Electrolytic Generation of Nucleophiles. IV.* Reductive Alkylation and Acylation of Disulfides

PALLE E. IVERSEN and HENNING LUND

Department of Organic Chemistry, University of Aarhus, DK-8000 Aarhus C, Denmark

Mayer and coworkers [3] have briefly reported on the electrolytic reductive methylation of various disulfides with dimethyl sulfate in aqueous isopropanol on a rather small scale. We have extended the reaction to aprotic medium with a variety of electrophiles to present a general alternative way of preparing sulfide derivatives and demonstrate another example of *in situ* reaction of electrochemically generated nucleophilic species.

The electrolytic reduction of a disulfide bond leads to a thiolate anion which could either be protonated to give the corresponding mercapto derivative [3] or react with an appropriate electrophile present, thus creating a new C–S linkage:

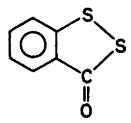
$$R-S-S-R \xrightarrow{2e^-} 2RS^- \xrightarrow{H^+} RSH$$
$$\qquad\qquad\qquad\qquad\quad \xrightarrow{R'X} R-S-R'+X^-$$

In the present investigation have been employed readily available (mostly symmetric) disulfides which yielded products of relatively low volatility (Tables 1 and 2). One advantage of the electrochemical method was already pointed out by Mayer and coworkers:[3] Derivatives can be made from disulfide precursors where the corresponding thiols are unstable or not known as in the case of 3*H*-1,2-benzodithiol-3-one and -3-thione. Another feature is that controlled potential electrolysis can work selectively on substrates which contain other reducible functions as exemplified by bis(2-nitrophenyl)disulfide. This is of course also possible by normal chemical procedures, if a suitable reducing agent can be found.

For a given disulfide the choice of the electrophile is restricted by the fact that the S–S bond must be easier reducible than the electrophile itself. Methyl chloride in an aprotic polar solvent, such as *N*,*N*-dimethylformamide (DMF), was found to be a convenient and efficient methylating reagent for the reductive methylation of most disulfides in DMF (Table 1). This has also recently been used by Simonet and coworkers [4] in electrolytic reductive alkylation of sulfonyl chlorides. Results from experiments with some other alkylating and acylating agents are given in Table 2 showing that the alkylations mostly give better yields than the acylations. In the experiment with *N*,*N*-dimethylcarbamoyl chloride, the electrophile was reduced at the potential applied, so that a good yield was not to be expected. However, the fact that our attempts to prepare the wanted dimethylthiocarbamoyl dimethylcarbamoyl sulfide by conventional methods [5] were unsuccessful, makes the relatively low yield (44 % crude) more acceptable. The addition of pyridine did not affect the product yield significantly

* *Cf.* Refs. 1–2.

Table 1. Results from reductive methylation of disulfides (5.0 g or 5.0 ml) with CH_3Cl in DMF/0.5 M LiCl.



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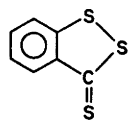

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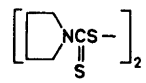

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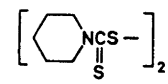

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Starting material	$-E$ (V) *vs.* Ag/AgCl/0.5 M Cl^-	Product yield (%) Crude	Isolated	B.p./mmHg or M.p. (°C)	n_D^{25}
$[C_6H_5CH_2S-]_2$	1.2	95	82	84–87/10	1.5608
$[C_6H_5S-]_2$	0.85	95	83.5	70–71/9	1.5835
$[p\text{-}CH_3C_6H_4S-]_2$	1.0	95	85.5	85–88/10	1.5730
$[C_6H_5COS-]_2$	0.8	90	70	112–120/10	1.5820
$[o\text{-}NO_2C_6H_4S-]_2$	0.3	94	91	67–68	
$[o\text{-}C_2H_5O-CO-C_6H_5S-]_2$	0.6	95	89	106–109/0.15	1.5754
1	0.15	98	85.5	53–54	
2	0.35	84	78	59–60	
$[(CH_3)_2NCSS-]_2$	1.0	98	81	46–47	
3	0.8	94	88	90–91	
4	1.2	86	78	36–37	

Table 2. Results from reductions of disulfides (5.0 g or 5.0 ml) with other electrophiles in DMF/0.5 M LiCl.

