Synthesis of 3-(Arylthio)propionic Acids from Nonactivated Aryl Iodides and their Use as Odorless Aryl Mercaptan Surrogates

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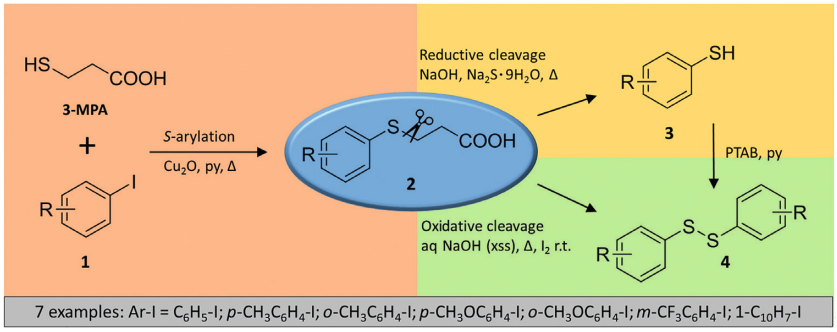

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Abstract The reaction of aryl iodides, 3-mercaptopropionic acid, and Cu_2O in refluxing pyridine resulted in the formation of 3-(arylthio)propionic acids in good to excellent yield. The latter 3-(arylthio)propionic acids — as novel aryl mercaptan equivalents — gave aryl mercaptans or diaryl disulfides, respectively, on reductive (Na_2S) or oxidative (I_2) cleavage in alkaline media. The symmetrical disulfides can also be prepared by oxidizing their precursor mercaptans with phenyltrimethylammoniumtribromide in pyridine at ambient temperature.

Key words 3-mercaptopropionic acid, sulfur-transfer reagent, 3-(arylthio)propionic acid, reverse Michael reaction, copper(I) oxide

3-(Arylthio)propionic acids are important compounds in biochemistry and pharmaceutical chemistry. They are used as sulfur-transfer reagents and building blocks for the synthesis of compound families with diverse biological activity. For example, **5** has anticancer activity,[1] **6** is a monoamine oxidase inhibitor,[2] **7** has antihepatitis effects[3] and Meniere's disease can be treated with **8**[4] (Figure 1). Furthermore, other important active pharmaceutical ingredients, such as (thio)pyranones, piperidones,[5] and benzodiazepines[6] are easily synthesized from 3-(arylthio)propionic acid derivatives. 3-(Arylthio)propionic acids have usually been synthesized from their precursor aryl mercaptans by conjugated addition reactions using acrylic acid, acrylic esters or acrylonitrile,[7] or by the alkylation of thiophenol derivatives using β-halopropionic acids or esters, or β-propiolactone.[8,9] They can also be synthesized by nickel-catalyzed S-arylation of 3-mercaptopropionic acid (3-MPA) with aryl iodides.[10] On the other hand, methyl 3-(arylthio)propionates are accessible by base-induced cleavage of sulfonium salts, prepared by condensation of electron-rich arenes and appropriate sulfoxides.[11]

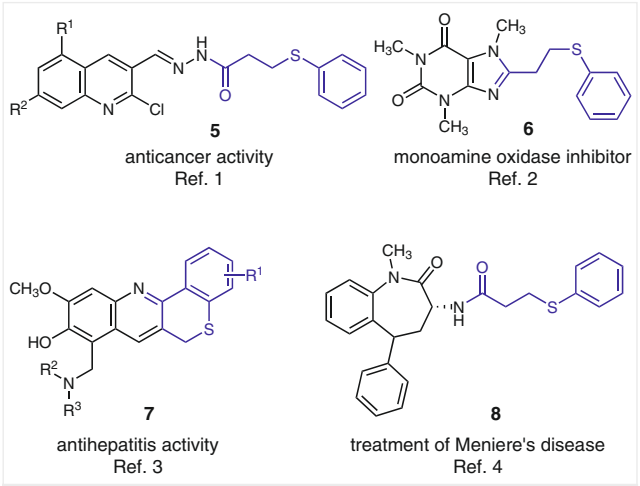


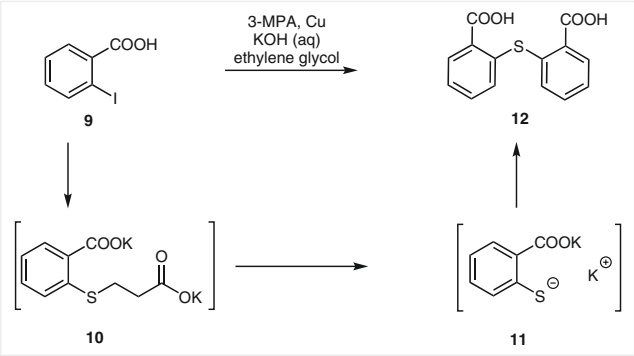
Figure 1 3-(Arylthio)propionic acids as building blocks and transfer reagents in active pharmaceutical ingredients (APIs)

3-(Arylthio)propionic acids are shelf-stable sources of thiols.[12] Thiols are an important class of compounds because of the special ability of the mercapto group to bind to metals and regulate redox reactions.[13] Aromatic thiols are often used for the synthesis and stabilization of metal nanoparticles[14] and for modification of metal or metal oxide surfaces.[15] Mercaptans also have biological activity, they play an important role in the regulation mechanism of redox systems with biological importance,[16] and this moiety can be found in anti-HIV and anticancer agents.[17] Diaryl and dialkyl disulfides are stable sources of thiols[18] and starting materials of several sulfur-containing reagents,

