3-Mercaptopropionic Acid: A New Tool in the Synthesis of Symmetrical Diaryl Sulfides from Unactivated Aryl Iodides as Substitute for Anhydrous Sodium Sulfide

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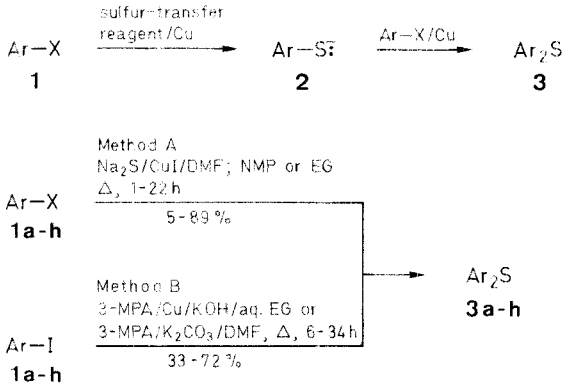
A series of symmetrical diaryl sulfides has been prepared by the copper-catalyzed reaction of 3-mercaptopropionic acid with unactivated aryl iodides. The yields are comparable with those obtained using anhydrous sodium sulfide under optimized reaction conditions.

The reaction of sodium sulfide with appropriate halides is a well known method for the preparation of symmetrical sulfides.[1] In this procedure, alkyl, benzyl, and activated aryl halides react under usual reaction conditions,[1] while unactivated aryl halides require high temperature and pressure.[2] These forcing conditions can be diminished to some extent by the use of copper catalysts[3] or dipolar aprotic solvents.[4] The role of the copper catalyst[5] and solvent[6] is well documented.

We report here two one-pot procedures for the synthesis of symmetrical diaryl sulfides **3**. These involve both the copper-catalyzed *in situ* formation of the intermediate arenethiolate anions **2** from the unactivated aryl halides **1**, and the subsequent arylation of **2** by **1** (Scheme **A**). Both anhydrous sodium sulfide[7] (Method A) and 3-mercaptopropionic acid (**4**) (Method B) offer powerful sulfur nucleophiles for this reaction. These methods have some advantages:

- the starting halides are accessible;
- there is no need for aromatic thiols as starting materials;
- the pure sulfides are obtained by conventional work-up; and
- the yields are good.



3-MPA = $HSCH_2CH_2CO_2H$ (**4**)
NMP = *N*-methylpyrrolidone
EG = ethylene glycol

	X (1)	Ar (1–3, 5)		X (1)	Ar (1–3, 5)
a	I	Ph	**d**	I	4-$HO_2CC_6H_4$
b	I	2-$HO_2CC_6H_4$	**e**	I	2-$H_2NO_2SC_6H_4$
b-Br	Br	2-$HO_2CC_6H_4$	**f**	I	2-$(CH_3)HNO_2SC_6H_4$
b-Cl	Cl	2-$HO_2CC_6H_4$	**g**	I	8-carboxy-1-naphthyl
c	I	3-$HO_2CC_6H_4$	**h**	I	1-naphthyl

Scheme **A**

The efficiency of different copper catalysts and various solvents on the formation of 2,2′-thiodibenzoic acid (**3b**) was studied using potassium 2-iodo-, 2-bromo-, and 2-chlorobenzoates. Table 1 shows that all copper(I) compounds and copper bronze used are equally efficient, while cupric sulfide, which is actually not a simple copper(II) compound,[8] affords the appropriate sulfide only in impure state. Without catalyst there is no sulfide formation. The reaction of **1b** to **3b** is faster in dimethylformamide than in ethylene glycol. The reactivity of aryl halides decreases in the order of ArI > ArBr > ArCl, thus only the aryl iodides **1a–h** were used for the synthesis of the sulfides **3a–h**.

