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Nucleophilic properties of thiourea towards aromatic halides.

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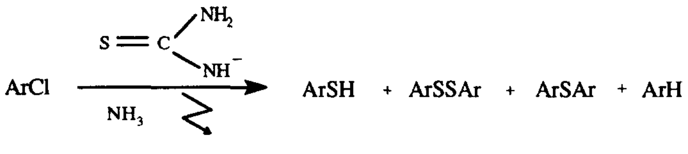
Abstract: *Arylsulfides (and diaryldisulfides obtained spontaneously by oxidation of the arylsulfides during the work-up) and diarylsulfides can be obtained by substituting aryl radicals by the thiourea anion in liquid ammonia under an electrochemical inducement.*

The formation of bonds between an aryl moiety and elements from the IVA (C, Si,..), VA (P, Sn,..), VIA (S, Se, Te,..) groups can be achieved by the $S_{RN}1$ reaction.[1] Among the anions which make possible the formation of carbon-sulfur bonds, aliphatic thiolates,[1] thiophenoxide[2] and the anions of mercapto-pyridine or -pyrimidine[3] may be mentionned but the anion of thiourea is not described as a nucleophile under $S_{RN}1$ conditions. Its nucleophilic properties are only known towards alkyl halides to give thiols after hydrolysis in a basic medium. We report here the results of the electrosyntheses of different aromatic halides with the anion of thiourea under $S_{RN}1$ conditions in liquid ammonia and we propose a mechanism for the reaction.

The reaction was carried out by means of an already described indirect electrochemical procedure.[4,5] When it was performed without an electrochemical inducement, no conversion of the starting compounds was observed. It was carried out in an undivided electrochemical cell containing 80 mL of liquid ammonia maintained at -40°C, 16 mmoles of potassium bromide as supporting electrolyte, 4 mmoles of aromatic chloride, 20 mmoles of thiourea, 21 mmoles of potassium *tert*-butoxide and 2 mmoles of mediator. A constant current density of 0.5 $A.dm^{-2}$ is imposed between a stainless steel grid and a magnesium rod, till the disappearance of the starting aromatic chloride. When the reaction was over, ammonia was evaporated and the organic phase was extracted with diethylether. The mineral phase was washed with acidic water and the organic products were also extracted with diethylether.

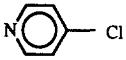
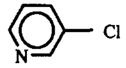
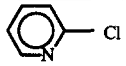
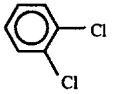
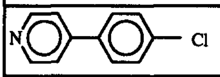
Starting from the aromatic chloride ArCl, the reaction generally leads to 4 products:



Products ArSAr were obtained from the organic extraction performed just after ammonia evaporation and products ArSH and ArSSAr from the mineral phase. Reduction products ArH have not been isolated.

The yields in the different isolated products are reported in Table I together with the numbers of Faradays consumed per mole of aromatic chloride.

Table 1
Results of the electrolyses with the anion of thiourea as nucleophile.

ArCl		mediator	ArSH (%)	ArSSAr (%)	ArSAr (%)	Ar_S[a] (%)	n[b] (F/mol)
	1	4,4'-dipyridyl	34	13	14	88	0.4
	2	2,4'-dipyridyl	75	-	5	85	0.25
	3	2,2'-dipyridyl	_	8	25	66	0.4
	4	2,2'-dipyridyl	23[c]	-	-	23	0.7
	5	benzonitrile	16[d]	-	-	16	0.95
	6[e]	4,4'-dipyridyl	32[f]	-	-	32	1.1

[a] percent of ArCl transformed into sulfur products (%Ar_S = %ArSH + 2%ArSSAr + 2 %ArSAr). [b] number of Faradays consumed per mole of ArCl. [c] determined by HPLC by comparison to an authentic sample. [d] the product is thiophenol. [e] prepared according to ref. 6. [f] identification in ref. 15.

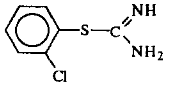
The following observations may be made:

(i) In the case of **1-3** the yields in sulfur products are higher than 65% , i.e. the reaction is efficient. The yields obtained with **4-6** are lower since the reactivity of the aryl radicals involved is smaller: the 2-pyridyl, chlorophenyl and pyridiniophenyl radicals are largely less reactive in $S_{RN}1$ reactions than the 4-cyanophenyl, 3- and 4- pyridyl radicals (cf Table 2).

(ii) The number of Faradays per mole is always lower than 2. Since the electrical yield has not been optimized and the main secondary product is the reduction product ArH whose formation consumes 2 electrons per mole, the sulfuration reaction may be postulated as electrocatalytic.

