Heteroatom Chemistry
Volume 11, Number 6, 2000

On Acidification of Thiols to Produce the Corresponding Disulfides

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Received 30 April 2000; revised 7 June 2000

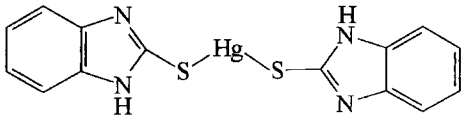
ABSTRACT: *Thiophenol* **1**, *2-mercaptobenzimidazole (***3a***), 4,5-diphenylimidazole-2-thione* **3b**, *and 5-mercapto-2-aryl-1,2,4-s-triazoles (***6a–b***) are chemically oxidized using the acidified acetic acid method to the corresponding disulfides* **2, 5a–b** *and* **7a–b**, *respectively. The structures of the disulfides thus formed were established both chemically and by spectral analysis.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 16:399–402, 2000

INTRODUCTION

The chemistry and biological activity of thiols and disulfides have been well known for many years and have been studied in depth [1–6]. Numerous methods had been reported for synthesis of the disulfides [7–19]. The selected thiols **1, 3a–b** and **6a–b** are important reagents for the dimerization to the corresponding disulfides **2**, **5a–b**, and **7a–b** in very good yields.

Interaction of the thiophenol **1** with acetic acid containing a catalytic amount of concentrated sulfuric acid afforded, after neutralization with iced NH_4OH, the corresponding diphenyl disulfide **2** in 73% yield (Scheme 1).

The formation of disulfide **2** has prompted us to study this reaction with different heterocyclic thiols. Oxidation of 2-mercaptobenzimidazole **3b** with iodine directly or that via the mercury derivative **4** leads to di-(2-benzimidazolyl)disulfides [9,20]. The oxidation with dilute aqueous hydrogen peroxide [21] and electrochemical oxidation [22] produce the same result.



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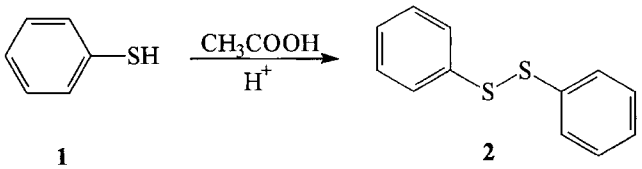
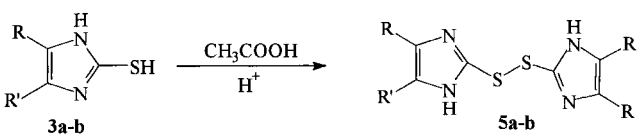
Similarly, by use of other heterocyclic thiols such as 4,5-diphenylimidazole-2-thiol **3a** and 2-mercaptobenzimidazole **3b**, the corresponding diheterocyclic disulfides **5a–b** were obtained in good yields (Scheme 2).

Oxidation of triazoline-5-thiols to the corresponding bistriazolyl disulfides, carried out using



1 **2**

SCHEME 1



3a-b **5a-b**

5a; R = R' = C_6H_5,

5b; R, R' = CH = CH - CH = CH

SCHEME 2

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hydrogen peroxide or iodine or by electrolytic oxidation in 5% hydrochloric acid in the presence of a platinum-iridium electrode at a potential of 0.7 to 1.0 volts, has also been demonstrated. In addition, treatment of triazoline-5-thiones with ozone or with a mixture of $NaNO_2$ and sodium hydrogen sulfate as an oxidant gave the corresponding disulfides [23–28].

When the acidified acetic acid method was applied on other thiol compounds such as 5-mercapto-3-phenyl-1,2,4-s-triazole **6a** or 5-mercapto-3-benzyl-1,2,4-s-triazole **6b**, the corresponding disulfides **7a–b** were also obtained in good yields (Scheme 3).

On the other hand, a Japanese group recently reported that, in the reaction of **8** with acetic acid, only the disulphide **9** was unexpectedly obtained as the only isolable product [29] (Scheme 4).

