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An efficient and convenient synthesis of unsymmetrical disulfides from thioacetates

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ABSTRACT

We have developed convenient methods for the synthesis of functionalized unsymmetrical dialkyl disulfides under mild conditions in very good yields. The designed method is based on the reaction of (5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)-disulfanyl derivatives **1** with functionalized alkyl thiolate anions, generated in situ from thioacetates **2** and sodium methoxide or butylamine. The developed method allows the preparation of unsymmetrical disulfides bearing additional hydroxy, carboxy, amino, azido, biotin, or maleimide functionalities.

The synthesis of unsymmetrical disulfides is an important transformation in modern organic synthesis and medicinal chemistry.[1] The recent developments in disulfide bond formation have been reviewed.[2] Disulfides have also been used for the preparation of self-assembled monolayers (SAMs)[3] and monolayer-protected clusters (MPCs) with a number of versatile properties.[4]

Thioesters are readily available from alcohol, alkyl halide, or alkene derivatives,[5] and traditionally are converted into the corresponding thiols. Deprotection of the thiol group by removal of the acyl group can occur under basic, acidic, or neutral conditions. However, the formation of symmetrical disulfides, instead of the expected thiol, is observed very frequently when deprotection is performed under basic conditions, when open to the atmosphere or when solvent with dissolved oxygen from air is used.[6]

Thiols are relatively labile under ambient atmosphere and thus a transformation is highly desired in which protected thiols can be directly converted into disulfides, especially unsymmetrical examples. Convenient one-pot syntheses of symmetrical disulfides from thioacetates by nickel boride catalyzed methanolysis and disproportionation,[7] hydrolysis catalyzed by sodium azide[6b] or treatment with alkoxystannanes and ferric chloride[8] have been reported. Treatment of thiobenzoates with piperidine[9] or samarium diiodide[10] can also afford symmetrical disulfides. Much more interesting from the synthetic point of view is the direct conversion of thioesters into unsymmetrical disulfides. Cosstick and co-workers have presented the preparation of *S*-nucleosidyl *S*-aryl disulfides[11] from the corresponding *S*-nucleosidyl thiobenzoates.

We have previously demonstrated the preparation of functionalized unsymmetrical molecules such as dialkyl disulfides, alkyl-aryl disulfides,[12] 'bioresistant' disulfides,[13] unsymmetrical disulfides of L-cysteine and L-cystine,[14] and diaryl disulfides[15] based on the readily available 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane-2-disulfanyl derivatives **1**. These disulfanyl derivatives **1** of phosphorodithioic acid were also convenient for the preparation of α-sulfenylated carbonyl compounds,[16] and symmetrical[17] and unsymmetrical[18] trisulfides. In continuation of our interest in using disulfanyl derivatives **1** of phosphorodithioic acid for the preparation of functionalized unsymmetrical disulfides, herein we report an efficient and convenient synthesis of unsymmetrical disulfides directly from thioacetates (Table 1).

The idea is based on the chemoselective deprotection of thioacetates with sodium methoxide (method A, Table 1) or butylamine (method B, Table 1) in the presence of disulfanyl derivatives **1**. The generated thiolate anion reacts quickly with electrophilic disulfanyl derivative **1** to produce the corresponding functionalized unsymmetrical disulfide **3**. We have found that the use of a small excess of compound **1** (1.05 equiv) was required to avoid potential disulfide–thiol exchange and formation of symmetrical disulfides. This is important, especially in the case when the symmetrical product cannot be separated from the unsymmetrical derivative by column chromatography.

