

## Versatile and Efficient Synthesis of $\omega$ -Functionalized Asymmetric Disulfides via Sulfenyl Bromide Adducts

Janusz Kowalczyk,<sup>†</sup> Piotr Barski,<sup>†</sup> Dariusz Witt,<sup>\*,‡</sup> and Bartosz A. Grzybowski<sup>\*,§</sup>

*ProChimia Surfaces, ul. Zacisze 2, 81-823 Sopot, Poland, Department of Organic Chemistry, Chemical Faculty, Gdansk University of Technology, Narutowicza 11/12, 80-952 Gdansk, Poland, and Department of Chemical and Biological Engineering, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208*

Received October 12, 2006. In Final Form: November 24, 2006

Various types of asymmetric disulfides can be synthesized under mild conditions and in excellent yields by a method involving dialkoxylthiophosphoranesulfenyl halide precursors. This straightforward, rapid procedure is used to prepare a series of disulfides bearing neutral, acidic, and basic terminal groups as well as groups commonly used in biospecific self-assembled monolayers.

This letter describes a straightforward, general, efficient method of synthesizing asymmetric disulfides (ADs) for applications in self-assembled monolayers (SAMs) on gold or other metals.<sup>1–3</sup> Although good-quality SAMs can be prepared both from thiols and disulfides,<sup>1</sup> the latter offer several practical advantages: they are more stable, significantly less prone to oxidation, and avoid problems associated with intra/intermolecular reactivity of the thiol group.<sup>4</sup> In addition, ADs give monolayers of well-defined surface compositions, in some cases avoid phase separation,<sup>5</sup> and eliminate cooperative effects associated with the co-adsorption of binary solutions of corresponding thiols.<sup>6</sup> The ability to tailor surface composition with ADs has been used, for instance, in DNA immobilization via intercalation,<sup>7</sup> in double-stranded DNA–protein microarrays,<sup>8</sup> in fundamental studies on surface reactions on nanoparticles,<sup>6</sup> and more recently, in electrostatic self-assembly of nanostructured materials.<sup>9</sup>

ADs can be synthesized by a variety of methods. The simplest procedure is based on the oxidation of a mixture of desired thiols<sup>10</sup> to give a statistical ratio of disulfides. Although the AD product is favored when the two thiol reagents are sufficiently structurally

different (e.g., oxidation of a primary thiol in the presence of an aromatic one), the method usually gives low yields and requires laborious purification. The alternative thiol–thiol coupling using diethyl azodicarboxylate (DEAD) can give better yields, but the high reactivity of DEAD toward other (than thiol) functional groups makes this approach less versatile. Similarly, high toxicity limits the use of sodium tellurite (Na<sub>2</sub>TeO<sub>3</sub>), which otherwise gives excellent yields and chemoselectivities under mild phase-transfer conditions.<sup>12</sup> Although several other procedures have been reported (with *N*-sulfenylphthalimides,<sup>13</sup> Bunte salts,<sup>14</sup> and sulfenyl chlorides<sup>15</sup>), the most common and versatile one is the thiolysis of disulfides with thiols (effectively a thiol–disulfide exchange reaction), especially using 2-pyridyldisulfide derivatives obtained from Aldrithiol.<sup>16</sup> This reaction is promoted by a wide range of different catalysts, including DMAP,<sup>17</sup> perchloric acid and triphenylphosphine,<sup>18</sup> and acetic acid,<sup>19</sup> but requires long reaction times and gives only moderate yields.

Here, we describe a new, versatile synthetic route to ADs by the use of easy-to-obtain dialkoxylthiophosphoranesulfenyl halides.<sup>20</sup> Our procedure is very rapid (~15 min), proceeds under mild conditions in excellent yields (~90%), and can be used to make disulfides from thiols bearing both neutral and basic or acidic functionalities.

The synthetic strategy is illustrated in Scheme 1. The starting bis-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl)disulfide (**1**) is stable and readily available in multigram quantities.<sup>21</sup> Its treatment with bromine at 0 °C affords (5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl)sulfenyl bromide (**2**), which can then be reacted directly with a desired thiol. As an example, we used

\* Corresponding authors. E-mail: grzybor@northwestern.edu, dwitt@chem.pg.gda.pl.

<sup>†</sup> ProChimia Surfaces.

<sup>‡</sup> Gdansk University of Technology.

<sup>§</sup> Northwestern University.

