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Mechanistic Investigation on the Formation of Indolizines from 2-Enynylpyridines

Inma R. Lahoz, Cristina Sicre, Armando Navarro-Vázquez, Carlos Silva López,* and María-Magdalena Cid*

Departamento de Química Orgánica, Facultade de Química, Campus Lagoas-Marcosende, 36310 Vigo, Spain

mcid@uvigo.es; csilval@uvigo.es

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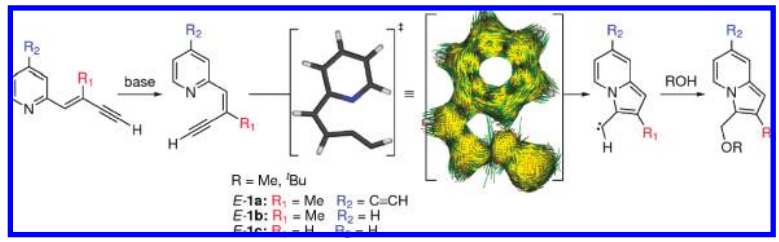
ABSTRACT



2,3,7-Trisubstituted indolizines were obtained from *E*- or *Z*-2-enynyl-4-substituted pyridines. The mechanistic pathway involves a base-catalyzed double-bond isomerization, if the *E*-isomer is the starting material, followed by a concerted pseudocoarctate cyclization.

During the past decade, the pharmacological potential of indolizines, pyridine-fused heterocycles, has been well recognized. Many indolizines have shown important biological activities, including anti-inflammatory,[1] muscular relaxant,[2] antioxidant,[3] and potential usage as dyes and fluorophores.[4] Although a variety of methods for their synthesis have emerged,[5] there is still significant need for more direct methods to afford functionalized indolizine derivatives. During their work on the practical synthesis of (*Z*)-heteroaromatic vinylacetylenes,[6] Hayford et al. serendipitously found the formation of indolizines upon desilylation of (*Z*)-2-

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pyridine-silylated vinylacetylene with cesium or potassium fluoride and different alcohols as solvents or cosolvents (Figure 1).[7] A mechanistic pathway involving a Michael-type addition to the vinylacetylene and subsequent six-electron electrocyclic ring closure to afford the indolizine was proposed (Figure 1).

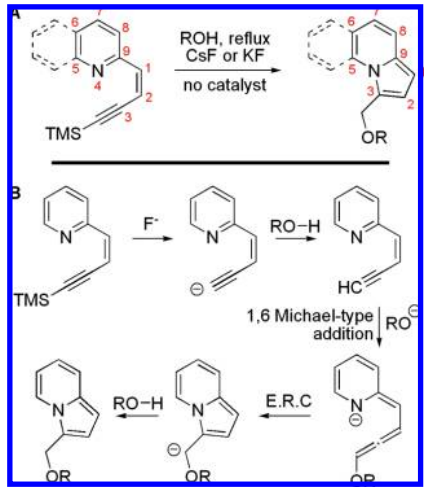
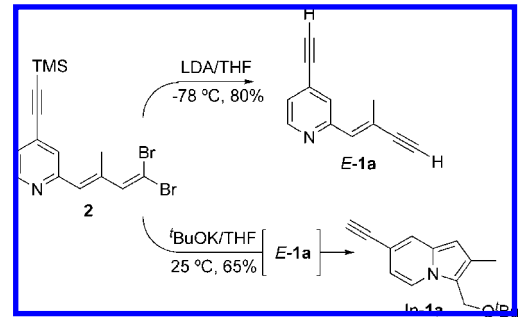


Figure 1. Preliminary studies by Hayford and co-workers. (A) Preparation of indolizines from (Z)-2-pyridine- and quinoline-silylated vinylacetylenes (numbering relative to the indolizine structure). (B) Proposed mechanism for the formation of indolizines from enynylpyridines.

During our studies on the synthesis of the ocular pigment A2E,[8] we observed that the reaction conditions in the preparation of 2-enynylpyridine *E*-**1a** from dibromodienylpyridine **2** were crucial. A range of bases and temperatures led to different results (Scheme 1). When dibromoolefin **2** was treated with a high excess of LDA in THF at −78 °C, enynylpyridine *E*-**1a** was produced in good yield, whereas the use of ^{t}BuOK led to a complex mixture of products.[8] Only when ^{t}BuOK was added in large excess at 25 °C, a single fluorescent product was obtained, which showed high-field shifted ^{1}H NMR signals (7.88, 7.47, and 6.49 ppm) compared to the pyridine moiety. On the basis of NMR analysis (^{1}H, ^{13}C, COSY, HSQC, and HMBC) this compound was identified as the indolizine derivative In-**1a**.