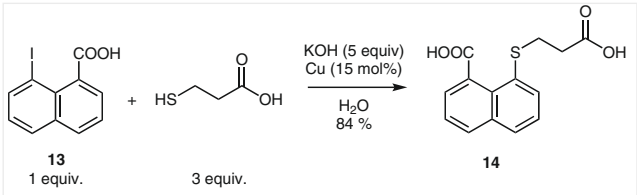
such as sulfenic acids,[19] sulfinic esters,[20] sulfinyl chlorides,[21] and thiocarbamates.[22] They are also used as antitumor[23] and anti-HIV agents.[24]

Although many procedures are known for the preparation of aryl mercaptans[25] and diaryl disulfides,[26] only a few involve the reaction of nonactivated aryl iodides with appropriate sulfur-transfer reagents such as copper(I) thiobenzoate[27] or copper(I) thiocyanate.[26b] The latter methods provide some advantages starting from accessible aryl iodides and reagents, but they involve the use of a carcinogenic solvent, HMPT.

In biological systems, thioethers are often used for reversible conjugation of thiols,[28] where the appropriate thiols are liberated by retro-Michael reaction. This approach is of intense interest for the development of fluorescent probes[29] and drug-delivery systems.[30] 3-(Arylthio)propionic acids **2** also can be cleaved by retro-Michael reaction to afford the appropriate thiolates **11** under laboratory conditions.[31] In our previous work, 3-MPA was used as a sulfur-transfer reagent in the synthesis of symmetric diaryl sulfides (Scheme 1).[32] We proposed that the reaction went through a 3-(arylthio)propionic acid intermediate **10**, which, in the next step, was cleaved to afford the arylthiolate intermediate **11**. The thiolate intermediate was isolated only in one specific case, when we adjusted the pH of the system to prevent the decomposition of 3-(8-carboxy-1-naphthylthio)propionic acid (**14**) into 8-mercapto-1-naphthalene-carboxylate, which, on acidification, gave the appropriate thiolactone (Scheme 2).[32]



Scheme 1 Synthesis of a symmetrical diaryl sulfide via 3-(arylmercapto)propionic acid **10** and arenethiolate **11** intermediate (cf. Ref.[19])



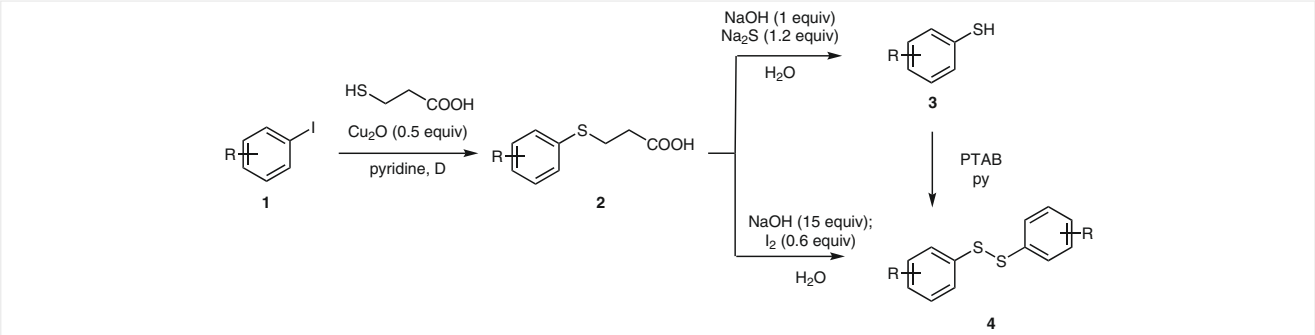
Scheme 2 Synthesis of 3-(8-carboxy-1-naphthylthio)propionic acid

In this study, as opposed to our earlier method allowing the synthesis of symmetrical diaryl sulfides in a one-pot reaction, we modified the reaction conditions to enable the isolation of 3-(arylthio)propionic acids **2** as the main products of the reaction of 3-MPA and aryl iodides.

3-(Arylthio)propionic acids **2** can be synthesized by copper-mediated C–S bond formation of 3-mercaptopropionic acid and nonactivated aryl iodides **1**. These compounds are important intermediates in the synthesis of arylmercaptans **3** and diaryl disulfides **4** (Scheme 3). To find the optimal reaction conditions, the solvent, the amount of Cu_2O, and the reaction time were varied (Table 1).

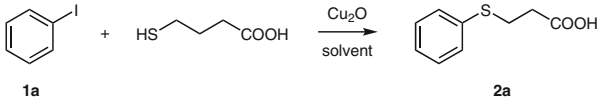
3-(Phenylthio)propionic acid was synthesized in good yield by using equivalent amounts of iodobenzene, 3-mercaptopropionic acid, and 0.5 equiv of Cu_2O in refluxing pyridine for 6 h (Table 1, entry 2). Substituted 3-(arylthio)propionic acids **2a–g** were prepared with good yields (Table 2).

