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A convenient route to 4-mercapto-1,2-dithiole-3-thiones from terminal alkynes

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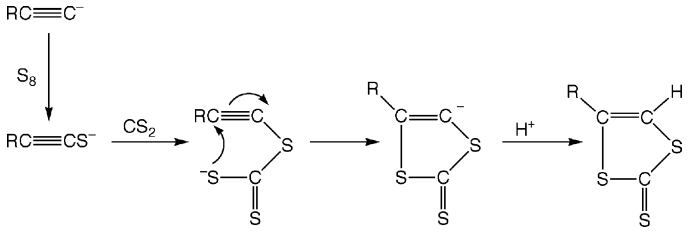
Abstract—4-Mercapto-1,2-dithiole-3-thiones are easily prepared by deprotonation of terminal alkynes followed by sequential treatment with carbon disulfide, sulfur and acid; addition of alkylating agents at the last stage gives 4-alkylthio-1,2-dithiole-3-thiones instead.

Compounds containing the 3*H*-1,2-dithiole-3-thione ring system have been known for many years, and have recently attracted interest as cancer preventive agents. In particular, Oltipraz (4-methyl-5-pyrazinyl-3*H*-1,2-dithiole-3-thione), a compound originally developed as an anti-schistosomal agent, has undergone large scale clinical trials in this respect, and simpler derivatives can also be effective.[1] There are many methods available for the synthesis of such compounds,[2] the majority of which require the use of sulfurising agents such as P_2S_5,[3] Lawesson's reagent, H_2S[4] or sulfur at high temperatures.[5] Our involvement in this area began when we recently discovered an interesting organometallic route to an otherwise inaccessible example.[6] We now report an extremely useful one-pot route to simple 5-substituted 4-mercapto-1,2-dithiole-3-thiones from terminal alkynes. The advantages of this method are twofold: all the stages of the reaction take place at or below room temperature, and the only sources of sulfur involved are carbon disulfide and elemental sulfur itself.

A recent paper by Otsubo and co-workers described the synthesis of 1,3-dithiole-2-thiones by sequential addition of sulfur and CS_2 to deprotonated terminal alkynes (Scheme 1).[7] We reasoned that it might be possible to produce the isomeric 1,2-dithiole-3-thiones by addition of the same reagents in the opposite order (Scheme 2). At first this idea did not look promising: we were able to find only one literature example of the addition of an alkynyl-lithium (MesC≡CLi) to CS_2,[8] and although methylation of the resulting anion gave a stable dithiocarboxylate ester, those derived from smaller aryl groups were described as thermally unstable. However, our initial investigations revealed that simple alkynyl-lithiums do add readily to CS_2 to give red solutions, which are stable at room temperature for at least several



Scheme 1. Otsubo's synthesis of 1,3-dithiole-2-thiones (Ref. 7).

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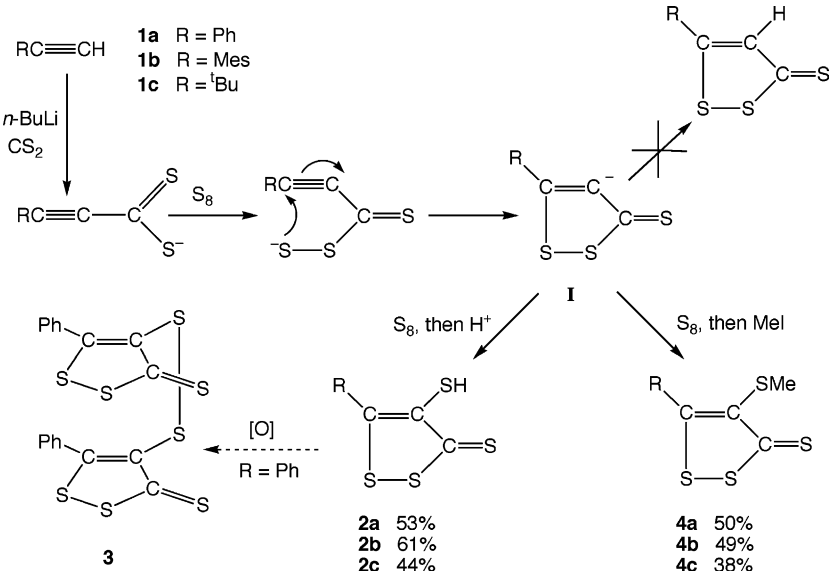

