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The hetero Diels–Alder reaction featuring 2-phenyl-4-dimethylamino-1-thia-3-azabuta-1,3-diene as diene component: a clear example of a thermodynamically-controlled process

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Abstract—Cycloaddition reactions of diene **1a** with various dienophiles lead to *trans* 4,5-disubstituted dihydro-1,3-thiazine adducts. We demonstrate that a thermodynamically-controlled process, in which the adduct N-3 nitrogen plays a prominent role, accounts for the observed *trans* relative configuration. © 2002 Elsevier Science Ltd. All rights reserved.

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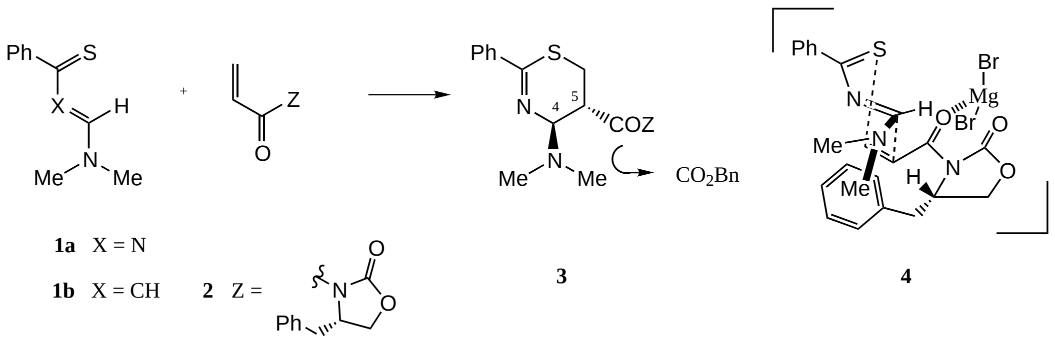
1. Introduction

Some years ago, we disclosed the first asymmetric synthesis of the dihydro-1,3-thiazine **3** by means of a highly diastereoselective [4+2] heterocyclisation between diene **1a** and chiral dienophile **2**, followed by a chiral auxiliary recovery step.[1] The *trans* relative configuration between the adjacent stereocenters at C-4 and C-5 in adduct **3** is particularly noteworthy. This disposition can be accounted for by an '*exo*-like' transition state topography as pictured in Scheme 1.

In a parallel study of the cycloaddition reaction of diene **1a** with a series of dienophiles (both chiral and achiral)[2] we were most surprised to observe that, independently of the experimental conditions used (thermal, high pressure or Lewis acid activations in a wide range of temperatures) the *trans* adducts, as in the above example, were the sole isolated compounds. These results are in sharp contrast with those reported in the literature for related 2-*N*,*N*-disubstituted amino-1-thia-3-azabuta-1,3-dienes which give *cis* adducts after



Scheme 1.

Keywords: hetero Diels–Alder reaction; thermodynamic control; Lewis acid; basic alumina.

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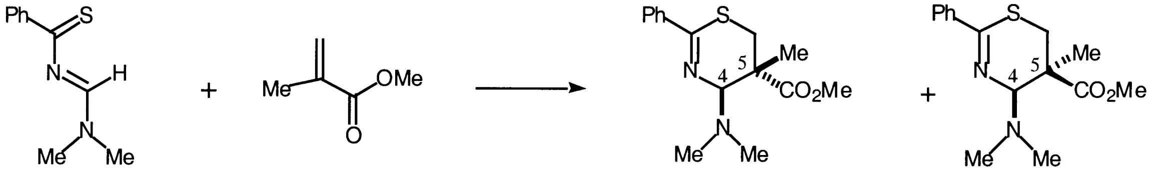
cycloaddition.[3] Subsequent work in this laboratory[4] revealed that diene **1b**, an analogue of **1a** lacking the N-3 nitrogen atom (N→CH), reacts with various dienophiles at 0°C or below giving mixtures of *cis* and *trans* adducts which could be equilibrated towards the calculated more stable *trans* adducts by elevation of the reaction temperature. Following these observations it appears that the N-3 atom in **1a**, or in its cycloaddition products, plays a crucial role in the events that lead to the final and exclusive formation of *trans* adducts (e.g. **3**). Since calculations at the PM3 level have shown that the *trans* adducts of type **3** are significantly more stable than their *cis* diastereomers (>12 kJ mol^{-1}) the first question arising was to determine whether or not the *trans* adducts are the result of a thermodynamically-controlled process. To answer that question we have engaged an experimental study and we disclose, herein, several arguments that unambiguously demonstrate that the intracyclic N-3 nitrogen triggers an exceptionally facile cycloreversion–cycloaddition process (thermodynamic control) ultimately responsible for the *trans* configuration of the reaction products.

