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Periselective intramolecular [4+2] cycloadditions of ketenimines: synthesis of pyrido[1,2-*a*]benzimidazoles

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Abstract

A new synthesis of pyrido[1,2-*a*]benzimidazole derivatives is described. Easily available *N*-(2-propenylideneaminophenyl)ketenimines underwent an intramolecular [4+2] cycloaddition reaction, in which the cumulated C=C bond of the ketenimine fragment acts as the 2π-electron component and the α,β-unsaturated imine function as the 4π-electron component, yielding the titled compounds in a periselective manner.

The last 20 years have witnessed the raise of a plethora of new reactions involving ketenimines as substrates or intermediates for the synthesis of heterocyclic compounds.[1] Amongst the pericyclic reactions of ketenimines, [4+2] cycloadditions in which these heterocumulenes play the role of the 4π-electron component have proven to be particularly useful and have been widely reported as efficient methods for the synthesis of six-membered rings.[2] By contrast, reports on the use of ketenimines as 2π-electron components in [4+2] cycloadditions are notably scarce. In such cases, either the C=N or C=C bond of the ketenimine could be the one involved in the cyclization process. To our knowledge, a few examples of participation of the C=N bond of ketenimines in that kind of pericyclic reactions have been disclosed.[3] Concerning the participation of the cumulated C=C bond, this has been shown to occur only when ketenimines are reacted intermolecularly with α,β-unsaturated aldehydes,[4] and intramolecularly with *C*-aryl hydrazones, when both functionalities are linked by a proper tether.[5]

Herein we describe the successful intramolecular [4+2] cycloaddition of imino-ketenimines **3** where the C=C bond of the ketenimine is the dienophile in respect to the α,β-unsaturated imino function which acts as the diene. Both functional groups are linked by an *ortho*-phenylene tether connecting the ketenimino and imino nitrogen atoms. This new cycloaddition reaction is also

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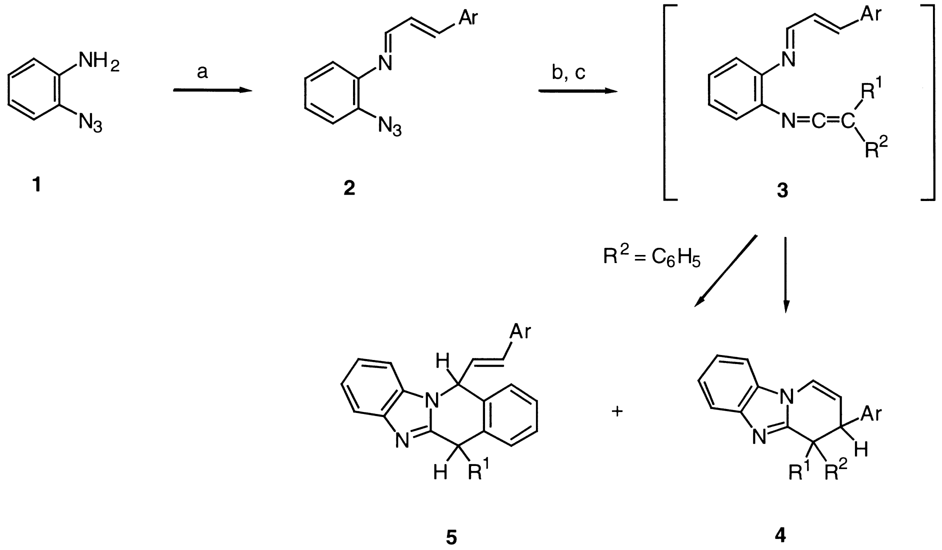
shown here to be periselective when other plausible pericyclic reaction paths of the same substrates are ocurring.

A number of *N*-(2-azidophenyl)imines **2** were prepared by reaction of 2-azidoaniline **1**[6] with different substituted cinnamaldehydes under standard reaction conditions (Scheme 1). A Staudinger reaction[7] of **2** with 1 equivalent of a 1 M toluene solution of trimethylphosphane, and subsequent reaction of the resulting non-isolated trimethylphosphazene with an equivalent amount of trimethylsilylketene in the same reaction flask led to the corresponding 3-aryl-3,4-dihydropyrido[1,2-*a*]benzimidazoles **4a–c** in moderate yields, after chromatographic (column, silica gel) purification (Table 1, entries a–c).



Scheme 1. Reagents and conditions: (a) Ar–CH=CH–CHO, EtOH, cat. AcOH, reflux, 30 min; (b) PMe_3, toluene, rt, 30 min; (c) $R^1R^2C{=}C{=}O$, toluene, rt, 1 h

Table 1
Pyrido[1,2-*a*]benzimidazoles **4** and benzimidazo[1,2-*b*]isoquinolines **5** prepared

Entry	Ar	R^1	R^2	**4** (%)[a]	**5** (%)[a]
a	C_6H_5	H	H	44	-
b	2-CH_3O-C_6H_4	H	H	52	-
c	2-O_2N-C_6H_4	H	H	40	-
d	4-Cl-C_6H_4	C_6H_5	C_6H_5	52	19
e	4-CH_3O-C_6H_4	C_6H_5	C_6H_5	67	15
f	2-O_2N-C_6H_4	C_6H_5	C_6H_5	46	41
g	4-Cl-C_6H_4	CH_3	C_6H_5	58	33
h	4-CH_3O-C_6H_4	CH_3	C_6H_5	58	33
i	2-O_2N-C_6H_4	CH_3	C_6H_5	32	40

[a] Yield of pure isolated product.