(iii) It may be assumed that the reaction leads first to ArS^-, whose oxidation gives ArSSAr and whose coupling with the aryl radicals generated during the reduction of ArCl yields ArSAr. When CPG/MS of the crude was carried out exactly once the electrolysis had been stopped, no ArSSAr was detected; therefore the oxidation of ArS^- does not occur during the electrolysis, but during the work-up. The amount of diaryldisulfide increases with the duration of the work-up.

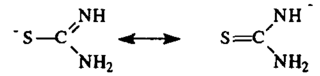
(iv) In the case of 1,2-dichlorobenzene (**5**) a product whose mass corresponds to that of:



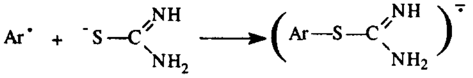
could be detected by GC/MS.

From these observations, a mechanism can be postulated for the reaction.

Among the two mesomeric structures of the anion of thiourea:

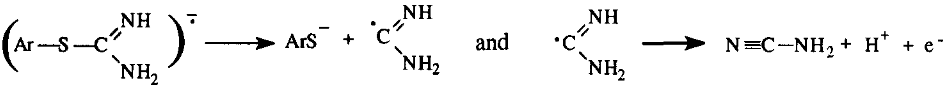


the first one is the only one to react under SRN1 conditions with the aryl radicals Ar$^•$ generated during the reduction of the aromatic chloride:



$$\mathrm{Ar}^{\bullet} + {}^{-}\mathrm{S{-}C({=}NH)NH_2} \longrightarrow \left(\mathrm{Ar{-}S{-}C({=}NH)NH_2}\right)^{\bullet -} \qquad \mathrm{I}$$

The formation of the transient anion-radical is followed by a cleavage reaction to yield the corresponding thiophenoxide and a radical which undergoes an oxidation:



$$\left(\mathrm{Ar{-}S{-}C({=}NH)NH_2}\right)^{\bullet -} \longrightarrow \mathrm{ArS^-} + {}^{\bullet}\mathrm{C({=}NH)NH_2} \quad \text{and} \quad {}^{\bullet}\mathrm{C({=}NH)NH_2} \longrightarrow \mathrm{N{\equiv}C{-}NH_2} + \mathrm{H^+} + \mathrm{e^-}$$

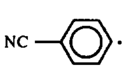
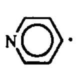
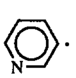
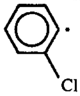
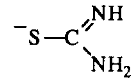
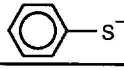
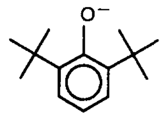
Cyanamide is a highly reactive product which gives guanidine in the presence of ammonia; the acidic hydrolysis of guanidine during the work-up releases carbon dioxide and ammonia:[7]

$$\mathrm{N{\equiv}C{-}NH_2} \xrightarrow{\mathrm{NH_3}} \mathrm{HN{=}C(NH_2)_2} \qquad \text{and} \qquad \mathrm{HN{=}C(NH_2)_2} \xrightarrow[\mathrm{3\,H^+}]{\mathrm{2\,H_2O}} \mathrm{CO_2} + 3\,\mathrm{NH_4^+}$$

The rate constants of the coupling reaction I were determined by perturbed redox catalysis.[2] They are collected in Table 2 together with those corresponding to 2 classical nucleophiles in SRN1 reactions: thiophenoxide and 2,6-di-*tert*-butylphenoxide.

Table 2

Rate constants ($M^{-1}s^{-1}$) of the coupling reaction between aryl radicals and nucleophiles under SRN1 conditions.

Nu$^-$ \ Ar$^•$					
	$4.2\ 10^9$	$3.3\ 10^9$	$0.98\ 10^9$	$0.27\ 10^9$	$0.5\ 10^9$
	$3.4\ 10^9$ [2]	-	$10\ 10^9$ [2]	$0.10\ 10^9$ [2]	-
 [4]	$3.6\ 10^9$ [4]	$1.2\ 10^9$ [4]	$3.2\ 10^9$ [4]	$< 10^8$ [4]	- [a]

[a] about $0.3\ 10^9$ for the 4-chlorophenyl radical.[8]

The values of the coupling reaction rate constants are in agreement with the SRN1 mechanism since the higher the rate constant, the higher the total yield of sulfur products. The reactivity of the thiourea anion is of the same order of magnitude as that of thiophenoxide or 2,6-di-*tert*-butylphenoxide. The coupling rate constant of the N,N-diphenylthiourea anion towards the 4-cyanophenyl radical has also been estimated ($< 10^8\ M^{-1}s^{-1}$); it is lower than that observed with the thiourea anion, which can be explained by a decrease of the nucleophilicity of the anion due to the delocalization of the negative charge on the phenyl rings.

