ORGANIC LETTERS

2009
Vol. 11, No. 6
1365−1368

Unexpected Formation of 2,1-Benzisothiazol-3-ones from Oxathiolano Ketenimines: A Rare Tandem Process

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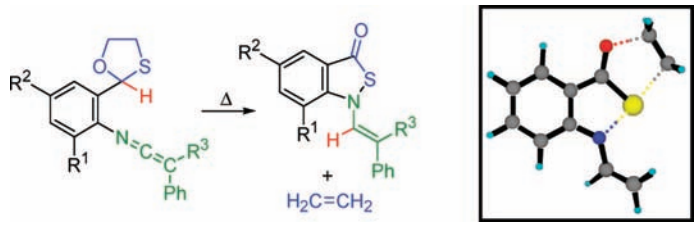
Received January 26, 2009

ABSTRACT

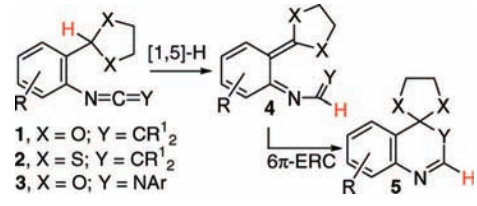


A rare one-pot reaction, a tandem [1,5]-H shift/1,5 electrocyclization/[3 + 2] cycloreversion process, leading from *N*-[2-(1,3-oxathiolan-2-yl)]phenyl ketenimines to 1-(*β*-styryl)-2,1-benzisothiazol-3-ones and ethylene, is disclosed and mechanistically unraveled by means of a computational DFT study. The two latter stages of the tandem process are calculated to occur in a single mechanistic step via a transition structure of pseudopericyclic characteristics.

In the course of our studies on the chemistry of ketenimines,[1] we have reported a number of sigmatropic rearrangements of atoms or groups of atoms to the central carbon atom of the heterocumulenic function.[2] Particularly relevant for the contents of this report are the recently unveiled hydricity-promoted [1,5]-H shifts in acetalic ketenimines and carbodiimides (Scheme 1).[2e]

The cyclic (dithio)acetal function of ketenimines **1**,**2** and carbodiimides **3** promotes the [1,5] shift of the acetalic proton to the central carbon atom of the heterocumulene fragment, under thermal conditions, for yielding carbonyl-protected 4-quinolones **5** (Y = CR_2) or 4-quinazolinones **5** (Y = NAr), via further 6π-electrocyclic ring closure of the initially formed transient *o*-quinomethanimines **4**.

Scheme 1. Reaction Path Converting **1**−**3** into **5**



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10.1021/ol9001416 CCC: $40.75
Published on Web 02/26/2009

While exploring the ability of other acetalic functions for activating similar processes, we tested ketenimines **9** bearing 1,3-oxathiolane rings, which were easily prepared from the respective 2-azidobenzaldehydes **6**. Surprisingly, after heating toluene solutions of ketenimines **9** under reflux for a few hours, these compounds did not convert into the expected quinolines **11**, but instead 1-(*β*-styryl)-2,1-benzisothiazol-3-ones **10** were obtained in fair to good yields (Scheme 2, Table 1).

Scheme 2. Preparation of 2,1-Benzisothiazol-3-ones **10**

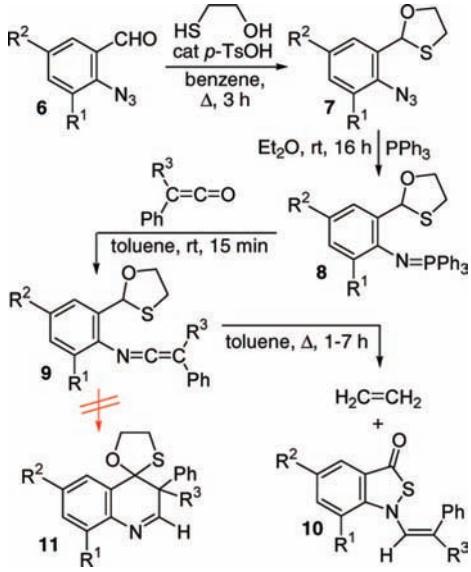


Table 1. 1-(*β*-Styryl)-2,1-benzisothiazol-3-ones **10**

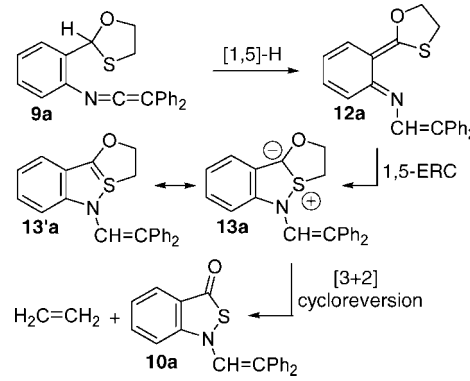
compd	R^1	R^2	R^3	yield (%)
10a	H	H	Ph	73
10b	CH_3	H	Ph	92
10c	H	Cl	Ph	74
10d	H	CH_3	Ph	92
10e	H	H	Me	81[a]

[a] Total yield for the *E* + *Z* isomers; ratio *E*/*Z* = 4:1.