Ketenimines **3** ($R^1 = Me_3Si$, $R^2 = H$), resulting from the aza-Wittig reaction[8] of the silylketene with the phosphazene derived from **2**, are reasonably the first transient intermediates in the sequence leading to **4a–c**, which should then undergo the new type of intramolecular [4+2] cycloaddition which results in the tricyclic pyrido[1,2-*a*]benzimidazole core. The protodesilylation of **4** ($R^1 = Me_3Si$, $R^2 = H$) to yield the finally isolated 4-unsubstituted **4a–c** ($R^1 = R^2 = H$), an uncommon but not unprecedented result,[9] must occur during the chromatographic purification step. The analytical and spectroscopic data[10] of the new compounds **4a–c** were unequivocal in assigning their structures.

The use of *C*-arylketenes instead of trimethylsilylketene in the sequence depicted in Scheme 1 opens the way to new pericyclic reaction paths. We have previously reported[2] that imino-ketenimines containing the same tether connecting both functionalities as that in imino-ketenimines **3**, but bearing two phenyl groups on the carbon terminus of the ketenimine function and one aryl group on the iminic carbon atom, experimented an intramolecular [4+2] cycloaddition in which the *C*-phenyl cumulenic unit behaved as the 4π-electron diene component, whereas the iminic C=N bond served as the dienophile, thus resulting in the formation of benzimidazo[1,2-*b*]isoquinolines (similar to compounds **5** in Scheme 1).

When diphenyl (entries d–f) or methyl phenyl ketene (entries g–i) were employed as reactants in step (c) of Scheme 1, mixtures of pyrido[1,2-*a*]benzimidazoles **4** and benzimidazo[1,2-*b*]isoquinolines **5** were obtained in good combined yields (71–91%) in which the tricyclic compounds **4** were clearly predominant, with the exception of the examples in entries f and i in which the ratio of products was nearly 1:1. In all cases the mixtures were easily resolved into their pure components by column chromatography (SiO_2 gel, mixtures of hexane and ethyl acetate). For entries g, h and i compounds **4** were obtained as nearly equimolecular mixtures of *cis*- and *trans*-isomers. Compounds **5** were formed as mixtures of *cis*- and *trans*-isomers of variable ratios, which equilibrated in solution as previously reported.[2]

These results illustrate the periselectivity of such reactions, in which the combination of the α,β-unsaturated imino portion of intermediates **3** as the 1-azabutadiene component with the dienophilic C=C bond incorporated into the ketenimine function leading to **4** is preferred to some extent to the alternative interaction between the iminic C=N bond as heterodienophile with the *C*-aryl ketenimine part of **3** as an all-carbon diene yielding **5**. Whereas it is well-known that azadienes are reluctant to participate in Diels–Alder reactions, it has been stated that the entropic assistance provided by the intramolecular variant of that reaction is sufficient in most instances to override that reluctance.[11] Moreover, the incorporation of the dienophile into a reactive system (typically a heterocumulene, e.g. the ketenimine function of **3**) has been shown to contribute notoriously for allowing otherwise non-amenable cycloadditions.[12] In the present case both effects contribute to make possible and to favour the hetero-Diels–Alder process **3** to **4** over the alternative pericyclic reaction path **3** to **5**.

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10. Satisfactory ^{1}H, ^{13}C NMR, mass spectra and elemental analyses were obtained for all new compounds. Compound **4a**: yellow prisms (diethyl ether). M.p. 140–142°C; IR (Nujol) 1652 (C=N), 1615, 1528, 1320, 1221, 1077, 966, 855, 742 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.20 (dd, J = 16.6, 9.6 Hz, 1H), 3.45 (dd, J = 16.6, 7.3 Hz, 1H), 3.87–3.94 (m, 1H), 5.61 (dd, J = 7.7, 3.7 Hz, 1H), 7.07 (dd, J = 8.0, 2.1 Hz, 1H) 7.14–7.35 (m, 8H), 7.64–7.68 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 32.21 (t), 38.72 (d), 108.39 (d), 115.50 (d), 119.72 (d), 121.37 (d), 122.68 (d), 122.98 (d), 127.24 (d), 127.28 (d), 129.02 (d), 131.81 (s), 142.71 (s), 143.05 (s), 149.60 (s); MS *m*/*e* (EI) 246 (100, M$^+$). Anal. calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 82.78; H, 5.59; N, 11.63.
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