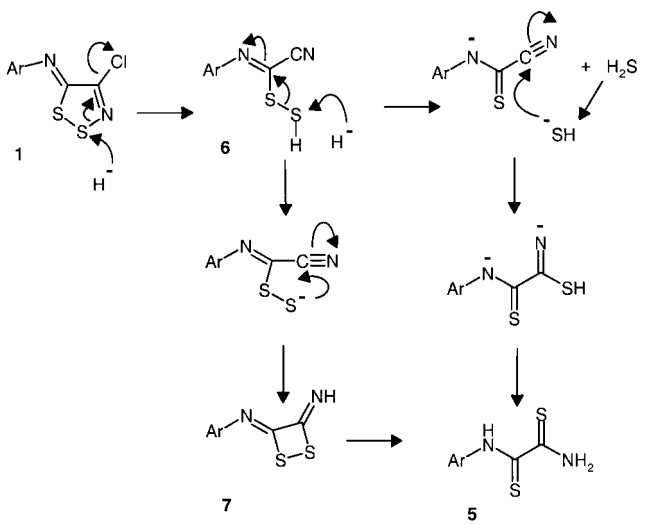


Product	Ar	Appearance	Yield (%)
5a	Ph	red needles	34
5b	4-$MeOC_6H_4$	red needles	45
5c	3,4,5-$(MeO)_3C_6H_2$	orange needles	35
5d	2-ClC_6H_4	red needles	25
5e	3,4-$F_2C_6H_3$	orange needles	43
5f	2-$HOCH_2CH_2C_6H_4$	orange needles	40
5g		red needles	37
5h	8-quinolinyl	orange needles	16
5i	3-quinolinyl	orange needles	40

The highly coloured products **5** are derivatives of rubeanic acid (dithiooxamide)[6] which has a long history as a chelating ligand, an analytical reagent, particularly for copper, cobalt and nickel,[7] and as a stabilizer of ascorbic acid solutions.

This conversion of arylimino-1,2,3-dithiazoles **1** into dithiooxamides **5** is unusual since, i) it is the first reaction of **1** in which all the C, N, and S atoms have been retained in the product (see Scheme 1) with no loss of sulfur in spite of the strongly reducing conditions, and ii) the connectivity of the heterocyclic ring atoms has changed, with the original S-2 atom becoming bound to carbon, indicating a molecular rearrangement or an elimination-addition pathway.

Whilst we have no firm evidence for a particular mechanism, it seems likely[2–4] that the reduction starts by attack at S-2 with opening of the heterocyclic ring to give the cyano intermediate **6** (Scheme 2). The disulfide bond of **6** would presumably be readily reduced to give the cyanothioformanilide **3** and its anion, together with hydrogen sulfide and HS^-. This last would then be expected to add to the cyano group of **3** to give the observed thioamide **5** (Scheme 2). The well known base-catalysed addition of hydrogen sulfide to cyanides[8] has already been demonstrated for cyanothioformamides.[9, 10]



Scheme 2

It is also possible, though perhaps less likely, that the LAH reaction could be intramolecular. Thus the anion of **6** (Scheme 2) could cyclise to give the dithietane[11] **7** which should then be rapidly reduced with cleavage of the disulfide bond to give dithiooxamide **5**.

The simple method described here for the conversion of a primary aromatic amine into the corresponding *N*-aryldithiooxamide **5** has the advantage of giving none of the symmetrical compound, ArNHCSCSNHAr.

IR spectra were recorded on a Perkin-Elmer paragon 1000PC instrument. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM LA (400MHz) spectrometer (Laboratoire Commun d'Analyse, Université de la Rochelle, France) ; chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS, which was used as internal standard. UV spectra were recorded on a Perkin-Elmer Lambda 16 UV/Vis. spectrometer. Mass spectra were recorded on a Varian MAT311 in the Centre Régional de Mesures Physiques de l'Ouest (C.R.M.P.O.), Université de Rennes, France. Chromatography was carried out on silica gel 60 at medium pressure with the mixtures preadsorbed onto silica. TLC was performed on Merck Kieselgel 60 F_{254} aluminium backed plates. Light petroleum ether refers to the fraction bp 40–60°C.

