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A traceless, one-pot preparation of unsymmetric disulfides from symmetric disulfides through a repeated process involving sulfenic acid and thiosulfinate intermediates

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ABSTRACT

A variable group of unsymmetric disulfides was prepared under mild reaction conditions and in high yields through the reaction of symmetric disulfides with sulfuryl chloride followed by treatment with thiols in the presence of water.

1. Introduction

Disulfides are found in numerous natural products and biologically significant functional materials.[1] Numerous disulfides occur naturally, and the study of their biogenesis should lead to fascinating results. For example, diallyl disulfide is the active constituent of garlic and the antibacterial disulfide monoxide (a thiosulfinate) also present is allicin.[2] Some disulfides express antitumor activity.[3] Although symmetric disulfides can be prepared by the direct transformation of thiols, through treatment with hydrogen peroxide, iodine, chromates, bromine or sulfuryl chloride, efficient synthetic methods, for unsymmetric disulfides are still in need.[4] The synthetic methodologies of unsymmetric disulfides reported in literatures over the past three decades were classified into three categories: First, the thiolysis of reactive sulfenylating agents such as sulfenyl chlorides,[5] sulfenamides,[6] sulfenimides,[7] sulfenyl hydrazides,[8] thiobenzotriazoles,[9] thiotriphenylphosphonium salts,[10] sulfenyl thiocarbonates,[11] thionitriles[12] and immobilized thiosulfonates[13] through nucleophilic S_N2 attack of thiol or thiolate anions to yield unsymmetric disulfides (Eq. 1). In this method, the isolation of the reactive sulfenylating agent intermediate should be done in advance in most of the cases. Second, syntheses through a thio-disulfide interchange reaction of symmetric disulfides, such as bistetrazole disulfide,[14] dithiobis(benzothiazole),[15] *N*-alkylpyridyl disulfide[16] or dithiopyridine N-oxides[17] (Eq. 2). Third, syntheses using metal complex catalyst (Eq. 3).[18] In a number of other approaches, a microwave assisted transformation was involved.[19] The drawback of most of these reported synthetic methodologies is the necessity of preparation of the reactive sulfenylating agents or thio-disulfide interchangeable symmetric disulfides in advance. In addition, the elimination of the leaving sulfenylating moiety (HL or R_3SH) or the symmetric disulfide, byproduct resulted from using excess thiol, at the end of the reaction is another drawback of the reported syntheses of unsymmetric disulfides.[20]

$$R_1{-}SH + R_2{-}S{-}L \rightarrow R_1{-}S{-}S{-}R_2 + HL \quad (1)$$

$$R_3{-}S{-}S{-}R_3 \xrightarrow{R_4{-}SH} \underset{+\ R_3{-}SH}{R_4{-}S{-}S{-}R_3} \xrightarrow{R_5{-}SH} \underset{+\ R_3{-}SH}{R_4{-}S{-}S{-}R_5} \quad (2)$$

$$(R_6{-}S)_2 + (R_7{-}S)_2 \xrightarrow{\text{metal catalyst}} R_6{-}S{-}S{-}R_7 \quad (3)$$

Herein, we report a simple and convenient preparation of unsymmetric disulfides under mild reaction conditions and in high yields from symmetric disufides through thiosulfinate intermediates. This is a practical synthesis of unsymmetric disulfides through thiolysis using thiosulfinate as a reactive sulfenylating agent. In addition, an important advance in this new methodology is the traceless preparation of unsymmetric disulfides in a one-pot reaction without separation of leaving sulfenylating moiety.

In the course of development of new herbicides, it was important to synthesize a new triazolyl phenyl disulfide **1** as an intermediate. The retrosynthetic analysis of this intermediate is shown in Scheme 1. According to this retrosynthetic analysis, a nucleophilic attack by the sulfur atom of 3-mercapto-1,2,4-triazole **3** at the

