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The Rearrangement of α-Imino-thioaldehydes into Dihydro-1,3-thiazoles

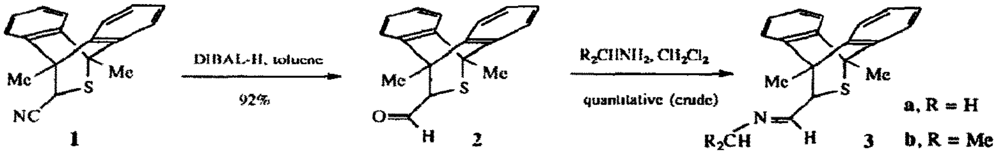
Roger Arnaud[a], Nadia Pelloux-Léon[a], Jean-Louis Ripoll[b] and Yannick Vallée[a]*

[a] L.E.D.S.S., laboratoire associé au CNRS, Université Joseph Fourier, B.P. 53X, 38041 Grenoble, France
[b] Laboratoire de Chimie des Composés Thioorganiques, associé au CNRS, ISMRA, 14050 Caen, France.

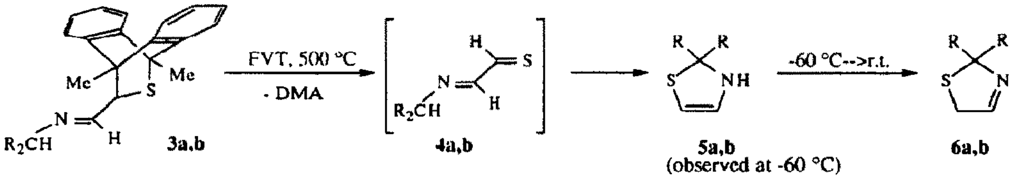
Abstract : α-Imino-thioaldehydes were generated by retro-Diels-Alder reaction under flash vacuum thermolysis conditions. They were found to be unstable and cyclized to 2,3-dihydro-1,3-thiazoles. This cyclization was investigated by *ab initio* calculations.

The chemistry of thioaldehydes is a rapidly growing area.[1] Most of these reactive species have been detected by spectroscopic methods at low temperature or in the gas phase[2] and trapped *in situ* by suitable reagents. Thioaldehydes bearing an electron-withdrawing group α to the C=S double bond are of special interest because of their high reactivity as dienophiles in the Diels-Alder reaction. Thioxoethanal (HCSCHO) has been generated photochemically in an argon matrix[3] and by flash vacuum thermolysis.[4] FVT has also been used to generate thioformyl cyanide (HCSCN).[5] When prepared *in situ*, this thioaldehyde, as well as various α-thioxoacetates ($HCSCO_2R$), undergoes [4π + 2π] cycloadditions with dienes, generally with high regio- and stereoselectivity.[6] Good enantioselectivity has been observed with chiral α-thioxoacetates.[7] In this communication we present our first results concerning our attempts to characterize the previously unknown α-imino-thioaldehydes.

Our synthetic pathway towards these compounds involved the retro-Diels-Alder reaction[8] and started from the thioformyl cyanide-dimethylanthracene (DMA) adduct **1** [9], which was reduced into the corresponding aldehyde **2** [10] by DIBAL-H in toluene. Compound **2** was then treated with methyl or isopropyl amine in dichloromethane in the presence of molecular sieves to give the two imines **3a,b** as pure *trans* isomers.[11] When heated in refluxing toluene for 3 h, these adducts underwent a quantitative retro-Diels-Alder reaction to DMA. However, under these conditions, we were not able to characterize any evolution product of the expected transient thioaldehydes **4a,b** and our efforts to trap them chemically remained unsuccessful.

