Pergamon

Tetrahedron Letters, Vol. 36, No. 42, pp. 7713-7716, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01570-1

Remarkably High Diastereoselective *Exo* Diels-Alder Reactivity of 4-Vinyl Isothiazoline-3-one-1-oxides: The Sulphoxide *Syn* effect.

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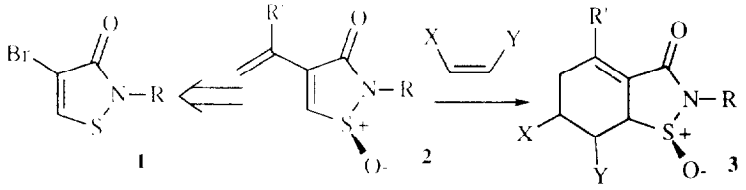
Abstract: Semi cyclic sulphoxide containing dienes, 4-vinyl-1,2-isothiazoline-3-one-1-oxides, generated *in situ via* Stille coupling methodology dimerise with remarkably high diastereoselectivity *via* an unusual *exo syn* transition state. X-ray analysis confirms the diastereoselectivity which was predicted by semi-empirical transition state calculations.

The Diels-Alder reaction remains one of the most powerful methods for the construction of cyclic systems with the potential for absolute stereochemical control at up to 4 contiguous centres in one step[1]. This control is derived from the regiochemistry, relative stereochemistry (*endo* or *exo*) and absolute stereochemistry, or facial selectivity, of the interacting diene and dienophile during the cycloaddition. The presence of sulphinyl groups on either of the cycloaddends has attracted particular attention due to their ability to induce a high degree of diastereoselectivity. Our aim was to produce a reactive homochiral diene (**2**, **Scheme 1**) utilising a sulphoxide group, to impart both reactivity and facial selectivity in the subsequent Diels-Alder chemistry to yield adducts **3**.



1 **2** **3**

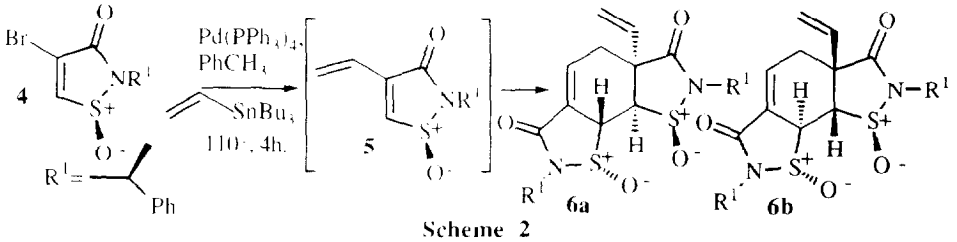
Scheme 1

Overman *et al.*[2] found semi-cyclic sulphoxide containing dienes to be strongly *anti* directing in reactions with N-phenyl maleimide. The *endo anti* selectivity was rationalised in terms of destabilising interactions between the sulphoxide oxygen and the imide carbonyl of N-phenyl maleimide in the less favoured *syn endo* transition state. In contrast, Jones *et al.*[3] found the facial selectivity of sulphoxide containing dienes reacting in the presence of Lewis acids to be *syn*. The preferred *endo syn* transition state was rationalised in terms of Lewis acid co-ordination between the sulphoxide oxygen and the ester carbonyl of the dienophile. More recently the *endo anti* selectivity of enantiomerically pure 1-p-tolylsulphinyl dienes[4] was explained using similar steric and electrostatic repulsion arguements in line with Overman's findings. The same facial selectivity occured in the presence of Lewis acids[4] which could also be explained *via* the Lewis acid co-ordination arguements proposed by Jones *et al.*[3]. Fallis discussed sulphoxide induced facial selectivity in cyclopentadienes[5] and thiophene oxide dienes[6]. The preferential addition *syn* to the sulphoxide oxygen was rationalised in terms of Cieplak's theory[7] of preferential addition *anti* to the better σ-donor.

During the course of our work directed towards the synthesis of novel homochiral Diels-Alder dienes, we identified (2-(*S*)-α-methylbenzyl)-1,2-isothiazoline-3-one-1-oxide as a highly functionalised

