ORGANIC LETTERS

2006
Vol. 8, No. 24
5645−5648

Hydricity-Promoted [1,5]-H Shifts in Acetalic Ketenimines and Carbodiimides

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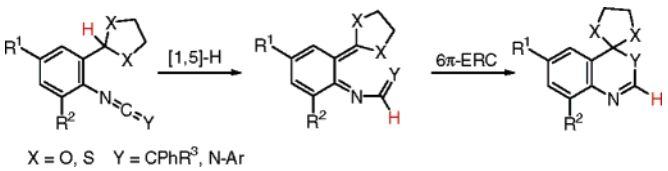
Received September 27, 2006

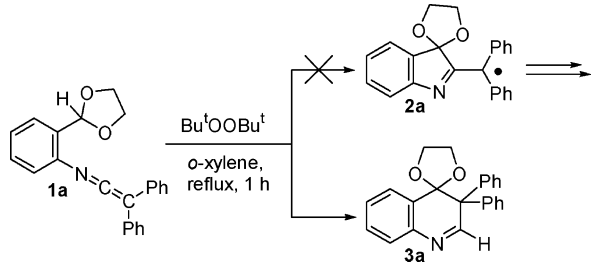
ABSTRACT



2-Monosubstituted 1,3-dioxolanes and dithiolanes act as hydride-releasing fragments, transferring intramolecularly their acetalic H atom to the central carbon of ketenimine functions. The presumed products of these migrations, *o*-quinomethanimines, undergo in situ 6π-electrocyclization. A computational study supports this mechanism and the hydride-shift character of the first step. Carbodiimides were also suitable substrates, although less reactive.

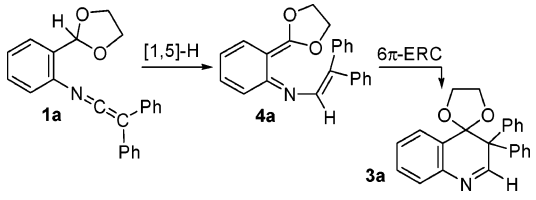
While investigating the addition of carbon radicals to ketenimines[1] we attempted the generation of a "protected acyl" radical by abstracting the acetalic H atom of the acetal-ketenimine **1a** with *tert*-butoxy radicals.[2] Our aim was that once formed, the new radical would add to the central carbon atom of the ketenimine function for leading to the (2-indolyl)-(diphenyl)methyl radical **2a** and from this to more complex indoles.[1a−c] We found that the actual product of this reaction turned out to be the carbonyl-protected 4-quinolone **3a** (Scheme 1). In compound **3a** the original acetalic hydrogen of **1a** is now situated at carbon 2 of its 3,4-dihydroquinoline ring system, whereas the new six-membered ring appearing in **3a** is formed by connecting the original acetalic carbon of **1a** with the terminal carbon of its ketenimine function.

Scheme 1. Cyclization of Ketenimine **1a**



We interpreted this result in mechanistic terms as the [1,5] migration of the acetalic proton of **1a** to the central heterocumulenic carbon, thus leading to the reactive intermediate *o*-quinomethanimine **4a**, followed by its 6π-electrocyclization to **3a** (Scheme 2).

Scheme 2. Proposed Mechanism for the Conversion **1a** → **3a**



In fact, we proved that the conversion **1a** → **3a** occurred by refluxing a toluene solution of **1a** for 1 h, in the absence

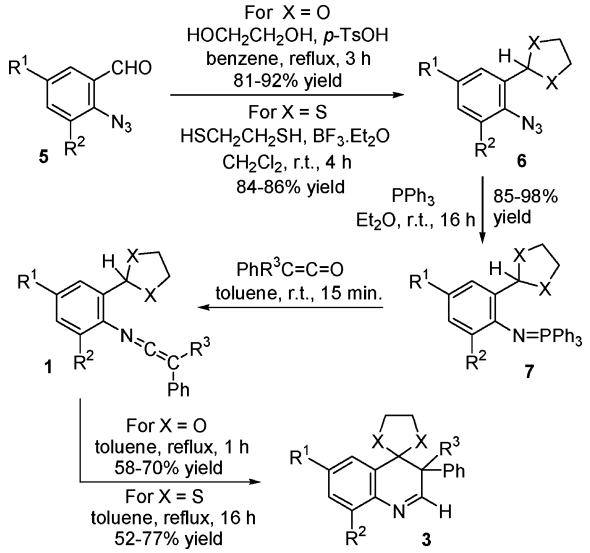
(1) (a) Alajarín, M.; Vidal, A.; Ortín, M.-M. *Tetrahedron Lett.* **2003**, *44*, 3027. (b) Alajarín, M.; Vidal, A.; Ortín, M.-M. *Org. Biomol. Chem.* **2003**, *1*, 4282. (c) Alajarín, M.; Vidal, A.; Ortín, M.-M.; Bautista, D. *New J. Chem.* **2004**, *28*, 570. (d) Alajarín, M.; Vidal, A.; Ortín, M.-M.;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