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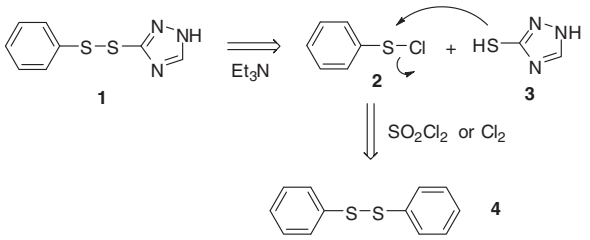
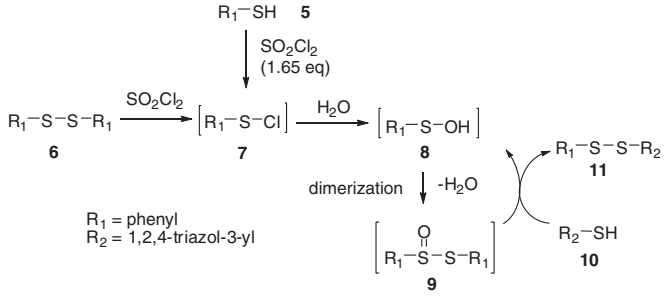


Scheme 1. Retrosynthetic analysis for triazolyl phenyl disulfide **1**.

sulfur atom of the benzenesulfenyl chloride **2**, that is prepared from diphenyldisulfide **4** in the presence of triethylamine, would be expected to give the unsymmetric disulfide **1**.

The benzenesulfenyl chloride intermediate **2** was prepared by the reaction of diphenyldisulfide **4** with sulfuryl chloride in dried benzene, and was then treated with 3-mercapto-1,2,4-triazole **3** in the presence of triethylamine under nitrogen atmosphere and at room temperature to yield the target unsymmetric disulfide **1** (see Scheme 1). Under these reaction conditions, the yield was very low and the starting disulfide **4** was recovered unchanged. Similar results were obtained by repeating the reaction at ambient temperature, and the yields were less than 40% in all these trials. Prudent experiments with protection from moisture showed a tendency towards lower yields of the product. Therefore, we tried to repeat the reaction in moist tetrahydrofuran instead of dried benzene as a solvent. Surprisingly, the reaction proceeded smoothly as monitored by TLC. Thus, it is conceivable that the addition of water would be a critical factor in obtaining high yields of the products. Accordingly, the reaction was repeated for several times using different molar equivalents of water in order to determine the optimum water equivalent for the highest yields. It was found that the highest yields of product were obtained when 5–10 M equiv of water were used.

A suggested mechanism of the reaction is shown in Scheme 2. The sulfenyl chloride **7** was obtained from either treatment of **5** with sulfuryl chloride (1.65 M equiv) or chlorinolysis of the disulfide **6** by treatment with sulfuryl chloride (1.1 M equiv).[5] In the presence of water the sulfenyl chloride **7** initially reacts with water to form the corresponding sulfenic acid **8**, which dimerizes into thiosulfinate **9** upon loss of water.[21,22] The nucleophilic attack of the sulfur atom of the thiol **10** (R_2SH) at the sulfenyl sulfur of **9** results in the desired unsymmetric disulfide **11** with the regeneration of the sulfenic acid **8**.[23] The generated sulfenic acid **8** dimerizes again to repeat the cycle. The net result is that the symmetric disulfide **6** was converted to the unsymmetric disulfide **11** in the presence of water and in high yield. On the basis that greater than 50% isolated yield of the product was obtained and the absence of any thiosulfonate or thiosulfonate-derived products, we concluded that disproportionation[22] did not take place in these reaction conditions. Although the mechanism of formation of unsymmetric disulfide by nucleophilic displacement at sulfur of thiosulfinate by thiol was previously proposed,[24] no such examples were reported. Recently, the transformation of thiosulfinate intermediate produced by oxidation of diallyl disulfide by the action of cytochrome P450 in *allium* tissues into unsymmetric disulfide was proposed in living system, mediated by enzymatic metabolic transformation.[25] However, a practical chemical synthesis of the unsymmetric disulfide by the mechanism depicted in Scheme 2 has not been reported until now according to our knowledge.



Scheme 2. The proposed mechanism for the formation of the disulfide **11** through the intermediates sulfenic acid **8** and thiosulfinate **9**.

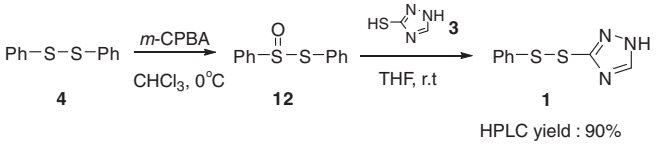
Evidence in support of the proposed reaction mechanism in Scheme 2 was that the thiosulfinate **12** prepared by the oxidation of the diphenyl disulfide **4** with *m*-chloroperoxoybenzoic acid[26] was found to react with triazolyl thiol **3** (2.0 M equiv) smoothly under anhydrous conditions to afford the unsymmetric disulfide **1** in a high yield (90%) (Scheme 3, see experimental in Supplementary data).

