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Allylic Disulfide Rearrangement and Desulfurization: Mild, Electrophile-Free Thioether Formation from Thiols

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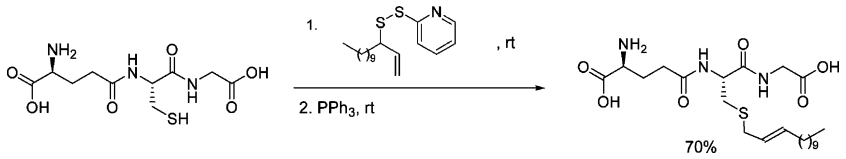
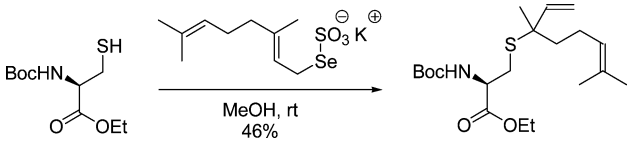
ABSTRACT



Secondary and tertiary allylic 2-pyridyl and 2-benzothiazolyl disulfides react with thiol groups at room temperature to give secondary and tertiary allyl alkyl disulfides. On the addition of a phosphine, a desulfurative sigmatropic rearrangement takes place at room temperature to give thioethers.

We recently reported a new functionalization method for thiols and cysteine derivatives which proceeds at room temperature in protic media. The chemistry involves the deselenative [2,3]-sigmatropic rearrangement of allylic selenosulfides (Scheme 1) and is best suited for the synthesis of tertiary allylic sulfides from primary selenosulfides as exemplified by the introduction of linalyl and nerolydyl groups.[1]

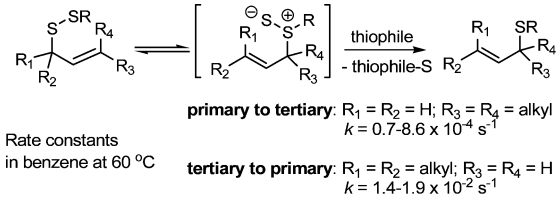
Scheme 1. Chemical Ligation via Se−Allyl Selenosulfides



However, this method is not as well adapted for the preparation of primary allyl sulfides because of complications in the synthesis of the required tertiary selenosulfides. To access primary allylic sulfides from thiols, we have now examined and report on the analogous rearrangement of allylic disulfides.

As first described by Baldwin,[2a] allylic disulfides are in equilibrium with allylic thiosulfoxides by virtue of a [2,3]-sigmatropic rearrangement of undetermined stereoselectivity (Scheme 2).[2] The equilibrium, which strongly favors the allylic disulfide, can be displaced toward the formation of an allylic sulfide by the addition of a thiophilic agent. At 60 °C in benzene, rate constants for the rearrangement with

Scheme 2. Allylation of Thiols via Allylic Disulfides



(1) Crich, D.; Krishnamurthy, V.; Hutton, T. K. *J. Am. Chem. Soc.* **2006**, *128*, 2544.

(2) (a) Höfle, G.; Baldwin, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 6307. (b) Baechler, R. D.; Hummel, J. P.; Mislow, K. *J. Am. Chem. Soc.* **1973**, *95*, 4442. (c) Block, E.; Iyer, R.; Grisoni, S.; Saha, C.; Belman, S.; Lossing, F. P. *J. Am. Chem. Soc.* **1988**, *110*, 7813. (d) Kutney, G. W.; Turnbull, K. *Chem. Rev.* **1982**, *82*, 333. (e) Moore, C. G.; Trego, G. R. *Tetrahedron* **1962**, *18*, 205. (f) Evans, M. B.; Higgins, G. M. C.; Moore, C. G.; Porter, M.; Saville, B.; Smith, J. F.; Trego, B. R.; Watson, A. A. *Chem. Ind.* **1960**, 897. (g) Pilgram, K.; Phillips, D. D.; Korte, F. *J. Org. Chem.* **1964**, *29*, 1844.