10.1021/ol062373w CCC: $33.50 © 2006 American Chemical Society
Published on Web 10/28/2006

of radical-promoting reagents. The proposed intermediate **4a** was neither isolated nor detected by following the reaction by ^{1}H and ^{13}C NMR experiments (toluene-d_8, 100 °C, 1.5 h), in which starting **1a** and final **3a** revealed as the only components of the reaction mixture.

Following these initial experiments, we examined similar transformations for a series of acetal-ketenimines **1a**−**e** (X = O) and dithioacetal-ketenimines **1f**−**h** (X = S), prepared from the corresponding 2-azidobenzaldehydes **5** by the synthetic sequence summarized in Scheme 3, via the azido-

Scheme 3. Preparation of 3,4-Dihydroquinolines **3**



acetals and dithioacetals **6**, their respective iminophosphoranes **7**, and finally by the aza-Wittig reaction of the latter with disubstituted ketenes. When toluene solutions of acetal-ketenimines **1a**−**e** (X = O) were heated at reflux temperature for 1 h, the corresponding spiro[1,3-dioxolane-2,4′(3′*H*)-quinolines] **3a**−**e** (X = O), members of a previously unknown heterocyclic system, were cleanly obtained in fair to good yields (Table 1). In a similar way, the dithioacetal-

Table 1. Quinolines **3**

compd	X	R^1	R^2	R^3	yield (%)
3a	O	H	H	Ph	70
3b	O	H	H	CH_3	58
3c	O	CH_3	H	Ph	68
3d	O	Cl	H	Ph	68
3e	O	H	CH_3	Ph	67
3f	S	H	H	Ph	74
3g	S	H	H	CH_3	52
3h	S	Cl	H	Ph	77

ketenimines **1f**−**h** (X = S) were converted into the spiro-heterocycles **3f**−**h** (X = S), although with the remarkable difference of requiring longer reaction times (16 h in refluxing toluene).

Whereas ketenimines are known to participate in a variety of cycloaddition reactions and 6π-electrocyclizations,[3] only a few examples of sigmatropic rearrangements[4] and sigmatropic shifts of atoms or groups of atoms[5] in ketenimines have been reported so far.

From these latter, the [1,3] sigmatropic shifts of different electron-rich groups to the central carbon of ketenimines reported by Wentrup[5a−h] are the best studied. To our knowledge, only five cases of [1,5] sigmatropic shifts[5m−r] involving ketenimine functions have been reported, four of them involving a H transfer to their central carbon.[5m−p]

One of these, also due to Wentrup,[5o] is closely related to our present results. It occurs in *N*-aryl ketenimines bearing a methyl group at the ortho position, which experience [1,5] shift of one of the CH_3 protons and subsequent 6π-electrocyclization to 3,4-dihydroquinolines when they were generated under flash vacuum thermolysis conditions (400−700 °C). To check if such *N*-(*o*-tolyl)ketenimines would also behave similarly under the mild thermal conditions of the conversion **1** → **3** we submitted the known ketenimine **8**[6] to heating in toluene solution at reflux temperature, but after 48 h it still remained unchanged (Scheme 4). After the same solution was heated in a sealed tube at 180 °C for 24 h compound **8** was also recovered intact.

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(3) 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, UK, 1980; Part 2, p 701. (e) Alajarín, M.; Vidal, A.; Tovar, F. *Targets Heterocycl. Syst.* **2000**, *4*, 293.