It has been reported that sulfenyl halides react rapidly with water to produce the corresponding sulfenic acids and thiosulfinates, which are vulnerable to attack by nucleophiles.[21] Therefore, an immediate dropwise addition of a freshly prepared solution of the sulfenyl chloride **7** in THF, prepared by chlorinolysis of symmetric disulfide, into a solution of the thiol **10**, triethylamine and water at the same solvent below room temperature is preferable in order to obtain high product yield and to avoid formation of byproducts.

For an extension of this new methodology for the preparation of various unsymmetric disulfides, a group of variable symmetric disulfides and thiols were used and the results are summarized in Table 1.

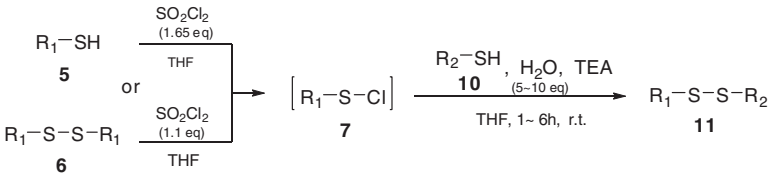
The structures of the prepared unsymmetric disulfides were confirmed by ^{1}H NMR, ^{13}C NMR, HRMS spectral data and X-crystallographic analysis. The ^{1}H NMR and ^{13}C NMR spectra of the prepared compounds were in agreement with the structures. The molecular ions (M^+ or MH^+) of the prepared unsymmetric disulfides **11** were successfully obtained by using Direct Analysis in Real Time ion source installed on a high-resolution time-of-flight mass spectrometer.[27] Further proof of the structure was established by means of an X-ray crystallographic analysis (Fig. 1) for compound **11j**.[28] Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-791710. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Since the symmetric disulfides could be prepared by oxidation of the corresponding thiols and a lot of thiols are commercially available it is most likely that this new methodology would be very useful for the preparation of unsymmetric disulfides.

In summary, we have prepared a variable group of unsymmetric sulfides under mild reaction conditions and in high yield. Treatment of symmetric disulfides with sulfuryl chloride followed by the reaction with thiols in the presence of water without isolation of sulfenic acid and thiosulfinate intermediates gave unsymmetric disulfides. The reagents were used in equimolar ratios and the reaction proceeded in a nearly quantitative yield. Little trace



Scheme 3. The reaction of thiosulfinate intermediate **12** and triazolyl thiol **3**.

Table 1
Physical properties and isolated yields of the prepared unsymmetric disulfides **11**



Entry	Compounds	R_1	R_2	Mp (°C)	Yields[a] (%)
1	**11a**	C_6H_4(4-Cl)	1,2,4-triazol-3-yl	88	71
2	**11b**	C_6H_4(4-Cl)	C_6H_4(4-CH_3)	95	87
3	**11c**	C_6H_4(4-Cl)	Benzothiazol-2-yl	63	81
4	**11d**	Cyclohexyl	1,2,4-triazol-3-yl	90	78
5	**11e**	Cyclohexyl	C_6H_4(4-OCH_3)	Oil	81
6	**11f**	Cyclohexyl	Benzothiazol-2-yl	Oil	63
7	**11g**	*t*-Butyl	C_6H_4(4-CH_3)	Oil	86
8	**11h**	*t*-Butyl	C_6H_4(4-OCH_3)	Oil	76
9	**11i**	*t*-Butyl	1,2,4-Triazol-3-yl	91	57
10	**11j**	*t*-Butyl	Benzothiazol-2-yl	82	47
11	**11k**	*n*-Propyl	C_6H_4(4-CH_3)	Oil	84
12	**11l**	*n*-Propyl	C_6H_4(4-OCH_3)	Oil	92
13	**11m**	*n*-Propyl	1,2,4-Triazol-3-yl	Oil	65
14	**11n**	*n*-Propyl	Benzothiazol-2-yl	Oil	71
15	**11o**	*n*-Propyl	C_6H_4(4-Cl)	Oil	96
16	**11p**	C_6H_5	1,2,4-Triazol-3-yl	109	91
17	**11q**	C_6H_5	C_6H_4(4-Cl)	Oil	46
18	**11r**	C_6H_5	C_6H_4(4-OCH_3)	Oil	83
19	**11s**	C_6H_5	Benzothiazol-2-yl	Oil	72

[a] Yields: either isolated yields (solid) by crystallization or isolated yields (oil) by flash chromatography.