Under alkaline conditions, thioether groups that are in the γ-position relative to a carbonyl group can be cleaved by retro-Michael reaction. This reaction was first observed by Holmberg and Schjånberg. They reported that diphenyl disulfide and 3-hydroxypropionic acid are formed when an aqueous NaOH solution of 3-(phenylthio)propionic acid was exposed to air, but no formation of dibenzyl disulfide was observed under the same conditions using 3-(benzylthio)propionic acid.[31] These observations can be interpreted by considering the higher acidity of thiophenol



Scheme 3 Synthesis of arylmercaptans and diaryl disulfides via 3-arylmercaptopropionic acid intermediate

Table 1 Optimization of the Synthesis of 3-(Phenylthio)propionic Acid

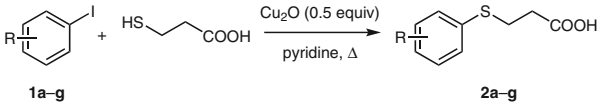


1a 2a

Entry	Cu_2O (equiv.)	Solvent	Reaction time (h)	Yield (%)
1	0.5	py	3	54
2	0.5	py	6	67
3	0.5	py	12	52
4	0.5	DMF	3	48
5	0.5	DMF+ 4 eq py	3	47
6	1.0	py	3	14
7	0.05	py	3	0

(pK_a 6.52) when compared to benzyl mercaptan (pK_a 9.43), thus the former is a better leaving group than the latter. In a control experiment we found that 3-(*n*-butylthio)propionic acid (*n*-C_4H_9S-$CH_2CH_2CO_2H$) was also stable to aq-NaOH in the presence of air (cf. *n*-butyl mercaptan, pK_a 10.66).[35] Retro-Michael reaction also took place at neutral pH, promoted by excess thiol.[29] In this case, the formed acrylic acid is quenched, thus the equilibrium is shifted towards the cleavage reaction. Acrylic acid also reacts in situ with sulfide[36] or hydroxide nucleophiles. On the other hand, the equilibrium can be shifted by oxidation of the formed mercaptides.

Table 2 Synthesis of 3-(Arylthio)propionic Acids



1a–g 2a–g

Entry	R	Product	Yield (%)	Lit.[a]
1	H	**2a**	67	7a,8c
2	4-CH_3	**2b**	77	8b
3	2-CH_3	**2c**	68	9
4	4-OCH_3	**2d**	69	7a,33
5	2-OCH_3	**2e**	66	7a,8d
6	3-CF_3	**2f**	59	34
7	1-naphthyl	**2g**	51	8b

[a] The same product was synthesized by a different method.

In our first set of experiments, 3-(arylthio)propionic acids **2a–g** were reacted with sodium hydroxide in the presence of excess sodium sulfide under nitrogen atmosphere. Arylmercaptans **3a–g** were isolated from the reaction mixture in good to excellent yield (Table 3). The synthesis of 4-methylbenzenethiol (**3b**) was reproduced in D_2O. In this case, the retro-Michael reaction took place in 2 h. The acrylic acid concentration was low during the reaction, since the formed acrylic acid reacted with the excess sodium sulfide present in the reaction mixture (Figure 2). ^{13}C NMR spectrum of the isolated byproduct is consistent with the structure of the disodium salt of 3-mercaptopropionic acid (3-MPA).

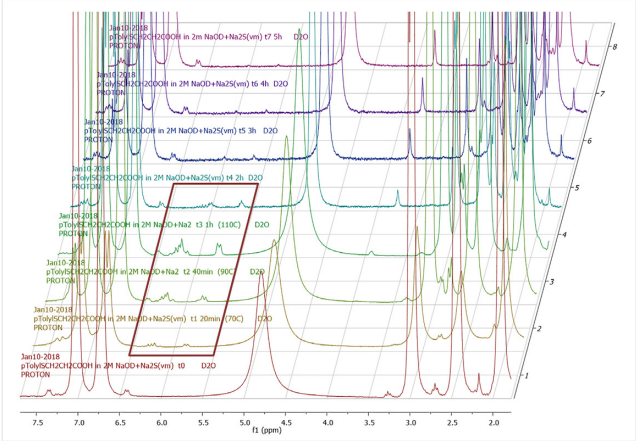


Figure 2 ^1H NMR spectra of the reaction mixture of the synthesis of **3b**

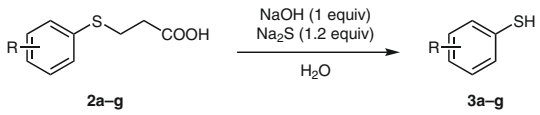
In the second set of experiments, arylmercaptans **3** formed in the retro-Michael reaction were oxidized in situ by iodine[37] to afford diaryl disulfides **4a–g** in good yield (Table 4).

We have found that mercaptans **3a–g** could also be oxidized to symmetrical disulfides **4a–g** in high yields under homogeneous conditions in pyridine with phenyltrimethylammonium tribromide (PTAB) at room temperature (Table 5).

In addition, the stench originating from minute amounts of aryl mercaptans in the glassware can be eliminated quickly by rinsing them with a few milliliters of PTAB/pyridine solution because of their oxidation to less volatile and odorous disulfides. This shelf-stable PTAB reagent has been used for the selective oxidation of sulfides to sulfoxides.[42]

In conclusion, arylmercaptans and diaryl disulfides were synthesized via 3-(arylmercapto)propionic acid intermediates in good yields. The availability of aryl iodides and reagents used, coupled with easy product isolation, make these synthetic methods attractive.