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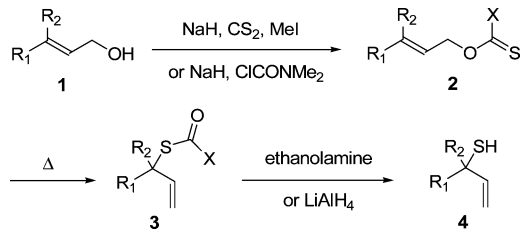
transfer of sulfur to triphenylphosphine were found to be strongly dependent on the substitution pattern.[2a] Whereas the desulfurative rearrangement was reported to be slow for primary allylic disulfides (R_1,R_2 = H and R_3,R_4 = H/alkyl; $k = 0.7 \times 10^{-4}$ to $8.6\ 10^{-4}\ s^{-1}$), a significant rate acceleration was observed with secondary and tertiary allylic disulfides (R_1,R_2 = alkyl and R_3,R_4 = H; $k = 1.4 \times 10^{-2}$ to $1.9\ 10^{-2}\ s^{-1}$).[2a] On the basis of early observations,[2a,e] we reasoned that use of polar solvents to stabilize the polar thiosulfoxide intermediate would enable the reaction to be conducted at room temperature, thereby providing a mild and selective functionalization method for thiols, complementary to the allylic selenosulfide methodology. We describe here the successful realization of this concept and its application to the functionalization of thiols under mild, electrophile-free conditions and provide the first insights into the stereoselectivity of this process.

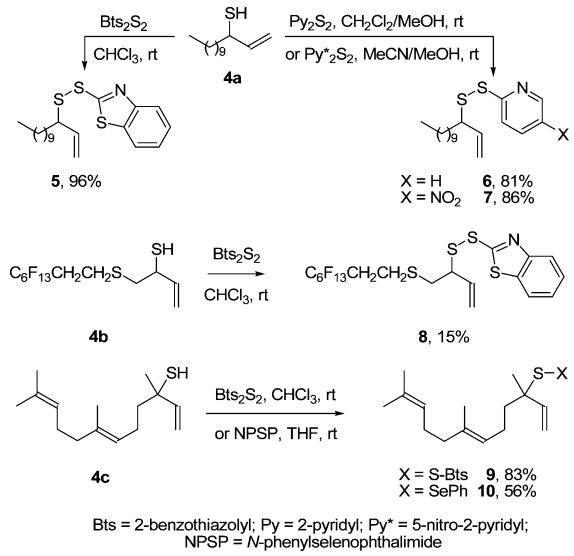
A series of secondary and tertiary allylic thiols were prepared by exploiting the ease of formation of allylic xanthates and thiocarbamates and their thermal [3,3]-sigmatropic rearrangement to dithiocarbonates and thiocarbamates (Scheme 3).[3]

Scheme 3. Synthesis of Secondary and Tertiary Allylic Thiols



Thiols **4a**−**c** were activated for disulfide formation by conversion to their corresponding benzothiazolyl and pyridyl disulfide derivatives (Scheme 4). Analogous sulfenylating agents have found wide applications for the synthesis of mixed disulfides, especially pyridyl derivatives owing to the spectroscopic properties of pyridine-2-thiones which enable successful monitoring of sulfydryl group modifications.[4] For **4a**, the benzothiazolyl derivative **5**, as well as pyridyl disulfides **6** and **7**, were prepared and proved to be easily purified and perfectly stable.[5,6] The recent use of selenosulfides for formation of disulfide-linked neoglycopeptides[7] motivated us to prepare the selenosulfide **10** and compare the efficiency of different sulfenylating agents in the context

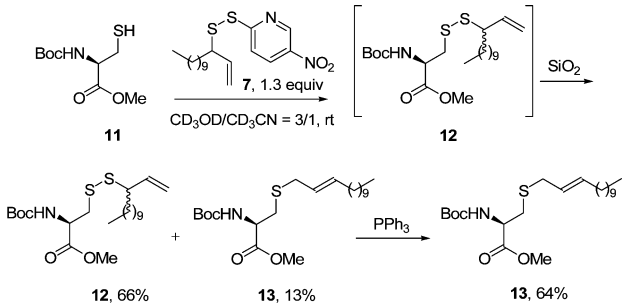
Scheme 4. Synthesis of Sulfenylating Agents from Allylic Thiols



of this new functionalization method. It is noteworthy that such sulfenylating agents, derived from hindered allylic thiols, have drawn little attention so far and that only a limited number of benzothiazolyl disulfides[8] and thiosulfinates[9] have been reported.