Scheme 2. Synthesis of 4-mercapto-1,2-dithiole-3-thiones.

hours, from which the alkynyldithiocarboxylates can be isolated by coordination to metal centres.[9]

When a red solution formed by addition of CS_2 to PhC≡CLi in THF was treated with elemental sulfur, a rapid colour change to red-purple occurred. After stirring for 1 h, the reaction was subjected to acidic work-up and extraction into dichloromethane, followed by column chromatography, from which an orange powder was isolated. However its ^{1}H NMR spectrum did not match that of 5-phenyl-1,2-dithiole-3-thione,[4] and the mass spectrum indicated the incorporation of an extra sulfur atom. Moreover the peak at δ 5.98 in the ^{1}H NMR spectrum, integrating as 1H, disappeared when the sample was treated with a drop of D_2O. We therefore identified the product as 5-phenyl-4-mercapto-1,2-dithiole-3-thione (**2a**), formed by further attack of the intermediate anion **I** on sulfur prior to work-up. This compound was briefly mentioned in the literature as a product of the sulfuration of 1-phenylpropene by sulfur and H_2S, though to our knowledge a full report of this reaction has never appeared.[10]

Crystallisation of compound **2a** from THF/ethanol provided dark orange crystals suitable for X-ray diffraction. The resulting structure is shown in Figure 1. While confirming our identification of **2a**, the result was slightly unexpected in that the compound had been oxidised during crystallisation to the corresponding disulfide **3** (a reaction well documented for the isomeric 4-substituted-5-mercapto-1,2-dithiole-3-thiones).[11,12] Although the disulfide is much less soluble than **2a**, we were able to confirm the absence of the –SH proton resonance in the ^{1}H NMR spectrum of the crystals used for the structure determination.

Extension of the reaction to other terminal alkynes resulted in the preparation of the analogous mesityl (**2b**) and *t*-butyl (**2c**) derivatives in comparable yields. Moreover, when the reaction mixtures were quenched with

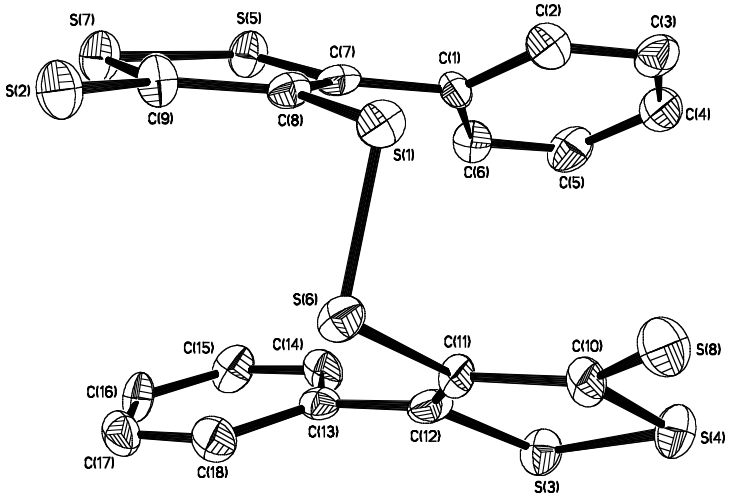

Figure 1. Molecular structure of $[PhCSSC(=S)CS]_2$ **3** in the crystal. Selected bond lengths (Å): S(1)–S(6) 2.057(3), S(1)–C(8) 1.761(10), S(2)–C(9) 1.647(10), S(5)–C(7) 1.734(11), S(5)–S(7) 2.066(4), S(7)–C(9) 1.716(9), C(7)–C(8) 1.390(14).

