ORGANIC LETTERS

2005
Vol. 7, No. 23
5281−5284

From Ketenimines to Ketenes to Quinolones: Two Consecutive Pseudopericyclic Events

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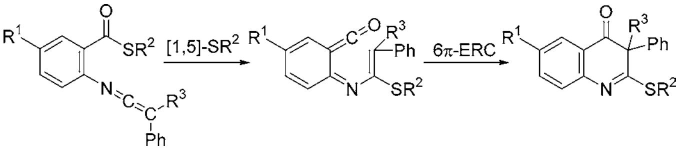
Received September 12, 2005

ABSTRACT



N-[2-(Alkyl- or arylthio)carbonyl]phenyl ketenimines undergo cyclization under mild thermal conditions to afford 2-alkyl(aryl)thio-3*H*-quinolin-4-ones by means of the 1,5-migration of the alkyl(aryl)thio group from the carbonyl carbon to the central carbon atom of the ketenimine fragment followed by the 6π-electrocyclization of the resulting vinyliminoketene. These 1,5-migration and electrocyclization processes occur via transition states whose pseudopericyclic characteristics have been established on the basis of their magnetic properties, geometries, and NBO analyses.

Ketenimines are nitrogenated heterocumulenes $R^1N{=}C{=}CR^2R^3$ whose reactivity can be explained by (1) the electrophilic character of their central carbon atom, accounting for the addition of a variety of nucleophiles[1] and radicals[2] to that center, (2) the nucleophilic nature of their nitrogen atom, which undergoes the attack of electrophilic species and behaves as a donor atom in the formation of metal σ complexes,[3] and (3) their participation in pericyclic processes such as electrocyclic ring closures, [2 + 2] and [4 + 2] cycloaddition reactions, and sigmatropic rearrangements.[1e]

Among the above reactions, the sigmatropic rearrangements of ketenimines have received minor attention. In 1965, Brannock and Burpitt reported the conversion of *N*-(2-alkenyl)amides into 4-pentenenitriles by the action of phosphorus pentachloride and triethylamine.[4] They postulated *N*-(2-alkenyl)ketenimines as reaction intermediates, suggesting that these species undergo a 3-aza-Claisen rearrangement to the unsaturated nitriles. Afterward, Walters[5] and some of us[6] carried out an extensive investigation of this [3,3] rearrangement, which has been also employed as a key step in an efficient asymmetric synthesis of chiral natural products

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[1] For reviews in the chemistry of ketenimines, see: (a) Krow, D. R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 435. (b) Gambaryan, N. P. *Usp. Khim.* **1976**, *45*, 1251. (c) Dondoni, A. *Heterocycles* **1980**, *14*, 1547. (d) Barker, M. W.; McHenry, W. E. In *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai, S., Ed.; Wiley-Interscience: Chichester, U.K., 1980; Part 2, p 701. (e) Alajarín, M.; Vidal, A.; Tovar, F. *Targets Heterocycl. Syst.* **2000**, *4*, 293.

[2] (a) Alajarín, M.; Vidal, A.; Ortín, M.-M. *Tetrahedron Lett.* **2003**, *44*, 3027. (b) Alajarín, M.; Vidal, A.; Ortín, M.-M. *Org. Biomol. Chem.* **2003**, *1*, 4282. (c) Alajarín, M.; Vidal, A.; Ortín, M.-M.; Bautista, D. *New J. Chem.* **2004**, *28*, 570. (d) Alajarín, M.; Vidal, A.; Ortín, M.-M.; Bautista, D. *Synlett* **2004**, 991.

[3] (a) Aumann, R. *Chem. Ber.* **1993**, *126*, 1867. (b) Merlic, C. A.; Burns, E. E. *Tetrahedron Lett.* **1993**, *34*, 5401.

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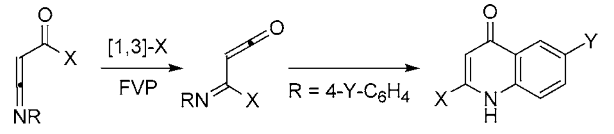
[6] (a) Molina, P.; Alajarín, M.; López-Leonardo, C. *Tetrahedron Lett.* **1991**, *32*, 4041. (b) Molina, P.; Alajarín, M.; López-Leonardo, C.; Alcántara, J. *Tetrahedron* **1993**, *49*, 5153.

