Pergamon

Tetrahedron Letters 43 (2002) 6259–6261

TETRAHEDRON LETTERS

Highly stereocontrolled [2+2] cycloaddition versus unprecedented imino-ene reactions of imino-ketenimines

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Received 3 June 2002; revised 26 June 2002; accepted 27 June 2002

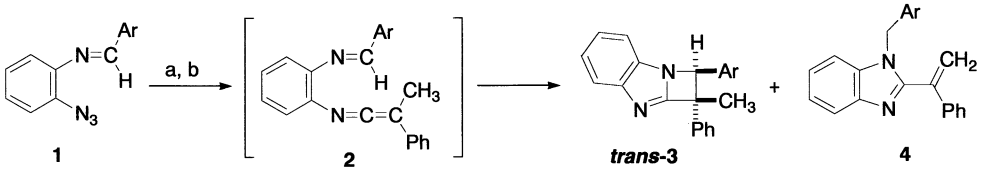
Abstract—*N*-[(2-Benzylideneamino)phenyl]-*C*-methylketenimines undergo intramolecular cyclization via two different reaction pathways, a [2+2] cycloaddition and a rare imino-ene reaction, to yield azeto[1,2-*a*]benzimidazoles and 2-(α-styryl)benzimidazoles, respectively. The results are interpreted in terms of a two-step mechanism involving two stereoisomeric conjugated betaines as intermediates.

Probably the most versatile chemical behavior of ketenimines is their participation in formal pericyclic processes, such as cycloaddition reactions, electrocyclic ring closures and sigmatropic rearrangements.[1–6] Amongst these reactions of ketenimines, [4+2] and [2+2] cycloaddition processes have attracted most attention, whereas electrocyclic ring closures and sigmatropic rearrangements are also well documented. By contrast, the participation of ketenimines in ene-type reactions is practically unknown.

Recently, we have reported on the intramolecular cyclizations of some imino-ketenimines where the nitrogen atoms of both functionalities are linked by an *ortho*-phenylene backbone.[7,8] In these reactions the ketenimine function played the role of either the 2- or 4-atom component in formal [4+2] cycloaddition processes. Herein we describe that imino-ketenimines of similar structure, bearing a methyl group on the terminal carbon atom of the ketenimine fragment, undergo intramolecular cyclization via two other reaction pathways: a [2+2] cycloaddition and a rare imino-ene reaction.

Imino-ketenimines **2** were prepared by sequential treatment of *N*-(2-azidophenyl)imines **1** with trimethylphosphane and methyl phenyl ketene, following a well-established protocol.[7,8] Compounds **2**, which could be detected in the reaction medium by IR spectroscopy (2000 cm^{-1}, C=C=N) shortly after the ketene addition, rapidly disappeared out of the toluene solution at room temperature, giving rise to a mixture of compounds that fortunately could be resolved into their components by column chromatography, yielding the *trans* azeto[1,2-*a*]benzimidazoles **3**, and the 2-(α-styryl)benzimidazoles **4** in variable yields and ratios (Scheme 1 and Table 1).

Azeto[1,2-*a*]benzimidazoles **3** are representative examples of a previously unknown heterocyclic system, and they have been characterized by their analytical and spectroscopic data.[9] In this respect, their ^{13}C NMR spectra are specially significant, showing the signals due to the two newly formed sp^3 carbon atoms, C1 and C2, near 74 and 62 ppm, respectively. The *trans* relative configuration at C1 and C2 was assigned unequivocally by NOE experiments. The formation of compounds **3**



Scheme 1. *Reagents and conditions*: (a) PMe_3, toluene, rt, 30 min; (b) $Ph(CH_3)C{=}C{=}O$, rt, 1 h.

Keywords: ketenimines; imines; cycloadditions; ene reactions.