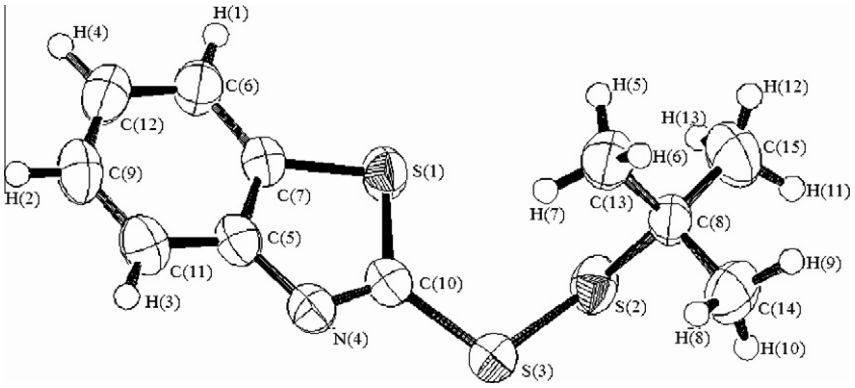


Figure 1. ORTEP plots of prepared unsymmetric disulfide **11j**.

byproducts were produced from the reaction through the cyclic process involving the intermediates.

2. General procedure for the synthesis of unsymmetric disulfides 11

2.1. Step 1: The preparation of the sulfenyl chloride 7

Method A: To a solution of the thiol **5** (1.0 mmol) in tetrahydrofuran (THF) (5.0 mL) at 0 °C under ice-bath was added slowly SO_2Cl_2 (1.65 mmol). The reaction mixture was stirred for 1 h at the same temperature. This solution was used immediately in the next step.

Method B: To a solution of the disulfides **6** (0.5 mmol) in THF (5.0 mL) at 0 °C under ice-bath was added dropwise SO_2Cl_2 (0.55 mmol). The reaction mixture was stirred for 30 min at the same temperature and the resulted solution was used immediately in the next step.

2.2. Step 2: The preparation of the unsymmetric disulfides 11

To a solution of the thiol **10** (1.0 mmol), triethylamine (2.2 mmol) and water (10 mmol) in THF (4.0 mL) at room temperature was added the pre-prepared solution of sulfenyl chloride (1.0 mmol) dissolved in THF while stirring. The reaction mixture was stirred for 1–6 h at room temperature. The reaction progress was monitored by TLC. The reaction mixture was diluted with methylene chloride (20 mL), washed sequentially with aqueous saturated $NaHCO_3$ solution and water and then dried over anhydrous $MgSO_4$. The solvent was removed by evaporation, and the residue was purified by flash chromatography on silica gel to obtain the corresponding unsymmetric disufide **11**.

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Supplementary data

The ^{1}H NMR, ^{13}C NMR and HRMS data for all the prepared compounds, experimental procedure for preparation of the unsymmetric disulfide **1** (Scheme 3). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.042.

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28. Crystallographic data of compound **11j**: $C_{11}H_{13}NS_3$, MW = 255.41, triclinic, space group $P\bar{1}(\#2)$; a = 5.9806(9), b = 9.526(2), c = 11.421(2) Å, α = 83.223°, β = 79.387°, γ = 77.541°, V = 622.4 Å^3, Z = 2, D_c = 1.363 g/cm^3, $F(0\,0\,0)$ = 268.00, μ(Mo-Kα) = 5.62 cm^{-1}, crystal dimensions 0.30 × 0.20 × 0.10 mm was used for measurement on Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-Kα radiation. $I > 2\sigma(I)$. Final indices: R_1 = 0.049, wR_2 = 0.158. The crystal structure of compound **11j** was solved by direct method SIR92 (Altomare, 1994) and expanded using difference Fourier technique, refined by the program SHELXL-97 (Sheldrick, 1997) and the Full-matrix least-squares on F^2 calculations.