Versatile and Efficient Synthesis of ω-Functionalized Asymmetric Disulfides via Sulfenyl Bromide Adducts

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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 difulfides (ADs) for applications in self-assembled monolayers (SAMs) on gold or other metals.[1−3] Although good-quality SAMs can be prepared both from thiols and disulfides,[1] 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.[4] In addition, ADs give monolayers of well-defined surface compositions, in some cases avoid phase separation,[5] and eliminate cooperative effects associated with the co-adsorption of binary solutions of corresponding thiols.[6] The ability to tailor surface composition with ADs has been used, for instance, in DNA immobilization via intercalation,[7] in double-stranded DNA−protein microarrays,[8] in fundamental studies on surface reactions on nanoparticles,[6] and more recently, in electrostatic self-assembly of nanostructured materials.[9]

ADs can be synthesized by a variety of methods. The simplest procedure is based on the oxidation of a mixture of desired thiols[10] 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_2TeO_3), which otherwise gives excellent yields and chemoselectivities under mild phase-transfer conditions.[12] Although several other procedures have been reported (with *N*-sulfenylphthalimides,[13] Bunte salts,[14] and sulfenyl chlorides[15]), 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.[16] This reaction is promoted by a wide range of different catalysts, including DMAP,[17] perchloric acid and triphenylphosphine,[18] and acetic acid,[19] 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.[20] 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.[21] Its treatment with bromine at 0 °C affords (5,5-dimethyl-2-thiono-1,3,2-dioxophosphorinanyl)sulfenyl bromide (**2**), which can then be reacted directly with a desired thiol. As an example, we used

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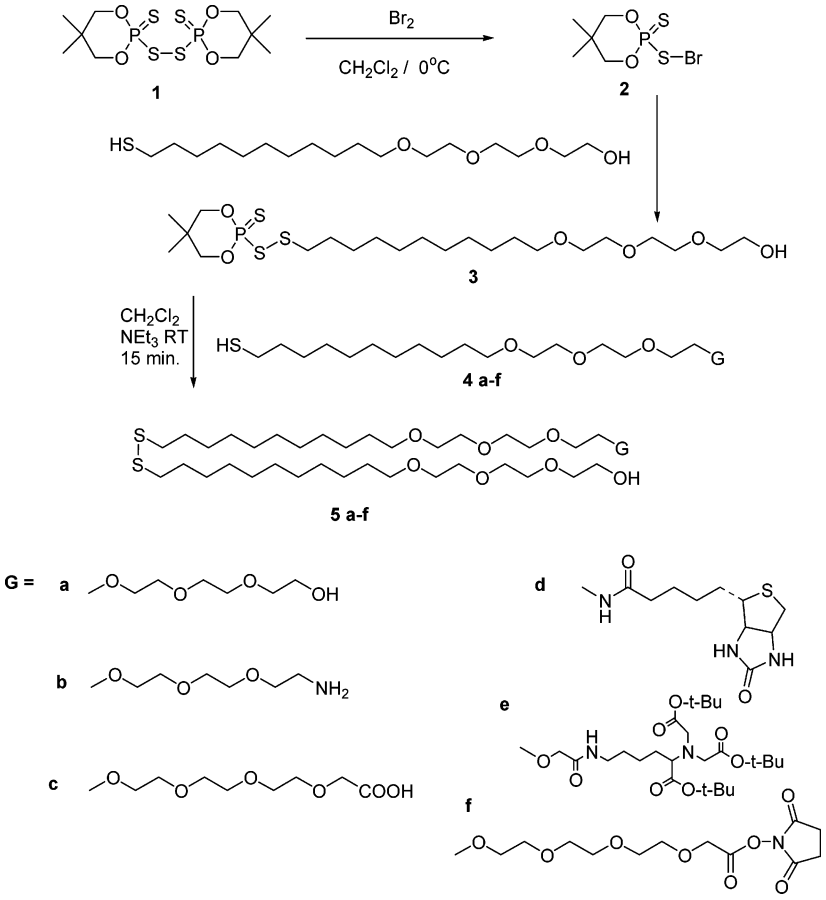
Scheme 1. Strategy for the Synthesis of Asymmetric Disulfides via Sulfenyl Bromide Adducts



11-(mercaptoundecyl)-triethylene glycol (ProChimia, Poland), a thiol commonly used to form "bioresistant" monolayers that resist the nonspecific adsorption of proteins and reduce the adhesion of cells,[1,22] to obtain **3** in 95% yield (after column chromatography in 50:1 CH_2Cl_2/MeOH). This adduct was stable at room temperature for several days, could be stored at −10 °C for several weeks without signs of decomposition or symmetrization, and could be reacted with a partner thiol to give a desired asymmetric disulfide.

