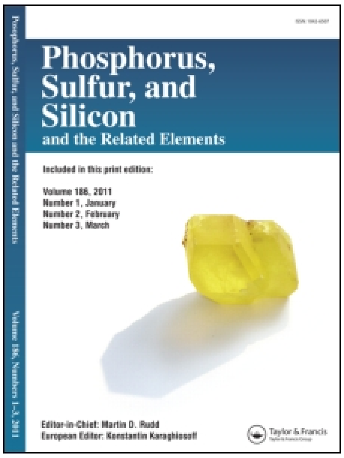

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The Organophosphorus Sulfenyl Bromides as Versatile Reagents for Cysteine Derivatives Functionalization by Unsymmetrical Disulfide Bond Formation

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We have developed a convenient method for the synthesis of L-cysteine unsymmetrical disulfides under mild conditions with good to excellent yields. Described method is based on the straightforward preparation of the organophosphorus sulfenyl bromide readily available from bis-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) disulfide. The unsymmetrical disulfides can be obtained for L-cysteine derivatives and thiols bearing neutral or acidic functionalities.

Keywords L-cysteine; sulfenyl bromide; thiols; unsymmetrical disulfides

INTRODUCTION

Recently, we have discovered that readily available S-thioacyl dithiophosphates are excellent thioacylating agents. These mixed anhydrides chemoselectively thioacylated nitrogen or sulfur nucleophiles in the presence of hydroxyl groups. That property allowed to obtained hydroxythioamides, hydroxydithioesters, and thiohydroxamic acids as well, from nonprotected substrates on oxygen atom.[1–4] We were encouraged by those results, so we decided to design a synthetic strategy for preparation of unsymmetrical disulfides based on the mixed anhydrides of dithiophosphoric acids. Disulfides are important compounds for both chemical and biological processes.[5,6] There are many biologically active L-cysteine derivatives, peptides and peptide mimetics possess unsymmetrical disulfide bonds.[7] The new efficient strategy for preparation of L-cysteine unsymmetrical disulfides is based on the organophosphorus

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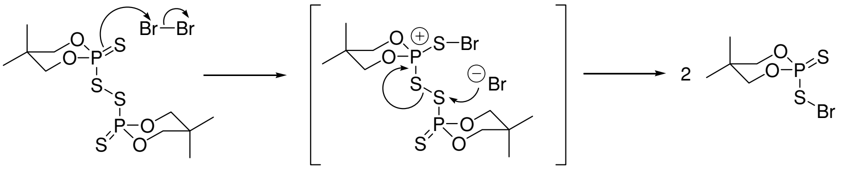
sulfenyl bromides, mixed anhydrides of dithiophosphoric acid, and hydrobromic acid as activating agents for unsymmetrical disulfide bond formation.

RESULTS

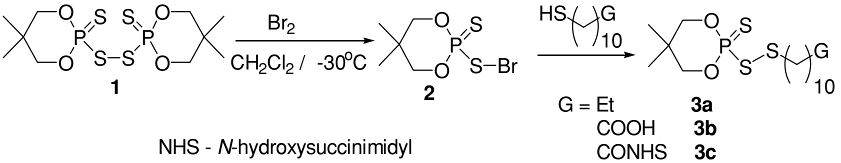
The stable and readily available bis-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) disulfide **1**[8] was treated with bromine at −30°C to afford quantitatively (5,5-dimethyl-2-thiono-1,3,2-dioxophosphorinanyl) sulfenyl bromide **2**.[9–10] The mechanism of formation of compound **2** is presented in Scheme 1.



SCHEME 1 The formation mechanism of sulfenyl bromide 2.

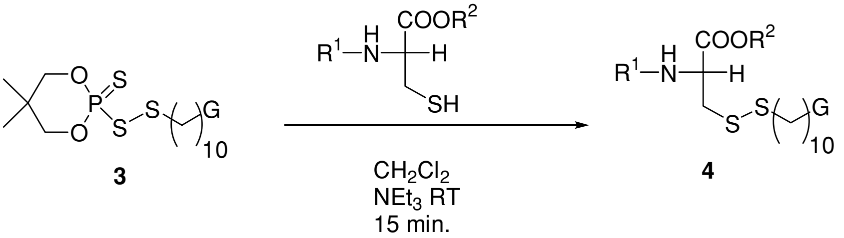
The organophosphorus sulfenyl bromide **2** was unstable at room temperature and upon isolation afforded mainly 5,5-dimethyl-2-thiono-1,3,2-dioxophosphorinanyl bromide.