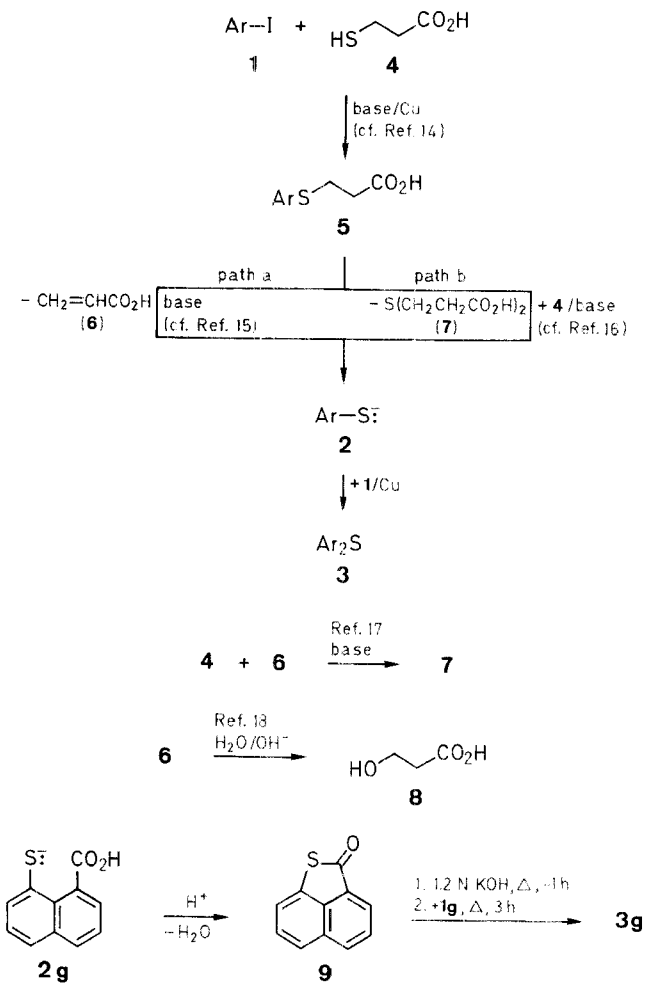
Table 1. Effect of Catalyst and Solvent on Formation of **3b** by Method A

Substrate	Catalyst[a]	Time (h)	Solvent[b]	Yield (%)
1b	none	4	EG	0
1b	Cu[c]	4	EG	80
1b	CuI	4	EG	89
1b	Cu_2S	4	EG	89
1b	Cu_2O	4	EG	80
1b	CuS[d]	4	EG	85[e]
1b	CuI	1	DMF	87
1b-Br	CuI	7	EG	64
1b-Cl	CuI	28	EG	0
1b-Cl	CuI	14	DMF	0
1b-Cl	CuI	8	NMP	5

[a] 10 Mmol of catalyst used for 100 mmol of aryl halide.
[b] EG = ethylene glycol, NMP = 1-methyl-2-pyrrolidinone.
[c] „Naturkupfer C" (copper bronze), product of C.A.F. Kahlbaum Chemische Fabrik, Berlin.
[d] Formulated as $Cu_2^ICu^{II}(S_2)S$ in Ref. 8.
[e] Contaminated with 2,2′-dithiodibenzoic acid (TLC).

In an improved laboratory procedure, a 2:1 molar mixture of aryl iodide and anhydrous sodium sulfide was refluxed under an argon atmosphere in ethylene glycol (~ 200 °C) or dimethylformamide (~ 150 °C) solution in the presence of copper(I) iodide (10 mol %) for the time given in Table 2. Carboxylic acids were converted to their potassium salts before use. The presence of a potential chelating group (e.g. CO_2H, SO_2NHR) in the *ortho*- or *peri*-position of the aryl halide has a marked activating effect (cf. reaction time, solvent and yield data for Method A in Table 2).

We have found that 3-mercaptopropionic acid (**4**, 3-MPA) can also be used as sulfur-transfer reagent. In our new one-pot procedure a water/ethylene glycol solution of aryl iodides and 3-MPA is refluxed (~ 120 °C) under an argon atmosphere with a large excess of potassium hydroxide and a catalytic amount of copper bronze, to afford diaryl sulfides. This method was very effective for iodo-arenecarboxylic acids and -sulphonamides (Table 2), but failed with the water-insoluble parent aryl iodides (iodobenzene and 1-iodonaphthalene). However, substituting potassium carbonate for potassium hydroxide, and using dimethylformamide as solvent allowed the preparation of diphenyl sulfide (**3a**) and bis(1-naphthyl)sulfide (**3h**) in fair to good yield (Table 2). Aryl bromides and chlorides (e.g. 2-bromo- and 2-chlorobenzoic acid) were ineffective under both conditions described above.