The mechanism of the reaction may involve an imidazole-2-thione such as **15**, as an intermediate. To provide a rationale for the formation of the disulfides chemically several reactions have been carried out using ketones in acidified acetic acid to form the thiazolo[3,2-*a*]-benzimidazoles or thiazoloimidazoles, respectively. Details of this mechanism were shown in our previous work [30]. Heating of 2-mercaptobenzimidazole (**3a**) in $AcOH/H_2SO_4$ gave the dimeric product **5b**, which acts as a starting material for the synthesis of the corresponding thioacetophenones **11a–b** and thiazolo[3,2-*a*]benzimidazoles **12a–b** [31]. The reaction of benzimidazolyl disulfide **5b** with ketones **10a–b** (a, Ar = C_6H_5–; b, Ar = $C_6H_4CH_4$-*p*) in a mixture of AcOH/H_2SO_4 yielded mixtures of the corresponding **11a–b** and **12a–b**, the major products being **11a–b** [30] (Scheme 5).

Reaction of 4,5-diphenylimidazole-2-thione **15** with acetone, butanone, pentan-2-one, and acetophenone using the acidified acetic acid method gave 2-(4,5-diphenylimidazolyl)thioketone derivatives **13a–d** [31] in good yields. Ring closure of **13a–d** using acidified acetic acid in addition to acetic anhydride afforded the corresponding thiazoloimidazole derivatives **14a–d** in very good yields (Scheme 6).

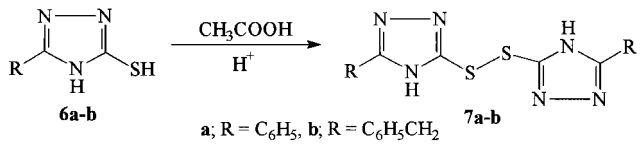
EXPERIMENTAL

General

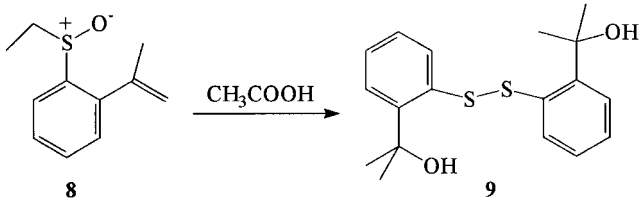
Melting points were uncorrected. IR Spectra were measured on a Perkin-Elmer spectrometer. For ^{1}H-NMR spectra (90 MHz and 200 MHz), TMS was used as an internal standard. Mass spectra were recorded on a MAT 312 spectrometer. Elemental analyses were performed by the microanalytical unit (Chemistry Department, Faculty of Science, Assiut University, Assiut 71516, Egypt).

Synthesis of Di-aryl/heteroaryl Disulfides **2** *and* **7a–b**

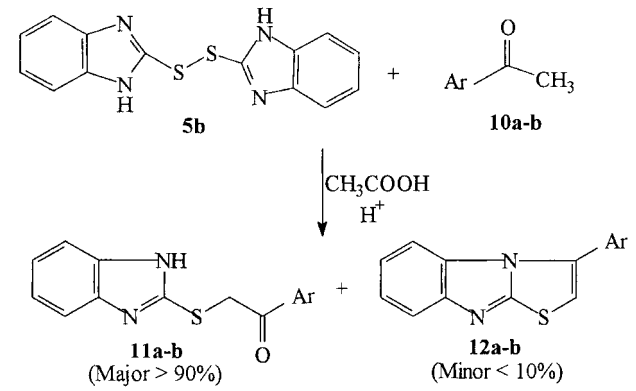
To a 1.0 g sample of thiol, **1** or **6a–b** in acetic acid (10 mL), a few drops of concentrated H_2SO_4 was



