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# 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.


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**.

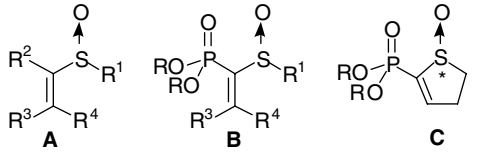
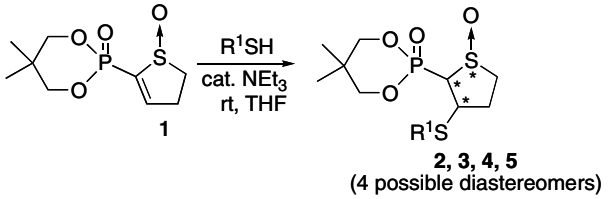



**Figure 1.**

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 $NaIO_4$ 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




**Scheme 1.**

*Keywords*: Chiral sulfoxide; α-Sulfinylphosphonates; Phosphonothiolanes; Diastereoselective Michael additions.
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double bond having obviously a *Z* geometry and the S=O bond quasi-perpendicular to the ring (torsional angles: $\Phi$[O1 S1 C2 C3] = 90.3°; $\Phi$[O1 S1 C5 C4] = 81.1°).[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 ($R^1$ = Ph), thiocresol ($R^1$ = 4-Tol), hexanethiol ($R^1$ = *n*-Hex), and *tert*-butanethiol ($R^1$ = *t*-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 (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 $CH_2Cl_2$/MeOH (30/1) as the eluent, the main product was characterized and identified as one of the diastereomers of adduct **7**.

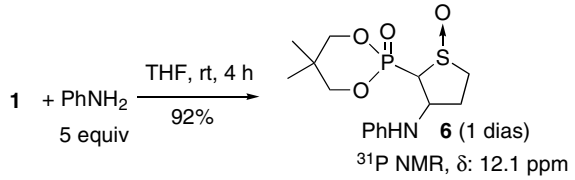
We then turned our attention to the stereochemical outcome of the reaction. According to literature suggestions, acyclic vinyl sulfoxides can adopt three reactive conformations which are favored during their reactions with nucleophiles: *s*-cis and *eclipsed lone pair* conformations, in the case of (*E*) 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

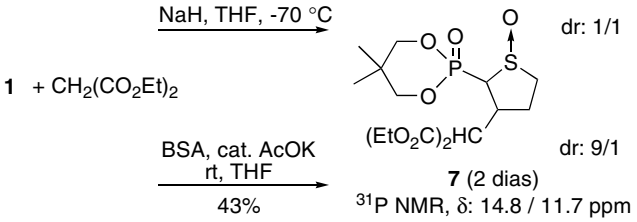
**Table 1.** Michael additions of thiols to **1**

| $R^1$ | Adduct (*n* dias)[a] | $^{31}$P NMR, $\delta$ (ppm) | Reaction time | Isolated yield (%) |
|---|---|---|---|---|
| Ph | **2** (1) | 13.3 | 1 min | 87 |
| 4-Tol | **3** (1) | 13.4 | 10 min | 89 |
| *n*-Hex | **4** (2, 2/1[b]) | 13.9/11.0 | 3 h | 78 |
| *t*-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 3.

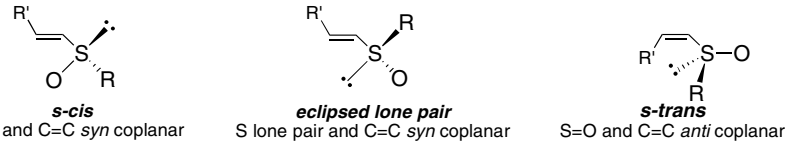
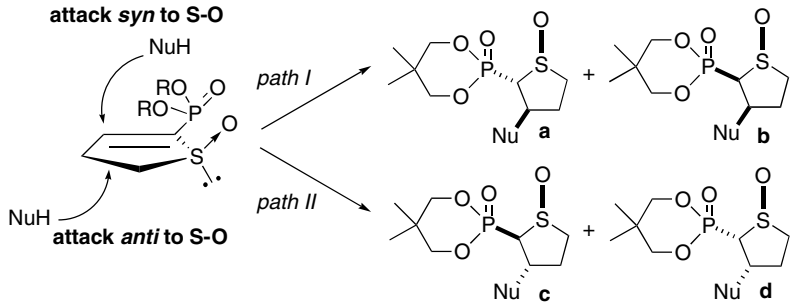



**Figure 2.** Reactive conformations for (*E*) and (*Z*) acyclic vinyl sulfoxides.




**Scheme 4.**

above to rationalize the stereochemical outcome of the reaction.