Reaction of disulfide **7** with cysteine derivative **11** at room temperature in CD_3OD/CD_3CN resulted in the formation of expected disulfide **12** accompanied by only traces of rearranged product **13** (Scheme 5).[10]

Scheme 5. Functionalization of a Cysteine Derivative



Interestingly, during an attempt to purify **12** on silica gel, a significant amount of **13** was obtained, thereby establishing

(3) (a) Harano, K.; Taguchi, T. *Chem. Pharm. Bull*. **1972**, *20*, 2348. (b) Harano, K.; Taguchi, T. *Chem. Pharm. Bull*. **1972**, *20*, 2357. (c) Harano, K.; Taguchi, T. *Chem. Pharm. Bull*. **1975**, *23*, 467. (d) Harano, K.; Ohizumi, N.; Hisano, T. *Tetrahedron Lett*. **1985**, *26*, 4203. (e) Nakai, T.; Ari-Izumi, A. *Tetrahedron Lett*. **1976**, *17*, 2335. (f) Nakai, T.; Mimura, T.; Ari-Izumi, A. *Tetrahedron Lett*. **1977**, *18*, 2425. (g) Ueno, Y.; Sano, H.; Okawara, M. *Tetrahedron Lett*. **1980**, *21*. 1767.

(4) (a) Talgoy, M. M.; Bell, A. W.; Duckworth, H. W. *Can. J. Biochem.* **1979**, *57*, 822. (b) Kimura, T.; Matsueda, R.; Nakagawa, Y.; Kaiser, E. T. *Anal. Biochem.* **1982**, *122*, 274.

(5) For examples of preparation of benzothiazolyl disulfides and pyridyl disulfides as well as their application to the synthesis of mixed disulfides, see: (a) Brzezinska, E.; Ternay, A. L. *J. Org. Chem.* **1994**, *59*, 8239. (b) Rabanal, F.; DeGrado, W. F.; Dutton, P. L. *Tetrahedron Lett.* **1996**, *37*, 1347. (c) Stoner, E. J.; Negrón, G.; Gaviño, R. In *Handbook of Reagents for Organic Synthesis: Reagents for Glycoside, Nucleotide and Peptide Synthesis*; Crich, D., Ed.; Wiley: London, 2005; p 330. (d) Lundblad, R. L. *Chemical Reagents for Protein Modification*, 3rd ed.; CRC Press: Boca Raton, 2005.

(6) Disulfides **5**−**10** were kept at 0 °C for several months with no evidence of rearrangement or degradation.