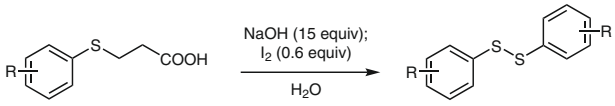
Table 3 Synthesis of Arylmercaptans



2a–g 3a–g

Entry	R	Product	Yield (%)
1	H	**3a**	65
2	4-CH_3	**3b**	78
3	2-CH_3	**3c**	99
4	4-OCH_3	**3d**	97
5	2-OCH_3	**3e**	100
6	3-CF_3	**3f**	81
7	1-naphthyl	**3g**	92

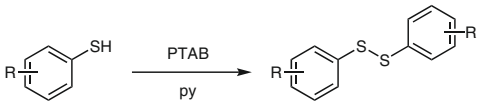
Table 4 Synthesis of Diaryl Disulfides from 3-(Arylthio)propionic Acids



Entry	R	Product	Yield (%)	Lit.[a]
1	H	**4a**	94	[38]
2	4-CH_3	**4b**	98	[39]
3	2-CH_3	**4c**	95	[39]
4	4-OCH_3	**4d**	65	[39]
5	2-OCH_3	**4e**	88	[40]
6	3-CF_3	**4f**	88	[41]
7	1-naphthyl	**4g**	94	[39]

[a] The same product was synthesized by a different method.

Table 5 Synthesis of Diaryldisulfides by Oxidizing Thiols



Entry	R	Product	Yield (%)
1	H	**4a**	88
2	4-CH_3	**4b**	53
3	2-CH_3	**4c**	61
4	4-OCH_3	**4d**	78
5	2-OCH_3	**4e**	63
6	3-CF_3	**4f**	56
7	1-naphthyl	**4g**	53

^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 250 MHz instrument using a 5 mm ^{1}H- and BB-channel probe head at r.t. (295±2 K) in $CDCl_3$. Chemical shifts (δ) are given in ppm units relative to the internal standards: TMS (δ = 0.00 ppm for ^{1}H). Melting points were determined with a Boetius micro melting point apparatus and are uncorrected.

3-(8-Carboxy-1-naphthylthio)propionic Acid (14)[32]

A mixture of 3-mercaptopropionic acid (3-MPA) (5.29 mL, 60.7 mmol), KOH (5.68 g, 101 mmol) in water (16 mL), 8-iodo-1-naphthoic acid (6.0 g, 20.1 mmol) and Cu powder (0.2 g, 3.15 mmol) was stirred and heated at reflux for 5 h under Ar. Then the mixture was diluted with water (80 mL), filtered through Celite, and the filtrate was acidified with 6 M HCl to pH 1. The pale-yellow precipitate was filtered and washed with cold water. Then it was dissolved in aq-$KHCO_3$, filtered and acidified with 6 M HCl to pH 1, and dried in a dessicator over KOH pellets.

Yield: 4.58 g (16.9 mmol, 84%); white needles; mp 158–159 °C. The physical and spectral properties of the product are identical with those reported.[19]

Preparation of 3-(Arylthio)propionic Acids (2a–g); General Procedure

A mixture of 3-MPA (8.7 mL, 100 mmol), Cu_2O (7.15 g, 50 mmol), and aryl iodide (100 mmol) in absolute pyridine (80 mL) was heated and stirred at 120–130 °C under N_2 atmosphere for 6 h. The solvent was then evaporated in vacuo, 6 M HCl (80 mL) was added to the residue and the mixture was stirred for 30 min at 90 °C. The reaction mixture was cooled to r.t., filtered, washed with water (3 × 20 mL) and dried over cc H_2SO_4. The anhydrous solid material was extracted with boiling acetone (3 × 100 mL), and the combined filtrates were evaporated under reduced pressure. 1 M $KHCO_3$ (120 mL) was added to the residue and the unreacted aryl iodide was steam-distilled from the mixture. Charcoal was added to the residue and the mixture was stirred for 5 min. The filtered solution was acidified with 6 M HCl to pH 1. The precipitate was filtered, washed with water (20 mL) and dried over P_2O_5. This product was used in the next reaction step without further purification or recrystallized to afford pure samples.

3-(Phenylthio)propionic Acid (2a)[7a]

3-MPA (8.7 mL, 10.61 g, 100 mmol) was reacted with Cu_2O (7.15 g, 50 mmol) and iodobenzene **1a** (11.2 mL, 20.40 g, 100 mmol).

Yield: 12.21 g (67%); white crystals; mp 60–61 °C (EtOH-H_2O) as reported

^{1}H NMR (250 MHz, $CDCl_3$): δ = 11.52 (s, 1 H, SCH_2CH_2COOH), 7.50–7.10 (m, 5 H, Ar-H), 3.15 (t, $^3J_{H-H}$ = 7.5 Hz, 2 H, SCH_2CH_2COOH), 2.64 (t, $^3J_{H-H}$ = 7.5 Hz, 2 H, SCH_2CH_2COOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.6 (SCH_2CH_2COOH), 135.3 (Ar-C1), 130.7 (Ar-C2), 129.5 (Ar-C3), 127.1 (Ar-C4), 34.6 (SCH_2CH_2COOH), 29.2 (SCH_2CH_2COOH).