Under the optimized reaction conditions, the scope and generality of the disulfide formation were explored (Table 1).[19] In general, the yields of the unsymmetrical dialkyl disulfides **3** were

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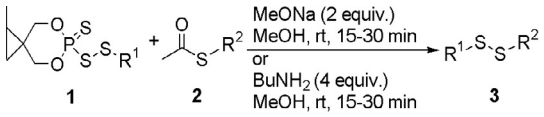
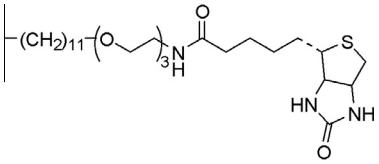
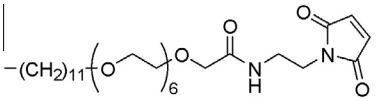
Table 1
Reaction of disulfanyl derivatives **1** with thioacetates **2**[a]



1 **2** **3**

Entry	R^1	**1**	R^2	**2**	Product	Yield[b] (%)	
						Method A	Method B
1	$(CH_2)_{11}CH_3$	**1a**	$(CH_2)_{11}OH$	**2a**	**3a**	86	92
2	$(CH_2)_{11}CH_3$	**1a**	$(CH_2)_{11}NHBoc$	**2b**	**3b**	91	95
3	$(CH_2)_{11}CH_3$	**1a**	$(CH_2)_{10}CO_2H$	**2c**	**3c**	92	94
4	$(CH_2)_{11}OH$	**1b**	$(CH_2)_{11}CH_3$	**2d**	**3a**	87	94
5	$(CH_2)_{11}NHBoc$	**1c**	$(CH_2)_{11}CH_3$	**2d**	**3b**	89	93
6	$(CH_2)_{10}CO_2H$	**1d**	$(CH_2)_{11}CH_3$	**2d**	**3c**	89	91
7	$(CH_2)_{11}N_3$	**1e**	$(CH_2)_{11}OH$	**2a**	**3d**	90	92
8	Ph	**1f**	$(CH_2)_{11}(OCH_2CH_2)_3OH$	**2e**	**3e**	65	70
9	$(CH_2)_{11}(OCH_2CH_2)_3OH$	**1g**	$(CH_2)_{11}(OCH_2CH_2)_6OH$	**2f**	**3f**	95	97
10	$(CH_2)_{11}(OCH_2CH_2)_3OH$	**1g**	$(CH_2)_{11}(OCH_2CH_2)_6OCH_2CO_2H$	**2g**	**3g**	85	89
11	$(CH_2)_{11}(OCH_2CH_2)_3OH$	**1g**		**2h**	**3h**	89	.92
12	$(CH_2)_{11}(OCH_2CH_2)_3OH$	**1g**		**2i**	**3i**	65	—
13	$(CH_2)_{11}OH$	**1b**	$(CH_2)_{10}CHO$	**2j**	**3j**	74	—

[a] Conditions. Method A: **1** (1.05 mmol), **2** (1.0 mmol), MeONa (2.0 mmol), MeOH (20 mL), 0 °C then rt, 15–30 min, under nitrogen. Method B: **1** (1.05 mmol), **2** (1.0 mmol), $BuNH_2$ (4.0 mmol), MeOH (20 mL), 0 °C then rt, 15–30 min, under nitrogen.
[b] Isolated yield based on **2**.

very high. Functional groups such as hydroxy, carboxy, azido, or Boc-protected amino were very well tolerated. Protection of the amino group was recommended to avoid potential acetyl transfer from thioacetates **2**. As shown in Table 1, the same unsymmetrical disulfide **3** can be obtained in two different ways. For example, **3a** can be prepared from **1a** and **2a** (entry 1), or from **1b** and **2d** (entry 4). Both approaches gave product **3a** in very good yield (Table 1). However, the formation of aryl alkyl disulfide **3e** was accomplished in moderate yield. It seems that the versatility of the method is limited by a very fast thiol–disulfide exchange reaction in the case of aryl alkyl disulfides. Probably, aromatic groups can promote this side reaction because the arylthiolate anion is a very good leaving group, and the generated thiolates from thioacetates **2** can react with either disulfanyl derivatives **1** or unsymmetrical product **3** to produce symmetrical disulfides.