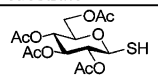
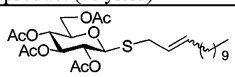
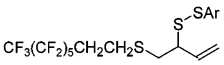
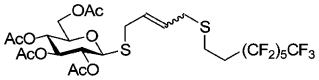
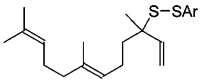
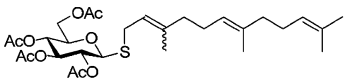
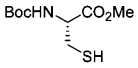
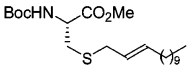
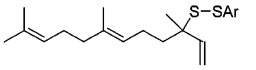
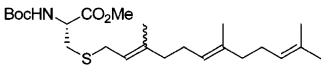
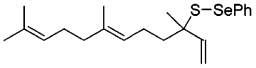
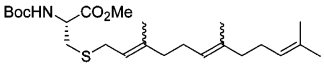
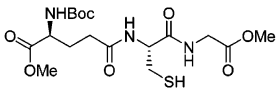
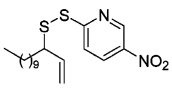
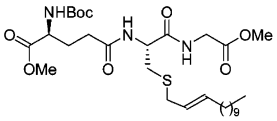
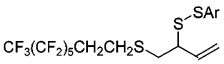
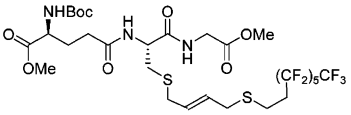
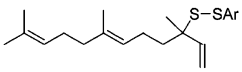
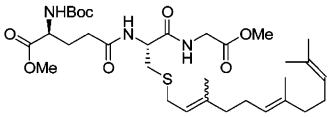
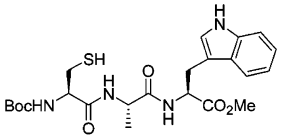
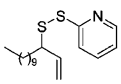
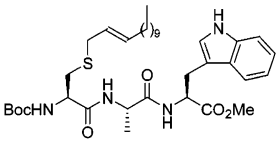
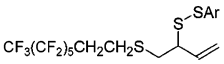
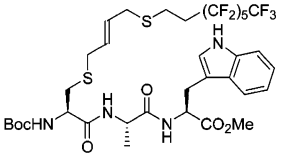
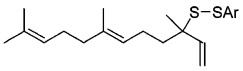
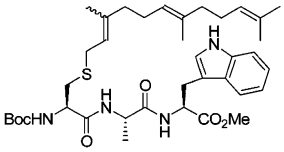
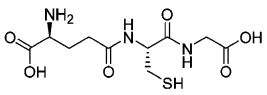
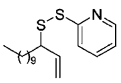
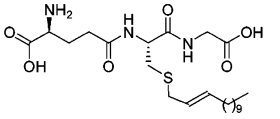
(7) Gamblin, D. P.; Garnier, P.; van Kasteren, S.; Oldham, N. J.; Fairbanks, A. J.; Davis, B. G. *Angew. Chem., Int. Ed*. **2004**, *43*, 828.

(8) (a) Watson, A. A. *J. Chem. Soc. (C)* **1964**, 2100. (b) Morrison, N. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 101.

(9) Braverman, S.; Pechenick, T. *Tetrahedron Lett*. **2002**, *43*, 499.

(10) Only traces of allylic sulfide **13**, arising from the [2,3]-rearrangement with loss of sulfur, were identified by NMR.

Table 1. Application to Thiols, Cysteine Derivatives, and Cysteine-Containing Peptides

entry	substrate	sulfenating agent[a]	product (% yield)[b]
1[c,e]	 **14**		 **18** (73) ds: 12/1
2[c,e]	**14**		 **19** (75) ds: 7.9/1
3[c,e]	**14**		 **20** (66) ds: 1.8/1
4[f]	 **11**		 **13** (85)
5[d,e,g]	**11**		 **21** (84) ds: 1.87/1
6[d,e,g]	**11**		 **21** (80) mixture of isomers
7[d,f]	 **15**		 **22** (70)
8[c,e]	**15**		 **23** (75)
9[c,e,g]	**15**		 **24** (70) ds: 1.7/1
10[c,e]	 **16**		 **25** (80)
11[c,e]	**16**		 **26** (79)
12[c,e,g]	**16**		 **27** (79) ds: 1.6/1
13[h,e]	 **17**		 **28** (70)

[a] Ar = 2-benzothiazolyl. [b] The double-bond configuration of **13**, **18**, **22**, **23**, **25**, **26**, and **28** was determined by a homonuclear spin decoupling experiment ($J \sim 15$ Hz). The *E* and *Z* isomers of **21** and **24** were separated by preparative HPLC, and double-bond configurations were determined on the basis of ^{13}C γ effects. [c] Reactions were performed in benzene at 0.05 M with 1.3 equiv of disulfide and 3 equiv of phosphine. Et_3N (3 equiv) was added to accelerate the disulfide bond formation (minutes instead of hours). The disulfide bond formation was carried out at room temperature, and the rearrangement was carried out at reflux. [d] Reactions were performed at room temperature in MeCN/MeOH (1:1) at 0.05 M with 2 equiv of disulfide and 3 equiv of phosphine. [e] PPh_3 was used as the thiophile. [f] $Ph_2P(4\text{-}C_6H_4NMe_2)$ was used as the thiophile. [g] Et_3N (5 equiv) was added. [h] Reaction was performed at room temperature in a mixture of Tris buffer/MeCN/THF (2:1:1) at 0.02 M with 3 equiv of disulfide and 5 equiv of phosphine.