3-(4-Tolylthio)propionic Acid (2b)[8b]

3-MPA (8.7 mL, 10.61 g, 100 mmol) was reacted with Cu_2O (7.15 g, 50 mmol) and 4-iodotoluene **1b** (21.80 g, 100 mmol).

Yield: 15.11 g (77%); white crystals; mp 71–72 °C (ligroin).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 11.37 (s, 1 H, SCH_2CH_2COOH), 7.29 (d, $^3J_{H-H}$ = 8.3 Hz, 2 H, Ar-H2), 7.11 (d, $^3J_{H-H}$ = 8.3 Hz, 2 H, Ar-H3), 3.09 (t, $^3J_{H-H}$ = 7.5 Hz, 2 H, SCH_2CH_2COOH), 2.60 (t, $^3J_{H-H}$ = 7.5 Hz, 2 H, SCH_2CH_2COOH); 2.28 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.7 (SCH_2CH_2COOH), 137.5 (Ar-C4), 131.7 (Ar-C3), 131.4 (Ar-C1), 130.2 (Ar-C2), 34.7 (SCH_2CH_2COOH), 29.9 (SCH_2CH_2COOH), 21.4 (CH_3).

3-(2-Tolylthio)propionic Acid (2c)[9]

3-MPA (8.7 mL, 10.61 g, 100 mmol) was reacted with Cu_2O (7.15 g, 50 mmol) and 2-iodotoluene **1c** (12.73 mL, 21.80 g, 100 mmol).

Yield: 13.35 g (68%) white crystals, mp 93–94 °C (C_6H_6-hexane).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 11.11 (s, 1 H, SCH_2CH_2COOH), 7.45–7.05 (m, 4 H, ArH), 3.12 (t, $^3J_{H-H}$ = 7.5 Hz, 2 H, SCH_2CH_2COOH), 2.64 (t, $^3J_{H-H}$ = 7.5 Hz, 2 H, SCH_2CH_2COOH), 2.37 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.3 (SCH_2CH_2COOH), 139.0 (Ar-C2), 134.6 (Ar-C1), 130.7 (Ar-C5), 129.7 (Ar-C6), 126.9 (Ar-C4,C3), 34.4 (SCH_2CH_2COOH), 28.3 (SCH_2CH_2COOH), 20.8 (CH_3).

3-((4-Methoxyphenyl)thio)propionic Acid (2d)[7a]

3-MPA (8.7 mL, 10.61 g, 100 mmol) was reacted with Cu_2O (7.15 g, 50 mmol) and 4-iodoanisole **1d** (23.40 g, 100 mmol).

Yield: 14.64 g (69%); white crystals; mp 81–82 °C (C_6H_6-petrol ether).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 11.26 (s, 1 H, SCH_2CH_2COOH), 7.36 (d, $^3J_{H-H}$ = 9.0 Hz, 2 H, Ar-H3), 6.82 (d, $^3J_{H-H}$ = 9.0 Hz, 2 H, Ar-H2), 3.76 (s, 3 H, CH_3), 3.01 (t, $^3J_{H-H}$ = 7.5 Hz, 2 H, SCH_2CH_2COOH), 2.58 (t, $^3J_{H-H}$ = 7.5 Hz, 2 H, SCH_2CH_2COOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.6 (SCH_2CH_2COOH), 159.9 (Ar-C4), 134.8 (Ar-C1), 125.2 (Ar-C2), 115.1 (Ar-C3), 55.7 (CH_3), 34.8 (SCH_2CH_2COOH), 31.2 (SCH_2CH_2COOH).

3-((2-Methoxyphenyl)thio)propionic Acid (2e)[7a]

3-MPA (8.7 mL, 10.61 g, 100 mmol) was reacted with Cu_2O (7.15 g, 50 mmol) and 2-iodoanisole **1e** (13.0 mL, 23.40 g, 100 mmol).

Yield: 14.01 g (66%); pale-yellow crystals; mp 89 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 11.47 (s, 1 H, SCH_2CH_2COOH), 7.40–7.10 (m, 3 H, Ar-H3,H4,H6), 6.88 (dt, $^3J_{H-H}$ = 7.5 Hz,$^4J_{H-H}$ = 1.7 Hz, 1 H, Ar-H5), 3.83 (s, 3 H, CH_3), 3.09 (t, $^3J_{H-H}$ = 7.5 Hz, 2 H, SCH_2CH_2COOH), 2.62 (t, $^3J_{H-H}$ = 7.5 Hz, 2 H, SCH_2CH_2COOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.6 (SCH_2CH_2COOH), 158.5 (Ar-C2), 131.8 (Ar-C6), 128.7 (Ar-C4), 123.0 (Ar-C1), 121.5 (Ar-C3), 111.2 (Ar-C5), 56.2 (CH_3), 34.7 (SCH_2CH_2COOH), 27.5 (SCH_2CH_2COOH).

3-((3-(Trifluoromethyl)phenyl)thio)propionic Acid (2f)[34]

3-MPA (8.7 mL, 10.61 g, 100 mmol) was reacted with Cu_2O (7.15 g, 50 mmol) and 3-(trifluoromethyl)iodobenzene **1f** (27.20 g, 100 mmol).

