

Diastereoselective Michael additions to α,β -unsaturated α -sulfinyl phosphonates in the thiolane series

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Abstract—A chiral racemic 2-phosphono-2,3-didehydrothiolane sulfoxide was used as a Michael acceptor in the reactions with several nucleophiles, in particular thiols. In most cases the reactions were fully diastereoselective. The relative configuration of the resulting adducts was determined.

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Chiral α,β -unsaturated sulfoxides **A** (Fig. 1) are versatile chiral partners in Michael addition reactions, which are known for their numerous applications in asymmetric syntheses.¹ Various structures have been described, however, new stereoselective routes to synthesize original structures are still investigated. In a previous paper,² some of us reported the synthesis of 2-phosphono-2,3-didehydrothiolane sulfoxides **C**, which are cyclic analogs of known α -sulfinylvinylphosphonates **B**.³

While chiral compounds **B** were already used as intermediates in asymmetric syntheses, in particular in cycloadditions, cyclopropanations, and Michael additions,⁴

compounds of type **C** have never been studied and used to this end. Due to the double activation of the C–C double bond by both phosphonyl and sulfinyl groups, and to the particular geometry of the unsaturated five-membered ring, 2-phosphono-2,3-didehydrothiolane sulfoxides **C** represent interesting substrates for stereoselective reactions. This paper describes our results on the Michael addition of several nucleophiles, in particular thiols, to cyclic vinyl sulfoxide of type **C**.

We selected for this study thiolane *S*-oxide **1** containing the 5,5-dimethyl-1,3,2-dioxaphosphorinane moiety, as a model substrate. This compound was easily prepared in racemic form by oxidation of the corresponding sulfide using NaIO₄ as an oxidizing agent.² The analysis by X-ray diffraction of a single crystal of **1**, revealed that the didehydrothiolane ring is quasi-planar, with the

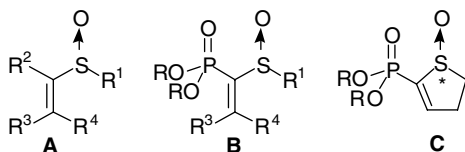
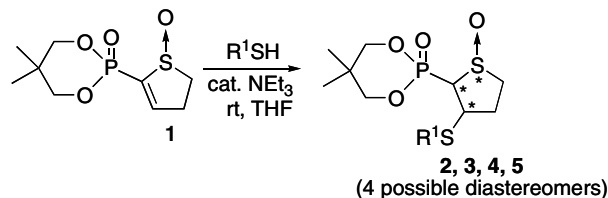


Figure 1.

Keywords: Chiral sulfoxide; α -Sulfinylphosphonates; Phosphonothiolanes; Diastereoselective Michael additions.

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Scheme 1.

double bond having obviously a *Z* geometry and the S=O bond quasi-perpendicular to the ring (torsional angles: $\Phi[\text{O1 S1 C2 C3}] = 90.3^\circ$; $\Phi[\text{O1 S1 C5 C4}] = 81.1^\circ$).²

The addition reactions were performed with racemic substrate **1**. We started the study using thiols as nucleophiles (Scheme 1). The reactions were carried out at room temperature, in THF, in the presence of a catalytic amount of a base (0.1 equiv of NEt_3).⁵ The experimental results obtained with four selected thiols: thiophenol ($\text{R}^1 = \text{Ph}$), thiocresol ($\text{R}^1 = 4\text{-Tol}$), hexanethiol ($\text{R}^1 = n\text{-Hex}$), and *tert*-butanethiol ($\text{R}^1 = t\text{-Bu}$), are listed in Table 1. The reactions were monitored by TLC and stopped after completion. The reactions were faster with the two aromatic thiols, which are the more acidic derivatives.⁶ In each case, the diastereomeric ratio was determined by ^{31}P NMR of the crude mixture. With three thiols (thiophenol, thiocresol, and *tert*-butanethiol), the reactions were fully diastereoselective, leading to adducts **2**, **3**, and **5**, respectively, as a single diastereomer. In contrast, hexanethiol adduct **4** was obtained as a mixture of two diastereomers in a 2/1 ratio, which were separable by column chromatography. All adducts were obtained in good yields, after purification by simple precipitation in ether.