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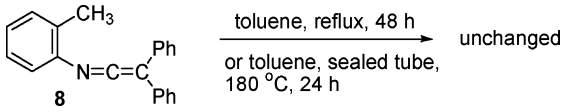
(5) For articles dealing with [1,3] migrations in ketenimines, see: (a) Cheikh, A. B.; Chuche, J.; Manisse, N.; Pommelet, J. C.; Netsch, K.-P.; Lorencak, P.; Wentrup, C. *J. Org. Chem.* **1991**, *56*, 970. (b) Kappe, C. O.; Kollenz, G.; Leung-Toung, R.; Wentrup, C. *J. Chem. Soc., Chem. Commun.* **1992**, 487. (c) Kappe, C. O.; Kollenz, G.; Netsch, K.-P.; Leung-Toung, R.; Wentrup, C. *J. Chem. Soc., Chem. Commun.* **1992**, 488. (d) Fulloon, B.; El-Nabi, H. A. A.; Kollenz, G.; Wentrup, C. *Tetrahedron Lett.* **1995**, *36*, 6547. (e) Fulloon, B. E.; Wentrup, C. *J. Org. Chem.* **1996**, *61*, 1363. (f) Ramana Rao, V. V.; Wentrup, C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2583. (g) Wentrup, C.; Ramana, Rao, V. V.; Frank, W.; Fulloon, B. E.; Moloney, D. W. J.; Mosandl, T. *J. Org. Chem.* **1999**, *64*, 3608. (h) Finnerty, J. J.; Wentrup, C. *J. Org. Chem.* **2004**, *69*, 1909. (i) Aumann, R.; Heinen, H. *Chem. Ber.* **1988**, *121*, 1739. (j) Clarke, D.; Mares, R. W.; McNab, H. *J. Chem. Soc. Chem. Commun.* **1993**, 1026. (k) Clarke, D.; Mares, R. W.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1799. (l) Amsallem, D.; Mazières, S.; Piquet-Fauré, V.; Gornitzka, H.; Baceiredo, A.; Bertrand G. *Chem. Eur. J.* **2002**, *8*, 5306. For articles dealing with [1,5] migrations in ketenimines, see: (m) Goerdeler, J.; Lindner, C.; Zander, F. *Chem. Ber.* **1981**, *114*, 536. (n) Morel, G.; Marchand, E.; Foucaud, A. *J. Org. Chem.* **1985**, *50*, 771. (o) Ramana, Rao, V. V.; Fulloon, B. E.; Bernhardt, P. V.; Koch, R.; Wentrup, C. *J. Org. Chem.* **1998**, *63*, 5779. (p). Alajarín, M.; Vidal, A.; Ortín, M.-M. *Tetrahedron* **2005**, *61*, 7613. (q) Alajarín, M.; Ortín, M.-M.; Sánchez-Andrada, P.; Vidal, A.; Bautista, D. *Org. Lett.* **2005**, *7*, 5281. (r) Alajarín, M.; Ortín, M.-M.; Sánchez-Andrada, P.; Vidal, A. *J. Org. Chem.* **2006**, *71*, 8126−8139.

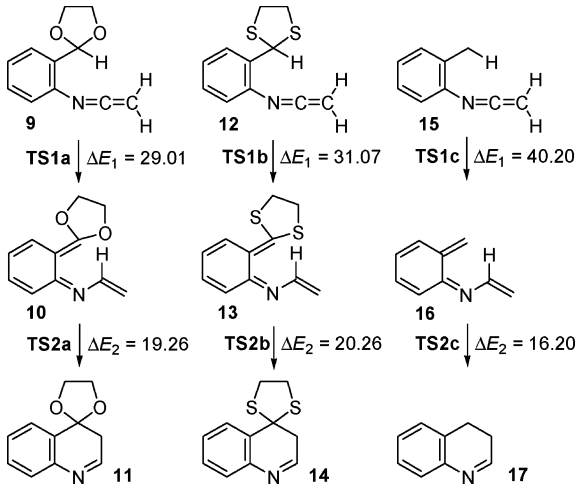
(6) Stevens, C. L.; Singhal, G. H. *J. Org. Chem.* **1964**, *29*, 34.

Scheme 4. Thermal Treatment of Ketenimine **8**



The comparison of the thermal stability of **8** in solution with the easy transformation of ketenimines **1** into spiroheterocycles **3** under milder conditions clearly reveals that the acetal function of **1** (and, to a lesser extent, the dithioacetal group) favors the occurrence of the tandem [1,5]-H shift/electrocyclization. To find reasons for explaining the beneficial influence of the acetal and dithioacetal functions to such conversions we carried out a computational study at the B3LYP/6-31+G** theoretical level of the three reaction sequences shown in Scheme 5: model ketenimines with

Scheme 5. B3LYP/6-31+G** Energy Barriers (kcal·mol^{-1})



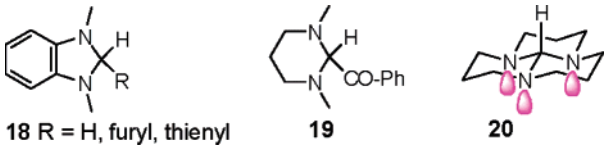
acetal (**9** → **11**) and dithioacetal (**12** → **14**) functions at the benzylic carbon and the unsubstituted case (**15** → **17**) for comparison. The results of this study are summarized in that scheme.

