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Selective Electrolytic Cleavage of a Side-Chain Carbon–Sulfur Bond of Heterocyclic Compounds. Formation of Di-2-thienyl Disulfides and 2-Mercaptothiazoles

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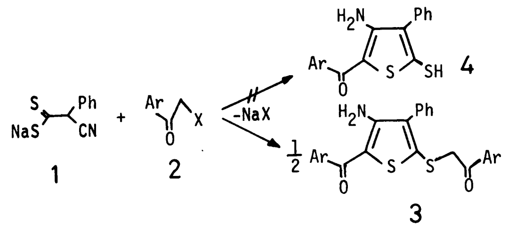
Synopsis. Highly selective cleavage of a side-chain carbon–sulfur bond of thiophene and thiazole derivatives containing acyl, cyano, and ethoxycarbonyl groups was successfully performed by electroreduction to provide the corresponding disulfides and thiols respectively in excellent to good yields.

In the course of our intensive synthetic studies of heterocyclic compounds,[1,2] we found a facile synthesis of 2-acyl-3-aminothiophene derivatives (**3**) from two equiv of α-halo ketones (**2**) and sodium cyanophenyldithioacetate (**1**) in the presence of triethylamine (Scheme 1).[3] Even though equimolar amounts of **1** and **2** were used in this reaction, **3** was always obtained and any 2-acyl-3-amino-5-mercapto-4-phenylthiophenes (**4**) were not formed.

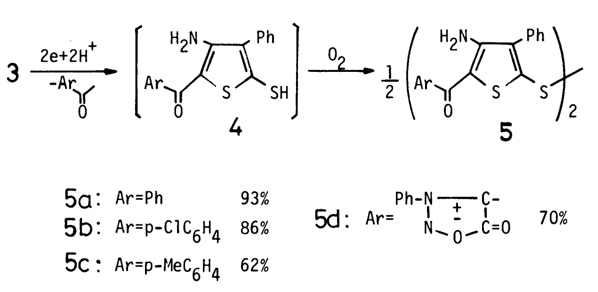
It is well known that the desulfurization of phenacyl sulfides[4] and phenacyl sulfoxides[5] can be easily achieved by chemical reduction with zinc/AcOH or alminum amalgam to provide the corresponding ketones.

Since the molecular structure of **3** is similar to phenacyl sulfides, its chemical reduction was first carried out in a manner similar to that reported.[4,5] However, our attempts to obtain **4** were not successful.

Recently, electrochemical methods have been shown to be useful for the deprotection of sulfur moieties for organic synthesis, especially for that of natural products.[6,7] These facts prompted us to attempt the electroreduction of **3**. After several attempts, the constant current electroreduction was successfully carried out at a mercury cathode in DMF containing phenol as a proton source to give rise to **4**. In these electrolyses, after slightly excess of theoretical amount of electricity ($2.2\times96480\ \mathrm{C\,mol^{-1}}$) had been passed, the cell voltage was found to increase remarkably and the electrolysis was stopped.



Scheme 1.

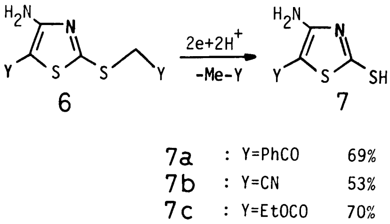


Scheme 2.

As shown in Scheme 2, the electroreduction proceeded smoothly and cleanly, and the desired **4** could be obtained as the corresponding disulfide (**5**) in good yields. The structure of **5** was determined mainly by the mass spectra together with IR and elemental analysis. The disulfide **5** showed its molecular ion peak and/or its fragments such as M^+-S, M^+-SH, and $M^+/2$. These fragmentation is well known to be characteristic of diaryl disulfides.[8]

Although a typical mesoionic compound, sydnone is interesting for its chemical, physical, and biological properties, its synthesis seems to be limitted, because the sydnone ring is unstable to acid, alkali, and heat.[9] Since the sydnone ring is also easily reduced chemically and electrochemically to decomposition products,[10] no report of the preparative electroreduction of sydnone compounds has been published except for one reported by us[11] and only a few papers deal with polarography of sydnones.[12] From this point, the electroreduction of a sydnone derivatives of **3** was also attempted. It was found that the selective reduction proceeded without any decomposition of the sydnone ring to provide pure **5d** without purification. The isolated disulfides **5** seem to be formed during the work-up by the air-oxidation of **4** once formed by the electroreduction.