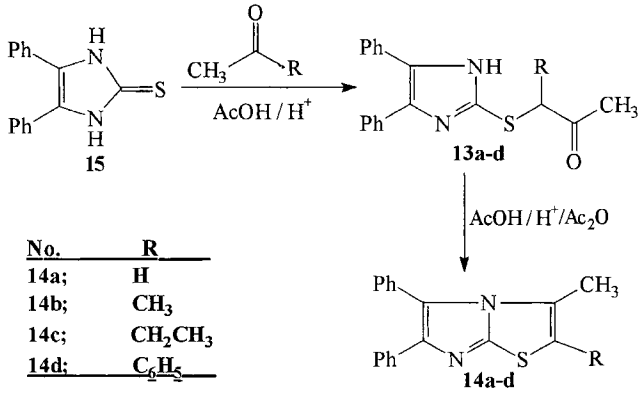
SCHEME 3



SCHEME 4



SCHEME 5



SCHEME 6

added at once. A yellow color developed after stirring for 3 minutes, and the mixture was refluxed for 3 hours. The reaction mixture was cooled and neutralized with NH_4OH solution. The resulting precipitate was extracted with chloroform. The extract was dried ($CaCl_2$), and the solvent was removed under reduced pressure. The separated compounds were crystallized from ethanol to give the corresponding disulfides **2** and **7a–b**.

Diphenyl Disulfide (*2*). This compound was obtained in 73% yield, m.p. 59–60°C; lit. [32] m.p. 58–60°C. ^{1}H NMR ($CDCl_3$) δ = 7.1–7.6 (m, 10H, arom-H).

Bistriazolyl Disulfides (**7a–b**). **7a**: R = Ph, 64% yield. IR (KBr) ν = 3150m, 3030m, 2920m, 1600m, 1570s, 1490s, 1445s, 1070s, 735s, 720s cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ = 7.0–7.4 (m, 10 H, arom-H). **7b:** R = $PhCH_2$, m.p. 184°C, 60% yield. IR (KBr) ν = 3150m, 3020m, 2910m, 2700m, 1600m, 1575s, 1490s, 1440s, 1060s, 730s, 720s cm^{-1}. ^{1}H NMR ($CDCl_3$) δ = 4.1 (s, 4H, 2 CH_2S), 7.3 (m, 10 H, arom-H).

Bis(4,5-diphenyl-2-imidazolyl) Disulfide (**5a**). 4,5-Diphenylimidazole-2-thione (**3a**: 2.5 g, 10 mmol) was heated for 30 minutes in refluxing acetic acid (20 mL) containing a few drops of concentrated H_2SO_4. The reaction mixture was cooled and neutralized by NH_4OH solution. The resulting precipitate was crystallized from chloroform to give the corresponding disulfide **5a** in 90% yield, m.p. 175°C. The dihydrochloride salt of **5a** was separated by adding conc. HCl to the disulfide solution in chloroform, m.p. 220°C; lit. m.p. 220–222°C [11]. ^{1}H NMR (DMSO-d_6) δ = 7.0–7.75 {m, 22H (20H, arom-H and 2NH)}. MS: *m/e* 502.8 [M^+] (12.17), 470 (90.29), 438 (32.35), 218.1 (100). Anal. calcd. for $C_{30}H_{22}N_4S_2$ (502.7): C, 71.69; H, 4.41; N, 11.15; S, 12.76. Found: C, 71.87; H, 4.14; N, 11.31; S, 12.74. Anal. calcd. for $C_{30}H_{24}N_4Cl_2S_2$ (575.6): C, 62.60; H, 4.20; N, 9.73; S, 11.14; Cl, 12.32. Found: C, 62.68; H, 4.18; N, 9.65; S, 11.15; Cl, 12.68.

Bisbenzimidazolyl Disulfide (**5b**). To a 1.0 g sample of 2-mercaptobenzimidazole (**3b**) in acetic acid (10 mL), a few drops of concentrated H_2SO_4 was added at once. The reaction mixture was refluxed for 3 hours and then cooled and neutralized with cold ammonia solution. The resulting precipitate was extracted with chloroform. The extract was dried ($CaCl_2$), and the solvent was removed under reduced pressure. The separated compound was crystallized from ethanol to give the disulfide **5b** in 67% yield.

IR (KBr) ν = 3150s, 1620s, 1505s, 1460s, 1350s, 1080s, 740s, 705s cm^{-1}. ^{1}H NMR (DMSO-d_6) δ = 7.15–7.35 (m, 4H, arom-H), 7.45–7.70 (m, 4H, arom-H), 13.50 (b, 2H, 2NH exchangeable with D_2O). MS *m/e* (%) = 298 [M^+] (2), 297 (3), 265 (2), 231 (3), 207 (3), 181 (2), 167 (2), 150 (100), 122 (17), 118 (21), 106 (27), 96 (10), 91 (18), 78 (11), 65 (27).