By comparing the computed energy barriers it seems obvious that in all cases the [1,5]-H shift is the rate determining step, and that the presence of the acetal function is favorable (lowering more than 11 kcal·mol^{-1} the barrier of the first step, in relation to the unsubstituted case) as well as that of the dithioacetal group although in a lesser extent, in coincidence with the experimental work.

How to explain the positive role of the acetal and dithioacetal functions in these [1,5]-H shifts? Our proposal is that these migrations can be understood as *hydride shifts*[7] and are facilitated by the *hydricity* of the acetalic functions.

The term *hydricity* has been coined as substitutive of hydride transfer (or hydride donor) ability. Typical chemicals possessing hydricity are mainly the metal hydrides, but also NADH-like compounds and triarylmethane derivatives.[8] The thermodynamic[8,9] and kinetic[10] hydricities of some of these hydride donors have been measured, and some hydricity scales are available.[8,9a,c] Apart from these, other classes of "organic hydride" systems have emerged in the last years, mainly in the search of new opportunities for chemical hydrogen storage. Among them there are nitrogenated heterocycles such as *N*,*N*-dimethylbenzimidazoles **18**,[7c,11] 2-benzoyl-*N*,*N*-dimethylperhydropyrimidine **19**,[9c] and orthoformamides **20**[12] (Chart 1).

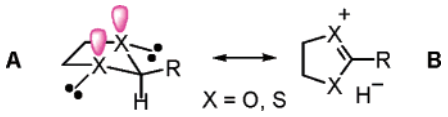
Chart 1. Examples of "Organic Hydride" Systems



The remarkable hydricity of **20** is explained as a consequence of its preference for the conformation drawn in Chart 1, in which the central C−H bond is weakened and polarized by the three antiperiplanar lone pairs at nitrogen.[12] It is a hyperconjugative interaction between the lone pair electrons and the σ^*(C−H) orbital that induces a weakening of the C−H bond and an increase of negative charge density at the hydrogen atom.

Although the 1,3-dioxolane and dithiolane functions have not been explicitly recognized as imparting hydricity yet,[13] they count with two antiperiplanar O or S atom lone pairs which can confer hydride-like character to their H atoms at C2, as represented in structure **A** and expressed by resonance with the canonical structure **B** (Chart 2). Taking this into

Chart 2. 2-Monosubstituted 1,3-Dioxolanes and 1,3-Dithiolanes



account as well as the electrophilic nature of the central carbon atom of a ketenimine function,[3d] the [1,5]-H shift occurring in compounds **1** can be reasonably qualified as a *hydride shift*.

(7) Many H shifts have been qualified as "hydride shifts". For a review on hydride shifts and transfers, see: (a) Watt, C. I. F. *Adv. Phys. Org. Chem.* **1988**, *24*, 57. For some representative recent examples, see: (b) Kawai, H.; Takeda, T.; Fujiwara, K.; Suzuki, T. *J. Am. Chem. Soc.* **2005**, *127*, 12172. (c) Schwarz, D. E.; Cameron, T. M.; Hay, P. J.; Scott, B. L.; Tumas, W.; Thorn, D. L. *Chem. Commun.* **2005**, 5919. (d) Birsa, M. L.; Jones, P. G.; Hopf, H. *Eur. J. Org. Chem.* **2005**, 3263. (e) O'Leary, J.; Formosa, X.; Skranc, W.; Wallis, J. D. *Org. Biomol. Chem.* **2005**, *3*, 3273. (f) Burk, S.; Gudat, D.; Nieger, M.; Du Mont, W.-W. *J. Am. Chem. Soc.* **2006**, *128*, 3946.

(8) Ellis, W. W.; Raebiger, J. W.; Curtis, C. J.; Bruno, J. W.; DuBois, D. L. *J. Am. Chem. Soc.* **2004**, *126*, 2738.