Yield: 14.76 g (59%); crystalline material; mp 56 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 11.24 (s, 1 H, SCH_2CH_2COOH), 7.65–7.30 (m, 4 H, ArH), 3.19 (t, $^3J_{H-H}$ = 7.5 Hz, 2 H, SCH_2CH_2COOH), 2.63 (t, $^3J_{H-H}$ = 7.5 Hz, 2 H, SCH_2CH_2COOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.5 (SCH_2CH_2COOH), 137.2 (Ar-C1), 133.1 (Ar-C5), 131.9 (q, $^2J_{C-F}$ = 32.5 Hz, Ar-C3), 129.8 (Ar-C6), 126.5 (q, $^3J_{C-F}$ = 3.7 Hz, Ar-C2), 125.3 (q, $^1J_{C-F}$ = 272.5 Hz, CF_3), 123.6 (q, $^3J_{C-F}$ = 3.7 Hz, Ar-C4), 34.4 (SCH_2CH_2COOH), 28.7 (SCH_2CH_2COOH).

3-((Naphthalen-1-yl)thio)propionic Acid (2g)[8b]

3-MPA (8.7 mL, 10.61 g, 100 mmol) was reacted with Cu_2O (7.15 g, 50 mmol) and 1-iodonaphthalene **1g** (14.6 mL, 25.41 g, 100 mmol).

Yield: 11.85 g (51%); crystalline material; mp 89–90 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.85 (s, 1 H, SCH_2CH_2COOH), 8.00–7.25 (m, 6 H, ArH), 8.43 (dd, $^3J_{H-H}$ = 6.5 Hz, $^4J_{H-H}$ = 2.0 Hz, 1 H, Ar-H8), 3.17 (t, $^3J_{H-H}$ = 7.5 Hz, 2 H, SCH_2CH_2COOH), 2.62 (t, $^3J_{H-H}$ = 7.5 Hz, 2 H, SCH_2CH_2COOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.9 (SCH_2CH_2COOH), 134.5 (Ar-C9), 133.8 (Ar-C10), 132.3 (Ar-C5), 130.6 (Ar-C1), 129.0 (Ar-C6), 128.7 (Ar-C2), 127.1 (Ar-C7), 126.7 (Ar-C4), 125.9 (Ar-C8), 125.6 (Ar-C3), 34.2 (SCH_2CH_2COOH), 29.5 (SCH_2CH_2COOH).

Preparation of Arylmercaptans (3a–g); General Procedure

To a solution of 3-(arylthio)propionic acid (100 mmol) in 2 M NaOH (50 mL) $Na_2S{\cdot}10H_2O$ (28.8 g, 120 mmol) was added, then the mixture was heated at reflux under N_2 atmosphere for 5 h. The solution was cooled to r.t., water (100 mL) was added and the mixture was acidified with 6 M HCl to pH 2. The mixture was extracted with $CHCl_3$ (3 × 100 mL), the combined organic phases were washed with 5% $NaHCO_3$ (2 × 50 mL) and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by distillation under N_2. All products **3a–g** showed higher than 98% assay as determined by iodometric SH titration.

Thiophenol (3a)[43]

Compound **2a** (18.22 g, 100 mmol) was reacted with $Na_2S{\cdot}10H_2O$ (28.8 g, 120 mmol).

Yield: 7.16 g (65%); colorless liquid; bp 169 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.3–6.9 (m, 5 H, ArH), 3.34 (s, 1 H, SH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 130.8 (Ar-C1), 129.3 (Ar-C3), 128.9 (Ar-C2), 125.5 (Ar-C4).

4-Methylbenzenethiol (3b)[44]

Compound **2b** (19.93 g, 100 mmol) was reacted with $Na_2S{\cdot}10H_2O$ (28.8 g, 120 mmol).

Yield: 9.69 g (78%); crystalline material; mp 41–43 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.19 (d, $^3J_{H-H}$ = 8.3 Hz, 2 H, Ar-H2), 7.06 (d, $^3J_{H-H}$ = 8.3 Hz, 2 H, Ar-H3), 3.36 (s, 1 H, SH), 2.29 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.6 (Ar-C4), 129.9 (Ar-C3), 129.8 (Ar-C2), 126.6 (Ar-C1), 20.9 (CH_3).

2-Methylbenzenethiol (3c)[45]

Compound **2c** (19.93 g, 100 mmol) was reacted with $Na_2S{\cdot}10H_2O$ (28.8 g, 120 mmol).

Yield: 12.30 g (99%); colorless liquid; bp 195 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.3–6.9 (m, 4 H, ArH), 3.17 (s, 1 H, SH), 2.23 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.2 (Ar-C2), 131.2 (Ar-C1), 130.5 (Ar-C5), 130.1 (Ar-C6), 126.8 (Ar-C4), 126.1 (Ar-C3), 21.2 (CH_3).

4-Mercaptoanisole (3d)[45]

Compound **2d** (21.23 g, 100 mmol) was reacted with $Na_2S{\cdot}10H_2O$ (28.8 g, 120 mmol).

Yield: 13.60 g (99%); colorless liquid; bp 100–103 °C / 13 mmHg.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.17 (d, $^3J_{H-H}$ = 8.7 Hz, 2 H, Ar-H3), 6.72 (d, $^3J_{H-H}$ = 8.7 Hz, 2 H, Ar-H2), 3.65 (s, 3 H, CH_3), 3.35 (s, 1 H, SH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.5 (Ar-C4), 132.3 (Ar-C2), 119.9 (Ar-C1), 114.7 (Ar-C3), 55.2 (CH_3).