When sulfenyl bromide **2** was treated at −30°C without isolation with a 1-dodecanethiol, 11-mercaptoundecanoic acid, or *N*-hydroxysuccinimidyl 11-mercaptoundecanoate, then the 5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl-2-disulfanylderivatives **3a–c** were isolated with 100, 92 and 96% yield, respectively (Scheme 2).



SCHEME 2 The synthesis of 5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl-2-disulfanylderivatives 3

The compounds **3a–c** were treated with variety of L-cysteine derivatives to examine the scope and limitation for the designed method of preparation compounds **4** (Scheme 3). The results are summarized in Table I.



SCHEME 3 The reaction of L-cysteine derivatives with compounds 3.

DISCUSSION

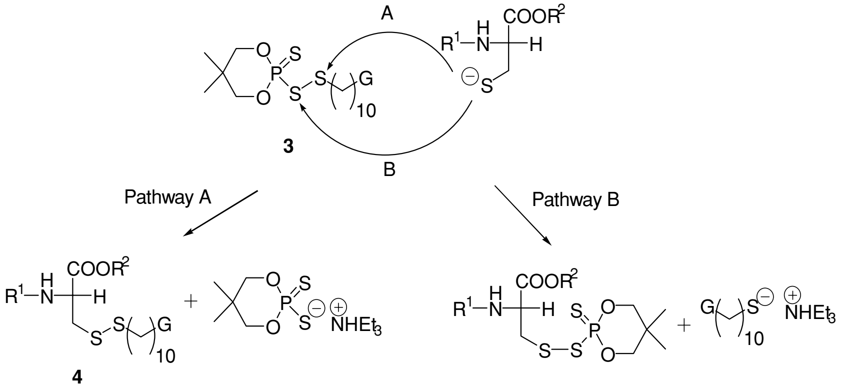
The reaction of sulfenyl bromide **2** with 1-dodecanethiol afforded disulfanyl derivative **3a** with excellent yield and the formation of HBr as the side product was observed. However, the same reaction in the presence of NEt_3 gave di-dodecyl disulfide (symmetrical disulfide) as major product (98%) and formation of compound **3a** was not observed. Moreover, the reaction of disulfanyl derivative **3a** did not occur with Ac-Cys in the absence of NEt_3 and after several hours only traces of unsymmetrical disulfide **4a** were detected by TLC in the reaction mixture. When NEt_3 was added to the reaction mixture, then reaction was accomplished in 15 minutes to afford unsymmetrical disulfide **4a** exclusively. All these observations confirmed reported S_N2-S type mechanism for disulfide exchange reaction where acidic conditions slow down process and basic conditions speed up by increasing amount of thiolate anion in the reaction mixture. From this point of view, the preparation of disulfanyl derivatives **3** has to be performed in the acidic conditions to minimize symmetrical disulfide formation. On other hand, further reaction of

TABLE I The Synthesis of Unsymmetrical Disulfides of L-cysteine Derivatives 4

Run		G	R^1	R^2		Yield (%)
1.	**3a**	Et	Ac	H	**4a**	99
2.	**3b**	COOH	Ac	H	**4b**	96
3.	**3c**	CONHS	Ac	H	**4c**	90
4.	**3a**	Et	H	Et	**4d**	98
5.	**3b**	COOH	H	Et	**4e**	97
6.	**3a**	Et	Boc	Et	**4f**	99
7.	**3b**	COOH	Boc	Et	**4g**	95
8.	**3c**	CONHS	Boc	Et	**4h**	97

Ac = acetyl; and Boc = t-butoxycarbonyl.

compounds **3** with cysteine derivatives to afford unsymmetrical disulfide **4** should be performed in the basic conditions. From the theoretical point of view, the thiolate anion from cysteine can attack both sulfur atoms in the disulfanyl derivative **3**. All these possibilities are presented in Scheme 4 (Pathway A and B).



SCHEME 4 The reaction of disulfanyl derivative 3 with cysteine nucleophile.

The success of the method (Scheme 4, Pathway A) depends on the selective reactivity of 5,5-dimethyl-2-thiono-1,3,2-dioxophosphorinanyl-2-disulfanyl derivatives **3** toward cysteine derivatives to afford exclusively unsymmetrical disulfides **4**. The observed selectivity emerged from excellent leaving group property for dithiophosphate anion (pK_a 2 for corresponding acid). This property is crucial for the short time required for the transformation and minimizes further disulfide exchange between product **4** and used cysteine derivative.

In conclusion, a convenient, versatile, functionalization method of cysteine derivatives by unsymmetrical disulfide bond formation has been developed. Simple procedure combined with excellent yields make this method an attractive alternative to other reported procedures.

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