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

B. Menczinger
A. Nemes
A. Csámpai
J. Rábai
Eötvös Loránd University, Institute of Chemistry, Pázmány Péter sétány 1/A, 1117 Budapest, Hungary
rabai@elte.hu

Abstract
The reaction of aryl iodides, 3-mercaptopropionic acid, and Cu₂O 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 (Na₂S) or oxidative (I₂) 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. 6 is a monoamine oxidase inhibitor. 7 has antihepatitis effects and Meniere’s disease can be treated with 8 (Figure 1). Furthermore, other important active pharmaceutical ingredients, such as (thio)pyranones, piperidones, and benzodiazepines 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, or by the alkylation of thiophenol derivatives using β-halopropionic acids or esters, or β-propiolactone. They can also be synthesized by nickel-catalyzed S-arylation of 3-mercaptopropionic acid (3-MPA) with aryl iodides. 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.

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

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

Although many procedures are known for the preparation of aryl mercaptans and diaryl disulfides, only a few involve the reaction of nonactivated aryl iodides with appropriate sulfur-transfer reagents such as copper(I) thio-benzoate or copper(I) thiocyanate. 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, where the appropriate thiols are liberated by retro-Michael reaction. This approach is of intense interest for the development of fluorescent probes and drug-delivery systems. 3-(Arylthio)propionic acids can also be cleaved by retro-Michael reaction to afford the appropriate thiolates under laboratory conditions. In our previous work, 3-MPA was used as a sulfur-transfer reagent in the synthesis of symmetrical diaryl sulfides (Scheme 1). We proposed that the reaction went through a 3-(arylmercapto)propionic acid intermediate, which, in the next step, was cleaved to afford the arylthiolate intermediate. 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 into 8-mercaptop-1-naphthalene-carboxylate, which, on acidification, gave the appropriate thiolactone (Scheme 2).

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 as the main products of the reaction of 3-MPA and aryl iodides. 3-(Arylthio)propionic acids can be synthesized by copper-mediated C–S bond formation of 3-mercaptopropionic acid and nonactivated aryl iodides. These compounds are important intermediates in the synthesis of arylmercaptans and diaryl disulfides (Scheme 3). To find the optimal reaction conditions, the solvent, the amount of Cu$_2$O, 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$_2$O in refluxing pyridine for 6 h (Table 1, entry 2). Substituted 3-(arylthio)propionic acids 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. These observations can be interpreted by considering the higher acidity of thiophenol
(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-C4H9S-CH2CH2CO2H) was also stable to aq-NaOH in the presence of air (cf. n-butyl mercaptan, pK_a 10.66).25

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 sulfide36 or hydroxide nucleophiles. On the other hand, the equilibrium can be shifted by oxidation of the formed mercaptides.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu2O (equiv.)</th>
<th>Solvent</th>
<th>Reaction time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>py</td>
<td>3</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>py</td>
<td>6</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>py</td>
<td>12</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>DMF</td>
<td>3</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
<td>DMF + 4 eq py</td>
<td>3</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>1.0</td>
<td>py</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>0.05</td>
<td>py</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

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 D2O. 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). 13C NMR spectrum of the isolated byproduct is consistent with the structure of the disodium salt of 3-mercaptopropionic acid (3-MPA).

In the second set of experiments, arylmercaptans 3 formed in the retro-Michael reaction were oxidized in situ by iodine37 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 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>R Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H 3a</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>4-CH₃ 3b</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>2-CH₃ 3c</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>4-OCH₃ 3d</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>2-OCH₃ 3e</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>3-CF₃ 3f</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>1-naphthyl 3g</td>
<td>92</td>
</tr>
</tbody>
</table>

*The same product was synthesized by a different method.*

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>R Product</th>
<th>Yield (%)</th>
<th>Lit. a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H 4a</td>
<td>94</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>4-CH₃ 4b</td>
<td>98</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>2-CH₃ 4c</td>
<td>95</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>4-OCH₃ 4d</td>
<td>65</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>2-OCH₃ 4e</td>
<td>88</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>3-CF₃ 4f</td>
<td>88</td>
<td>41</td>
</tr>
<tr>
<td>7</td>
<td>1-naphthyl 4g</td>
<td>94</td>
<td>39</td>
</tr>
</tbody>
</table>

Table 5  Synthesis of Diaryldisulfides by Oxidizing Thiols

<table>
<thead>
<tr>
<th>Entry</th>
<th>R Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H 4a</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>4-CH₃ 4b</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>2-CH₃ 4c</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>4-OCH₃ 4d</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>2-OCH₃ 4e</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>3-CF₃ 4f</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>1-naphthyl 4g</td>
<td>53</td>
</tr>
</tbody>
</table>

1H and 13C NMR spectra were recorded with a Bruker Avance 250 MHz instrument using a 5 mm 1H- and 80 MHz 13C NMR probes. Chemical shifts (δ) are in ppm units relative to the internal standards: TMS (δ = 0.00 ppm for 1H). Melting points were determined with a Boetius micro melting point apparatus and are uncorrected.

