A Versatile and Convenient Preparation of Unsymmetrical Diaryl Disulfides

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Received 5 February 2008; revised 4 March 2008

Abstract: We have developed a convenient method for the synthesis of unsymmetrical diaryl disulfides under mild conditions in excellent yields. The described method is based on the straightforward preparation of 5,5-dimethyl-2-thioxyp-1,3,2-dioxaphosphorinan-2-sulfenyl bromide from readily available 5,5-dimethyl-2-sulfonyl-2-thioxo-1,3,2-dioxophosphorinan or bis(5,5-dimethyl-2-thioxo-1,3,2-dioxophosphorinan-2-yl) disulfide. The unsymmetrical diaryl disulfides can be obtained from aromatic thiols derivatives bearing electron-withdrawing or electron-donating groups.

Key words: unsymmetrical diaryl disulfides, sulfenyl bromide, aromatic thiols, arenes, heterocycles

The synthesis of unsymmetrical disulfides is an important transformation in modern organic synthesis and medicinal chemistry.1 Although there are many different approaches for the preparation of disulfides, the majority of them are not applicable to the synthesis of unsymmetrical diaryl disulfides, due to the fast thiol–disulfide exchange reaction. Furthermore, preparative methods that are efficient for the preparation of symmetrical diaryl disulfides are very often ineffective for the preparation of unsymmetrical diaryl disulfides. The most common methods for obtaining unsymmetrical diaryl disulfides include the thioalkylation of a thiol or its derivative by sulfenyl derivatives: sulfenyl chlorides,2 N-(trifluoracetyl)arenesulfenamides,3 benzotriazolyl sulfides,4 S-arylarenethiosulfonates,5 4-nitroarenesulfenamides,6 and toluene-4-sulfonic acid.7 Other practical procedures involve disulfide exchange catalyzed by rhodium,8 triphenylphosphine,9 or tetrathiomolybdate.10

Several unsymmetrical substituted aromatic donor–acceptor disulfides have been analyzed for their second-order nonlinear optical properties. These compounds exhibited moderately high first hyperpolarizability with excellent transparency in the visible region.11 Although this class of molecules has potential application in optical data processing and communication, these disulfides are provided in only moderate or poor yield by the available synthetic methods.

We have previously demonstrated the preparation of functionalized unsymmetrical molecules, such as dialkyl disulfides, alkyl aryl disulfides,12 ‘bioreistant’ disulfides,13 and unsymmetrical disulfides based on L-cysteine and L-cystine derivatives.14 The excellent results encouraged us to extend the strategy to the preparation of unsymmetrical diaryl disulfides based on organophosphorus sulfenyl bromides as activating agents for unsymmetrical disulfide bond formation.

Treatment of the stable and readily available bis(5,5-dimethyl-2-thioxo-1,3,2-dioxophosphorinan-2-yl) disulfide (1)15 with bromine at −30 °C quantitatively affords 5,5-dimethyl-2-thioxyp-1,3,2-dioxophosphorinan-2-sulfenyl bromide (3) (Table 1). Subsequent treatment, without prior isolation, of sulfenyl bromide 3 with arenethiols provides the corresponding aryl 5,5-dimethyl-2-thioxyp-1,3,2-dioxophosphorinan-2-yl disulfides 4a–f, which can be isolated in very good yields (Table 1, method A, entries 1–6). These compounds are stable at room temperature for several months; formation of symmetrical disulfides or decomposition by moisture was not observed. Moreover, compounds 4a–f can be prepared from 5,5-dimethyl-2-sulfonyl-2-thioxyp-1,3,2-dioxophosphorinan (2)15 in similar, very high yields (Table 1, method B, entries 1–6). Although the use of dithiophosphoric acid derivative 2 is simpler with regard to the availability of reagents required for the preparation of sulfenyl bromide 3, the formation of hydrogen bromide as side product was observed. In some cases strong acidic conditions are responsible for the removal of protective group and poor reaction yield.14 From this point of view, method B can only be applied to the preparation of disulfide derivatives 4 from thiols without acid-sensitive groups. The results for both methods are summarized in Table 1.