Scheme **B**

We assume that Method B is based on a set of consecutive and parallel reactions (Scheme **B**). The formation of intermediate arenethiolate anions **2** involves a copper-catalyzed nucleophilic substitution on the unactivated aryl iodide **1**[14] affording 3-arylthiopropionic acid intermediate **5**, from which **2** is formed either by base-catalyzed elimination[15] of acrylic acid **(6)** (path a), or to a minor extent, by nucleophilic substitution of **4** at the α-carbon followed by elimination of 3,3'-thiodipropionic acid **(7)** (path b).[16] For compounds **1**, **5** and **6** there is a competition to react with 3-MPA **(4)** yielding **5**, **2** + **7** and **7**[17], respectively (Scheme **B**). From these facts, it follows that the optimal ratio of aryl iodide **(1)** to 3-MPA **(4)** lies between 2:1 and 1:1. However, the large excess of base, which converts **6** into 3-hydroxypropionic acid **(8)**,[18] decreases the amount of **6** available for the above competition. Thus, the use of **1** and **4** in a 2:1 molar ratio usually results in good yields of diaryl sulfides **3** formed, like in Method A, by arylation of **2** as closing step.

Under optimized conditions (experimental) the hydrolyzable[19] 8-iodo-1-naphthoic acid **(1g)** was converted to thiolactone **9** by acidifying the arenethiolate **2g** intermediate. On subsequent arylation the thiolactone afforded the corresponding diaryl sulfide **3g** in high yield. In this case the 3-arylthiopropionic acid intermediate **5g** and the by-product, 3,3'-thiodipropionic acid **(7)**, were also isolated (Scheme **B**).

Melting points were determined on a Boëtius micro melting point apparatus and are corrected. IR spectra were taken on a Specord IR 75 (Zeiss, Jena) spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian A60 D spectrometer. Analytical TLC plates were purchased from Merck (No. 5554) and the following solvent systems were used: benzene/dioxane/AcOH (9:2.5:4); benzene/$CHCl_3$/AcOH (4:1:2; 8:1:1) and $CHCl_3$/AcOH (4:1).

Aryl halides **1a–d**, **1b**-Br, **1b**-Cl and **1h**, and 3-MPA **(4)** are commercially available. Aryl iodides **1e**,[20] and **1g**[21] were prepared according to literature procedures.

Table 2. Preparation of Symmetrical Diaryl Sulfides **3** and Thiolactone **9**

Substrate	Product[a]	Method[b]	Solvent[c]	Reaction Time (h)	Yield[d] (%)	mp (°C)[e] (solvent)	Molecular Formula[f] or Lit. mp (°C)	IR (KBr) (cm^{-1})[g]
1a	**3a**	A	DMF	22	67	296	296[9]	1580, 1476, 1438 (C=C_{ar}); 738 (γ_{CH}), 690 ($\gamma_{C=C}$, monosubstitution)
		B	DMF	22	42	(1.6328)	(1.6327)[9]	
1b	**3b**	A	EG	5	89	234–236	233.5–236[10]	3300–2100 (OH); 1690 (C=O); 1581, 1553, 1460 (C=C_{ar}); 1293, 1271, 1250 (C–O); 930 (γ_{OH}); 742 ($\gamma_{ar-CH(1,2)}$)
		B	aq-EG	6	72	(AcOH)		
1c	**3c**	A	DMF	12	52	302–304	$C_{14}H_{10}O_4S$	3200–2100 (OH); 1690 (C=O); 1590, 1571 (C=C_{ar}); 1312, 1258 (C–O); 938 (γ_{OH}); 896, 748, 721 ($\gamma_{ar-CH(1,3)}$)
		B	aq-EG	6	70	($EtCO_2H$)	(274.3)	
1d	**3d**	A	EG	5	45	335	335[11]	3300–2100 (OH); 1680 (C=O); 1591, 1565 (C=C_{ar}); 1295 (C–O); 930 (γ_{OH}); 802 ($\gamma_{ar-CH(1,4)}$)
		B	aq-EG	6	45	($EtCO_2H$)		
1e	**3e**	A	DMF	6	16	206–208	$C_{12}H_{12}N_2O_4S_3$	3371, 3253 (NH_2); 1532 (δ_{NH_2}); 1320, 1161 (SO_2); 902 (γ_{NH_2}); 761 ($\gamma_{ar-CH(1,2)}$)
		B	H_2O	10	61	(EtOH/H_2O)	(344.4)	
1f	**3f**	A	EG	5	49	181–182[h]	$C_{14}H_{16}N_2O_4S_3$	3346, 3318 (NH); 1570 (δ_{NH}); 1328, 1314, 1169, 1162, 1152 (SO_2); 842 (γ_{NH}); 765, 755 ($\gamma_{ar-CH(1,2)}$)
		B	aq-EG	6	60	(MeOH/H_2O)	(372.5)	
1g	**3g**	A	EG	5	67	239–241	$C_{22}H_{14}O_4S$	3300–2000 (OH); 1702, 1638 (C=O); 1587, 1564, 1500 (C=C_{ar}); 1273, 1203 (C–O); 825, 764 ($\gamma_{ar-CH(1,2,3)}$)
		(**9** + **1g**)	H_2O	3	86	(EtOH/H_2O)	(374.4)	
1g	**9**	B	H_2O	8	89	145–146 (EtOH/H_2O)	144.5–145.5[12]	1686 (C=O); 1615, 1586, 1488 (C=C_{ar}); 815, 760 ($\gamma_{ar-CH(1,2,3)}$)
1h	**3h**	A	DMF	22	69	110	110[13]	1590, 1561, 1500 (C=C_{ar}); 764 ($\gamma_{ar-CH(1,2)}$); 792, 662 ($\gamma_{ar-CH(1,2,3)}$)
		B	DMF	34	33	(MeOH)		