***N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)anilines 1**

These were prepared from 4,5-dichloro-1,2,3-dithiazolium chloride and the primary amines as previously described.[1–4]

Aryl Dithiooxamides 5a–i: General Procedure

Under an argon atmosphere, a solution of *N*-aryliminodithiazoles **1** (0.7 mmol) in anhyd THF (5 mL) was treated with $LiAlH_4$ (27 mg, 0.7 mmol) and stirred for 15 min at r.t. The reaction mixture was diluted with EtOAc (7 mL) and washed with satd aq $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and the solvent evaporated. The residue was column-chromatographed on silica gel using CH_2Cl_2/EtOAc as eluent, and the products were crystallised from light petroleum/CH_2Cl_2.

***N*-Phenyldithiooxamide (5a)**

Red needles (34%), mp 101–102°C (light petroleum/CH_2Cl_2) (Lit.[9a] mp 99°C).

UV (EtOH): λ_{max} (log ε) = 232(4.16), 323 (4.04), 375 nm (3.66)

IR (KBr): ν = 3292, 3135, 1589, 1539, 1490, 1443, 1237, 1102, 1020 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32 (t, 2 H, *J* = 7.45 Hz, H_{arom}), 7.46 (t, 2 H, *J* = 7.55 Hz, H_{arom}), 7.85 (br s, 1 H, NH), 8.00 (d, 1 H, *J* = 8.20 Hz, H_{arom}), 9.73 (br s, 1 H, NH), 12.00 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 121.96, 127.56, 129.09, 138.11, 179.40 (C=S), 189.55 (C=S) .

MS (EI, 70 eV) : *m*/*z* (%) = 196 (M^+, 100), 136 ($M^+ - CSNH_2$, 56), 77 (89).

HRMS: *m*/*z* calc. for $C_8H_8N_2S_2$ 196.0129, found 196.0134.

***N*-(4-Methoxyphenyl)dithiooxamide (5b)**

Red needles (45%); mp 138–140°C (light petroleum/CH_2Cl_2) (Lit.[9b] mp 142–143°C).

UV (EtOH): λ_{max} (log ε) = 237 (4.18), 324 (4.05), 397 nm (3.84).

IR (KBr): ν = 3322, 3221, 3028, 2835, 1594, 1547, 1506, 1450, 1242, 1171, 1033 cm^{-1} .

^1H NMR (400 MHz, $CDCl_3$): δ = 3.01 (s, 3 H, CH_3O), 6.97 (d, 2 H, *J* = 8.90 Hz), 7.87 (br s, 1 H, NH), 7.95 (d, 2 H, *J* = 8.90 Hz), 9.77 (br s, 1 H, NH), 11.96 (br s, 1 H, NH) .

MS (EI, 70 eV): *m*/*z* (%) = 226 (M^+, 100), 195 ($M^+ - CH_3O$, 17), 166 ($M^+ - CSNH_2$, 31).

HRMS: *m*/*z* calc. for $C_9H_{10}N_2OS_2$ 226.0234, found 226.0238.

***N*-(3,4,5-Trimethoxyphenyl)dithiooxamide (5c)**

Orange needles (35%); mp 176–178°C (light petroleum/CH_2Cl_2).

UV (EtOH): λ_{max} (log ε) = 322 (3.99), 398 nm (3.79).

IR (KBr): ν = 3290, 3145, 1595, 1531, 1505, 1430, 1236, 1123 cm^{-1}.

^1H NMR (400 MHz, DMSO): δ = 3.66 (s, 3 H, CH_3O), 3.75 (s, 6 H, 2 × CH_3O), 7.45 (s, 2 H, H_{arom}), 9.80 (br s, 1 H, NH), 10.34 (br s, 1 H, NH), 11.94 (1 H, br s, NH) .

^{13}C NMR (100 MHz, DMSO): δ = 55.91, 60.92, 100.25, 134.51, 135.68, 152.41, 188.80 (C=S), 195.11(C=S) .

MS (EI, 70 eV): *m/z* (%) = 286 (M^+, 100), 226 ($M^+ – CSNH_2$, 24).

HRMS: *m/z* calc.for $C_{11}H_{14}N_2O_3S_2$ 286.0446, found 286.0458.