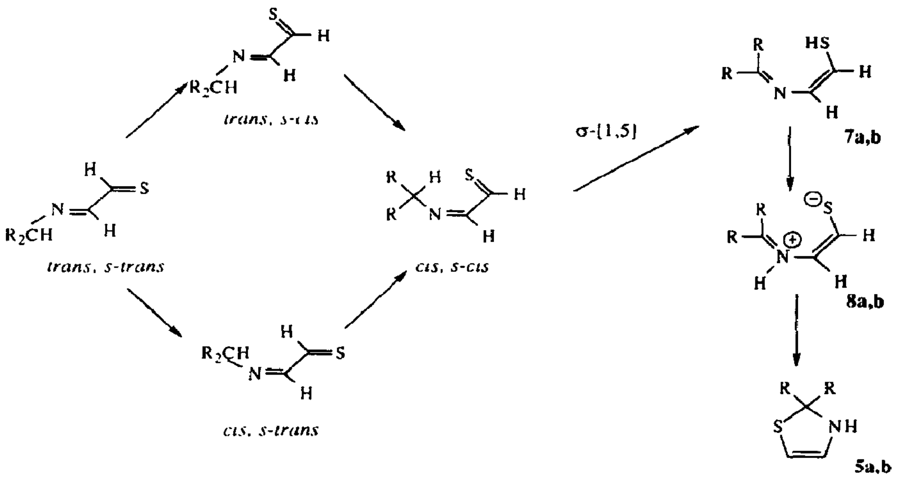


FVT being a well suited method for the investigation of reactive species, we then effected the thermolysis of the imines **3a,b** in the gas phase at 500 °C (oven : 12 x 1.6 cm, P = 10^{-5} hPa). The obtained volatile products were collected in a cold trap and their ^{1}H and ^{13}C NMR spectra were recorded at -60 °C. As expected, the presence of the α-iminothioaldehydes **4a,b** was not observed. The ^{1}H NMR spectrum obtained after the thermolysis of **3b** consists mainly in a methyl singlet at 1.68, two doublets at 3.46 (J = 3.0 Hz) and 5.32 (J = 4.5 Hz) and a doublet of doublet at 6.01 ppm (J = 4.5 and 3.0 Hz) (integration *ca.* 6/1/1/1)[12], in agreement with the cyclic structure **5b**. In particular, it is very similar to the previously reported spectrum of the N-acetylated derivative of **5b**.[13] We also identified compound **5a**[12] after thermolysis of **3a**. Compounds **5a,b** having a secondary enamines structure, were expected to be poorly stable and to readily isomerize to the corresponding imines **6a,b**. In fact, **6a** was observed as a minor product in the low temperature spectra recorded after the thermolysis of **3a** (ratio **5a/6a** : 8/1).[12] The isomerization of **5a** into **6a** was complete at room temperature. In the same way, even at -60 °C, the enamine **5b** was contaminated with some imine **6b** (**5b/6b** : 4/1) and at room temperature only **6b**, a previously known compound,[13] was observed. FVT-low temperature (-196 °C) IR coupling experiments were also performed and confirmed the formation of the enamines **5a,b** (**5a** ν_{NH} = 3200, $\nu_{C=C}$ = 1585, **5b** ν_{NH} = 3240, $\nu_{C=C}$ = 1580 cm^{-1}) and their transformation into the imines **6a,b** (**6a** $\nu_{C=N}$ = 1620, **6b** $\nu_{C=N}$ = 1635 cm^{-1}).

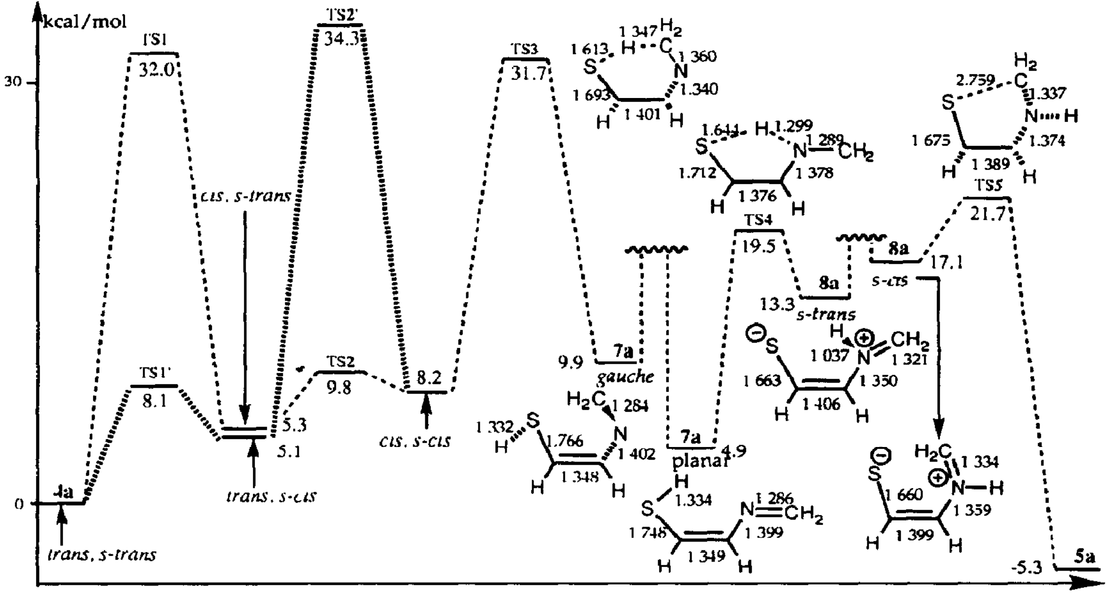


The transformation of the α-iminothioaldehydes **4a,b** into the enamines **5a,b** must be a multistep process. We propose that it occurs *via* the enethiolization of the thioaldehydes into the imino-enethiols **7a,b**. Addition of the thiol group onto the new C=N double bond would then lead to the enamines *via* the ionic intermediates **8a,b**. The formation of **7a,b**, however, could occur only from the *cis* isomers of **4a,b**. The ethanoanthracenic compounds **3a,b** being obtained as pure *trans* imines, this necessitates a *trans* -> *cis* isomerization of the transient imines **4a,b**. Such an isomerization may occur at high temperature in the oven and be followed by a rapid allowed [1,5] sigmatropy leading to the enethiols **7a,b** ready for cyclization, in the *cis, s-cis* conformation. In contrast, the [1,3] sigmatropy involved in the enamine-imine isomerization (**5** -> **6**) is not an allowed process and is possibly catalyzed by the acidity of $CDCl_3$.