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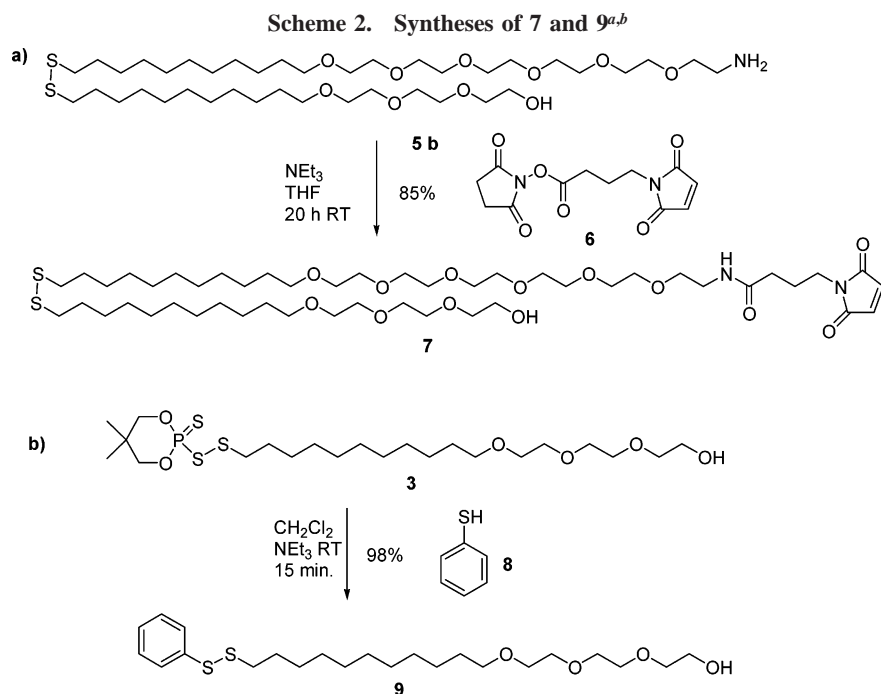
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<sup>a</sup> Asymmetric disulfides prepared from sulfenyl bromide adducts can be further reacted in good yields without the purification of intermediates (here **5b**). The mixed maleimide disulfide (**7**) forms SAMs that capture thiol-terminated peptide and carbohydrate ligands and has been used in detection biochips.<sup>26</sup> <sup>b</sup>Our synthetic method works well with both aliphatic and aromatic thiols (e.g., thiophenol **8**).

**Table 1. Yields for the Syntheses of Asymmetric Disulfides**

| 5a–e |   | G | Yield of disulfide 5 |
|------|---|---|----------------------|
| 1.   | a |   | 87%                  |
| 2.   | b |   | 86%*                 |
| 3.   | c |   | 91%                  |
| 4.   | d |   | 93%                  |
| 5.   | e |   | 96%                  |
| 6.   | f |   | 92%                  |

\*disulfide **5b** was isolated as hydrochloride salt

**4**, and the short times required for the transformation minimizes further disulfide exchange between product **5** and thiol **4**.

Short times, high yields, and ease of purification are the major advantages of our method over the popular scheme involving Aldrithiol, in which reaction times are between 20 and 36 h, the yields for similar disulfides such as those described here range from 65 to 85%, and the formation of symmetrical disulfide byproducts is sometimes observed. The latter is a serious drawback because these byproducts are hard to separate from the desired ADs.

Finally, we note that the method is not limited to alkyl disulfides and works equally well with aromatic thiols. One example is

illustrated Scheme 2b, which shows an almost qualitative synthesis (98% yield) of a mixed aromatic/aliphatic disulfide. Other types and combinations of aromatic thiols can be used with comparable efficiencies.

In summary, we have described a new synthetic route to  $\omega$ -functionalized alkane asymmetric disulfides that is, to our knowledge, simpler and more efficient than other procedures currently in use. We envision the uses of these and other structurally related compounds in biochip applications (cf. ref 4 for the use of disulfide **7**, ref 29 for **5b**, and ref 30 for **5f**) and for the adjustment of electrostatic charges<sup>9b</sup> (e.g., **5b** or **5c**) on nanoscopic objects used in electrostatic self-assembly.<sup>9a</sup>

**Acknowledgment.** We thank ProChimia Poland for the generous gift of thiol precursors. B.A.G. gratefully acknowledges financial support from the Pew Scholars Program in Biomedical Sciences, an NIH/NCI CCNE grant, and a 3M Non-Tenured Faculty Award.

**Supporting Information Available:** Detailed synthetic procedures and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

LA063013K