The reaction of disulfide 4a with one equivalent of 4-methylbenzenethiol in the presence of triethylamine afforded unsymmetrical disulfide 5a in moderate yield (67%), together with the other symmetrical disulfides. However, in the presence of a 5% excess of 4a relative to 4-methylbenzenethiol, the same reaction gave product 5a in excellent yield (97%) (Table 2). These observations show that unsymmetrical disulfide 5a forms very fast from 4-methylbenzenethiol and compound 4a, and that further disulfide exchange takes place in the presence of thiolate anion. Therefore, unsymmetrical disulfides 5 need to be prepared in the presence of only a small excess of reagent 4. The influence of the thiolate anion on the disulfide exchange reaction was confirmed by treatment of isolated unsymmetrical disulfide 5a with 4-methylbenzenethiol (5 mol%) in the presence of triethylamine. After 15 minutes an equal amount of both symmetrical disulfides was observed and after 30 minutes only 65% of starting 5a was present in the reaction mixture (confirmed by TLC and 1H NMR).
The development of an effective protocol for the reliable synthesis of unsymmetrical disulfides 5 was the most challenging. When triethylamine was added to the solution of 4f in dichloromethane, a yellow and then brownish color appeared very fast. Further treatment with a benzenethiol did not afford the corresponding unsymmetrical disulfide 5. This is probably because compound 4f reacted with triethylamine to form 4-thioxocyclohexa-2,5-dienone (Scheme 1).

However, when triethylamine is added to a mixture of 4f and the arenethiol in dichloromethane, complete conversion into the unsymmetrical disulfide 5 takes place, without significant formation of either symmetrical disulfide or 4-thioxocyclohexa-2,5-dienone (Table 2). In general, because arenethiols are stronger acids than the corresponding phenols, triethylamine abstracts the proton from the thiol group, and the intramolecular elimination shown in Scheme 1 is not observed. The thiolate anion is generated in the presence of a small excess of 4f, so that thiol–disulfide exchange is limited, and unsymmetrical product 5 forms exclusively. Finally, after modification of the conditions, unsymmetrical disulfides 5e, 5j, 5n, 5r, 5t, and 5w were obtained from 4f in excellent yields (Table 2).

Compounds 4a–f were treated with a variety of arenethiol to examine the scope and limitation of this method for the preparation of 5 (Table 2).

As shown in Table 2, the same unsymmetrical disulfide can be obtained by two different ways. For example, 5a can be prepared from 4a and 4-methylbenzenethiol or from 4b and methyl 2-sulfanylbenzoate. Both approaches gave product 5a in excellent yield (Table 2). Moreover, it seems that steric hindrance and the presence of electron-

### Table 1 Synthesis of Aryl 5,5-Dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl Disulfides 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Product 4</th>
<th>Yield (%) by method A</th>
<th>Yield (%) by method B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-MeO₂CC₆H₄</td>
<td>4a</td>
<td>94</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>4-Tol</td>
<td>4b</td>
<td>95</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>4c</td>
<td>92</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>2-Naph</td>
<td>4d</td>
<td>97</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>PMP</td>
<td>4e</td>
<td>91</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>4-HOC₆H₄</td>
<td>4f</td>
<td>93</td>
<td>97</td>
</tr>
</tbody>
</table>