[a] Homogeneous by TLC.
[b] Sulfur-transfer reagents: Na_2S (Method A), 3-MPA (Method B).
[c] aq-EG = aqueous ethylene glycol (10 N KOH/EG = 1:1 v/v; see experimental).
[d] For recrystallized products based on **1**.
[e] In case of **3a**, bp (1 atm) and (n_D^{20}) are given.
[f] Satisfactory microanalyses obtained: C ±0.40, H ±0.18, S ±0.31; exception **3c**: C −0.75.
[g] Refers to ν, unless otherwise stated (δ or γ).
[h] ^{1}H-NMR ($CDCl_3$/TMS): δ = 2.61 (d, 3H, J = 5 Hz, CH_3); 5.55 (q, 1H, J = 5 Hz, NH exchangeable with D_2O); 7.2–7.65 (m, 3H_{arom}); 8.0–8.3 (m, 1H_{arom}).

N-Methyl-2-iodobenzenesulfonamide (1f):
A 4.5 N solution of CH_3NH_2 in THF (300 mL) is added to a stirred solution of 2-iodobenzenesulfonyl chloride[22] (180 g, 0.6 mol) in dioxane (600 mL) at room temperature. The mixture is allowed to stand overnight and the solvent is evaporated *in vacuo*. The solid residue is suspended in water (500 mL), filtered and recrystallized to afford a white solid; yield: 166 g (94%); mp 119–121 °C (MeOH/H_2O).

$C_7H_8INO_2S$	calc.	C 28.29	H 2.71	I 42.71	N 4.71	S 10.79
(297.1)	found	28.53	2.72	42.53	4.50	10.60

IR (KBr): ν = 3312 (NH); 1318, 1162, 1156 (SO_2); 830, 760 cm^{-1}

^{1}H-NMR ($CDCl_3$/DMSO-d_6, 10:3/TMS): δ = 2.60 (d, 3H, J = 5 Hz, CH_3); 6.35 (br, 1H, NH, exchangeable with D_2O); 7.0–8.3 (m, 4 H_{arom}).

Diaryl Sulfides 3a–h; General Procedures:
Method A (Table 2): A solution or suspension of aryl halide **1** (100 mmol) and anhydrous K_2CO_3 (6.9 g, 50 mmol, for **1b–e, g**) in ethylene glycol (100 mL) or in DMF (100 mL) is made by heating on a steam bath for a few min. After the addition of anhydrous Na_2S (4.3 g, 55 mmol) and CuI (1.9 g, 10 mmol) the mixture is refluxed under an argon atmosphere for the time shown in Table 2. Water (500 mL) is then added, and the mixture is boiled with activated carbon. It is filtered while hot into an excess of 6N HCl (50 mL). The precipitate formed on cooling to room temperature is filtered, washed with water, and recrystallized.