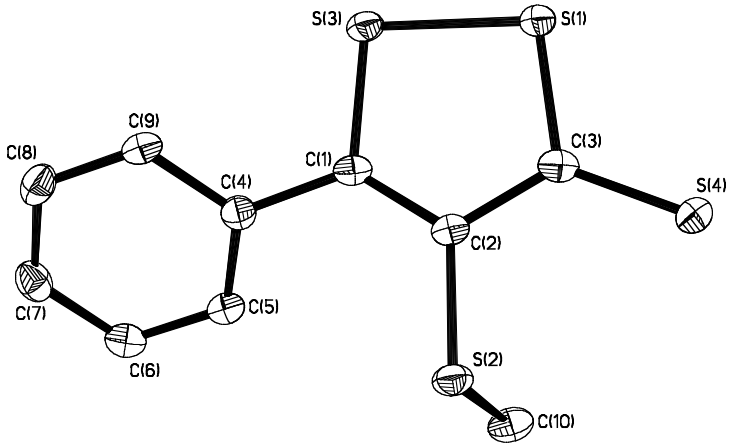

Figure 2. Molecular structure of PhCSSC(=S)C(SMe) **4a** in the crystal. Selected bond lengths (Å): S(1)–C(3) 1.741(3), S(1)–S(3) 2.0518(10), S(2)–C(2) 1.766(3), S(3)–C(1) 1.737(3), S(4)–C(3) 1.651(3), C(1)–C(2) 1.376(4).

methyl iodide rather than HCl, work-up afforded 4-methylthio-5-substituted-1,2-dithiole-3-thiones **4a**–**c**, again in similar yields. Of these, **4a** is the only one prepared previously, most effectively by a reaction involving sequential treatment of $PhCOCH_2SMe$ with KH, CS_2, $S(SiMe_3)_2$ and C_2Cl_6.[13] To confirm the nature of the product, the crystal structure of **4a** was also determined and is shown in Figure 2, with selected bond lengths and angles given in the caption. The heterocyclic ring lies almost coplanar with the phenyl substituent, with the methyl group attached as expected to S(2). Bond lengths within the ring are typical for this type of heterocycle.

In conclusion we have described a general synthesis of 4-thio-5-substituted-3*H*-1,2,-dithiole-3-thiones from readily available, relatively innocuous, and inexpensive starting materials, which occurs under unusually mild conditions in THF solution. Further investigations of the chemistry of these heterocycles are continuing.

Typical experimental procedure (synthesis of **2a**). A solution of phenylacetylene (0.29 mL, 2.64 mmol) in THF (18 mL), at −78 °C, was treated dropwise with *n*-BuLi (1.65 mL of a 1.6 M solution in hexanes) and allowed to warm to room temperature. After 30 min stirring the solution was cooled again to −78 °C and CS_2 (0.15 mL, 2.5 mmol) was added. The pale yellow solution was allowed to warm to room temperature and then stirred for 1 h, giving a red solution of the alkynyldithiocarboxylate, to which was added sulfur (0.25 g, 7.92 mmol), causing a rapid further colour change to magenta. After stirring for a further 1 h, an excess of 2 M HCl was added, giving an orange-red mixture. The solvent was removed and the residue partitioned between CH_2Cl_2 and water; the organic layer was dried (Na_2SO_4) and evaporated, then chromatographed (silica gel). Elution with light petroleum–CH_2Cl_2 (9:1) afforded a yellow band, which produced an orange powder of **2a** on evaporation. Yield 0.3409 g, 53%.

Selected spectroscopic data (^{1}H NMR 250.13 MHz, ^{13}C NMR 62.9 MHz, all in $CDCl_3$). Compound **2a**: mp 116–118 °C. ^{1}H NMR δ 7.75–7.55 (m, 5H, Ph), 5.98 (s, 1H, SH). ^{13}C NMR: δ 206.0 (C=S), 160.9, 139.1 (C=C), 134.1–128.8 (m, Ph). Found: C, 44.60; H, 2.21; S, 52.69%. Calcd for $C_9H_6S_4$: C, 44.60; H, 2.50; S, 52.89%. MS *m*/*z* 242 (M^+), 209 ($M-SH)^+$.

Compound **2b**: yield 61%. Mp 119–121 °C. ^{1}H NMR: 7.05 (s, 2H, CH), 5.35 (s, 1H, SH), 2.37 (s, 3H, Me), 2.15 (s, 6H, 2 Me). ^{13}C NMR: δ 207.1 (C=S), 160.3, 140.5 (C=C), 140.8 (CMe), 136.8 (2CMe), 129.0 (CH), 21.2 (Me), 19.5 (2Me). Found: C, 50.88; H, 4.49; S, 43.63%. Calcd for $C_{12}H_{12}S_4$: C, 50.67; H, 4.25; S, 45.07%. MS *m*/*z* 284 (M^+), 269 ($M-Me)^+$.