10.1021/ol052189v CCC: $30.25

such as (+)-canadensolide, (+)-santolinolide B, and (−)-santolinolide A.[7]

Wentrup has extensively studied the reversible acyl ketenimine to imidoyl ketene rearrangement via [1,3] sigmatropic shifts of a range of atoms and groups of atoms under flash vacuum pyrolysis (FVP) conditions (Scheme 1).[8a−h] Within this framework, (*N*-aryl)imidoyl ketenes underwent further 6π-electrocyclization to quinolones.[8b,d−f,9]

Scheme 1. [1,3] Sigmatropic Shifts in Acylketenimines

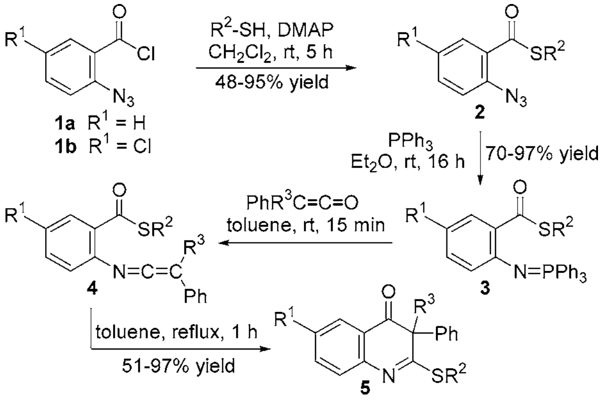


Only three examples of [1,5] sigmatropic shifts in ketenimines have been reported, and all of them involve a [1,5] hydrogen atom transfer to the central carbon atom of the keteminine.[10]

In our effort to develop new reactions of ketenimines, we decided to prepare *N*-[2-(alkyl- or arylthio)carbonyl]phenyl ketenimines, with the aim of testing the viability of the [1,5] migration of the electron-rich alkyl(aryl)thio group from the carbonyl carbon to the electron-deficient central carbon atom of the ketenimine fragment. Here, we report the results obtained in the thermally induced cyclization of such ketenimines, which, in fact, undergo a facile [1,5] sigmatropic migration of the alkyl(aryl)thio group and subsequent 6π-electrocyclic ring closure (ERC) to afford 2-alkyl(aryl)thio-3*H*-quinolin-4-ones. We also present a computational study of the mechanism of these conversions showing that both the [1,5] migration and the electrocyclization steps take place through transition states of pseudopericyclic nature.

The reactions of 2-azidobenzoyl chloride **1a** and 2-azido-5-chlorobenzoyl chloride **1b** with alkyl and arylthiols, in dichloromethane solution and in the presence of a slight excess of 4-(dimethylamino)pyridine, afforded the 2-azidothiobenzoates **2**. Triphenylphosphazenes **3** were prepared by treating diethyl ether solutions of azides **2** with triphenylphosphane. Aza-Wittig reactions of compounds **3** with a stoichiometric amount of diphenylketene or methylphenylketene, in toluene solution, gave *N*-[2-alkyl(aryl)thiocarbonyl]phenyl ketenimines **4**, whose formation was confirmed by the presence of very strong absorptions around 2000 cm^{-1} in the IR spectra of the reaction mixtures, associated to the N═C═C grouping. Furthermore, ketenimine **4a** (R^1 = H; R^2 = 4-$CH_3C_6H_4$; R^3 = Ph) was isolated and fully identified. The toluene solutions containing ketenimines **4** were heated at reflux temperature up to total disappearance of the cumulenic band in their IR spectra, approximately for 1 h. Column chromatography of the final reaction mixtures obtained from this thermal treatment allowed the isolation of pure 2-alkyl(aryl)thio-3*H*-quinolin-4-ones **5** in acceptable yields (Scheme 2, Table 1).