At the second stage of this study, we applied this electrochemical technique to other heterocyclic compounds such as thiazoles. Three thiazole derivatives (**6**)[13] were chosen as model compounds. A highly selective electroreduction of **6** proceeded to provide the corresponding 2-mercaptothiazoles (**7**) in good yields as shown in Scheme 3. It is noticeable that disulfides **5** were always obtained as the products from thiophene derivatives **3** whereas thiols **7** were derived from thiazoles **6** in the electroreduction. In these electrolyses, reasonable amount of acetophenone derivatives, acetonitrile, and ethyl acetate were detected in the catholyte by GC analysis and any further reduction did not occur. From these results,



Scheme 3.

the electroreduction seemed to proceed via a two-electron step.

Although **3** and **6** contain other reducible groups such as carbonyl, nitrile, and ester groups, only reductive cleavage of the C-S bond took place selectively.

Since the reduction proceeded selectively and efficiently under quite mild conditions and did not need any reducing reagent, this clean electrochemical method seems to have a potential utility for organic synthesis.

Experimental

Starting Material. Thiophene and thiazole derivatives (**3** and **6**) were prepared using the method reported previously[3] and according to the reference.[13]

General Electrolytic Procedure. An H-type electrolytic cell divided with a glass filter diaphragm was used. A mercury pool (area 7.1 cm^2) and a platinum plate were used as a cathode and anode, respectively. The catholyte was 40 ml of 0.1 mol dm^{-3} $NaClO_4$-DMF solution containing 1.5 mmol of thiophenes **3** or thiazoles **6** together with 3.0 mmol of phenol. The constant current (0.57 A dm^{-2}) was passed at ca. 20 °C.

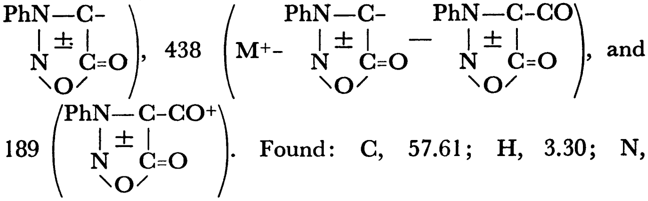
Analysis and Isolation of Products. After the electrolysis, the catholyte was evaporated under reduced pressure below 60 °C. The residue was mixed with water and neutralized. The resulting precipitated product was collected by filtration, washed with water or ether, and dried. The catholyte was subjected to gas chromatography (PEG 20M) for analysis of acetophenones, acetonitrile, and ethyl acetate.

Bis(4-Amino-5-benzoyl-3-phenyl-2-thienyl) Disulfide (5a): Mp 174 °C (from ethanol). IR (KBr) 3500, 3300 (νNH) and 1590 cm^{-1} (νC=O). MS m/z 620 (M$^+$), 588 (M$^+$−S), 587 (M$^+$−SH), 310 (M$^+$/2), and 105 (PhCO$^+$). Found: C, 65.79; H, 3.69; N, 4.52%. Calcd for $C_{34}H_{24}N_2O_2S_4$: C, 65.78; H, 3.90; N, 4.51%.

Bis[4-amino-5-(*p*-chlorobenzoyl)-3-phenyl-2-thienyl] Disulfide (5b): Mp 138 °C (from DMF). IR (KBr): 3450, 3300 (νNH) and 1580 cm^{-1} (νC=O). MS m/z 660 (M$^+$+4−S), 658 (M$^+$+2−S), 656 (M$^+$−S), 655 (M$^+$−SH), 346 (M$^+$+4/2), 345 (M$^+$+2/2), 344 (M$^+$/2), 141, and 139 (*p*-$ClC_6H_4CO^+$). Found: C, 59.16; H, 3.23; N, 4.45%. Calcd for $C_{34}H_{22}N_2S_4Cl_2$: C, 59.21; H, 3.21; N, 4.08%.