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In fact, the computed NBO analysis of ketenimines **9** and **12** shows that the $n_x \rightarrow \sigma^*_{C-H}$ hyperconjugative interactions are the dominant ones among those involving the acetalic C−H bond (see the Supporting Information). The "charge transfer" from the lone pairs at the O and S atoms weakens that C−H bond, and this interaction is stronger in acetal-ketenimine **9** than in dithioacetal-ketenimine **12**.[14]

We have also tested similar reactions involving carbodiimide functions in compounds **21**, easily prepared from iminophosphoranes **7** (X = O) and aryl isocyanates by aza-Wittig type reactions (Scheme 6). The cyclization of carbodiimides **21** to the spirocyclic dioxolanoquinazolines **22**, presumably via similar consecutive [1,5]-H shifts and electrocyclizations, required stronger conditions (refluxing *o*-xylene, 24−36 h) than their analogous ketenimines **1** (Scheme 6 and Table 2).

Scheme 6. Preparation of Spirocyclic Dioxolanoquinazolines **22**

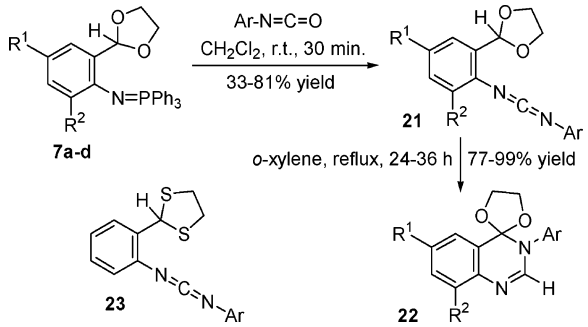

Table 2. Quinazolines **22**

compd	R^1	R^2	Ar	yield (%)
22a	H	H	4-CH_3O-C_6H_4	81
22b	H	CH_3	4-Br-C_6H_4	98
22c	H	CH_3	4-Cl-C_6H_4	97
22d	H	CH_3	4-CH_3-C_6H_4	99
22e	CH_3	H	4-Br-C_6H_4	77
22f	CH_3	H	4-Cl-C_6H_4	85

As expected, dithioacetalic carbodiimides **23** were less reactive and we were not able to achieve their cyclization under two different thermal conditions essayed (either *o*-xylene, reflux, 72 h or toluene, 180 °C, sealed tube, 48 h).

In summary, we have disclosed in this letter new [1,5]-H shifts that occur under unusually mild thermal conditions and proposed a rational explanation based on their characterization as *hydride shifts*. We believe that our results allow the inclusion of the monosubstituted 1,3-dioxolane and dithiolane functions into the ensemble of hydricity-imparting functionalities. To our knowledge this is the first synthetic utilization of hydride-releasing fragments for promoting intramolecular H shifts, a strategy that presumably will find further applications. Our current efforts are directed to this end.

Acknowledgment. This work was supported by the DGES and FEDER (Project CTQ2005-02323/BQU) and Fundación Séneca-CARM (Project 00458/PI/04). Two of us (M.-M.O. and B.B.) thank Fundación Cajamurcia and Fundación Séneca-CARM for the respective fellowships.

Supporting Information Available: Experimental details for the synthesis of compounds **6**, **7**, **1a**, **3**, **21**, and **22** and their full characterization; details of computational procedures, geometries, Cartesian coordinates, and energies for all the stationary points; selected interactions from the NBO analyses; and NMR spectra of compounds **1a**, **3**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062373W

(10) (a) Cheng, T.-Y.; Bullock, R. M. *Organometallics* **2002**, *21*, 2325. (b) Cheng, T.-Y.; Brunschwing, B. S.; Bullock, R. M. *J. Am. Chem. Soc.* **1998**, *120*, 13121. (c) Cheng, T.-Y.; Bullock, R. M. *Organometallics* **1995**, *14*, 4031.

(11) (a) Lee, I.-S. H.; Jeoung, E. H. *J. Org. Chem.* **1998**, *63*, 7275. (b) Montgrain, F.; Ramos, S. M.; Wuest, J. D. *J. Org. Chem.* **1988**, *53*, 1489.

(12) Brunet, P.; Wuest, J. D. *J. Org. Chem.* **1996**, *61*, 2020 and references cited therein.

(13) Exceptionally, the cationic polymerization of cyclic acetals has been proposed to be initiated by an hydride transfer step from the acetal to the cationic initiator, see: Penczek, S. *Makromol. Chem.* **1974**, *175*, 1217−1252 and references cited therein.

(14) It is known that the hyperconjugative interactions $n_x \rightarrow \sigma^*_{C-H}$ involving lone pairs at oxygen atoms are stronger than those involving sulfur atoms in analogous compounds. See: Alabugin, I. V. *J. Org. Chem.* **2000**, *65*, 3910−3919 and referenced cited therein.