The nucleophilic attack at the cyclic derivative can only occur *syn* or *anti* to the S=O group, thus leading to two possible diastereomers, **a** or **b** in the *syn* attack and **c** or **d**, in the *anti* attack (Scheme 4).

To gain information on the relative configuration of the products, a detailed NMR study[16] of thiophenol adduct **2** was undertaken. These NMR data undoubtedly revealed that the phosphoryl and the phenylsulfanyl groups are trans to each other. The coupling constant between $H^{2'}$ and $H^{3}$ ($J = 7.2$ Hz), indicates that these protons are in trans relation, and the NOESY and the coupling constant between $H^{2'}$ and $H^{5'}$ ($J = 1.1$ Hz) indicate that these protons are in an equatorial–equatorial relation (Fig. 3).

Although both structures **a** and **c** can have this stereochemical arrangement, diastereomer **a**, in which the phosphoryl group is located trans to the phenylsulfanyl group and trans to the sulfinyl oxygen atom, is supposed to be thermodynamically more stable. To support this hypothesis, the relative energies for the four possible diastereomers **a**–**d** were estimated by theoretical calculations. Both Hartree-Fock (6-31G*) and hybrid density functional (B3LYP/6-31+G*) level of theory were used and performed with Spartan software.[17] To avoid time consuming, we performed the calculations (structure optimization) on models **A**–**D** (Fig. 4). The structural differences between these models and the real molecules concern two points: the presence of a dimethyl phosphono ester and a methylthioether functions. Whatever the level of theory used, the results are consistent giving the lowest energy for compound **A**. These calculations are in good agreement with the experimental results. Indeed the relative configurations of **2a** (as determined by NMR experiments), and of compound **A** (with the lowest energy), are identical.

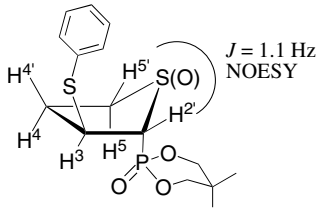
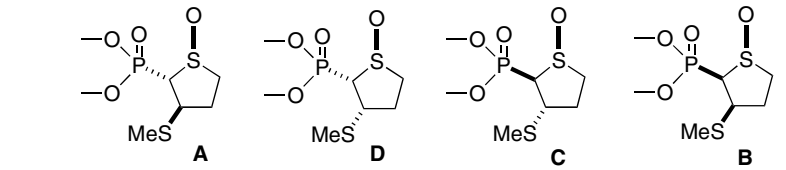



**Figure 3.**

Based on the consistency between the experimental results and calculation, we assume that adducts **2**, **3**, **4** major, **5**, **6**, and **7** major are formed under thermodynamic control (by nucleophilic attack occurring *syn* to the S=O group, as shown in Scheme 4, path I), and that their structures correspond to diastereomer **a**. Moreover, thiol adducts **2**, **3**, **4** major, and **5** display quite similar chemical shifts in $^{31}P$ NMR spectra (ranging between 13.3 and 13.9 ppm), which also suggests that these adducts have the same relative configuration. Concerning the minor diastereomer of **4**, the coupling constant between the vicinal C*H*P and C*H*SHex protons in the $^{1}H$ NMR spectra ($^{3}J_{HH} = 6.8$ Hz) suggests that these protons are in a trans arrangement,[18] which corresponds to the relative configuration of type **c**.

Trying to get more information on the diastereoselectivity, we enjoyed to isolate a single crystal (obtained after




| | A | D | C | B |
|---|---|---|---|---|
| 6-31G * | 0 | 4.3 | 6.3 | 6.8 |
| B3LYP/6-31+G * | 0 | 3.1 | 5.9 | 6.7 |

**Figure 4.** Theoretical calculation on models of compounds **4a**–**d** with HF-6-31G* and B3LYP/6-31+G* level of theory. Relative energies are expressed in kcal/mol.

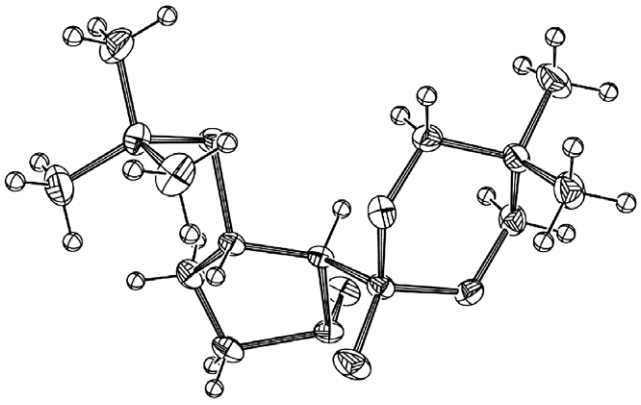


**Figure 5.** X-ray structure of **5**.

crystallization from benzene) of adduct **5**, obtained from **1** and *tert*-butanethiol and to perform its X-ray analysis[19] (Fig. 5).