***N*-(2-Chlorophenyl)dithiooxamide (5d)**
Red needles (25%); mp 152–154°C (petroleum ether/CH_2Cl_2) (Lit.[9c] mp 154–155°C).

UV (EtOH): λ_{max} (log ε) = 235 (4.11), 326 (4.01), 376 nm (3.58).

IR (KBr): ν = 3309, 3210, 3118,1598, 1518, 1441, 1370, 1226, 1041, 880 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (dt, 1 H, *J* = 7.60 Hz, *J* = 1.50 Hz, $H_{arom)}$, 7.37 (dt, 1 H, *J* = 7.65, 1.50 Hz, H_{arom}), 7.51 (dd, 1 H, *J* = 8.10, 1.50 Hz, H_{arom}), 7.75 (br s, 1 H, NH), 8.85 (dd, 1 H, *J* = 8.10, 1.50 Hz, H_{arom}), 9.65 (br s, 1 H, NH), 12.48 (br s, 1 H, NH) .

^{13}C NMR (100 MHz, $CDCl_3$): δ = 122.73, 127.16, 127.62, 128.11, 129.89, 135.19, 180.28 (C=S), 189.37 (C=S) .

MS (EI, 70 eV): *m/z* (%) = 230 (M^+, 10), 195(M^+ – Cl, 10), 170 ($M^+ – CSNH_2$, 17).

HRMS: *m/z* calc. for $C_8H_7ClN_2S_2$ 229.9739, found 229.9737.

***N*-(3,4-Difluorophenyl)dithiooxamide (5e)**
Orange needles (43%); mp 137–138°C (light petroleum/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.30 (m, 1 H, H_{arom}), 7.50–7.58 (m, 1 H, H_{arom}, HF), 7.82 (br s, 1 H, NH), 8.20–8.27 (m, 1 H, $H_{arom.}$, HF), 9.64 (1 H, br s, NH), 12.01 (1 H, br s, NH) .

^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.90, 112.11, 117.39, 117.57, 119.90, 119.93, 119.96, 120.00, 135.48, 135.51, 135.56, 135.60, 145.86, 145.99, 147.22, 147.25, 148.31, 148.43, 149.65, 149.79, 192.07 (C=S), 195.91 (C=S).

MS (EI, 70 eV): *m/z* (%) = 232 (M^+, 60), 198 ($M^+ – H_2S$, 40), 171 (M^+ – HCN, – H_2S, 100).

HRMS: *m/z* calc. for $C_8H_6F_2N_2S_2$ 231.9940, found 231.9954.

***N*-(2-Hydroxyethylphenyl)dithiooxamide (5f)**
Orange needles (40%); mp 100°C (light petroleum/CH_2Cl_2).

UV (EtOH): λ_{max} (log ε) = 232 (3.96), 322 nm (3.96).

IR (KBr): ν = 3430, 3292, 3096, 1598, 1512, 1442, 1365, 1254, 1179, 1041 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.70 (t, 2 H, *J* = 6.60 Hz, CH_2), 3.61 (t, 2 H, *J* = 6.60 CH_2), 4.85 (br s, 1 H, OH), 7.24–7.37 (m, 3 H, H_{arom}), 7.48–7.53 (m, 1 H, H_{arom}), 9.78 (s, 1 H, NH), 10.43 (s, 1 H, NH), 11.89 (s, 1 H, NH) .

^{13}C NMR (100 MHz, DMSO): δ = 34.38, 61.54, 126.00, 126.43, 127.53, 130.46, 135.65, 137.61, 190.23 (C=S), 193.55 (C=S).

MS (EI, 70 eV): *m/z* (%) = 240 (M^+, 100), 222 ($M^+ – H_2O$, 42), 162 ($M^+ – H_2O – CSNH_2$, 25), 128 (75), 118 (72).

HRMS: *m/z* calc. for $C_{10}H_{12}N_2OS_2$ 240.0362, found 240.0391.

***N*-(2,3-Dihydro-1,4-benzodioxan-6-yl)dithiooxamide (5g)**
Red needles (37%); mp 172°C (light petroleum/CH_2Cl_2).

UV (EtOH): λ_{max} (log ε) = 271 (3.92), 319 (3.97), 402 nm (3.79).