3-8-Carboxy-1-naphthyl)propionic Acid (14)**

A mixture of 3-mercaptocarboxylic acid (3-MPA) (5.29 mL, 60.7 mmol), KOH (5.68 g, 101 mmol) in water (16 mL), 8-iodo-1-naphthol (35.1 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-KOH solution, filtered and acidified with 6 M HCl to pH 1, and dried in a desiccator 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), Cu₂O (7.15 g, 50 mmol), and aryl iodide (100 mmol) in absolute pyridine (80 mL) was heated and stirred at 120–130 °C under Ar 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 c&lt;sub&gt;2&lt;/sub&gt;H₂SO₄. The anhydrous solid material was extracted with boiling acetone (3 × 100 mL) and the combined filtrates were evaporated under reduced pressure. 1 M KHCO₃ (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 P₂O₅. This product was used in the next reaction step without further purification or recrystallized to afford pure samples.

3-(Phenylthio)propionic Acid (2a)**

3-MPA (8.7 mL, 10.61 g, 100 mmol) was reacted with Cu₂O (7.15 g, 50 mmol) and iodobenzene (100 mmol) in absolute pyridine (80 mL) was heated and stirred at 120–130 °C 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-KOH solution, filtered and acidified with 6 M HCl to pH 1, and dried in a desiccator 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), Cu₂O (7.15 g, 50 mmol), and aryl iodide (100 mmol) in absolute pyridine (80 mL) was heated and stirred at 120–130 °C under Ar 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 c&lt;sub&gt;2&lt;/sub&gt;H₂SO₄. The anhydrous solid material was extracted with boiling acetone (3 × 100 mL) and the combined filtrates were evaporated under reduced pressure. 1 M KHCO₃ (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 P₂O₅. This product was used in the next reaction step without further purification or recrystallized to afford pure samples.

3-(Phenylthio)propionic Acid (2a)**

3-MPA (8.7 mL, 10.61 g, 100 mmol) was reacted with Cu₂O (7.15 g, 50 mmol) and iodobenzene (100 mmol) in absolute pyridine (80 mL) was heated and stirred at 120–130 °C 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-KOH solution, filtered and acidified with 6 M HCl to pH 1, and dried in a desiccator 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
Yield: 13.35 g (68%) white crystals, mp 93–94 °C (C6H6-hexane).

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

13C NMR (75 MHz, CDCl3): δ = 133.1 (Ar-C5), 131.9 (q, 2H, Ar-H5) and 3-(trifluoromethyl)iodobenzene
131.8 (Ar-C6), 128.7 (Ar-C4), 123.0 (Ar-C1), 121.5 (Ar-C3), 111.2 (Ar-CHOH), 29.9 (SCH2CH2COH), 21.4 (CH3).

3-(2-Tolylthio)propionic Acid (2e)
3-MPA (8.7 mL, 10.61 g, 100 mmol) was reacted with Cu2O (7.15 g, 50 mmol) and 2-iodoanisole
3-MPA (8.7 mL, 10.61 g, 100 mmol) was reacted with Cu2O (7.15 g, 50 mmol) and 4-iodoanisole

13C NMR (75 MHz, CDCl3): δ = 131.7 (Ar-C3), 131.4 (Ar-C1), 130.2 (Ar-C2), 34.7 (SCH2CH2COH), 29.9 (SCH2CH2COH), 21.4 (CH3).

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

13C NMR (75 MHz, CDCl3): δ = 134.8 (Ar-C1), 130.7 (Ar-C5), 129.7 (Ar-C6), 126.9 (Ar-C4,C3), 34.4 (SCH2CH2COH), 28.3 (SCH2CH2COH), 20.8 (CH3).

Preparation of Arylimercaptans (3a–g): General Procedure
To a solution of 3-(arylimerothio)propionic acid (100 mmol) in 2 M NaOH (50 mL) Na2S·10H2O (28.8 g, 120 mmol) was added, then the mixture was heated at reflux under N2 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 CHCl3 (3 × 100 mL) and dried over MgSO4. The solvent was evaporated and the crude product was purified by distillation under N2. All products 3a–g showed higher than 98% assay as determined by iodometric SH titration.

Thiophenol (3a)

Compound 2a (18.22 g, 100 mmol) was reacted with Na2S·10H2O (28.8 g, 120 mmol).

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

1H NMR (250 MHz, CDCl3): δ = 7.3–6.9 (m, 5 H, ArH), 3.34 (s, 1 H, SH).

13C NMR (75 MHz, CDCl3): δ = 130.8 (Ar-C1), 129.3 (Ar-C3), 128.9 (Ar-C2), 125.5 (Ar-C4).

4-Methylbenzenethiol (3b)

Compound 2b (19.93 g, 100 mmol) was reacted with Na2S·10H2O (28.8 g, 120 mmol).

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

1H NMR (250 MHz, CDCl3): δ = 7.19 (d, 3H, Ar-H2), 7.06 (d, δJHH = 8.3 Hz, 3H, Ar-H2), 3.36 (s, 1 H, SH), 2.29 (s, 3 H, CH3).