Scheme 2. Synthesis of 3*H*-Quinolin-4-ones **5**



The utilization of a chiral thiol in the sequence leading to **5i** yielded a 1:1 mixture of two diastereomeric quinolones.

The structural determination of the 2-alkyl(aryl)thio-3*H*-quinolin-4-ones **5** was achieved following their analytical and spectral data and unequivocally established by the X-ray

Table 1. 3*H*-Quinolin-4-ones **5**

compd	R^1	R^2	R^3	yield (%)
5a	H	4-$CH_3C_6H_4$	Ph	74
5b	H	4-$CH_3C_6H_4$	Me	52
5c	H	4-$CH_3OC_6H_4$	Ph	89
5d	H	4-C_5H_4N	Ph	79
5e	Cl	4-$CH_3C_6H_4$	Ph	97
5f	Cl	4-$CH_3OC_6H_4$	Ph	95
5g	Cl	4-$CH_3OC_6H_4$	Me	76
5h	H	4-$CH_3OC_6H_4CH_2$	Ph	83
5i	H	$C_6H_5(CH_3)CH$	Me	58[a]
5j	Cl	4-$CH_3OC_6H_4CH_2$	Ph	51
5k	H	$C_6H_5CH_2CH_2$	Ph	85
5l	H	2-$IC_6H_4CH_2CH_2$	Ph	90

[a] Isolated as a 1:1 mixture of two diastereoisomers

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structure determination of a monocrystal of **5a** ($R^1 = H$; $R^2 = 4\text{-}CH_3C_6H_4$; $R^3 = Ph$) (Figure 1).

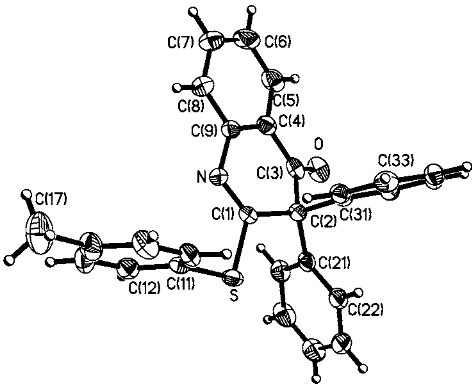
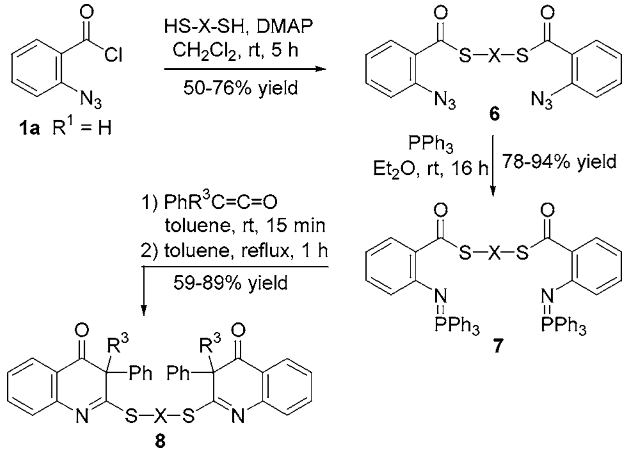


Figure 1. X-ray structure of **5a**.

The reactions of 2-azidobenzoyl chloride **1a** with α,ω-dithiols provided bis(azides) **6**, which by a sequence of reactions similar to that shown in Scheme 1 were converted into the bis(3*H*-quinolin-4-ones) **8** (Scheme 3, Table 2). In compounds **8**, two quinolin-4-one rings are linked via their respective C2 carbon atoms by a propylene, 1,2-phenylene, or 1,3-phenylene dithioether chain. Bis(3*H*-quinolin-4-ones) **8b**, **8d,** and **8f**, in which R^3 is a methyl group, were obtained as 1:1 mixtures of their two diastereoisomers.