### Table 2 Synthesis of Unsymmetrical Diaryl Disulfides 5

<table>
<thead>
<tr>
<th>Ar₁</th>
<th>Ar₂</th>
<th>2-MeO₂CC₆H₄</th>
<th>4-Tol</th>
<th>Ph</th>
<th>2-Naph</th>
<th>PMP</th>
<th>4-HOC₆H₄</th>
<th>4-O₂NC₆H₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>2-MeO₂CC₆H₄</td>
<td>5a (97)</td>
<td>5b (86)</td>
<td>5c (100)</td>
<td>5d (100)</td>
<td>5e (90)</td>
<td>5f (93)</td>
<td></td>
</tr>
<tr>
<td>4b</td>
<td>4-Tol</td>
<td>5a (93)</td>
<td>5g (98)</td>
<td>5h (100)</td>
<td>5i (100)</td>
<td>5j (98)</td>
<td>5k (100)</td>
<td></td>
</tr>
<tr>
<td>4c</td>
<td>Ph</td>
<td>5b (100)</td>
<td>5g (97)</td>
<td>5l (96)</td>
<td>5m (82)</td>
<td>5n (98)</td>
<td>5o (100)</td>
<td></td>
</tr>
<tr>
<td>4d</td>
<td>2-Naph</td>
<td>5c (100)</td>
<td>5h (97)</td>
<td>5l (96)</td>
<td>5p (92)</td>
<td>5r (84)</td>
<td>5s (98)</td>
<td></td>
</tr>
<tr>
<td>4e</td>
<td>PMP</td>
<td>5d (99)</td>
<td>5i (95)</td>
<td>5m (99)</td>
<td>5p (100)</td>
<td>5t (87)</td>
<td>5u (93)</td>
<td></td>
</tr>
<tr>
<td>4f</td>
<td>4-HOC₆H₄</td>
<td>5e (100)</td>
<td>5j (95)</td>
<td>5n (99)</td>
<td>5r (100)</td>
<td>5t (100)</td>
<td>5w (100)</td>
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</table>

* The yields (%) of the isolated product are reported in parentheses.
PAPER
Preparation of Unsymmetrical Diaryl Disulfides

4-Methylbenzenethiol, thiophenol, naphthalene-2-thiol, 4-methoxybenzenethiol, 4-sulfanylbenzenethiol, and 4-nitrobenzenethiol are available from Aldrich. Methyl 2-sulfanylbenzoate, 16 bis(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl) disulfide (1),15 and 5,5-dimethyl-2-sulfanyl-2-thioxo-1,3,2-dioxaphosphorinan (2)15 were synthesized by previously described procedures. CH2Cl2 was dried and distilled by standard procedures. Melting points are uncorrected. NMR spectra were recorded on a Varian Gemini 500-MHz or 200-MHz spectrometer. The residual solvent peak was used as internal reference (CDCl3; δ = 7.26 for 1H, δ = 49.0 for 13C); for 31P NMR spectroscopy an external reference (CDCl3: δ = 127.7, 127.5, 127.4, 126.9, 77.9 (d, Jp–C = 9.0 Hz) was used. ESI-MS spectra were recorded on a Mariner PerSeptive Biosystem spectrometer. Column chromatography was performed on silica gel 60 (230–400 mesh, Merck). Preparative TLC was performed on silica gel Polygram SIL G/UV254 (Macherey-Nagel).

Methyl 2-[5-(5,5-Dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)disulfanyl]benzoate (4a); Typical Procedure (Method A)

Br2 (0.96 g, 6.0 mmol) was added to a soln of 1 (2.76 g, 7.0 mmol) in anhyd CH2Cl2 (50 mL) at –30 °C and under N2. After 15 min, a sohn of methyl 2-sulfanylbenzoate (1.85 g, 11 mmol) in anhyd CH2Cl2 (5 mL) was added. Then the mixture was stirred at r.t. for 30 min, diluted with CH2Cl2 (50 mL), washed with H2O (50 mL), dried (MgSO4), filtered, and evaporated under vacuum. The residue was purified by column chromatography (silica gel, CH2Cl2–hexane, 1:1); this yielded 4a.

Yield: 3.77 g (94%); white solid; mp 106–108 °C.

1H NMR (200 MHz, CDCl3); δ = 0.95 (s, 3 H, CH3), 1.19 (s, 3 H, CH3), 3.94 (s, 3 H, OCH3), 3.98–4.30 (m, 4 H, POCH3), 7.20–7.36 (m, 1 H, Ar), 7.52–7.66 (m, 1 H, Ar), 8.02 (dd, J = 1.5, 7.8 Hz, 1 H, Ar), 8.16 (d, J = 8.1 Hz, 1 H, Ar).