In order to test this reaction mechanism, we have investigated by *ab initio* molecular orbital theory the potential energy surface for the rearrangement of **4a**. All calculations were carried out using the GAUSSIAN 92 system of programs.[14] The stationary points of the[C_3H_5NS] potential energy surface was initially located at the Hartree-Fock (HF) level with the polarized 6-31G(d,p) basis set[15] and characterized by harmonic vibrational frequencies at this level. Geometrical parameters were then refined at the second-order Möller-Plesset pertubation theory (MP2/6-31G(d,p)) level. After transition states were obtained, intrinsic reaction coordinate (IRC) calculations were carried out in order to verify that the saddle points obtained were associated with the reaction path originally assumed. The results obtained at the MP2/6-31G(d,p) level are summarized in the Figure.[16] The isomer of **4a** calculated as the most stable is the *trans, s-trans* one. Both enethiol **7a** and zwitterion **8a** are found to be local minima but are predicted to be respectively 9.9 and 17.1 kcal/mol higher in energy than the *trans, s-trans* isomer of **4a**. On the other hand the cyclic species **5a** and **6a** (the latter not shown in the Figure) lie respectively 5.3 and 16.7 kcal/mol below **4a** in energy.



Two pathways have been examinated for the 4a(*trans, s-trans*) -> 4a(*cis, s-cis*) step. In both cases, the *trans-cis* isomerization is predicted to occur by inversion at nitrogen (TS1 and TS2' transition structures have a planar S=C-C=N-C skeleton with a C=N-C angle close to 180°) rather than by rotation about the C=N bond. Similar results have been obtained by Pople *et al.* in their study of the potential energy surface of $H_2C=NH$.[17] With the assumption that the variations of the barrier heights are not altered by non potential energy terms (activation entropy, zero point vibrational energy, thermal energy correction) our results indicate that the rotation about the C-C bond followed by the *trans-cis* isomerization is the preferred pathway.



The calculated potential energy barrier (23.5 kcal/mol) for the [1,5] sigmatropic rearrangement (transition structure TS3 corresponding to a suprafacial H migration) is considerably lower than that calculated for the

[1,5] hydrogen shift of (Z)-1,3-pentadiene at the same level of theory (36.5 kcal/mol, experimental 38.8 kcal/mol).[18] This result is in agreement with an expected rapid [1,5] sigmatropy. The transition stucture connecting the minimum **7a**(planar) with the zwitterion **8a**(*s-trans*)appears to be a C_s structure and lies 14.6 kcal/mol above **7a**(planar). Finally, the exothemic cyclization step proceeds with an energy barrier of only 4.6 kcal/mol. Thus, our calculations predict that the *trans-cis* isomerization of **4a** is the rate determining step and support the mechanism above proposed.[19]

References and notes

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10. Compounds **2** and **3a,b** gave spectroscopical data (including HRMS) in agreement with their structure.
11. *trans* stucture determined by NOE experiments.
12. **5a** : ^{1}H NMR : 3.57 (m, NH), 4.76 (d, J = 3.7 Hz, CH$_2$), 5.46 (d, J = 4.3, SCH), 6.19 (dd, J = 2.7 and 4.3, NCH). ^{13}C NMR : 53.64, 100.50, 129.91. **5b** : ^{1}H NMR : see main text. ^{13}C NMR : 30.74, 75.36, 98.44, 127.11. **6a** : ^{1}H NMR : 3.94 (dt, J = 1.2 and 4.7, SCH$_2$C), 5.30 (dt, J = 2.7 and 4.7, SCH$_2$N), 7.52 (narrow m, HC=N). ^{13}C NMR : 44.07, 68.38, 161.37. **6b** : ^{1}H NMR : see ref[13]. ^{13}C NMR : 32.79, 45.12, 89.80, 156.76.
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15. Description of basis set and explanations of standard levels including Moller-Plesset pertubation theory may be found in : Here, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*, Wiley, New York, **1986**. The computations were performed on an IBM RS 6000/340 at the LEDSS.
16. Bond lengths in Å. For the sake of clearness, the rotational barriers for the **7a**(*gauche*) -> **7a**(planar) (1.6 kcal/mol) and the **8a**(*s-trans*) -> **8a**(*s-cis*) (24.3 kcal/mol) have been omitted in the figure.
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18. For a review of transition structures in hydrocarbon pericyclic reactions see : Houk, K. N.; Li, Y., Evanseck, J.D. *Angew. Chem. Int. Ed. Engl.*, **1992**, *31*, 682-708.
19. The complete geometry of all products, intermediates and transition states will be presented, along with a detailed study of the reaction hypersurface, in a forthcoming full paper.

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