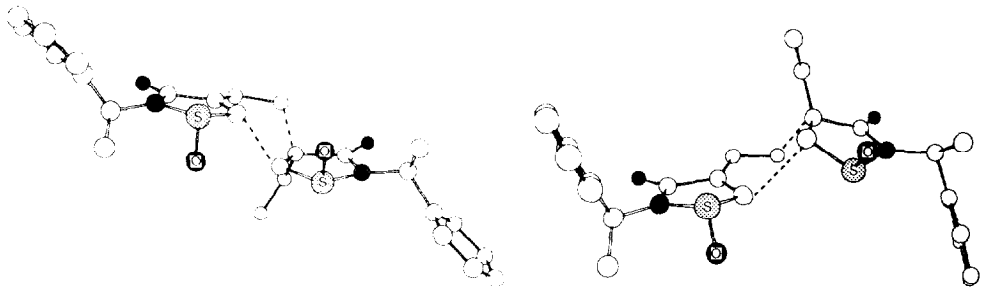
heterocycle and a potentially useful homochiral system. The isothiazoline nucleus was attractive due to its rigidity, ease of oxidation and its known Diels-Alder reactivity[8,9]. Racemic 1,2-isothiazoline-3-one-1-oxides have been successfully used as Diels-Alder dienophiles[8] and were found to be much more reactive than their unoxidised counterparts. Homochiral 1,2-isothiazoline-3-one-1-oxides[9] reacted in an *endo* fashion with azabutadienes and cyclopentene to give cycloadducts in excellent yields with excellent *anti* diastereoselectivity. Dienes **2** (**Scheme 1**) should be readily available *via* oxidation of bromides **1** followed by our previously established 4-vinylation methodology[10].

Oxidation of 2-(S)-α-methylbenzyl-4-bromo-1,2-isothiazoline-3-one with mCPBA formed two diastereoisomeric sulphoxides in the ratio 2.2 : 1. Waldner has reported X-ray data confirming the (S) chirality of the major isomer for the non brominated system[9] therefore we reasoned that the absolute stereochemistry at sulphur of the major isomer was also (S) by comparison. Additionally, calculation of the surface around the sulphur atom accessible to oxidation using a sphere probe of radius equivalent to water[11] also indicates a preference for (S) chirality at the sulphur as shown in **4** (**Scheme 2**).



Scheme 2

Whereas the parent 4-vinyl isothiazoline prepared using Stille methodology[10] was unreactive as a Diels-Alder diene, coupling of the major diastereoisomeric sulphoxide derivative with vinyltributyltin yielded a single product resulting from a diastereoselective Diels-Alder dimerisation. NMR revealed this to be one of two possible diastereoisomers **6a** or **6b** but it was not possible to obtain a crystal of X-ray quality. The product clearly results from a diastereoselective Diels-Alder dimerisation of the initially formed diene **5** exclusively *via* the less common *exo* transition state (**Scheme 2**). As the dimerisation occurs *in situ* and in the presence of both tin and palladium the observed selectivity could be explained *via* a stabilising metal chelation to the sulphoxide oxygens of both addends. In an attempt to predict which diastereoisomeric product had been formed, we performed semi-empirical calculations[11] to model the transition states leading to **6a** and **6b** respectively (**Figure 1**).



TS (*exo syn*) ΔHf = 53.50kcal TS (*exo anti*) ΔHf = 59.15kcal

Figure 1. Transition structures leading to **6a** and **6b**.

The results of these calculations summarised in **Figure 1**, predict a striking preference for *exo syn*

addition leading to **6a** *via* transition structure TS (*exo syn*) which is *ca* 6 kcal lower in energy than that leading to the adduct **6b**. Interestingly, for the *exo anti* transition state, the distance between the sulphoxide oxygens is 5.38Å which is too great to allow such a stabilising metal chelation.[12,13] However, in the *exo syn* transition state either metal can comfortably chelate to the sulphoxides with an optimal bond length, accomodating the required transition state geometry and with favourable alignment of the S-O electronic dipoles (see **Figure 2**). Thus in addition to dipole alignment, metal chelation may also greatly affect the diastereoselectivity. This may also explain the departure from the normal *endo* selectivity which would not allow such a stabilising alignment with the same regiochemistry.

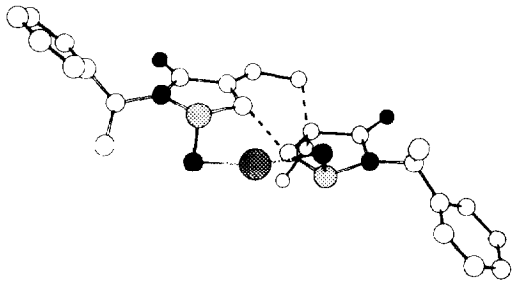
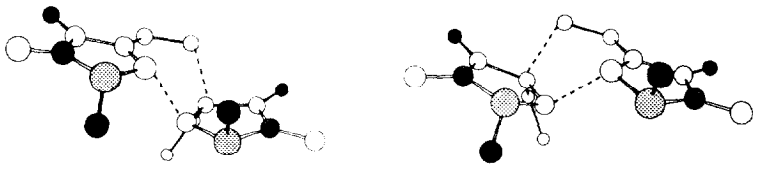