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0040-4039/02/$ - see front matter
PII: S0040-4039(02)01261-3

Table 1. Compounds **3** and **4** obtained via Scheme 1

Entry	Ar	Yield (%)[a,b]	Ratio *trans*-**3**:**4**[c]
a	4-CH_3O-C_6H_4	76	80:20
b	2-CH_3-C_6H_4	84	61:39
c	4-Cl-C_6H_4	79	76:24
d	3,4-Cl_2-C_6H_3	90	64:36
e	4-NC-C_6H_4	76	55:45
f	4-O_2N-C_6H_4	71	44:56
g	2-Cl-5-O_2N-C_6H_3	79	28:72
h	2,6-Cl_2-C_6H_3	84	6:94
i	2,6-$(CH_3)_2$-C_6H_3	70	0:100

[a] Total yield of isolated products (*trans*-**3**+**4**).

[b] In some entries (a, b, and e–g) minor amounts of benzimidazo[1,2-*b*]isoquinolines were isolated, never reaching 15% of the total yield. These compounds should be the result of an intramolecular [4+2] cycloaddition in ketenimines **2**, as described in Ref. 7.

[c] Values determined by ^1H NMR analysis of the crude reaction mixtures. The ratio of isolated pure products is, in all cases, similar.

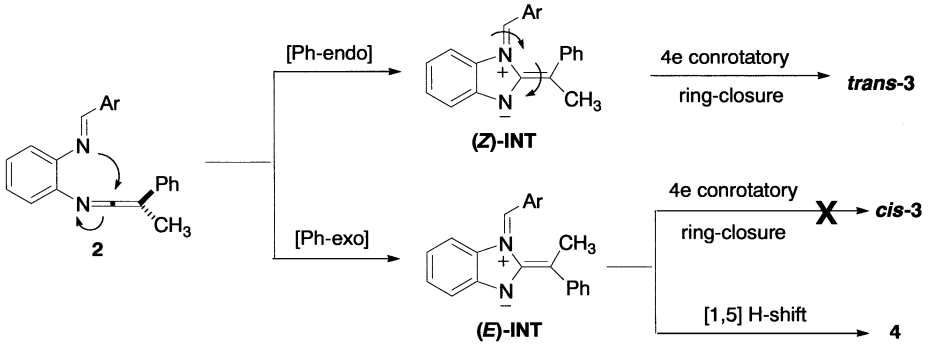
can be understood as resulting from a formal [2+2] cycloaddition between the imino C=N and the cumulated C=C bonds of the imino-ketenimines **2**. Such reaction seems to occur with a noticeable high degree of stereocontrol, as only the *trans* isomers were formed.

2-(α-Styryl)benzimidazoles **4** were found somewhat unexpectedly in the reaction mixtures resulting from all entries in Table 1, and in some of them they are the major components (entries f–i). Compounds **4** were easily identified by means of their analytical and spectral data.[9] Their two methylene carbons, benzylic and vinylic, appear near 46 and 122 ppm, respectively, in their ^{13}C NMR spectra. These compounds should be formed by an intramolecular imino-ene reaction occurring on imino-ketenimines **2**, in which the iminic C=N bond (enophile) removes an H atom from the methyl group on the *C*-terminus of the ketenimine (ene component) with concurrent formation of a single C–N bond. To the best of our knowledge this is the first report of a generalized ene-type reaction of ketenimines.[10]

The data presented in Table 1 show that the most effective way for shifting the **3**:**4** ratio towards the imino-ene product is the introduction of substituents into the *ortho* positions of the iminic Ar group (entries g–i). This effect could be rationalized on steric grounds by considering the reasonably higher steric demand of the [2+2] cycloaddition reaction when compared with the imino-ene process.

The present imino-ene reaction leading to benzimidazoles **4** is of type I following Oppolzer's classification of ene processes.[11] Imino-ene reactions have been recently reviewed.[12] Whereas in these processes C–C bond formation and H transfer to the N atom of the imine is the more common situation, in compounds **2** only C–N bond formation and H transfer to the methine carbon of the imine can occur, due to the stereoelectronic restraints imposed on the system by the intramolecularity of the reaction. Only a few examples that follow this last mechanistic pathway have been reported, as the intramolecular cyclizations of *N*-acyl imine derivatives via thermal imino ene reactions under FVT conditions.[13,14] The mechanism of ene reactions has been the subject of controversial discussions, and is now pictured in terms of a continuum from a concerted six-electron pathway to a stepwise process involving either biradical or zwitterionic intermediates.[12,15,16]

