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Graphical Abstract

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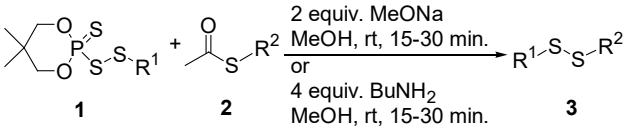

Efficient and convenient synthesis of unsymmetrical disulfides from thioacetates

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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 anion generated *in situ* from thioacetates **2** and sodium methoxide or butylamine. Developed method allows preparation of unsymmetrical disulfides bearing the 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 to the corresponding thiols. Deprotection of 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 the transformation is highly desired in which protected thiols can be directly converted to disulfides, especially unsymmetrical ones. A convenient one-pot synthesis of symmetrical disulfides from thioacetates by nickel boride catalyzed methanolysis and dispropotionation[7] or hydrolysis catalyzed by sodium azide[6b] or treatment with alkoxystannanes and ferric chloride[8] have been reported. The 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] symmetrical[17] and unsymmetrical[18] trisulfides. In continuation of our interest in using of disulfanyl derivatives **1** of phosphorodithioic acid for 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**. Generated thiolate anion reacts quickly with electrophilic disulfanyl derivative **1** to produce appropriate functionalized unsymmetrical disulfide **3**. We have noticed that small excess of compound **1** (1.05 equiv.) is required to avoid potential disulfide-thiol exchange reaction and formation of symmetrical disulfides. It is important especially in the case, when symmetrical product can not be separated from unsymmetrical on chromatography column.

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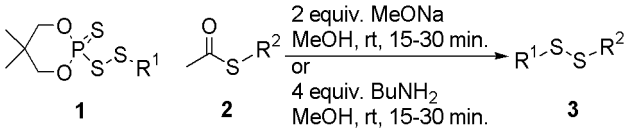
Table 1. Reaction of disulfanyl derivatives **1** with thioacetates **2**[a]



1 **2** **3**

Entry	R^1	**1**	R^2	**2**	Product **3**	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	$(CH_2)_{11}EG_3OH$	**1g**	$(CH_2)_{11}(OCH_2CH_2)_6OH$	**2f**	**3f**	95	97
10	$(CH_2)_{11}EG_3OH$	**1g**	$(CH_2)_{11}(OCH_2CH_2)_6OCH_2CO_2H$	**2g**	**3g**	85	89
11	$(CH_2)_{11}EG_3OH$	**1g**	$(CH_2)_{11}(OCH_2CH_2)_3NH$-Biotin	**2h**	**3h**	89	92
12	$(CH_2)_{11}EG_3OH$	**1g**	$(CH_2)_{11}(OCH_2CH_2)_6OCH_2CONH(CH_2)_2$Maleimide	**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), 0ºC 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), 0ºC then rt, 15-30 min., under nitrogen.

[b] Isolated yield based on **2**.

Under the optimized reaction conditions, the scope and generality of the disulfide formation were explored (Table 1).[19] General, yields of the unsymmetrical dialkyl disulfides **3** are very high. Functional groups such as hydroxyl, carboxyl, azido or Boc protected amino were very well tolerated under developed conditions. The protection of amino group is 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 with moderate yield. It seems that the versatility of the method is limited by 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, so 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 to react with **1g** and **1b** respectively (entries 12 and 13, Table 1). In these cases only method A can be applied because butylamine can react with 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 with good yield. As can be seen corresponding thiols from deprotection **2i** and **2j** can not be isolated due to the reaction of thiol group with aldehyde [20] or maleimide [21] functionalities. Although these thiols can not be isolated, their formation in the reaction mixture and reaction with electrophilic disulfanyl derivatives **1** to produce disulfides **3i-j** can be accomplished. It looks like the reaction of generated thiolate from thioacetate **2i-j** is faster with disulfanyl derivatives **1** than with aldehyde or maleimide functionalities respectively. It seems that the major advantage of developed method is the possibility of disulfide bond formation in the presence of highly reactive functionalities towards thiol group.

In summary, we have developed an efficient and convenient methods for the preparation of unsymmetrical dialkyl disulfides **3** bearing the additional hydroxy, carboxy, amino, azido, biotin or maleimide functionalities. Reactions of **1** with variety of **2** in the presence of sodium methoxide or butylamine in methanol at room temperature were generally complete within 30 minutes and gave unsymmetrical dialkyl disulfides **3** exclusively in good or very good yield after isolation. Since the reactions of the 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 very good yields make this method one of the most attractive approaches to the preparation of functionalized unsymmetrical dialkyl disulfides especially when the presence of highly reactive functionalities towards thiol group can not be avoided.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article consisting of experimental details and spectroscopic data for all compounds **3** are available in the online version.

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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 ºC under a N_2 atmosphere. Then, the ice bath was removed, and the mixture was stirred for 15-30 min at r.t. The progress of the reaction was controlled 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 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 ºC under a N_2 atmosphere. Then, the ice bath was removed, and the mixture was stirred for 15-30 min at r.t. The progress of the reaction was controlled 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 colorless oil; 397 mg (92%).
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