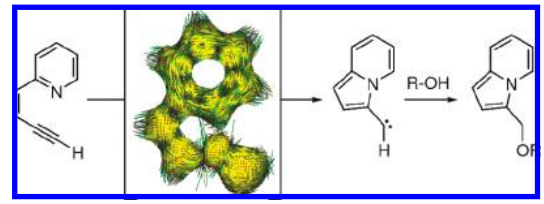
It is noteworthy that, unlike in the work reported by Hayford, the dienylpyridine **2** features a double bond of *E* configuration. This implies that the transformation of **2** into In-**1a** must encompass a double-bond isomerization along with, or previous to, the cyclization. This seems plausible taking into account the proposed mechanism since the Michael-type addition of the base sets a single bond between C1−C2 (Figure 1). However, Haley and Herges propose that similar heterocyclic structures undergo cyclization via a pseudocoarctate process.[9] A pseudocoarctate transition state can be conveniently identified by a disconnection in the

Scheme 1. Results Related to the Synthesis of the Ocular Pigment A2E



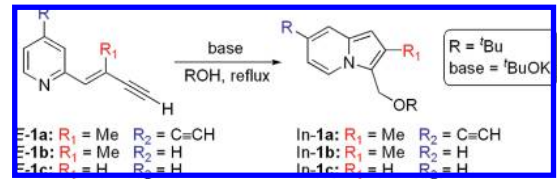
anisotropy of the current-induced density (ACID).[10] This concerted cyclization and its associated pseudocoarctate transition state is illustrated below (Scheme 2). The ACID isosurface at the TS clearly shows a disconnection characteristic to this type of reactions.[11]

Scheme 2. Proposed Pseudocoarctate Pathway for the Formation of Indolizines from Enynylpyridines



In order to gain further insight about this process, we carried out a reactivity study on the enynylpyridines *E*-**1a**, *E*-**1b**, and *E*-**1c** (Scheme 3). The preparation of these enynylpyridines is described in the Supporting Information.

Scheme 3. Enynylpyridines To Be Subjected to Experimental and Computational Reactivity Studies[12]



Interestingly, when submitted to cyclization conditions, enynylpyridine *E*-**1a** readily yielded the corresponding in-

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(12) R = Me for computed structures (see the computational methods).

dolizine In-**1a** at room temperature, and *E*-**1b** also yielded the indolizine product In-**1b** although it required a slightly higher temperature (65 °C). On the contrary, *E*-**1c** proved nonreactive. Different attempts to activate the reaction, such as thermal (115 °C in toluene), nucleophilicity enhancement of the $tBuO^-$ anion by adding a crown ether to capture the base counterion (15-crown-5), or activation of the alkyne with iodine, were unsuccessful.

Given this clear trend in reactivity, we decided to explore the energy landscape of the mechanistic alternatives to the formation of these indolizines. Due to the different nature of the reactions to be modeled (concerted and neutral vs nucleophilic and highly charged), slightly different methodologies where selected in order to accurately describe the species involved.

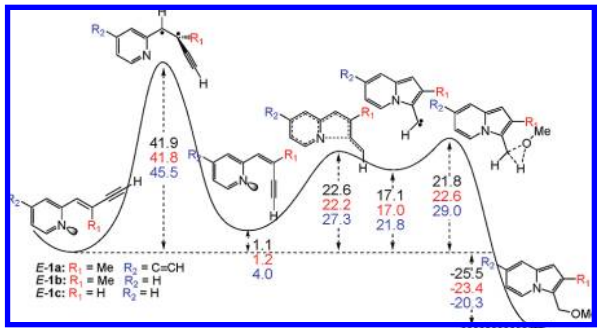

Figure 2. Free energy profile (kcal/mol, 298 K) for the concerted pathway from enynylpiridines *E*-**1a**, *E*-**1b**, and *E*-**1c** to the corresponding indolizines.