that the rearrangement and the subsequent loss of sulfur can be performed at room temperature.[11] The addition of a phosphine to a mixture of **12** and **13** resulted in the desulfurization of the thiosulfoxide and led to the primary allylic sulfide as a single *E*-isomer, without racemization of the cysteine moiety.[12] We next explored the possibility of conducting the reaction in one pot, at room temperature, using a mixture of methanol−acetonitrile as solvent. Fol-

lowing this strategy, the phosphine was simply added to the reaction mixture after consumption of the cysteine derivative. This protocol turned out to be not only more convenient but also more efficient with yields up to 85% (Table 1, entry 4). The nature of the sulfenylating agent (**5**, **6**, or **7**), or of the arylphosphine, has no significant impact on the yields, which were optimum with 2 equiv of sulfenylating agents.

We next explored the functionalization of carbohydrate-based thiols, cysteine derivatives, and small cysteine-containing peptides with 1-thio-β-D-glucose tetraacetate **14**, Boc-L-Cys-OMe **11**, Boc-(α-OMe)-γ-L-Glu-L-Cys-Gly-OMe **15**, and Boc-L-Cys-L-Ala-L-Trp-OMe **16**[1] (Table 1). These reactions were conducted following the one-pot/two-step procedure in various solvents, including protic ones. The reaction involving cysteine residues could be performed at room temperature, whereas the rearrangement of disulfides derived from 1-thio-β-D-glucose tetraacetate **14** required a higher temperature. Secondary disulfides **5**−**8** were employed under neutral conditions, but the more hindered tertiary disulfide **9** and the selenosulfide **10** required the addition of Et_3N to achieve the ligation to the cysteine derivatives. With selenosulfide **10**, the modified cysteine derivative **13** was isolated as a mixture of isomers, presumably arising from double-bond isomerization mediated by selenium-based byproducts (Table 1, entry 6).[13] The potential of this method for the ligation of organic molecules to cysteine-containing peptides was also demonstrated by allylation of free glutathione (Table 1, entry 13). It is noteworthy that this convenient and efficient thiol functionalization method is highly selective and compatible with the indole ring in tryptophan.

The results gathered in Table 1 give also the first insight into the stereochemistry of the [2,3]-sigmatropic rearrangement of allylic disulfides. At room temperature, high selectivity was observed for the formation of *E*-disubstituted double bonds, but the selectivity slightly decreased when the rearrangement was performed at 80 °C (Table 1, entries 1 and 2). On the other hand, trisubstituted double bonds were obtained with a modest *E*-selectivity (Table 1, entries 3, 5, 9, and 12). These results are consistent with features of other [2,3]-shifts, such as the Evans−Mislow or [2,3]-Wittig sigmatropic rearrangements.[14,15]

In summary, we describe a new and convenient functionalization method of thiols, combining the use of stable and easily prepared benzothiazolyl and pyridyl disulfides as sulfenylating agents with a phosphine-promoted desulfurative allylic rearrangement. As demonstrated by allylation of unprotected glutathione, this method has potential for the ligation to peptides and protein-based thiols, an area of considerable current interest. The facile synthesis of the allyl heteroaryl disulfides coupled with the applicability of the method to native peptides renders the method highly competitive with other routes to cysteine functionalized peptides, all of which require the use of electrophilic reagents or the prior derivatization of the peptide.[16]

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Sulfur extrusion appears to be favored by the presence of acid in the reaction mixture. In untreated $CDCl_3$, the disulfide **12** partially rearranged to allylic sulfide **13**, even in the absence of phosphine.

(12) Rearrangement of **12** to **13** in the presence of PPh_3 or 4-(Me_2-NC_6H_4)PPh_2 was complete in 12−15 h. Racemization was excluded by a reaction in $CDCl_3/CD_3OD$, with no deuterium incorporation.

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(14) Stereoselectivity of the allylic sulfoxide rearrangement. Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.

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