Figure 2. Metal chelation in TS (*exo syn*)

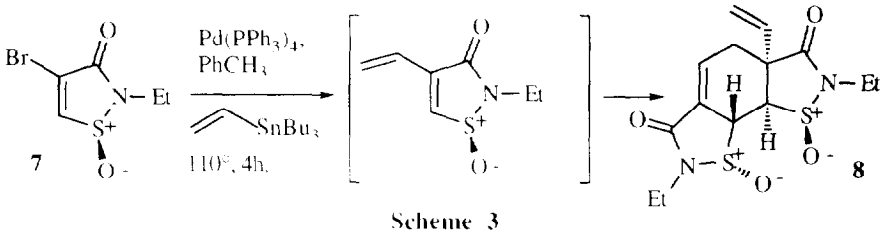
We also performed semi-empirical calculations[10] to model the transition structures for the 2-methyl analogues to ensure the predicted *exo syn* selectivity was not a function of the bulky 2-α-methyl benzyl substituent. The models again predict a clear preference for the *exo syn* cycloadduct which has a lower energy transition state (**Figure 3**).



TS(*exo syn*) ΔH_f = 3.766 kcal TS(*exo anti*) ΔH_f = 4.220 kcal

Figure 3. Transition State models of dimerisation of 2-methyl-4-vinyl-1,2-isothiazoline-3-one-1-oxides.

To elucidate the true selectivity and the validity of the predicted models we carried out vinylation of racemic 2-ethyl-4-bromo-1,2-isothiazoline-3-one-1-oxide (**7**, **Scheme 3**). The stereochemistry shown below is relative as the system is racemic. The reaction resulted in a single dimeric product which was found to have structure **8** by X-ray analysis (**Figure 3**). This closely fits the predicted cycloadducts for these systems and results exclusively from an *exo syn* transition state.



Scheme 3

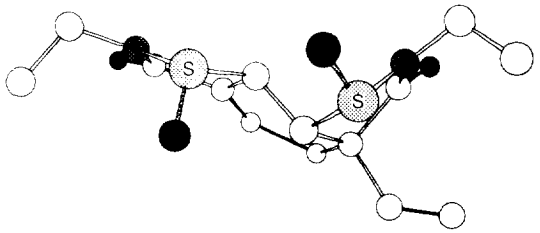


Figure 4. X-ray structure of **8**.

In addition to favourable sulphoxide dipole alignment, metal chelation may also be playing an important role in dictating the remarkable stereoselectivity of this Diels-Alder process. These intriguing results serve to further delineate the high degree of diastereoselectivity displayed around asymmetric sulphoxide moieties and serves to underline the potential of isothiazoline-1-oxides. Studies are now underway to explore the scope and synthetic potential of the Diels-Alder reactivity of such species.

Acknowledgement.

We are grateful to EPSRC and Pfizer Central Research for their financial support and to Mike Kinns, Christine Thompson, Carol Winslow of Pfizer Central Research, Sandwich and Jon Bordner and Debora DeCosta at the X-ray department, Pfizer, Groton for their help.

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11. The solvent accessible surface area was established using a radius of 1.4 Å. Molecular models were constructed on Silicon Graphics *Indigo* using Macro Model v3.0, developed by Professor W.C. Still. All models were fully optimised using AM1 Hamiltonian in MOPAC v6.0 which was optimised for parallel computation using a Silicon Graphics Challenge eight processor parallel computer. Transition structures were located *via* the SADDLE routine in MOPAC and optimised via the TS routine. Transition structures were characterised using FORCE within MOPAC.
12. Palladium to sulphoxide oxygen bond lengths are usually within the range 2.06-2.31Å. Recent examples include: Wang, C.; Bodenbinder, M.; Willner, H.; Rettig, S.; Trotter, J.; Aubke, F. *Inorg. Chem.* **1994**, *33*, 779, (2.159Å), Leoni, P.; Pasquali, M.; Sommovigo, M.; Albinati, A.; Lianza, F.; Pregosin, P.S.; Ruegger, H. *Organometallics* **1993**, *12*, 4503 (2.282Å) Palladium to sulphur co-ordination could also be accomodated within the *exo syn* transition state
13. Tin to sulphoxide oxygen bond lengths are usually in the range 2.10-2.62Å. Recent examples include: Engel, G.; Mattern, G. *Z. Anorg. Allg. Chem.* **1994**, *620*, 723, (2.345Å), Zhu, F. C.; Shao, P. X.; Yao, X. K.; Wang, R. J.; Wang, H. G. *Inorg. Chim. Acta.* **1990**, *171*, 85, (2.569Å).

(*Received in UK* 14 *July* 1995; *accepted* 18 *August* 1995)