Bis[4-Amino-5-(*p*-toluoyl)-3-phenyl-2-thienyl] Disulfide (5c): Mp 136 °C (from EtOH-DMF). IR (KBr): 3500, 3300 (νNH), 1605 and 1580 cm^{-1} (νC=O). MS m/z 616 (M$^+$−S), 615 (M$^+$−SH), 325 (M$^+$/2+H), and 120 (*p*-$MeC_2H_4CHO^+$). ^{1}H NMR (acetone-d_6) δ=2.44 (s, 6H, C$\underline{H}_3$), 3.08 (broad s, 4H, N$\underline{H}_2$), and 7.28—7.92 (m, 18H, Ar-$\underline{H}$). Found: C, 66.54; H, 4.49; N, 4.32%. Calcd for $C_{36}H_{28}N_2O_2S_4$: C, 66.64; H, 4.35; N, 4.32%.

Bis[4-Amino-5-(3-phenyl-4-sydnonylcarbonyl)-3-phenyl-2-thienyl] Disulfide (5d): Mp 194 °C (decomp). IR (KBr): 3480, 3320 (νNH), 1775 (νC=O of a sydnone ring), and 1580 cm^{-1} (νC=O). MS m/z 478 (M$^+$-PhN-CO-NO-



$$\text{PhN—C-}\left(\begin{array}{c}\text{PhN—C-}\\ |\ \pm\ |\\ \text{N}\quad\text{C=O}\\ \diagdown\text{O}\diagup\end{array}\right),\ 438\ \left(\text{M}^+\text{-}\ \begin{array}{c}\text{PhN—C-}\\ |\ \pm\ |\\ \text{N}\quad\text{C=O}\\ \diagdown\text{O}\diagup\end{array} — \begin{array}{c}\text{PhN—C-CO}\\ |\ \pm\ |\\ \text{N}\quad\text{C=O}\\ \diagdown\text{O}\diagup\end{array}\right),\ \text{and}\ 189\ \left(\begin{array}{c}\text{PhN—C-CO}^+\\ |\ \pm\ |\\ \text{N}\quad\text{C=O}\\ \diagdown\text{O}\diagup\end{array}\right).$$

Found: C, 57.61; H, 3.30; N, 10.54%. Calcd for $C_{38}H_{24}N_6O_6S_4$: C, 57.86; H, 3.07; N, 10.65%.

4-Amino-5-benzoyl-2-mercaptothiazole (7a): Mp 231 °C (from ethanol). IR (KBr): 3400, 3300 (νNH) and 1640 cm^{-1} (νC=O). MS m/z 236 (M$^+$), 235 (M$^+$−H), 159 (M$^+$−Ph), 130 (M$^+$−H-PhCO), and 105 (PhCO$^+$). Found m/z 236.0039. Calcd for $C_{10}H_8N_2OS_2$: 236.0077.

4-Amino-5-cyano-2-mercaptothiazole (7b): Mp 202—203 °C (from ethanol). IR (KBr): 3320, 3220, 3100 (νNH) and 2220 cm^{-1} (νC≡N). MS m/z 157 (M$^+$), 130 (M$^+$−HCN), and 98 (M$^+$−HCN-S). Found: C, 30.60; H, 1.81; N, 26.73%. Calcd for $C_4H_3N_3S_2$: C, 30.56; H, 1.81; N, 26.73%.

4-Amino-5-ethoxycarbonyl-2-mercaptothiazole (7c): Mp 192 °C (from ethanol). IR (KBr): 3400, 3320, 3220 (νNH) and 1670 (νC=O). MS m/z 204 (M$^+$), 176 (M$^+$−C_2H_4), 159 (M$^+$−EtO), and 130 (M$^+$−H-EtOCO). Found: C, 35.56; H, 3.83; N 13.61%. Calcd for $C_6H_8N_2O_2S_2$: C, 35.28; H, 3.95; N, 13.71%.

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