The structural determination of the 1-(*β*-styryl)-2,1-benzisothiazol-3-ones **10** was achieved following their analytical and spectral data, and unequivocally established by the X-ray structure determination of a monocrystal of **10a** ($R^1 = R^2 =$ H; R^3 = Ph) (see Supporting Information).

We obviously envisaged that the transformation **9** → **10** should occur with the concomitant formation of ethylene, although we made no efforts to detect it in the reaction exhausts. However, the results of the computational mechanistic study of such transformation (see below) support this assumption. The presence of the original acetalic proton of **9** at the styryl *β*-carbon of benzisothiazolones **10**, which was the central keteniminic carbon in **9**, suggest the involvement of a [1,5]-H shift as the initial step of the sequence leading from **9** to **10**. In our first mechanistic proposal, this step, converting **9** into the transient **12**, would be followed by a rare 1,5 cyclization of the latter involving S−N bond formation, thus providing the sulfur ylide **13**, which finally should undergo a [3 + 2] cycloreversion step to yield **10** plus ethylene (Scheme 3, **9a** is used for simplicity).

Scheme 3. Mechanistic Proposal for the Conversion **9** → **10**



Whereas the first step of this mechanistic proposal is precedented in the introduction above, the atom connectivity of the final products apparently leaves no room for mechanistic speculations other than the two final steps outlined in Scheme 3.

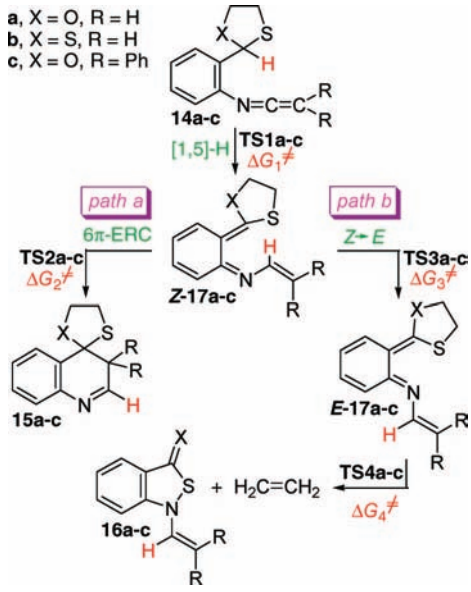
Taking into account that the thioanalogues of **12**, structures **4** (X = S), did not experience similar transformations but instead electrocyclize to quinolines **5**, it seems clear that the generation of a strong C═O bond in **10** should be a crucial fact for explaining its formation.

In order to gain insight into the mechanistic path of the transformation of ketenimines **9** into ethylene plus benzisothiazolones **10**, and also to answer why analogous dithiolanes **2** do not experience a similar transformation, we have carried out a computational DFT study at the B3LYP/6−31+G** level of theory using the Gaussian03 package (see Supporting Information).

First we approached the transformation of the oxathiolane ketenimine **14a** into the initially expected spiroquinoline **15a**, and also into the actual product benzisothiazolone **16a** (Scheme 4). The first step, common to both reaction channels, consists of a [1,5]-H shift, as anticipated, leading to the intermediate *o*-quinomethanimine ***Z*-17a** which further can follow the two alternative pathways (a and b) depicted in Scheme 4.

The most relevant outcome of these calculations is that formation of benzisothiazolone **16a** plus ethylene does not involve a transient sulfur ylide similar to **13**; instead, intermediate **E-17a** undergoes simultaneously the two following events, 1,5-electrocyclization and [3 + 2] cycloreversion, via the transition state **TS4a**. The optimized geometries of the four transition states involved in these transformations are depicted in Figure 1. The computations establish the same mechanistic paths for the conversion of the dithiolane ketenimine **14b** into the spiroquinoline **15b** or the benzisothiazole-3-thione **16b**. However, the energy barriers are quite different as shown in Table 2.