Compound **2c**: yield 44% of an orange-brown oil. ^{1}H NMR: δ 6.65 (^{1}H, SH), 1.55 (9H, Me). ^{13}C NMR: δ 207.0 (C=S), 174.9, 137.5 (C=C), 39.0 (*C*Me_3), 27.4 (Me). MS *m*/*z* 222 (M^+), 207 ($M-Me)^+$. HRMS (electrospray) *m*/*z* 222.9735 ($M+H^+$); calcd for $C_7H_{11}S_4$: 222.9744.

Compound **4a**: yield 50%. Mp 68–72 °C. ^{1}H NMR: 7.70–7.50 (m, 5H, Ph), 2.25 (s, 3H, Me). ^{13}C NMR: δ 213.6 (C=S), 174.3, 139.4 (C=C), 133.2–128.8 (m, Ph), 16.7 (Me). Found: C, 47.98; H, 3.16; S, 47.28%. Calcd for $C_{10}H_8S_4$: C, 46.87; H, 3.13; S, 50.00%. MS: *m*/*z* 256 (M^+), 241, 223. HRMS *m*/*z* 255.9510; calcd for $C_{10}H_8S_4$: 255.9509.

Compound **4b**: yield 49%. Mp 72–75 °C. ^{1}H NMR: δ 7.00 (2H, CH), 2.35 (3H, Me of mes), 2.25 (3H, SMe), 2.10 (6H, Me). ^{13}C NMR: δ 213.9 (C=S), 174.3 (C=C), 140.5 (CMe + C=C), 136.6 (2CMe), 128.9 (CH), 21.5, 20.3 (Me), 15.6 (SMe). Found: C, 52.67; H, 4.74; S, 43.39%. Calcd for $C_{13}H_{14}S_4$: C, 52.31; H, 4.73; S, 42.97%. MS *m*/*z* 298 (M^+), 283 ($M-Me)^+$.

Compound **4c**: yield 38% of an orange-brown oil. ^{1}H NMR: δ 2.40 (3H, SMe), 1.45 (9H, Me). ^{13}C NMR: δ 211.1 (C=S), 157.7, 129.6 (C=C), 38.0 (*C*Me_3), 30.6 (3Me), 21.3 (SMe). MS *m*/*z* 236 (M^+), 221 ($M-Me)^+$. HRMS (electrospray) *m*/*z* 236.9903 ($M+H^+$); calcd for $C_8H_{13}S_4$: 236.9900.

X-ray crystal structure data for **3**: $C_9H_5S_4$, $M = 241.37$, trigonal, space group $P32$, $a = b = 8.0049(9)$, $c = 26.433(4)$ Å, $\alpha = \beta = 90°$, $\gamma = 120°$, $V = 1466.9(3)$ Å^3, $Z = 6$. Mo Kα radiation, $\mu = 0.914\,mm^{-1}$, $T = 150(2)$ K, 9370 reflections collected, 3401 independent reflections ($R_{int} = 0.1786$), $R_1 = 0.0628$, $wR_2 = 0.1417$. Final R indices (all data) $R_1 = 0.1208$, $wR_2 = 0.1895$.

X-ray crystal structure data for **4a**: $C_{10}H_8S_4$, $M = 256.40$, monoclinic, space group $C2/c$, $a = 23.651(4)$, $b = 5.5964(9)$, $c = 16.126(3)$ Å, $\alpha = \gamma = 90$, $\beta = 90.781°$, $V = 2134.3(6)$ Å^3, $Z = 8$. Mo α radiation, $\mu = 0.843\,mm^{-1}$, $T = 150(2)$ K, 6163 reflections collected, 2577 independent reflections ($R_{int} = 0.0655$), $R_1 = 0.0422$, $wR_2 = 0.1033$. Final R indices (all data) $R_1 = 0.0640$, $wR_2 = 0.1127$.

Crystallographic data for the structure determinations of **3** and **4a** have been deposited with the Cambridge Crystallographic data centre, CCDC reference numbers 240542 and 240543, respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail deposit@ccdc.cam.ac.uk or Web: http://www.ccdc.cam.ac.uk).

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