Scheme 3. Synthesis of Bis(3*H*-quinolin-4-ones) **8**



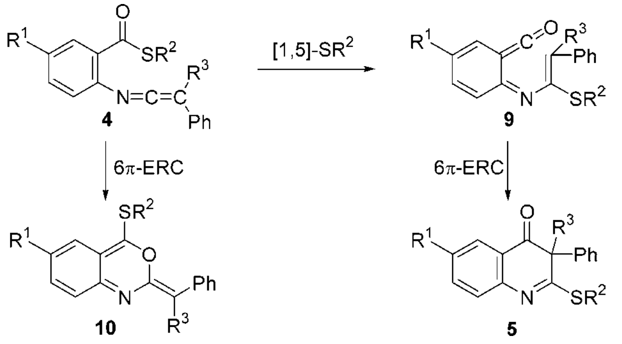
The most reasonable mechanistic explanation for the conversion of ketenimines **4** into the 3*H*-quinolin-4-ones **5** is as follows: first, the alkyl(aryl)thio group undergoes [1,5] migration from the carbonyl carbon to the central carbon atom of the ketenimine moiety, giving rise to vinyliminoketenes **9**, which, in turn, are converted into the final 3*H*-quinolin-4-ones **5** through a 6π electrocyclic ring closure that involves the conjugated 3-azatriene fragment of their 1-oxa-5-aza-1,2,4,6-heptatetraene system. It is conceivable that ketenimines **4** may experience cyclization by an alternative pathway: a 6π electrocyclization involving their conjugated 1-oxa-5-azahexatrienic system to give the 3,1-benzoxazines **10** (Scheme 4). This does not seem to be the case, as these compounds were not detected in the ^1H NMR spectra of the crude materials obtained from the thermal treatment of ketenimines **4** before the purification step.

Table 2. Bis(3*H*-quinolin-4-ones) **8**

compd	X	R^3	yield (%)
8a	$CH_2CH_2CH_2$	Ph	89
8b	$CH_2CH_2CH_2$	Me	61[a]
8c	1,2-C_6H_4	Ph	64
8d	1,2-C_6H_4	Me	63[a]
8e	1,3-C_6H_4	Ph	70
8f	1,3-C_6H_4	Me	59[a]

[a] Isolated as a 1:1 mixture of two diastereoisomers.

Scheme 4. Proposed Mechanism for the Conversion **4** → **5**



We have studied the mechanism of the sequence **4** → **9** → **5** by ab initio and DFT calculations using Gaussian 98.[11] Geometry optimizations were attempted first at the RHF/6-31G* level[12] and then with the B3LYP[13] functional using the 6-31+G* basis set. Second-order perturbation analyses were achieved with the NBO (natural bond orbital) method.[14]

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(11) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Repogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

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NICS (nucleus-independent chemical shifts) values were obtained at the B3LYP/6-31+G* level with the GIAO (gauge-independent atomic orbital) method.[15] For modeling the ketenimines **4** used in the experimental study, we selected the simplest structure **11** and explored the potential energy surface associated to its transformation into 2-thiohidroxy-4(3*H*)-pyridinone **13** (Figure 2). The theoretical study predicts that this transformation occurs by a two-step pathway starting by the [1,5] shift of the SH group via the transition structure **TS1** leading to the intermediate vinyliminoketene **12**. In the second step, this ketene undergoes a 6π-ERC through **TS2** providing the pyridinone **13**. At the B3LYP/6-31+G* theoretical level, the energy barriers associated to the first and second steps are 16.75 and 1.51 kcal·mol^{-1}, respectively. The overall transformation of ketenimine **11** into the pyridinone **13** is exothermic by 25.36 kcal·mol^{-1}.

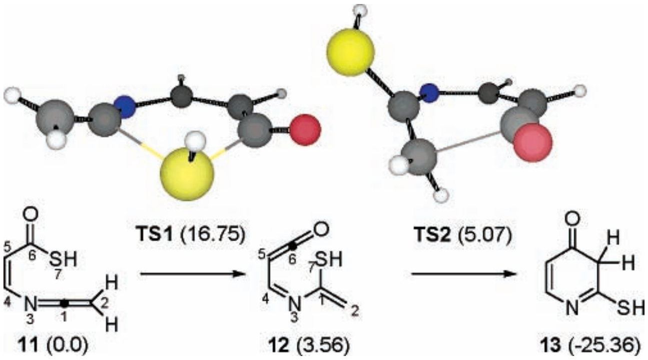

Figure 2. B3LYP/6-31+G*-optimized geometries and energetics for the [1,5]-SH shift of **11** leading to **12** and the 6π-ERC of **12** into **13**. Energies are given in kcal·mol^{-1} relative to reactant (zero-point vibrational energy corrections have been applied, but not scaled).