All the stationary points involved in this chemistry were computed within the density functional theory scheme.[13] The hybrid exchange functional by Becke[14] together with the correlation formula by Lee, Yang and Parr (LYP)[15] was used with the large 6-31++G(d,p) basis set for C, H, and O. Diffuse functions where included in the basis set due to the presence of negatively charged structures along the nucleophilic profile. Solvation effects were taken into account through a continuum dielectric model (PCM)[16] for the concerted pathway. In the nucleophilic mechanism, explicit microsolvation was included (the reaction was modeled with lithium methoxide complexed to the substrate and two dimethyl ether molecules). The base was modeled as MeOLi to reduce computational cost. Due to the presence of diradical structures, the unrestricted broken symmetry (BS) formulation[17] of B3LYP was employed and wave function stability was checked for all the computations included in this work.[18] The nature of the stationary points was established by analytical computation of harmonic frequencies. All the calculations were performed with the Gaussian03 package.[19]

A computational description of the concerted mechanistic alternative indicates that the double-bond isomerization preceding the pseudocoarctate cyclization involves a very high activation barrier (41.9, 41.8, and 45.5 kcal/mol for *E*-**1a**, *E*-**1b** and *E*-**1c**, respectively, see Figure 2).[20] The remaining steps show activation energies considerably lower. Accessible barriers at working temperatures can be observed for *E*-**1a** and *E*-**1b** (the rate-limiting step would involve an activation energy of ~22 kcal/mol), whereas *E*-**1c** seems to be less prone to undergo both, the pseudocoarctate cyclization (27.3 kcal/mol) and the carbene insertion (29.0 kcal/mol). The energy profiles for this pathway, thus, are quite consistent with the experimental reactivity trends if a low energy alternative for the double-bond isomerization of the *E*-enynylpyridines can be found.

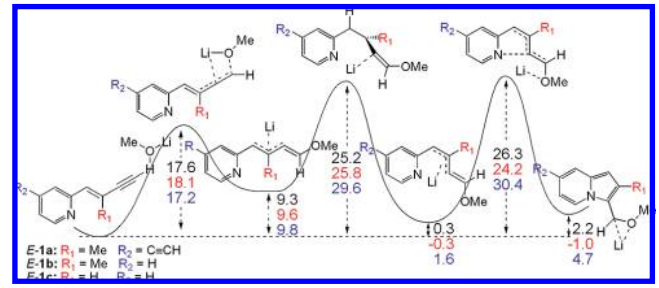

Figure 3. Free energy profile (kcal/mol, 298 K) for the nucleophilic pathway from enynylpiridines *E*-**1a**, *E*-**1b**, and *E*-**1c** to the corresponding indolizines.

The nucleophilic mechanistic alternative does seem compatible with the double-bond isomerization. An energy profile of this alternative is illustrated in Figure 3. After the deprotection of the TMS group, the first and key step in the this mechanism proposed by Hayford and co-workers is the addition of the alkoxide to the enyne. According to our calculations this step takes place with a low barrier of ~18 kcal/mol to give an intermediate complex.[21] According to the energy profile, double-bond isomerization is accessible for *E*-**1a** and *E*-**1b** (rate limiting steps of ~25 kcal/mol) whereas it is significantly higher in energy for *E*-**1c** (29.6 kcal/mol). The final cyclization step follows, approximately, the same trend and similar reaction barriers.

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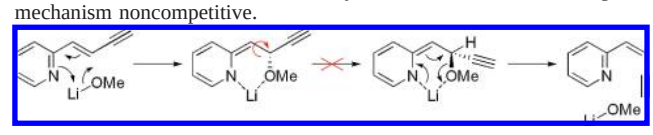
(19) Gaussian 03, Rev. E.01: Frisch, M. J. Gaussian, Inc., Wallingford CT, 2004. See the Supporting Information for the full citation.
(20) These values are, however, lower than the activation energies for ethylene isomerization since the diradical TS is stabilized by conjugation.
(21) An alternative six-centered addition of MeOLi to the substrate could alleviate the ring strain at the transition state. The bond rotation in this alternative is, however, "locked" by Li coordination, rendering this mechanism noncompetitive.