General Procedure for Synthesis of 5,6-Diphenyl-3-methyl-2-substituted Thiazolo[3,2-a]imidazoles (**14a–d**)

A mixture of 4,5-diphenylimidazole-2-thione (**5a**: 2.5 g, 10 mmol) and aliphatic ketones or acetophenone (10 mmol) was heated in refluxing acetic acid (20 mL) containing a few drops of concentrated H_2SO_4 for two hours. Then acetic anhydride (7 mL) was added to the reaction mixture, and the refluxing was continued for two hours. The reaction mixture was cooled and worked up to give the corresponding **14a–d** [34].

5,6-diphenyl-3-methylthiazolo[3,2-a]imidazole (**14a**). The thiazolo[3,2-*a*]imidazole **14a** was obtained as colorless crystals from benzene/methanol mixture in 40% yield, m.p. 180°C. IR (KBr): ν 1590 (C=N), 1490 cm^{-1} (C=C). ^{1}H NMR ($CDCl_3$): δ = 1.9 (s, 3H, CH_3), 6.3 (s, 1H, CH), 7.15–7.7 (m, 10H, arom-H). Anal. Calcd. for $C_{18}H_{14}N_2S$ (290.4): C, 74.45; H, 4.86; N, 9.65; S, 11.04. Found: C, 74.40; H, 4.92; N, 9.56; S, 11.08.

2,3-Dimethyl-5,6-diphenylthiazolo[3,2-a]imidazole (**14b**). The thiazolo[3,2-*a*]imidazole **14b** was obtained as colorless crystals from benzene/hexane mixture in 70% yield, m.p. 160–162°C. IR (KBr): ν = 590 (C=N), 1520 cm^{-1} (C=C). ^{1}H NMR ($CDCl_3$); δ = 1.75 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 7.1–7.6 (m, 10H, arom-H). MS: *m/e* (%) = 304 [M^+] (100), 305 [M^{+1}] (44), 306 [M^{+2}] (17.7), 303 [M^{-1}] (35). Anal. calcd. for $C_{19}H_{16}N_2S$ (304.4): C, 74.97; H, 5.30; N, 9.20; S, 10.53. Found: C, 74.60; H, 5.08; N, 8.89; S, 10.80.

5,6-diphenyl-2-ethyl-3-methylthiazolo[3,2-a]imidazole (**14c**). The thiazolo[3,2-*a*]imidazole **14c** was obtained as colorless crystals from benzene/hexane mixture in 63% yield, m.p. 118°C. IR (KBr): ν = 1590 (C=N), 1490 cm^{-1} (C=C). ^{1}H NMR ($CDCl_3$): δ = 1.2 (t, 3H, $CH_2\mathbf{CH_3}$), 1.7 (s, 3H, CH_3), 2.6 (q, 2H, $\mathbf{CH_2}CH_3$), 7.0–7.6 (m, 10H, arom-H). MS: *m/e* (%) = 318.8 [M^+] (44.9), 319.8 [M^{+1}] (12.3), 317.8 [M^{-1}] (100), 316.6 [M^{-2}] (15.3). Anal. calcd. for $C_{20}H_{18}N_2S$ (318.4): C, 75.44; H, 5.70; N, 8.80; S, 10.07. Found: C, 75.80; H, 5.80; N, 8.54; S, 10.00%.

3-Methyl-2,5,6-triphenylthiazolo[3,2-a]imidazole (**14d**). The thiazolo[3,2-*a*]imidazole **14d** was obtained as pale brown crystals from benzene/hexane mixture in 71% yield, m.p. 182°C. IR (KBr): ν = 1590 (C=N), 1490 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): δ 1.9 (s, 3H, CH_3), 7.1–7.6 (m, 15H, arom-H). Anal. calcd. for $C_{21}H_{18}N_2S$ (366.5): C, 78.66; H, 4.95; N, 7.64; S, 8.75. Found: C, 78.66; H, 5.05; N, 7.59; S, 8.81.

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