2-Mercaptoanisole (3e)[45]

Compound **2e** (21.23 g, 100 mmol) was reacted with $Na_2S·10H_2O$ (28.8 g, 120 mmol).

Yield: 13.88 g (99%); colorless liquid; bp 99 °C / 8 mmHg.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.3–6.7 (m, 4 H, ArH), 3.76 (s, 1 H, SH), 3.73 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.8 (Ar-C2), 129.3 (Ar-C6), 126.3 (Ar-C4), 121.1 (Ar-C5), 120.5 (Ar-C1), 110.7 (Ar-C3), 55.7 (CH_3).

3-(Trifluoromethyl)benzenethiol (3f)[46]

Compound **2f** (25.02 g, 100 mmol) was reacted with $Na_2S·10H_2O$ (28.8 g, 120 mmol).

Yield: 14.43 g (81%); colorless liquid; bp 161–163 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.8–7.0 (m, 4 H, ArH), 3.50 (s, 1 H, SH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.7 (Ar-C1), 132.4 (q, $^4J_{C–F}$ = 1.3 Hz, Ar-C5), 131.6 (q, $^2J_{C–F}$ = 32.4 Hz, Ar-C3), 129.4 (Ar-C6), 125.8 (q, $^3J_{C–F}$ = 3.9 Hz, Ar-C4), 123.9 (q, $^1J_{C–F}$ = 272.5 Hz, CF_3), 122.4 (q, $^3J_{C–F}$ = 3.9 Hz, Ar-C2).

Naphthalene-1-thiol (3g)[47]

Compound **2g** (23.23 g, 100 mmol) was reacted with $Na_2S·10H_2O$ (28.8 g, 120 mmol).

Yield: 14.74 g (92%); colorless liquid; bp 160–162 °C/20 mmHg.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.2–8.0 (m, 1 H, Ar-H8), 7.9–6.9 (m, 6 H, ArH), 3.40 (s, 1 H, SH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.2 (Ar-C9), 132.5 (Ar-C10), 128.9 (Ar-C5), 128.7 (Ar-C1), 128.4 (Ar-C6), 127.3 (Ar-C2), 126.7 (Ar-C7), 126.3 (Ar-C4), 125.9 (Ar-C8), 125.4 (Ar-C3).

Preparation of Diaryl Disulfides 4a–g; General Procedure

Method A

A solution of 3-(arylthio)propionic acid (10 mmol) in 2.5 M NaOH (60 mL) was heated at reflux for 1 h. The reaction mixture was then cooled to 0 °C and finely powdered iodine (1.52 g, 6 mmol) was added in portions at a rate such that the inner temperature of the reaction mixture was maintained below 10 °C. The mixture was acidified with cc HCl to pH 1 and a small amount of sat. $Na_2S_2O_5$ was added. The solution was extracted with $CHCl_3$ (3 × 20 mL), the combined organic phases were washed with 10% $KHCO_3$ (20 mL) and water (20 mL), and was dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by crystallization from petroleum ether.

Diphenyl Disulfide (4a)[38]

3-(Phenylthio)propionic acid **2a** (1.82 g, 10 mmol) was reacted with iodine (1.52 g, 6 mmol).

Yield: 1.02 g (94%); crystalline material; mp 59–60 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.6–7.1 (m, 5 H, ArH),

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.9 (Ar-C1), 128.9 (Ar-C2), 127.5 (Ar-C3), 127.0 (Ar-C4).

Di(*p*-tolyl) Disulfide (4b)[39]

3-(*p*-Tolylthio)propionic acid **2b** (1.99 g, 10 mmol) was reacted with iodine (1.52 g, 6 mmol).

Yield: 1.21 g (98%); crystalline material; mp 43–45 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.35 (d, $^3J_{H–H}$ = 8.3 Hz, 2 H, Ar-H2), 7.06 (d, $^3J_{H–H}$ = 8.3 Hz, 2 H, Ar-H3), 2.28 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.4 (Ar-C4), 133.9 (Ar-C1), 129.8 (Ar-C2), 128.5 (Ar-C3), 21.0 (CH_3).

Di(*o*-tolyl) Disulfide (4c)[39]

3-(*o*-Tolylthio)propionic acid **2c** (1.99 g, 10 mmol) was reacted with iodine (1.52 g, 6 mmol).

Yield: 1.17 g (95%); crystalline material; mp 30–34 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.5–7.0 (m, 4 H, ArH), 2.39 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.4 (Ar-C2), 135.4 (Ar-C1), 130.3 (Ar-C5), 128.7 (Ar-C6), 127.3 (Ar-C4), 126.7 (Ar-C3), 20.0 (CH_3).

Di(4-methoxyphenyl) Disulfide (4d)[39]

3-((4-Methoxyphenyl)thio)propionic acid **2d** (2.12 g, 10 mmol) was reacted with iodine (1.52 g, 6 mmol).