2. Results and discussion

In order to reveal the possible relation that exists between the *trans* configuration of the cycloaddition products and the presence of a nitrogen atom in their backbone, we first envisaged to study the [4+2] heterocyclisation between **1a** and methyl methacrylate. This approach to the problem originates from the fact that the enthalpy of formation for adduct **5**, arising from an '*exo*-like' transition state (cf. **4**, Scheme 1) was evaluated (PM3 calculations) only 4.68 kJ mol^{-1} under the corresponding calculated value for its diastereomer **6**. As a result, if cycloaddition reactions involving diene **1a** were governed by the occurrence of a thermodynamic control, a mixture of adducts **5** and **6** should be expected with methyl methacrylate as the dienophile (Scheme 2), contrary to examples featuring dienophiles having an α-unsubstituted acryloyl moiety.

Heating diene **1a** and methyl methacrylate at reflux of toluene for hours failed to give any condensation products. However, Lewis acids such as magnesium bromide or, preferably, diethylaluminum chloride did promote the cycloaddition reaction to give two diastereomeric adducts in an 80:20 ratio as observed by inspecting the CO_2Me, NMe_2 and Me signals in the NMR spectrum of the crude mixture. This mixture proved to be thermally unstable giving back the reactants as soon as a temperature of ca 40°C is applied. This observation accounts for the failure of the cycloaddition reaction at reflux of toluene solution (vide supra). Moreover, adducts **5** and **6** could not be purified by flash-chromatography since cycloreversion reaction occurred to some extent on silica. We were thus pleased to observe the formation of crystals by abandoning the **5**/**6** mixture in the refrigerator for several days. These crystals were shown by NMR analysis to correspond to the most abundant diastereomer which was identified as being **5** by a single crystal X-ray analysis (Fig. 1).[5] The less abundant diastereomer **6** was shown to exist mainly in the conformation depicted in Fig. 1 on the basis of its NMR spectrum displaying a W-type long range coupling (2.0 Hz) between the diequatorial protons located on carbons C-4 and C-6.

After having determined the structures of the reaction products **5** and **6** we turned our attention to investigating the reaction mechanism. In this context, crystals of **5** were subjected to the conditions used for the cycloaddition reaction (i.e. stirring in CH_2Cl_2 at rt for 3 h in the presence of 1 equiv. of Et_2AlCl). After work-up a mixture of **5** and **6** was recovered in an 80:20 ratio



1a **5** **6**

Scheme 2.

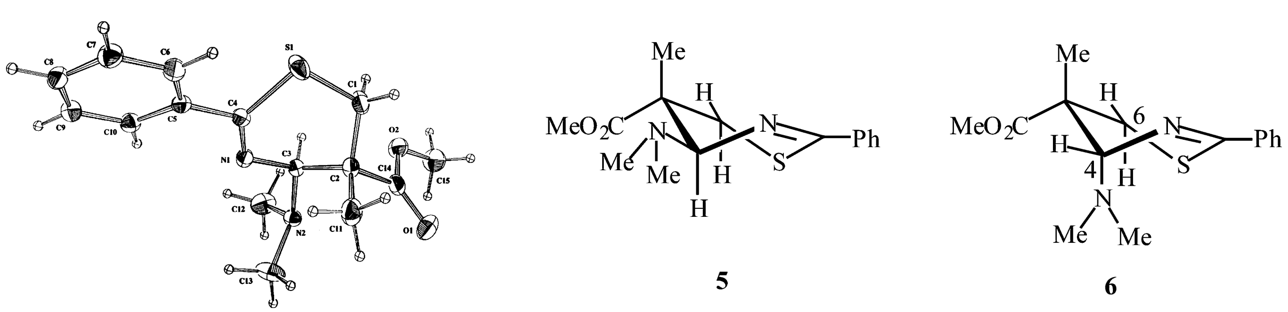
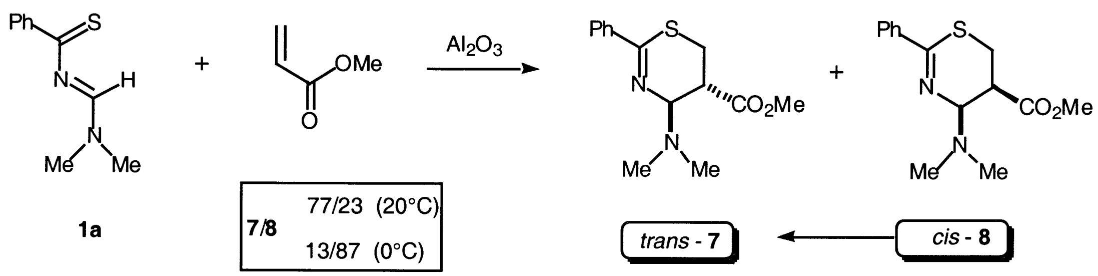


Figure 1. X-Ray crystal structure of **5** and calculated most stable conformations for **5** and **6**.