The model "partner" thiols that we used were all obtained from ProChimia (www.prochimia.com) and were chosen on the basis of the chemical properties of their end groups (**4a** neutral, **4b** basic, **4c** acidic) and/or their technological relevance (**4d**−**f**). For example, biotin-terminated thiol **4d** is commonly used in protein chip technology to immobilize streptavidin constructs onto surfaces;[23] tri-t-butyl-NTA thiol **4e** is a precursor to an NTA analog (by treatment with TFA) for the selective immobilization of His-tagged proteins;[24] and the NHS-terminated thiol allows for a variety of covalent in situ coupling schemes on SAMs.[1] In addition, these compounds were a challenging test bed for the efficiency of our method because the presence of the ethylene glycol linker usually complicates purification procedures (as we have often experienced with other synthetic schemes).

Reactions of thiols **4** with compound **3** in the presence of triethyl amine proceeded quantitatively (as verified by TLC, 25 :1 CH_2Cl_2/MeOH, and ^{1}H NMR of the crude reaction mixture), rapidly (usually starting material **3** was not detected by TLC after ca. 5 min), and without further disulfide exchange as confirmed by TLC and column separation. The yields of the pertinent reactions, after aqueous workup and column chromatography, are summarized in Table 1. We note that although postreaction purification was not necessary for possible further synthetic elaboration of crude products **5** (cf. Scheme 2a) it was nevertheless necessary for successful application of the disulfides in biospecific SAMs, where even minor contamination can cause serious untoward effects (e.g., cytotoxicity[25]). The purification step decreased the otherwise quantitative yields to those that we report because the aqueous workup removed not only the traces of dithiophosphate but also part of the ADs as a result of the hydrophilic character of the EG linker and/or the head groups.

The success of the method rests on the selective reactivity of (5,5-dimethyl-2-thiono-1,3,2-dioxophosphorinanyl)sulfenyl bromide (**2**) toward sulfur nucleophiles to produce intermediate **3**. As we have verified experimentally, the disulfide bond in intermediate **3** forms even in the presence of other nucleophilic groups (e.g., hydroxyl, amino, and carboxyl) so that these groups do not need to be protected prior to the thiolation reaction. Furthermore, because dithiophosphoric acids are very strong (pK_a $\approx$ 2), their anions are very good leaving groups. This property is crucial for the exclusive formation of disulfides **5** from **3** and

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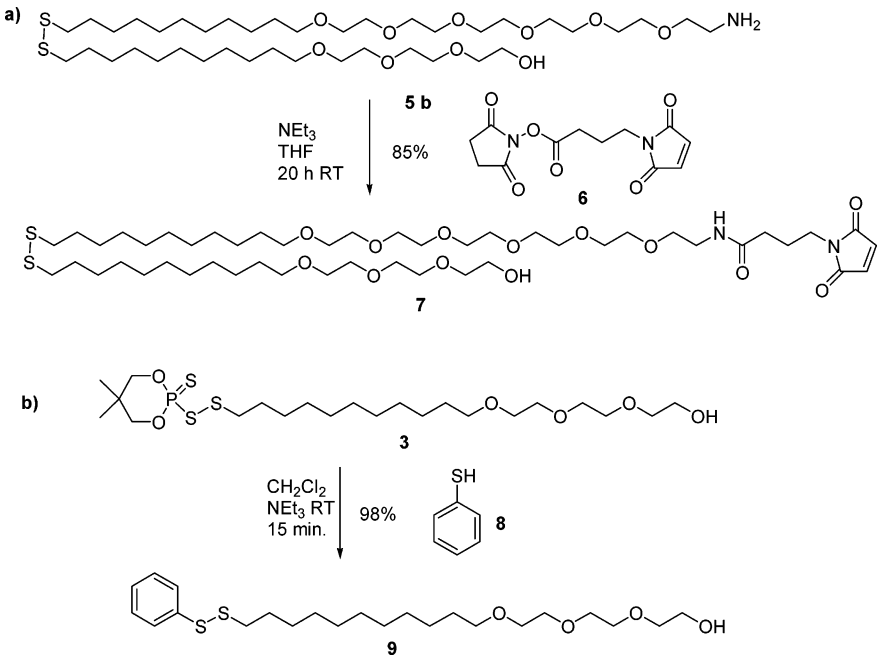
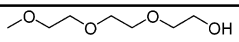
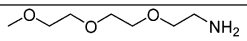
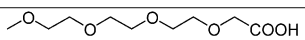
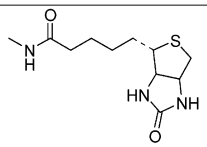
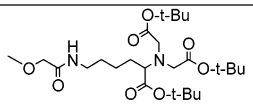
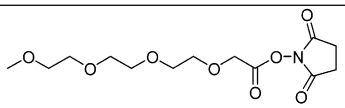
Scheme 2. Syntheses of 7 and 9[a,b]



[a] 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.[26] [b]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 ω-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[9b] (e.g., **5b** or **5c**) on nanoscopic objects used in electrostatic self-assembly.[9a]

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

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