Scheme 4. Alternative Mechanistic Paths for the Conversions of Ketenimines **14a−c** into **15a−c** and into **16a−c** Plus Ethylene



Several main conclusions can be inferred by comparing the first two entries of this table: (1) for both reaction paths in each entry (**14a,b→15a,b/16a,b**) the rate limiting step is the [1,5]-H shift; (2) the energy barrier for the 6π-electrocyclization of ***Z*-17** (path a) is identical in both entries (21.1 kcal·mol^{-1}); (3) concerning path b, the *Z*→*E* *C*=N isomerization involves always an easily surmountable barrier; (4) the barrier for the conversion of ***E*-17a** leading to the benzisothiazolone **16a** is considerably lower than that calculated for the thioanalogous transformation ***E*-17b→16b**; (5) the energy barrier of this latter conversion is higher than that of the alternative 6π-ERC leading to **15b**, whereas just the opposite occurs for the transformations of intermediate ***Z*-17a**, that is, the energy barrier for the 6π-ERC (***Z*-17a→15a**) is a little higher than that leading to **16a**; (6) the spiroquinoline **15b** is predicted to be the thermal and kinetically controlled product when starting from **14b**, whereas the benzisothiazolone **16a** is the kinetically controlled product when starting from **14a**. These conclusions are in accordance with the experimental results obtained in the thermal treatment of dithiolane ketenimines **2**, which results only into the corresponding spiroquinolines,[2e] whereas the calculations predict a small kinetic preference for the formation of benzisothiazolone **16a** versus spiroquinoline **15a**.

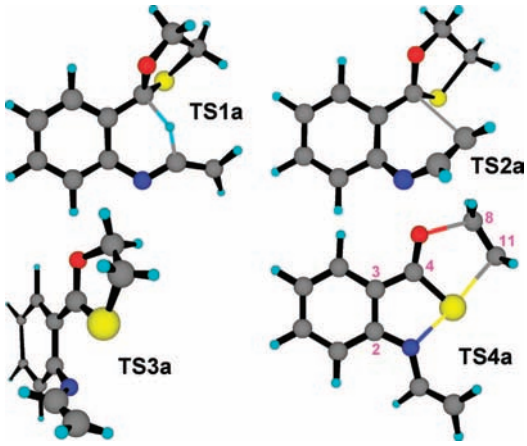


Figure 1. Optimized B3LYP/6−31+G** geometries of the transition structures involved in the transformations **TS1−4a**.

Table 2. Free Energy Barriers[a] (kcal·mol^{-1}) Calculated for the Conversions **14a−c→15a−c/16a−c** at the B3LYP/6-31+G** Level

14→15/16	$\Delta G^{\ddagger}_1$	$\Delta G^{\ddagger}_2$	$\Delta G^{\ddagger}_3$	$\Delta G^{\ddagger}_4$	ΔG_{rxn} path a	ΔG_{rxn} path b
a	31.7	21.1	9.5	19.2	−21.2	−12.5
b	33.3	21.1	10.2	27.5	−17.4	+2.0
c	26.9	26.4	9.5	20.5	−1.4	−10.7

[a] See Scheme 4 for the notation of the energy barriers $\Delta G^{\ddagger}_{1-4}$ (these energies are relative to those of the preceding stationary points).

It is conceivable that replacing H/H by Ph/Ph or Ph/Me at the sp^2 carbon atom of the ketenimine **14a**, as in the experimental substrates **9**, should considerably increase the barrier of the 6π-ERC step due to steric constrains. This is why we also studied the transformations **14c→15c/16c** involving a ketenimine fragment bearing two phenyl groups. The chief outcomes of this study are the increase of the energy barrier for the 6π-ERC step when compared with the unsubstituted case, which is now 5.3 kcal·mol^{-1} higher, whereas that of the last step in path b only increases by 1.3 kcal·mol^{-1}. In addition, spiroquinoline **15c** is higher in energy than benzisothiazolone **16c** by 9.3 kcal·mol^{-1}. Therefore, **16c** is clearly predicted to be the thermal and kinetically controlled product, accordingly with the experiments.

It is worth commenting on the special features of the mechanistic step converting ***E*-17** into **16**. It is a complex, apparently pericyclic process having no precedent in the literature. It looks like a 1,5-electrocyclization and a [3 + 2] cycloreversion taking place *simultaneously* through the transition state **TS4**. However, we have found in the literature neither 1,5-electrocyclizations of pentadienyl skeletons similar to the 1-thia-5-aza-2,4-pentadiene fragment of ***E*-17** nor [3 + 2] cycloreversions involving 1,3-oxathiolane rings, and these two transformations do not seem, independently, easily amenable. By contrary, the combination of both processes in a unique mechanistic step results in a process of a discrete activation energy, close to 20 kcal·mol^{-1}. Probably the two simultaneous transformations cooperate in a favorable way. For instance, now the 1,5-electrocyclization might be viable thanks to the formation of the strong C=O bond, occurring by virtue of the simultaneous ethylene extrusion, which in turn is favored by the initial S−N bond formation. Moreover, the aromaticity recovery at the benzene ring along the way to **16** and the inherent entropic assistance of this mechanistic step must be also decisive factors for determining its success.