Scheme 3.

identical to that initially formed by reacting **1a** and methyl methacrylate. Similarly, several mixtures of adducts **5** and **6**, in different ratios, invariably led to a same 80:20 mixture of **5** and **6** when subjected to the same protocol as above. In the light of these results it appears clearly that cycloaddition of diene **1a** with methyl methacrylate is governed by the establishment of an equilibrium between reactants and products which leads to an 80:20 thermodynamic mixture of adducts **5** and **6** and agrees with the results of theoretical calculations. By way of similarities it seems reasonable to postulate that changing methyl methacrylate for methacrylate, or other dienophiles bearing no substituent on the reacting double bond, would not alter the profile of the cycloaddition reactions and that the formation of *trans* adducts may thus be rationalised by the establishment of a thermodynamic control. This assertion could be fully ascertained after we observed that the cycloaddition reaction between diene **1a** and methylacrylate, both adsorbed on basic alumina, led to a mixture of *cis* and *trans* adducts. The *cis* adduct could be made predominant[6] (**7**:**8** = 13:87, Scheme 3) when the reaction was run and worked up at 0°C. The facile equilibrium between the two species was evidenced by briefly heating the reaction mixture in deuterated chloroform at 40°C which resulted in the transformation of the *cis* adduct toward the more stable *trans* adduct (**8**→**7**, Scheme 3).

3. Conclusions

We have shown that the hetero Diels–Alder reaction of 2-phenyl-4-dimethylamino-1-thia-3-azabuta-1,3-diene **1a** with common dienophiles is a thermodynamically-controlled process resulting in the formation of the most stable, generally *trans*, dihydrothiazine adducts. By comparison with the behaviour of the corresponding thiopyran adducts it clearly appears that the N-3 nitrogen greatly accelerates the process of cycloreversion.

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5. X-Ray analysis of compound **5**: $M_r = 292.40$, monoclinic, $P21/c$, $a = 12.126(5)$, $b = 8.256(2)$, $c = 15.501(4)$ Å, $\beta = 105.66(4)°$, $V = 1623(1)$ Å^{-3}, $Z = 4$, $D_X = 1.300$ Mg m^{-3}, λ (Mo Kα) = 0.71073 Å, $\mu = 2.095$ cm^{-1}, $F(000) = 672$, $T = 110$ K. The sample (0.22×0.24×0.24 mm) is studied on an automatic diffractometer CAD4 Enraf-Nonius with graphite monochromatised Mo Kα radiation. The cell parameters are obtained by fitting a set of 25 high-θ reflections. The data collection ($2\theta_{\max} = 54°$, scan $\omega/2\theta = 1$, $t_{\max} = 60$ s, range *hkl*: *h* 0.15, *k* 0.10, *l* –20.20, intensity controls without appreciable decay (0.2%) gives 3553 reflections from which 2489 were independent ($R_{\text{int}} = 0.011$) with $I > 3.0\sigma$ (I). After Lorentz and polarisation corrections the structure was solved with SIR-97,[7] which reveals the non-hydrogen atoms of the structure. After anisotropic refinement, all hydrogen atoms are found with a Fourier difference. The whole structure was refined[8] by the full-matrix least-square technique (use of F magnitude; x, y, z, β_{ij} for S, O, C and N atoms; x, y, z for H atoms; 242 variables and 2489 observations; $w = 1/(\sigma F_o)^2 = [\sigma^2(I) + (0.04F_o^2)^2]^{-1/2}$ with the resulting $R = 0.035$, $R_w = 0.034$ and $S_w = 0.84$ (residual $\Delta\rho \leq 0.34$ e Å^{-3}).
6. Some characteristic NMR values (ppm): NMe$_2$ (**7**: 2.44, s; **8**: 2.52, s); CO$_2$Me (**7**: 3.79, s; **8**: 3.75, s); H-4 (**7**: 4.42, d, $J = 10.2$ Hz; **8**: 4.62, d, $J = 4.0$ Hz).
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