IR (KBr): ν = 3296, 3152, 1603, 1537, 1502, 1321, 1285, 1246, 1167, 1126, 1063 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.29 [s, 4 H, $O(CH_2)_2O$], 6.92 (d, 1 H, *J* = 8.70 Hz, H-8), 7.35 (dd, 1 H, *J* = 2.50, 8.80 Hz, H-7), 7.77 (br s, 1 H, NH), 7.82 (d, 1 H, *J* = 2.50 Hz, H-5), 9.75 (br s, 1 H, NH), 11.92 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 64.32, 64.41, 111.00, 115.74, 117.43, 131.90, 142.81, 143.33, 178.12 (C=S), 189.74 (C=S).

MS (EI, 70 eV : *m/z* (%) = 254 (M^+, 100), 194 (M – $CSNH_2$, 27), 162 (M – $CSNH_2$ – S, 27) .

HRMS: *m/z* calc. for $C_{10}H_{10}N_2O_2S_2$ 254.0183, found 254.0182.

***N*-(Quinolin-8-yl)dithiooxamide (5h)**
Orange needles (16%); mp 204°C (light petroleum/CH_2Cl_2).

UV (EtOH): λ_{max} (log ε) = 242 (4.40), 287 (4.01), 332 (4.04), 390 nm (3.87).

IR (KBr): ν = 3285, 3128, 1594, 1528, 1489, 1420, 1324, 1081, 1027 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (dd, 1 H, *J* = 4.20, 8.25 Hz, H-3), 7.63 (t, 1 H, *J* = 8.10 Hz, H_{arom}), 7.76 (dd, 1 H, *J* = 1.20, 8.25 Hz, H_{arom}), 7.80 (br s, 1 H, NH), 8.23 (dd, 1 H, *J* = 1.70, 8.25 Hz, H-4), 9.01 (dd, 1 H, *J* = 1.70, 4.20 Hz, H-2), 9.68 (br s, 1 H, NH), 9.85 (dd, 1 H, *J* = 1.70, 7.30 Hz, H_{arom}), 14.35 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 117.50, 122.21, 125.73, 126.51, 128.11, 134.71, 136.35, 140.58, 149.25, 178.59 (C=S), 190.42 (C=S).

MS (EI, 70 eV): *m/z* (%) = 247 (M^+, 28), 187 ($M^+ – CSNH_2$, 100).

HRMS: *m/z* calc. for $C_{11}H_9N_3S_2$ 247.0238, found 247.0244.

***N*-(Quinolin-3-yl)dithiooxamide (5i)**
Orange needles (40%); mp 212°C (light petroleum/CH_2Cl_2).

UV (EtOH): λ_{max} (log ε) = 246 (4.32), 297 (3.98), 328 (3.96), 380 nm (3.69).

IR (KBr): ν = 3278, 3123, 1618, 1536, 1490, 1378, 1238, 1128 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (t, 1 H, *J* = 7.65 Hz, H_{arom}), 7.76 (t, 1 H, *J* = 7.65 Hz, H_{arom}), 7.85 (br s, 1 H, NH), 7.90 (d, 1 H, d, *J* = 8.10 Hz, H_{arom}), 8.12 (d, 1 H, *J* = 8.70 Hz, H_{arom}), 9.05 (d, 1 H, *J* = 2.70 Hz, H_{arom}), 9.44 (d, 1 H, *J* = 2.70 Hz, H_{arom}), 9.65 (br s, 1 H, NH), 12.31 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 125.73, 127.30, 127.71, 128.30, 129.34, 129.92, 131.76, 145.56, 146.51, 180.29 (C=S), 188.85 (C=S).

MS (EI, 70eV): *m/z* (%) = 247 (M^+, 100), 187 ($M^+ – CSNH_2$, 51), 128 (64) .

HRMS: *m/z* calc. for $C_{11}H_9N_3S_2$ 247.0238, found 247.0244.

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(10) The relatively low yields observed could result from the alternative sites available for nucleophilic attack on the dithiazole ring and the possibility of diversion or loss of hydrogen sulfide. The much lower yields of dithiooxamides **5** produced in the sodium hydride reactions (Scheme 1) could then result from substantial loss of hydrogen sulfide in the boiling THF medium.
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