We analyzed in detail some geometric and electronic parameters of the transition state **TS4a**. Its geometry does not resemble that expected for a [3 + 2] cycloreversion or an 1,5-

ERC. The three rings are in the same plane, in fact **TS4a** is nearly planar and only the exocyclic C=C double bond attached to the nitrogen atom projects out of the molecular plane. In a classical [3 + 2] cycloaddition the interacting π-systems in the transition state are parallel,[3] whereas in **TS4a** the developing π system of ethylene and that of the remaining molecular frame are perfectly perpendicular, indicating that, on going backward from **16a** plus ethylene to **TS4a**, the nonbonding lone pairs at the heteroatoms interact with the p orbitals of ethylene. In accordance, the second order perturbation analysis[4] along the IRC coordinate shows as the more relevant donor−acceptor interactions $Lp_1O \rightarrow \pi^*C_8-C_{11}$ and $\pi C_8-C_{11} \rightarrow \sigma^*N-S$. The geometry of the forming thiazole ring in **TS4a** does not correspond to that expected for a disrotatory 6π-electron 5-center electrocyclizations as all the atoms are in the molecular plane.[5] Going forward from ***E*-17a** to **TS4a** the most relevant donor−acceptor interactions along the IRC are $LpN \rightarrow \sigma^*S-C_{11}$, $Lp_1O \rightarrow \pi^*C_3-C_4$ and $\pi^*C_3-C_4 \rightarrow \pi^*N-C_2$. Therefore, the electronic movements in the direct and inverse reaction paths passing through **TS4a** could be represented as shown in Figure 2. Accordingly, the planar geometry and the orbital topology

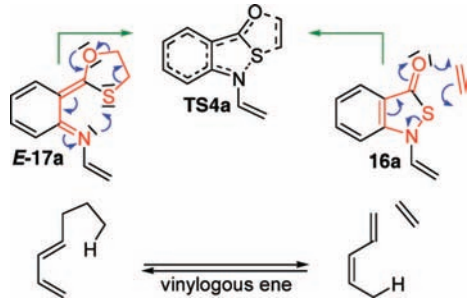


Figure 2. Electronic reorganization leading to **TS4a**.

of **TS4a**, containing orbital disconnections in the cyclic array of overlapping orbitals (where orthogonal bonding and non-bonding orbitals interchange roles), both confer pseudopericyclic[6] characteristics to this transition state.

As the electronic reorganization only takes place at the periphery of **TS4a**, and the single C_4-S bond not intervening, the transformation of ***E*-17a** into **16a** could also be viewed as a particular case of vinylogous retro-thia-ene reaction (Figure 2) in which the enophile component is ethylene and the vinylogous ene partner is triheterosubstituted, the migrating atom being sulfur.

In conclusion, we have experimentally unveiled and computationally scrutinized an unprecedented tandem reaction composed of a [1,5]-H shift and a further mechanistic step of pseudopericyclic characteristics which is structurally related with vinylogous ene reactions. As these latter processes are scarcely known,[7] the reactions reported here would require more indepth studies, a part of which is currently underway in our laboratory.

Acknowledgment. This work was supported by the Ministerio de Educacion y Ciencia of Spain and FEDER (Projects CTQ2005-02323/BQU and CTQ2008-05827/BQU), and Fundacion Seneca-CARM (Project 08661/PI/08). B.B. also thanks Fundacion Seneca-CARM for a fellowship.

Supporting Information Available: Experimental details for the synthesis of compounds **7**, **8** and **10**. Spectral data (NMR, IR, MS, elemental analyses) for compounds **7**, **8**, and **10**. CIF file of **10a**. ^1H and ^{13}C NMR spectra of compounds **10**. Details of computational procedures, geometries, Cartesian coordinates, IRC calculations on **TS4a**, and energies for all the stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) We could only locate two documents reporting on vinylogous ene reactions: (a) Gollnick, K.; Griesbeck, A. *Tetrahedron* **1984**, *40*, 3235–3250. (b) Maas, H.; Roeper, M. *Preparation of alkoxydodecatrienes and analogous by a vinylogous ene reaction*; BASF AG: Germany, DE 1995069, A1 20001005; CAN 2000, *133*, 281536. It is not surprising that all-carbon vinylogous ene reactions are so rarely reported. Whereas they would involve, if concerted, cyclic transition states involving eight electrons, they could hardly compete with the alternative Diels-Alder reaction and other classical six-electron ene processes. Only the special structural and electronic features of the transformation ***E*-17** into **16** (heteroatoms, lone-pair interactions, pseudopericyclic character, and aromaticity recovery) seem to explain why this process is easily amenable.