13C NMR (75 MHz, CDCl3): δ = 135.6 (Ar-C4), 129.9 (Ar-C3), 129.8 (Ar-C2), 126.6 (Ar-C1), 20.9 (CH3).

2-Methylbenzenethiol (3c)

Compound 2c (19.93 g, 100 mmol) was reacted with Na2S·10H2O (28.8 g, 120 mmol).

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

1H NMR (250 MHz, CDCl3): δ = 7.3–6.9 (m, 4 H, ArH), 3.17 (s, 1 H, SH), 2.23 (s, 3 H, CH3).

13C NMR (75 MHz, CDCl3): 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 (CH3).

4-Mercaptanisole (3d)

Compound 2d (21.23 g, 100 mmol) was reacted with Na2S·10H2O (28.8 g, 120 mmol).

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

1H NMR (250 MHz, CDCl3): δ = 7.17 (d, 3H, Ar-H2), 6.72 (d, δJHH = 8.7 Hz, 2 H, Ar-H2), 3.65 (s, 3 H, CH3), 3.35 (s, 1 H, SH).

13C NMR (75 MHz, CDCl3): δ = 158.5 (Ar-C4), 132.3 (Ar-C2), 119.9 (Ar-C1), 114.7 (Ar-C3), 55.2 (CH3).
2-Mercaptoanisole (3e)\(^{46}\)

Compound 2e (21.23 g, 100 mmol) was reacted with NaN\(_2\)-10H\(_2\)O (28.8 g, 120 mmol).

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

\(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta = 7.3–6.7\) (m, 4 H, ArH), 3.76 (s, 1 H, SH), 3.73 (s, 3 H, CH\(_3\)).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 154.8\) (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 NaN\(_2\)-10H\(_2\)O (28.8 g, 120 mmol).

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

\(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta = 7.8–7.0\) (m, 4 H, ArH), 3.50 (s, 1 H, SH).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 132.7\) (Ar-C1), 132.4 (q, \(J_{C,F} = 1.3\) Hz, Ar-C5), 131.6 (q, \(J_{C,F} = 32.4\) Hz, Ar-C3), 129.4 (Ar-C6), 125.8 (q, \(J_{C,F} = 3.9\) Hz, Ar-C4), 123.9 (q, \(J_{C,F} = 272.5\) Hz, CF\(_3\)), 122.4 (q, \(J_{C,F} = 3.9\) Hz, Ar-C2).

**Naphthalene-1-thiol (3g)\(^{47}\)**

Compound 2g (23.23 g, 100 mmol) was reacted with NaN\(_2\)-10H\(_2\)O (28.8 g, 120 mmol).

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

\(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta = 8.2–8.0\) (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\(_3\)): \(\delta = 134.2\) (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-(aryltiolo)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. NaN\(_2\)SO\(_4\) 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\(_2\)SO\(_4\). The solvent was evaporated and the crude product was purified by crystallization from petroleum ether.

**Diphenyl Disulfide (4a)\(^{18}\)**

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\(_3\)): \(\delta = 7.6–7.1\) (m, 5 H, ArH).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 136.9\) (Ar-C1), 128.9 (Ar-C2), 127.5 (Ar-C3), 127.0 (Ar-C4).

**Di(p-toly) Disulfide (4b)\(^{20}\)**

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\(_3\)): \(\delta = 7.35\) (d, \(J_{H,F} = 8.3\) Hz, 2 H, Ar-H2), 7.06 (d, \(J_{H,F} = 8.3\) Hz, 2 H, Ar-H3), 2.28 (s, 3 H, CH\(_3\)).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 137.4\) (Ar-C4), 133.9 (Ar-C1), 129.8 (Ar-C2), 128.5 (Ar-C3), 21.0 (CH\(_3\)).
Method B
To a solution of arylmercaptan (20 mmol) in absolute pyridine (10 mL) a solution of PTAB (3.9 g, 10.5 mmol) in absolute pyridine (10 mL) was added dropwise. The unreacted reagent was neutralized with sat. NaHCO₃, and the mixture was poured into a mixture of ice (100 g) and 6 M HCl (50 mL). The solution was extracted with CHCl₃ (3 × 40 mL), the combined organic phases were washed with 10% KHCO₃ (40 mL) and water (40 mL), and was dried over Na₂SO₄. 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: 1.69 g (53%).
The physical and spectral properties of the product were 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)⁴⁰
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(2-methoxyphenyl) Disulfide (4d)⁴¹
2-Mercaptoanilide 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(3-methoxyphenyl) Disulfide (4e)⁴²
2-Mercaptoanilide 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)⁴³
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)⁴⁴
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%).

Funding Information
National Research Development and Innovation Office (NN 117633).

Acknowledgment
The authors thank Dr. H. Medzihradszky-Schweiger for SH analyses.

Supporting Information
Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591771.

References
(34) Jacquignon, P.; Fravolini, A.; Feron, A.; Croisy, A. Experimentia 1974, 30, 452.