To further explore the scope of the reaction, thioacetates **2i,j** were employed in reactions with **1g** and **1b**, respectively (Table 1, entries 12 and 13). In these cases only method A could be applied because butylamine can react with the aldehyde or maleimide groups in the starting materials **2i,j** or products **3i,j**. Under the optimized reaction conditions (method A), both thioacetates **2i** and **2j** provided unsymmetrical disulfides **3i** and **3j**, respectively, in moderate yields. The corresponding thiols from deprotection of **2i** and **2j** could not be isolated due to the reaction of the thiol group with the aldehyde[20] or maleimide[21] functionalities. Although these thiols cannot be isolated, their formation in the reaction mixture and reaction with electrophilic disulfanyl derivatives **1** to produce disulfides **3i,j** can be accomplished. It appears that the reaction of the generated thiolate from thioacetates **2i,j** is faster with disulfanyl derivatives **1** than with aldehyde or maleimide functionalities. A major advantage of the developed method is the possibility of disulfide bond formation in the presence of functionalities that are highly reactive toward thiol groups.

In summary, we have developed efficient and convenient methods for the preparation of unsymmetrical dialkyl disulfides **3** bearing hydroxy, carboxy, amino, azido, biotin, or maleimide functionalities. Reactions of **1** with various thioacetates **2** in the presence of sodium methoxide or butylamine in methanol at room temperature were generally complete within 30 min, and gave unsymmetrical dialkyl disulfides **3** exclusively, in good or very good yields after isolation. Since the reactions of thioacetates **2** proceeded with a small excess of **1** under mild reaction conditions in a short time, thiol–disulfide exchange did not occur during the reaction. The simplicity and good yields should make this method an attractive approach for the preparation of functionalized unsymmetrical dialkyl disulfides, especially when the presence of functionalities highly reactive toward thiol groups cannot be avoided.

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Supplementary data

Supplementary data (experimental details and spectroscopic data for all compounds **3**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.056.

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19. *Method A.* A solution of MeONa (2.0 mmol) in dry MeOH (2 mL) was added to a solution of **1e** (447 mg, 1.05 mmol) and **2a** (246 mg, 1.0 mmol) in dry MeOH (20 mL) at 0 °C under an N_2 atmosphere. The ice bath was removed and the mixture was stirred for 15–30 min at rt. The progress of the reaction was monitored by TLC. The volatiles were removed under vacuum and the residue was purified by column chromatography (silica gel, CH_2Cl_2) to give **3d** as a colorless oil; yield: 388 mg (90%). All compounds were characterized by means of IR, ^{1}H NMR, ^{13}C NMR, and HRMS. Compound **3d**: IR (KBr): ν = 3413 (m), (OH), 2921 (s), 2851 (s), 2098 (m), (N_3), 1055, (m), 720 (w) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.64 (t, J = 6.5 Hz, OCH_2, 2H), 3.28 (t, J = 7.1 Hz, CH_2N_3, 2H), 2.69 (t, J = 7.3 Hz, SCH_2, 4H), 1.50–1.76 (m, CH_2, OH, 5H), 1.20–1.48 (m, CH_2, 32H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 63.0, 51.5, 39.2, 32.7, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 28.5, 28.6, 25.6, 22.8. Signals: expected, 22; observed, 14. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{22}H_{46}N_3OS_2$: 432.3082; found: 432.3084. *Method B.* A solution of *n*-butylamine (290 mg, 0.4 mL, 4.0 mmol) in dry MeOH (2 mL) was added to a solution of **1e** (447 mg, 1.05 mmol) and **2a** (246 mg, 1.0 mmol) in dry MeOH (20 mL) at 0 °C under an N_2 atmosphere. The ice bath was removed and the mixture was stirred for 15–30 min at rt. The progress of the reaction was monitored by TLC. After evaporation of the volatiles under reduced pressure, the residue was purified by column chromatography on a silica gel column to yield **3d** as a colorless oil; 397 mg (92%).
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