Compounds **3a, 3f** and **3h** are prepared without K_2CO_3. In the case of **3f**, NaOH (5.0 g, 125 mmol) is added to the reaction mixture diluted with water. For **3a** and **3h** the water diluted reaction mixtures are extracted with $CHCl_3$ (3 × 100 mL). The combined organic phase is washed with 2N NaOH (3 × 50 mL), and dried ($MgSO_4$). The solvent is removed and the crude products obtained are purified by distillation or recrystallization.

Method B (Table 2): To a magnetically stirred mixture of ethylene glycol (50 mL), 10N KOH (50 mL, 500 mmol) and Cu (0.5 g), 3-MPA (4.6 mL, 5.6 g, 53 mmol) and aryl iodide **1b–d, f** (100 mmol) are added under an argon atmosphere. The mixture is stirred and refluxed for the time shown in Table 2.

In the case of **3e**, a mixture of 3-MPA (9.2 mL, 11.2 g, 106 mmol), **1e** (28.3 g, 100 mmol) and Cu (0.5 g) is allowed to react in boiling 5N KOH (200 mL).

Compounds **3a** and **3h** are obtained by the reaction of 3-MPA (4.6 mL, 5.6 g, 53 mmol) with **1a** (11.2 mL, 20.4 g, 100 mmol) or **1h** (14.6 mL, 25.4 g, 100 mmol), respectively, in the presence of anhydrous K_2CO_3 (15 g, 109 mmol) and Cu (0.5 g) in boiling DMF (100 mL).

The rest of the procedure for the isolation of the sulfides **3a–f, h** is the same as given in Method A, except for using more 6N HCl (100 mL for **3b–d, f**; 200 mL for **3e**) for acidification of the water diluted reaction mixtures.

2*H*-Naphtho[1,8-*bc*]thiophen-2-one (9):
To 7N KOH (300 mL) and 3-MPA (**4**; 105 mL, 128 g, 1.2 mol) are added **1g** (119 g, 0.40 mol) and Cu (4 g) under an argon atmosphere and the mixture is refluxed for 5 h. The intermediate 3-(8-carboxy-1-naphthylthio)propionic acid (**5g**) can be isolated at this point by acidification of a sample with excess 6N HCl.

5g; white crystals; mp 158–159 °C (EtOH/H_2O).

$C_{14}H_{12}O_4S$	calc.	C 60.85	H 4.38	S 11.60
(276.3)	found	60.98	4.48	11.92

IR (KBr): ν = 3300–2100 (OH); 1688 (C=O); 1293, 1211 (C–O); 941, 833, 770 cm^{-1}.

^{1}H-NMR ($CDCl_3$/DMSO-d_6, 6:1/TMS): δ = 2.45 (t, 2H, J = 7 Hz, $SCH_2CH_2CO_2H$); 3.08 (t, 2H, J = 7 Hz, $SCH_2CH_2CO_2H$); 7.3–8.0 (m, 6 H_{arom}); 10.5 (2H, $2CO_2H$, exchangeable with D_2O).

To effect the alkaline cleavage of **5g**, 7N KOH (300 mL) is added to the above mixture and refluxed for 3 h. Water (800 mL) is then added and filtered into an excess of 6N HCl (800 mL). The precipitate obtained is filtered, washed with water, and dried. The crude product is purified by extraction with CH_2Cl_2 in a Soxhlet apparatus, followed by recrystallization; yield: 66.6 g (89%); yellow needles, mp 145–146 °C (EtOH/H_2O).

From the acidic (HCl) filtrate 3,3′-thiodipropionic acid (**7**) can be isolated by crystallization; yield: 70% based on **1g**, showing identical properties (mp, IR, TLC) with an authentic sample.

Bis(8-Carboxy-1-naphthyl) Sulfide (3g):
The thiolactone **9** (7.45 g, 40 mmol) is boiled with 1.2 N KOH (100 mL) under an argon atmosphere until it dissolves (ca. 1 h). Then Cu (0.4 g) and **1g** (11.9 g, 40 mmol) are added and the mixture is refluxed for 3 h. The subsequent procedure is the same as given in Method A.

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