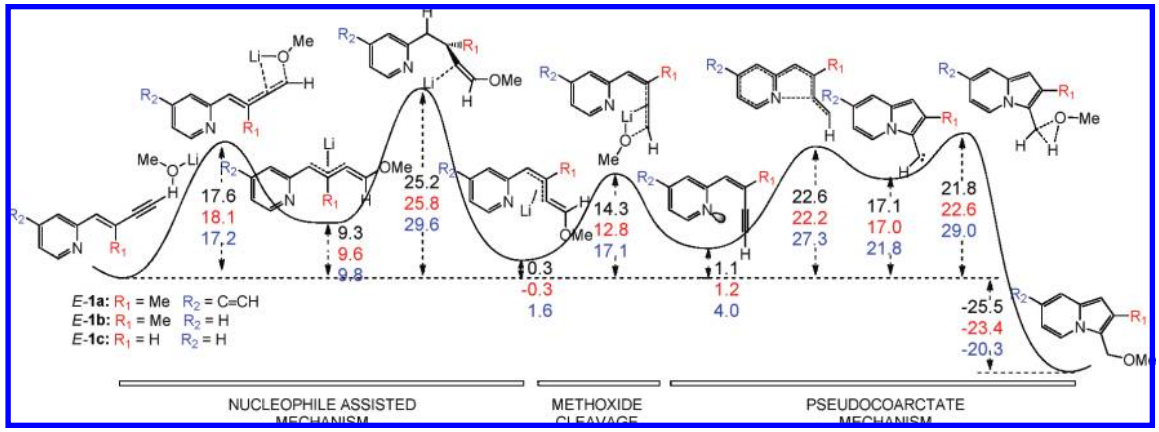
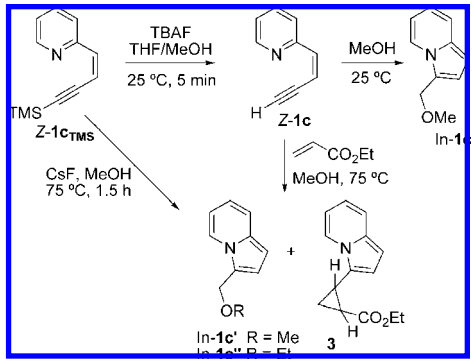


Figure 4. Free energy profile (kcal/mol, 298 K) for the proposed mechanism for the formation of indolizine derivatives from enynylpiridines *E*-**1a**, *E*-**1b**, and *E*-**1c**.

A qualitative comparison between the profiles in Figures 2 and 3 indicates that, indeed, the pseudocoarctate pathway is preferred once the Z-enynylpyridine is formed (the rate-limiting steps being ~23 and ~26 kcal/mol for the concerted and the nucleophilic alternatives, respectively). Thus, if the nucleophile cleavage is energetically accessible after the formal double-bond isomerization has occurred, the lowest energy pathway available to the *E*-enynylpyridine substrate combines both mechanisms: the nucleophile assisted *E*-*Z* isomerization followed by the pseudocoarctate cyclization. We have therefore computed the corresponding additional steps relevant to this hypothesis and illustrated the whole reaction profile in Figure 4. The nucleophile cleavage step involves a low energy transition state and it is therefore more likely to occur than the cyclization step shown in Figure 3.

Scheme 4. Base-Free Cyclization of Enynylpyridine *Z*-**1b** and Intermediate Carbene-Trapping Experiments



If this complex mechanism is indeed operating in the reaction flask, the following characteristics should apply: (1) the nucleophilic base is needed only to activate the double-bond isomerization process, and (2) a carbene intermediate is formed and could therefore be trapped.

The first statement means that any *Z* isomer of the enynylpyridines *E*-**1a** to *E*-**1c** should furnish the corresponding indolizine without base. It also implies that the lack of reactivity shown by the simpler substrate, *E*-**1c**, is due to the high activation barrier of the double-bond isomerization step (29.6 kcal/mol, Figures 3 and 4). The *Z*-**1a**, *Z*-**1b**, and *Z*-**1c** enynylpyridines only need to surmount 21.5, 21.4, and 25.0 kcal/mol rate-limiting barriers to furnish indolizines In-**1a** to In-**1c** via pseudocoarctate cyclization and carbene insertion. Actually, when *Z*-**1c** was subjected to base-free reaction conditions, In-**1c** was obtained (Scheme 4). Additionally, when enynylpyridine ***Z*-1c$_{TMS}$** was deprotected in the presence of ethyl acrylate,[22] the cyclopropane derivative **3**, among other products, was isolated revealing the intermediacy of a carbene.[23]

In summary, computational and experimental evidence supports that a combination of base catalyzed *E*−*Z* isomerization followed by a pseudocoarctate cyclization mechanism is responsible for the transformation of *E*-enynylpyridines into the corresponding indolizines.

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Supporting Information Available: Experimental and computational procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Due to the nucleophilicity of the carbene intermediate, an electrophilic agent is required for successful trapping.

(23) The particular reactivity of this carbene and further work on its cyclization to afford more complex indolizines are underway.