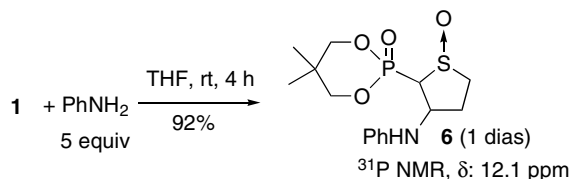
We then examined the Michael addition of aniline and diethylmalonate, a nitrogen and a carbon nucleophile, respectively, to vinyl sulfoxide **1**. The reaction with aniline did not require the addition of an external base (NEt_3), and was carried out using an excess of the nucleophile (5 equiv), in THF, at room temperature

Table 1. Michael additions of thiols to **1**

R^1	Adduct (<i>n</i> dias) ^a	^{31}P NMR, δ (ppm)	Reaction time	Isolated yield (%)
Ph	2 (1)	13.3	1 min	87
4-Tol	3 (1)	13.4	10 min	89
<i>n</i> -Hex	4 (2, 2/1 ^b)	13.9/11.0	3 h	78
<i>t</i> -Bu	5 (1)	13.5	4 h	74

^a Number of diastereomers determined by ^{31}P NMR.

^b Diastereomeric ratio determined by ^{31}P NMR.



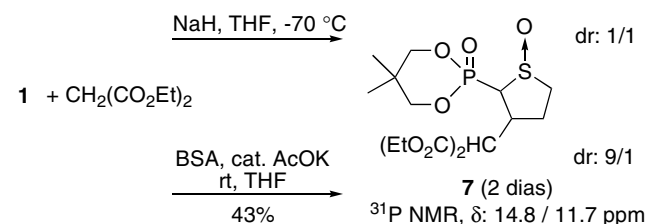
Scheme 2.

(Scheme 2). After completion (4 h), the product precipitated from the reaction solution. Aniline adduct **6** was obtained with a high diastereoselectivity (*de* > 98%), as measured by ^{31}P NMR.

When sodium malonate was added to **1** (using diethylmalonate and NaH , in THF, at -70°C), the crude mixture, analyzed by ^{31}P NMR, showed the formation of two diastereomeric adducts **7** in a 1/1 ratio, having phosphorus chemical shifts at 14.8 and 11.7 ppm, together with other unidentified by-products. In the second experiment, the malonate carbanion was generated using bis-trimethylsilylacetamide (BSA) and a catalytic amount of AcOK (Scheme 3). The two main products observed in the first experiment were also formed under these conditions, but in a 9/1 ratio (the major product at 14.8 ppm), and the reaction proceeded cleanly, without the formation of by-products. After purification by chromatography on silica gel using $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (30/1) as the eluent, the main product was characterized and identified as one of the diastereomers of adduct **7**.

We then turned our attention to the stereochemical outcome of the reaction. According to literature suggestions, acyclic vinyl sulfoxides can adopt three reactive conformations which are favored during their reactions with nucleophiles: *s*-cis and *eclipsed lone pair* conformations, in the case of (*E*) vinyl sulfoxides,⁷ and *s*-trans conformation, in the case of (*Z*) vinyl sulfoxides (Fig. 2).⁸ By assuming involvement of such conformations it was possible to explain the stereochemical outcome of the Michael addition of various nucleophiles (carbanions,⁹ C-radicals,¹⁰ amines,¹¹ alkoxides,¹² silylates,¹³ thiolates^{3,14,15}) to acyclic vinyl sulfoxides.

In our case, the peculiar geometric characteristics of the thiolane-oxide (didehydrothiolane ring quasi-planar, with the double bond having a *Z* geometry and the S=O bond quasi-perpendicular to the ring) do not allow the extrapolation of any of the three models mentioned



Scheme 3.

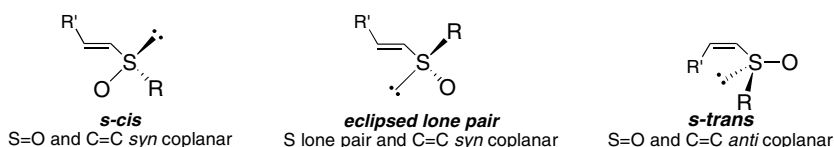


Figure 2. Reactive conformations for (*E*) and (*Z*) acyclic vinyl sulfoxides.

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