Both processes, i.e., the [1,5]-SH shift and the 6π-ERC, have energy barriers lower than those expected for normal pericyclic paths,[16,17] and the geometries of their transition structures, **TS1** and **TS2**, are also notably different than those expected for transition states with pericyclic topologies.

On the basis of the geometries and magnetic properties of **TS1** and **TS2** and the results of the second-order perturbation analyses showing the delocalization energies of electrons from filled NBOs into empty NBOs, we have established the *pseudopericyclic*[18,19] nature of both transition states. They are not aromatic (the computed NICS at the ring critical point of the electronic density[20] are +0.13 and −3.20 ppm·mol^{-1}, respectively). The NBO analysis of **TS1** shows bonding between a sulfur lone pair and the π*C1−N3 natural localized orbital ($\Delta E(2)_{\mathrm{Lp(2)S7}\rightarrow\pi^*\mathrm{C1-N3}}$ = 88.7 kcal·mol^{-1}). Thus, the new, partially formed σ-C1−S7 bond results from the interaction between a lone pair of the sulfur atom (which changes from non bonding sp^2 orbital to bonding sp^3 orbital) and a p orbital of the C1═N3 bond (the LUMO of the ketenimine moiety initially placed perpendicular to the molecular plane). In **TS2**, the forming σ-bond C2−C6 is due mainly to the interaction between the πC1−C2 and the π*C6−O (the LUMO of the ketene fragment placed in the molecular plane) natural localized orbitals ($\Delta E(2)_{\pi\mathrm{C1-C2}\rightarrow\pi^*\mathrm{C6-O}}$ = 20.6 kcal·mol^{-1}), instead of the interaction between the natural localized orbitals πC1−C2/π*C5−C6 and πC5−C6/π*C1−C2 expected for a transition state with normal pericyclic topology.

Acknowledgment. This work was supported by the MCYT and FEDER (Project BQU2001-0010) and Fundación Séneca-CARM (Project 00458/PI/04). M.-M.O. thanks Fundación Cajamurcia for a fellowship.

Supporting Information Available: Experimental details for the synthesis of compounds **2**−**5** and **6**−**8** and their characterization (NMR, IR, MS, elemental analyses). X-ray data and CIF file for **5a**. B3LYP/6-31+G*-optimized Cartesian coordinates for minima and transition structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The calculated energy barrier for the prototypical 6π-ERC of hexatriene into cyclohexadiene is 29.9 kcal·mol^{-1}; see: Guner, V. A.; Houk, K. N.; Davies, I. W. *J. Org. Chem.* **2004**, *69*, 8024 and references cited therein.

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(19) For reports on pseudopericyclic 6π-electrocyclic ring closures see ref 17a and: (a) Luo, L.; Bartberger, M. D.; Dolbier, W. R. *J. Am. Chem. Soc.* **1997**, *119*, 12366. (b) Zora, M. *J. Org. Chem.* **2004**, *69*, 1940. (c) Alajarín, M.; Sánchez-Andrada, P.; Cossío, F. P.; Arrieta, A.; Lecea, B. *J. Org. Chem.* **2001**, *66*, 8470. (d) Alajarín, M.; Sánchez-Andrada, P.; Vidal, A.; Tovar, F. *J. Org. Chem.* **2005**, *70*, 1340. (e) De Lera. A. R. ; Alvarez, R.; Lecea, B.; Torrado, A.; Cossío, F. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 557. (f) Cabaleiro-Lago, E. M.; Rodríguez-Otero, J.; Varela-Varela, S. M.; Peña-Gallego, A.; Hermida-Ramón, J. M. *J. Org. Chem.* **2005**, *70*, 3921.

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