On the basis of the results of our previous experimental and computational studies on the intramolecular [2+2] cycloaddition reaction between imines and ketenimines,[17–19] we can reasonably presume that the conversion of the present imino-ketenimines **2** into the [2+2] cycloadducts *trans*-**3** should occur in two steps, via the conjugated betaine **(*Z*)-INT** resulting from the nucleophilic ring-closure of **2** via a Ph-*endo*[17] transition state (Scheme 2). This betaine should convert into *trans*-**3** by a four-electron conrotatory ring closure. The experiments summarized in Scheme 1 and Table 1 show that the [2+2] cycloaddition leading to **3** is highly stereoselective as the *cis*-**3** adducts were never isolated nor detected. A rational explanation of this fact, which also accounts for the alternative formation of the imino-ene products **4**, becomes apparent by considering that the cyclization of **2** leading to the dipolar intermediate could also occur by the alternative, less sterically congested Ph-*exo* mode of addition, thus giving rise to the stereoisomeric betaine **(*E*)-INT**. This intermediate could cyclize by a **4e** conrotatory ring-closure to *cis*-**3**, but this is not experimentally observed. Instead, the results show that this betaine seems to prefer the evolution by a 1,5 sigmatropic H-shift from the methyl group to the iminic carbon leading to the imino-ene product **4**. A similar shift is not available in **(*Z*)-INT** due to geometric reasons.



Scheme 2.

In summary, the intramolecular cyclization of imino-ketenimines **2** yielding [2+2] cycloadducts *trans*-**3** and imino-ene products **4** can be understood as occurring by two divergent mechanistic routes, via two stereoisomeric conjugated betaines as intermediates. In silico exploration of the mechanistic steps represented in Scheme 2 by ab initio and DFT calculations are now underway and will be reported in due course.

Acknowledgements

This work was supported by the MCYT and FEDER (Project BQU2001-0010), and Fundación Séneca-CARM (Project PI-1/00749/FS/01). One of us (F.T.) thanks the MECD for a fellowship.

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9. Satisfactory ^{1}H and ^{13}C NMR, mass spectra and elemental analyses were obtained for all the new compounds.
   ***trans*-2-Methyl-1-(4-nitrophenyl)-2-phenylazeto[1,2-*a*]benzimidazole** (**3f**): mp 153–154°C; colorless prisms (diethyl ether); IR (Nujol) 1607, 1603, 1529, 1349 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 3H), 5.96 (s, 1H), 7.22–7.46 (m, 6H), 7.51–7.60 (m, 4H), 7.94 (d, 1H, $J=8.1$ Hz), 8.35 (d, 2H, $J=8.7$ Hz); ^{13}C NMR ($CDCl_3$): δ 22.52, 62.59 (s), 74.48, 110.81, 120.85, 122.98, 124.47, 126.12, 127.65, 128.02, 129.22, 133.20 (s), 141.06 (s), 142.48 (s), 147.03 (s), 148.30 (s), 161.41 (s), a methine carbon was not observed; mass spectrum m/z (relative intensity) 355 (M^+, 100). Anal. calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.10; H, 4.96; N, 11.70%.
   1-(4-Nitrobenzyl)-2-(α-styryl)benzimidazole (**4f**): mp 130–131°C; pale-yellow prisms (diethyl ether); IR (Nujol) 1609, 1515, 1342 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.18 (s, 2H), 5.79 (s, 1H), 5.97 (s, 1H), 7.03 (d, 2H, $J=8.6$ Hz), 7.16 (d, 1H, $J=7.3$ Hz), 7.24–7.38 (m, 7H), 7.89 (d, 1H, $J=7.3$ Hz), 8.05 (d, 2H, $J=8.6$ Hz); ^{13}C NMR ($CDCl_3$): δ 47.45, 109.85, 120.60, 122.16, 123.07, 123.69, 124.00, 126.84, 127.20, 128.88, 128.95, 135.37 (s), 137.74 (s), 139.22 (s), 142.95 (s), 143.34 (s), 147.51 (s), 153.53 (s); mass spectrum m/z (relative intensity) 355 (M^+, 100). Anal. calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.12; H, 4.75; N, 11.78%.
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