In conclusion, arylsulfides (and diaryldisulfides obtained spontaneously by oxidation of the arylsulfides during the work-up) and diarylsulfides can be obtained by substituting aryl radicals by the thioureate anion in liquid ammonia under an electrochemical inducement. It should be possible to obtain preferentially the arylsulfide by increasing the amount of thiourea or the diarylsulfide by increasing the amount of aromatic halide.[9] The sulfuration method proposed in this paper is softer than the alternative chemical routes which generally make use of alkaline monosulfides (NaSH, KSH) or phosphorus pentasulfide (P_2S_5) either in the presence of activated aromatic halides or at high temperature.[10-14]

References and notes

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9 From the kinetic equations: $\frac{d[ArS^-]}{dt} = k_1[Nu^-][Ar^\bullet] - k_2[ArS^-][Ar^\bullet]$ and $\frac{d[ArSAr]}{dt} = k_2[ArS^-][Ar^\bullet]$, the following differential equation ensues:
$k_2[ArS^-]d[ArSAr] = k_1[Nu^-]d[ArSAr] - k_2[ArS^-]d[ArS^-]$ *[1]*. Since $0 < [ArS^-] < [ArS^-]_{fin}$, equation *[1]* leads to the following range for $\frac{k_2}{k_1}$: $\frac{2[Nu^-][ArSAr]_{fin}}{[ArS^-]^2_{fin}+2[ArS^-]_{fin}[ArSAr]_{fin}} < \frac{k_2}{k_1} < \frac{2[Nu^-][ArSAr]_{fin}}{[ArS^-]^2_{fin}}$ *[2]* in which $[Nu^-]$ is supposed to be constant throughout the experiment and $[X]_{fin}$ corresponds to the concentration of X at the end of the electrolysis. An estimation of $\frac{k_2}{k_1}$ can be obtained from equation *[2]* since $(20\ mM - [Nu^-]_{fin}) < [Nu^-] < 20\ mM$:
$\frac{2\,(20-[Nu^-]_{fin})[ArSAr]_{fin}}{[ArS^-]^2_{fin}+2[ArS^-]_{fin}[ArSAr]_{fin}} < \frac{k_2}{k_1} < \frac{40[ArSAr]_{fin}}{[ArS^-]^2_{fin}}$ *[3]* with the concentrations expressed in mM.
When the reaction leads to ArS^- and ArSAr (case of **1-3**), the reaction can be made specific if the initial concentrations of ArCl and Nu^- are properly chosen. The conversion of ArCl is supposed total and the reduction of Ar into Ar^- negligible. In order to obtain preferentially ArSAr (for instance $[ArS^-]_{fin} = 0.1\ [ArSAr]_{fin}$), equation *[2]* leads to: $\frac{k_2}{400\,k_1} < \frac{[Nu^-]}{[ArX]_0} < \frac{k_2}{20\,k_1}$ *[4]*, whilst in order to obtain preferentially ArS^- (for instance $[ArSAr]_{fin} = 0.1\ [ArS^-]_{fin}$), equation *[2]* leads to $\frac{[Nu^-]}{[ArCl]_0} = 5\frac{k_2}{k_1}$ *[5]*.
The following ranges were obtained: for **1**: $2.4 < \frac{k_2}{k_1} < 4.1$ (mean value: 3.3); for **2**: $0.66 < \frac{k_2}{k_1} < 0.88$ (mean value: 0.77); for **3**: $19 < \frac{k_2}{k_1} < 82$ (mean value: 51). For **4-6**, k_2 is negligible when compared to k_1. Equations *[4]* and *[5]* have been applied using the mean values of $\frac{k_2}{k_1}$. The conditions found to obtain preferentially ArSAr involve large excesses of ArCl compared to Nu^- ($\frac{[ArCl]_0}{[Nu^-]}$: between 6.1 and 121 for **1**; between 26 and 520 for **2** and between 0.39 and 7.8 for **3**); they have to be calculated more precisely since with such excesses of ArCl, $[Nu^-]$ cannot be constant throughout the experiment and the above kinetic model is not valid. The conditions found to obtain preferentially ArS^- are the following: $\frac{[Nu^-]}{[ArCl]_0} = 17$ for **1**; 3.9 for **2** and 255 for **3**. From an experimental point of view the requirements to obtain preferentially ArSAr or ArSH are not always easily fulfilled since in some cases they involve very large excesses of either the aromatic halide or the nucleophile, which can make the work-up difficult.
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15 **4-(4-thiophenyl)pyridine.** mp = 171°C; ^1H NMR (300 MHz, $CDCl_3$), δ (ppm)= 7.32-7.48 (m, 2 H), 7.48-7.70 (m,2 H), 8.48-8.72 (m, 2 H); ^{13}C NMR (300 MHz, $CDCl_3$), δ (ppm)= 121.19 (2 CH), 127.56 (2 CH), 127.69 (2 CH), 136.94 (2 C), 137.86 (2 C), 147.07 (2 C), 150.22 (2 CH); MS (CPG/MS), m/z= 187.

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