13C NMR (50 MHz, CDCl3); δ = 166.8, 133.0, 131.0, 127.3, 125.8, 78.2 (d, Jp–C = 9.2 Hz), 52.4, 32.5 (d, Jp–C = 7.4 Hz), 22.0, 21.0. Signals: expected, 12; observed, 10.

13P NMR (200 MHz, CDCl3); δ = 81.31.


4-[5,5-Dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl]disulfanyl]anisole (4c)

Chromatography (hexane–CH2Cl2–hexane, 1:1:1); yield: 93%; mp 86–88 °C.

1H NMR (200 MHz, CDCl3); δ = 0.95 (s, 3 H, CH3), 1.19 (s, 3 H, CH3), 3.90–4.10 (m, 4 H, POCH3), 7.40–7.60 (m, 2 H, Ar), 7.70–7.93 (m, 4 H, Ar), 8.12–8.20 (m, 1 H, Ar).

13C NMR (50 MHz, CDCl3); δ = 133.2, 132.9, 130.1, 130.0, 129.0, 127.7, 127.5, 127.4, 126.9, 77.9 (d, Jp–C = 9.0 Hz), 32.4 (d, Jp–C = 7.4 Hz), 21.9, 21.0. Signals: expected; 14; observed, 13.

13P NMR (200 MHz, CDCl3); δ = 83.87.


4-[5,5-Dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl]disulfanyl]phenol (4f)

Chromatography (CHCl3); yield: 93%; mp 110–112 °C.

1H NMR (200 MHz, CDCl3); δ = 0.96 (s, 3 H, CH3), 1.21 (s, 3 H, CH3), 3.90–4.05 (m, 4 H, POCH3), 5.10 (br s, 1 H, OH), 6.76–6.87 (m, 2 H, Ar), 7.57–7.68 (m, 2 H, Ar).

Methyl 2-(4-Tolyldisulfanyl)benzoate (5a)

The residue was purified by column chromatography (silica gel, CH2Cl2–hexane, 1:1); this gave 4a.

Yield: 3.69 g (92%); white solid; mp 106–108 °C.

Compounds 4b–f were prepared similarly from 2, and the yields are reported in Table 1.

Methyl 2-(4-Methoxyphenyl)disulfanyl]benzoate (5d)

Chromatography (CH2Cl2–hexane, 1:2); yield: 86%; mp 53–55 °C.

1H and 13C NMR spectra identical to those reported previously.3,8a

13C NMR (50 MHz, CDCl3): δ = 172.2, 155.8, 141.6, 133.0, 132.9, 131.2, 131.0, 125.9, 125.4, 116.3, 116.1, 52.5. Signals: expected and observed, 12.


4-(Phenyl disulfanyl)toluene (5g)

Chromatography (CH2Cl2–hexane, 1:2); yield: 100%; mp 43–45 °C (Lit.3b 44–45 °C).

1H and 13C NMR spectra identical to those reported previously.3a

2-(Naphthyl disulfanyl)toluene (5h)

Chromatography (CH2Cl2–hexane, 1:2); yield: 98%; oil.

1H and 13C NMR spectra identical to those reported previously.3a

2-(4-Tolyldisulfanyl)naphthalene (5l)

Chromatography (CH2Cl2–hexane, 1:1); yield: 96%; mp 93–96 °C.

1H NMR (200 MHz, CDCl3): δ = 7.03 (s, 3 H, CH3), 7.05–7.16 (m, 2 H, Ar), 7.37–7.55 (m, 4 H, Ar), 7.56–7.66 (m, 1 H, Ar), 7.70–7.86 (m, 3 H, Ar), 7.92–8.00 (m, 1 H, Ar).

13C NMR (50 MHz, CDCl3): δ = 129.8, 129.7, 128.9, 128.8, 128.5, 127.7, 127.4, 126.6, 126.5, 126.3, 126.2, 125.6, 21.0. Signals: expected and observed, 15.


13C NMR (50 MHz, CDCl3): δ = 157.2, 135.4, 125.3, 113.2, 77.8 (d, J13C–1H = 85.71 Hz), 32.5 (d, J13C–1H = 7.2 Hz), 22.0, 21.0. Signals: expected and observed, 8.