Starting material	$-E$ (V) *vs.* Ag/AgCl/0.5 M Cl^-	Electrophile (ml)	Product yield (%) Crude	Isolated	B.p./mmHg or M.p. (°C)	n_D^{25}
$[CH_3S-]_2$	1.2	$C_6H_5CH_2Cl$ (18)	–	63	82–86/9	1.5604
$[CH_3COS-]_2$	0.8	» (5)	87	76.5	65–75/0.25	1.5564
$[C_6H_5S-]_2$	0.8	» (5.5)	98	92	41–42	
$[C_6H_5CH_2S-]_2$	1.2	$CH_3CHClCH_3$ (20)	90	75.5	100–104/10	1.5362
»	1.2	$(CH_3CO)_2O$[a] (15)	95	89.5	68–72/0.25	1.5564
$[o\text{-}NO_2C_6H_4S-]_2$	0.2	» [a] (15)	87	68.5	118–125/0.25	1.5910
»	0.2	CH_3COCl (10)	–	39	110–120/0.15	1.5912
»	0.3	CH_3I (2.2)	89	84	68–69	
»	0.3	$(CH_3O)_2SO_2$ (10)	98	91	66–68	
»	0.3	$(CH_3CH_2O)_2SO_2$ (20)	82	76.5	115–125/0.25	1.6234
$[(CH_3)_2NCSS-]_2$	0.4[b]	$(CH_3)_2NCOCl$[c] (5)	44	37	76–77	
$[C_6H_5COS-]_2$	0.4	CH_2Br_2 (2)	98	66[d]	118–119	
»	0.4	CH_2Cl_2 (1.2)	57	34[d]	108–110	

[a] 5 ml of pyridine added. [b] Solvent acetonitrile/0.8 M $NaClO_4$, sat. LiCl in the reference electrode. [c] 2 ml of pyridine added. [d] The product was di-*S*-thiobenzoylmethane.

in this particular case, but it proved to be advantageous for the reductions with acetic anhydride.

In most experiments DMF has been employed as the solvent, but acetonitrile may also be useful for reductive alkylations and acylations. In some cases, *e.g.* dibenzyldisulfide, the yield of methylated product was considerably lower in acetonitrile (82 %) than in DMF (95 %), whereas with *N*,*N*-dimethylcarbamoyl chloride as the electrophile the yield was higher in acetonitrile than in DMF. Ethanol and presumably other protic solvents are inferior to the aprotic solvents and a considerable amount of thiol was found as a side product in methylations with methyl chloride, but possibly dimethyl sulfate may be used instead.

Experimental. The electrolytic equipment has been described earlier.[1] The disulfides were either commercial products or prepared by literature methods. The DMF was dried over A4 molecular sieves. Boiling and melting points are uncorrected.

General procedure for electrolytic reductive alkylation and acylation. The disulfides (5.0 ml or 5.0 g) were reduced overnight at room temperature (cell surrounded by a water bath) in DMF (approx. 175 ml) containing 0.5 M lithium chloride. The reference electrode was Ag/AgCl/0.5 M LiCl in DMF, and working potentials and amounts of added electrophile are indicated in Tables 1 and 2. For some of the very easily reducible compounds the mercury cathode was polarized negatively before addition of the disulfide to avoid the formation of a black precipitate by reaction with the metal. The electricity consumption was usually very close to 2 F/mol of disulfide. After reduction an equal volume of benzene was added to the catholyte which was then washed 3 times with 1.5 l of water to remove the DMF. For experiments in acetonitrile the solvent was evaporated *in vacuo* before the extraction with benzene. The organic layer was dried over anh. magnesium sulfate, the solvent removed *in vacuo*, and the residue either fractionated *in vacuo* or recrystallized from ethanol. In a few experiments with diphenyl- and dibenzyldisulfide about 600 ml of water were added to the catholyte which was then extracted continuously with petroleum ether (16–20 h) and worked up as above. The extraction procedure was checked with benzyl methyl sulfide giving 95 % recovery. The prepared sulfide derivatives were known from the literature and identified by comparison with authentic specimens or literature data. Optimization of yields has not been attempted.

S-*Methyl(2-thiomethyl)thiobenzoate.* For this compound our m.p. (53–54 °C) did not agree with the reported[3] one (121–122 °C). NMR-spectrum (60 MHz, CCl_4, TMS): δ 2.35 (s, 3 H); δ 2.40 (s, 3 H); δ 6.9–7.9 (multiplet, 4 H). Strong IR-absorptions (KBr, cm^{-1}): 1660, 1205, 905. (Found: C 54.47; H 5.13; S 32.07. Calc. for $C_9H_9OS_2$: C 54.54; H 5.09; S 32.30). For comparison the NMR (CCl_4) *S*-methyl signals are given for S-*methylthiobenzoate:* δ 2.40 (s, 3 H) and S-*methyl(2-methylthio)dithiobenzoate*: δ 2.32 (s, 3 H) and δ 2.69 (s, 3 H).

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4. Jeminet, G., Simonet, J. and Courcy, J.-G. *Bull. Soc. Chim. Fr.* (1974) 1102.
5. White, R. W. *Can. J. Chem. 32* (1954) 867.

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