Yield: 0.90 g (65%); crystalline material; mp 35–37 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.35 (d, $^3J_{H–H}$ = 8.7 Hz, 2 H, Ar-H3), 6.81 (d, $^3J_{H–H}$ = 8.7 Hz, 2 H, Ar-H2), 3.74 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0 (Ar-C4), 132.8 (Ar-C2), 127.4 (Ar-C1), 114.7 (Ar-C3), 55.4 (CH_3).

Di(2-methoxyphenyl) Disulfide (4e)[40]

3-((2-Methoxyphenyl)thio)propionic acid **2e** (2.12 g, 10 mmol) was reacted with iodine (1.52 g, 6 mmol).

Yield: 1.23 g (88%); crystalline material; mp 119–121 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.5–6.9 (m, 4 H, ArH), 3.87 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4 (Ar-C2), 137.6 (Ar-C6), 127.3 (Ar-C4), 124.2 (Ar-C5), 121.1 (Ar-C1), 110.3 (Ar-C3), 55.6 (CH_3).

Bis(3-(trifluoromethyl)phenyl) Disulfide (4f)[32]

3-((3-(Trifluoromethyl)phenyl)thio)propionic acid **2f** (2.50 g, 10 mmol) was reacted with iodine (1.52 g, 6 mmol).

Yield: 1.56 g (88%); crystalline material; bp 95–100 °C/0.2 mmHg.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.8–7.1 (m, 4 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.0 (Ar-C1), 131.9 (q,$^2J_{C–F}$ = 32.5 Hz, Ar-C3), 130.9 (q,$^4J_{C–F}$ = 1.2 Hz, Ar-C5), 129.8 (Ar-C6), 124.5 (q,$^3J_{C–F}$ = 3.9 Hz, Ar-C2), 124.4 (q,$^3J_{C–F}$ = 3.9 Hz, Ar-C4), 123.8 (q,$^1J_{C–F}$ = 272.5 Hz, CF_3).

Di(naphthalen-1-yl) Disulfide (4g)[39]

3-((Naphthalen-1-yl)thio)propionic acid **2g** (2.32 g, 10 mmol) was reacted with iodine (1.52 g, 6 mmol).

Yield: 1.50 g (94%); crystalline material; mp 83–86 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.4–8.1 (m, 1 H, Ar-H8), 7.9–7.1 (m, 6 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.1 (Ar-C9), 132.6 (Ar-C10), 130.3 (Ar-C5), 129.9 (Ar-C1), 128.6 (Ar-C6), 128.0 (Ar-C2), 126.8 (Ar-C7), 126.5 (Ar-C4), 125.9 (Ar-C8), 125.1 (Ar-C3).

Method B

To a solution of arylmercaptan (20 mmol) in absolute pyridine (10 mL) a solution of PTAB (3.95 g, 10.5 mmol) in absolute pyridine (10 mL) was added dropwise. The unreacted reagent was neutralized with sat. $NaHSO_3$, and the mixture was poured into a mixture of ice (100 g) and 6 M HCl (50 mL). The solution was extracted with $CHCl_3$ (3 × 40 mL), the combined organic phases were washed with 10% $KHCO_3$ (40 mL) and water (40 mL), and was dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by crystallization from petroleum ether. The physical and spectral properties of the product were identical to those obtained by Method A.

Diphenyl Disulfide (4a)[38]

Thiophenol **3a** (2.05 mL, 2.20 g, 20 mmol) was reacted with PTAB (3.9 g, 10.5 mmol).

Yield: 1.92 g (88%).

The physical and spectral properties of the product are identical to those obtained by Method A.

Di(*p*-tolyl) Disulfide (4b)[39]

4-Methylbenzenethiol **3b** (2.48 g, 20 mmol) was reacted with PTAB (3.9 g, 10.5 mmol).

Yield: 1.31 g (53%).

The physical and spectral properties of the product are identical to those obtained by Method A.

Di(*o*-tolyl) Disulfide (4c)[39]

2-Methylbenzenethiol **3c** (2.35 mL, 2.48 g, 20 mmol) was reacted with PTAB (3.9 g, 10.5 mmol).

Yield: 1.50 g (61%).

The physical and spectral properties of the product are identical to those obtained by Method A.

Di(4-methoxyphenyl) Disulfide (4d)[39]

4-Mercaptoanizole **3d** (2.46 mL, 2.80 g, 20 mmol) was reacted with PTAB (3.9 g, 10.5 mmol).

Yield: 2.17 g (78%).

The physical and spectral properties of the product are identical to those obtained by Method A.

Di(2-methoxyphenyl) Disulfide (4e)[40]

2-Mercaptoanizole **3e** (2.43 mL, 2.80 g, 20 mmol) was reacted with PTAB (3.9 g, 10.5 mmol).

Yield: 1.75 g (63%).

The physical and spectral properties of the product are identical to those obtained by Method A.

Bis(3-(trifluoromethyl)phenyl) Disulfide (4f)[41]

3-(Trifluoromethyl)benzenethiol **3f** (3.56 g, 20 mmol) was reacted with PTAB (3.9 g, 10.5 mmol).

Yield: 1.98 g (56%).

The physical and spectral properties of the product are identical to those obtained by Method A.

Di(naphthalen-1-yl) Disulfide (4g)[39]

Naphthalene-1-thiol **3g** (2.77 mL, 3.21 g, 20 mmol) was reacted with PTAB (3.9 g, 10.5 mmol).

Yield: 1.69 g (53%).

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Supporting Information

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