Methyl 2-(4-Phenyl)disulfanyl]benzoate (5b)

Chromatography (CHCl3); yield: 100%; mp 61–63 °C (Lit.18 63–65 °C).

1H NMR (200 MHz, CDCl3): δ = 8.00 (s, 3 H, OCH3), 6.65–6.80 (m, 3 H, Ar), 7.23–7.35 (m, 3 H, Ar), 7.54–7.64 (m, 2 H, Ar).

13C NMR (50 MHz, CDCl3): δ = 167.2, 155.8, 141.6, 133.0, 132.9, 131.4, 131.0, 125.9, 125.4, 116.3, 116.1, 52.5. Signals: expected and observed, 12.


Methyl 2-(4-Butyl)disulfanyl]benzoate (5e)

Chromatography (CH2Cl2–hexane, 1:1); yield: 97%; mp 60–62 °C.

1H NMR (200 MHz, CDCl3): δ = 7.47–7.62 (m, 1 H, Ar), 7.95–8.07 (m, 1 H, Ar), 8.11–8.20 (m, 1 H, Ar).

13C NMR (50 MHz, CDCl3): δ = 124.9, 52.3. Signals: expected, 18; observed, 17.

ESI-HRMS: m/z [M + Na]+ calcd for C12H14NaO3S2: 283.0581; found: 283.0583.

Methyl 2-(4-Methyl)disulfanyl]benzoate (5c)

Chromatography (CHCl3); yield: 100%; mp 128–130 °C.

1H NMR (200 MHz, CDCl3): δ = 8.01 (s, 3 H, OCH3), 6.79–6.90 (m, 2 H, Ar), 7.25–7.31 (m, 3 H, Ar), 7.47–7.56 (m, 2 H, Ar).

13C NMR (50 MHz, CDCl3): δ = 159.5, 139.0, 133.9, 133.0, 130.6, 127.7, 117.1, 21.1. Signals: expected and observed, 9.


2-(4-Phenyl)disulfanyl]napthalene (5i)

Chromatography (CH2Cl2–hexane, 1:2); yield: 96%; mp 51–53 °C.

1H NMR (400 MHz, CDCl3): δ = 7.40–7.56 (m, 1 H, Ar), 7.57–7.67 (m, 1 H, Ar), 7.76–7.87 (m, 2 H, Ar), 7.96–8.06 (m, 2 H, Ar).

13C NMR (50 MHz, CDCl3): δ = 121.5, 126.5, 126.3, 126.2, 125.9, 125.8, 125.7, 125.5, 124.9, 123.9, 123.7, 123.4, 123.3, 123.1, 122.9, 122.7, 122.6, 122.5, 122.4, 122.3, 122.2, 121.8, 121.7, 121.6, 121.5, 121.4, 121.3. Signals: observed, 14.

4-(Phenyldisulfanyl)anisole (5m)
Chromatography (CH₂Cl₂–hexane, 2:1); yield: 92%; mp 116–118 °C.

4-(Phenyldisulfanyl)phenol (5n)
Chromatography (CH₂Cl₂–hexane, 1:1); yield: 98%; mp 117–119 °C (Lit. 20 118–120 °C).

1-H and 13C NMR spectra identical to those reported previously.

Unsymmetrical Diaryl Disulfides 4 from 4f; Typical Procedure
Et₂N (0.84 mL, 6.0 mmol) was added to a soln of 4f (1.69 g, 5.25 mmol) and the appropriate areniethiol ArSH (5.0 mmol) in CH₂Cl₂ (35 mL). After stirring for 15 min at rt, the mixture was diluted with CH₂Cl₂ (50 mL), washed with H₂O (35 mL), dried (MgSO₄), filtered, and evaporated under vacuum. The residue was purified by column chromatography; this gave 5e, 5j, 5m, 5r, 5t, or 5w (see Table 2 for yields).

Acknowledgment
We gratefully acknowledge the Polish Ministry of Science and Higher Education for financial support (grant no N204 4511 33).

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