The X-ray analysis revealed that the relative configuration of adduct **5** was identical with that represented by structure '**a**' (Scheme 4). The same configuration was also predicted on the basis of both NMR spectra and theoretical calculations.

In conclusion, the chiral racemic 2-phosphono-2,3-didehydrothiolane sulfoxide **1** was used as a new Michael acceptor in the reaction with several nucleophiles. In most cases the reactions were fully diastereoselective. The relative configurations of two obtained adducts were determined on the basis of the NMR data (for thiophenol adduct **2**) and X-ray analysis (for *tert*-butanethiol adduct **5**), and found to be identical. Based on theoretical calculations and NMR data, it can be assumed that the adducts obtained have the same relative configuration (phosphoryl group trans to the sulfanyl group and trans to the sulfinyl oxygen atom), which is a result of a thermodynamic control. Investigations on the asymmetric version of these Michael additions and some applications are currently in progress in our laboratories.

## Acknowledgments

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5. *Michael addition of thiophenol to* **1**. *Typical procedure*: Thiophenol (1.2 mmol) and $NEt_3$ (0.1 mmol) were added to racemic 2-phosphono-2,3-didehydrothiolane 1-oxide **1** (1 mmol), dissolved in dry THF (20 mL), at room temperature. The resulting mixture was stirred until the reaction was completed (monitored by TLC). The solvent was evaporated and the product was precipitated from the residue using $Et_2O$ to give pure adduct **2**: Yield = 87%; white solid, mp 139 °C; $^{31}$P NMR (161.9 MHz, $CDCl_3$) $\delta$ 13.2; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.99 (s, 3H, $CH_3$), 1.22 (s, 3H, $CH_3$), 2.77–2.81 (m, 2H, $CH_2$), 3.00 (m, 1H, C*H*HSO), 3.20 (m, 1H, CH*H*SO), 3.31 (ddd, $^4J_{HH} = 1.1$, $^3J_{HH} = 7.2$, $^2J_{HP} = 14.6$, 1H, PCH), 3.92–4.01 (m, 3H, PhSCH and $CH_2O$), 4.11–4.16 (m, 2H, $CH_2O$), 7.35–7.37 (m, 3H, $H^{arom}$), 7.54–7.57 (m, 2H, $H^{arom}$); $^{13}$C NMR (100.6 MHz, $CDCl_3$) 20.98 ($CH_3$), 21.69 ($CH_3$), 32.43 (d, $J = 6.8$, $(CH_3)_2C$), 34.77 (d, $J = 7.8$, $CH_2$), 48.26 (CHS), 53.29 (d, $J = 3.4$, $CH_2SO$), 68.52 (d, $J = 130.8$, PCH), 77.05 (d, $J = 6.6$, $CH_2O$), 77.33 (d, $J = 6.5$, $CH_2O$), 128.57 ($CH^{arom}$), 129.37 ($2 \times CH^{arom}$), 133.50 ($SC^{arom}$), 133.55 ($2 \times CH^{arom}$); IR (neat, $cm^{-1}$) 2969, 2894, 1582, 1475, 1270, 1055, 1006, 979, 836, 816, 746, 693; MSMS: *m*/*z* (%) 361 ($MH^+$, 22), 161 (100); HRMS calcd for $C_{15}H_{21}PO_4S_2$: 361.0697. Found: 361.0706.
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16. The following NMR experiments were done: $^{31}P$, $^{1}H$, $^{1}H\{^{31}P\}$, $^{13}C$, DEPT, COSY, NOESY, HMBC, HMQC.
17. http://www.wavefun.com.
18. By similarity with **2a** for which $^{3}J_{H2'H3} = 7.2$ Hz (in **4a** the proton signal corresponding to CHP is a multiplet).
19. The crystal structure of **5** has been registered at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 61129: $PS_2C_{13}H_{25}O_4$, $M_r = 340.42$, triclinic, $P1$, $a = 8.6925(5)$, $b = 10.7129(6)$, $c = 11.2020(6)$ Å, $\alpha = 114.582(3)$, $\beta = 110.381(4)$, $\gamma = 91.258(4)$, $V = 872.03(8)$ Å$^3$, $Z = 2$, $D_x = 1.296$ Mg m$^{-3}$, $\lambda$ (MoK$\alpha$) = 0.71073 Å, $\mu = 4.06$ cm$^{-1}$, $F(000) = 364$, $T = 150(1)$ K.