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Formal [4+2] Intramolecular Cycloaddition Ketenimine-Imine. Synthesis of Benzimidazo[1,2-*b*]isoquinolines

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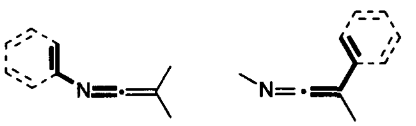
Abstract

Benzimidazo[1,2-*b*]isoquinolines have been prepared by a formal [4+2] intramolecular cycloaddition of ketenimines with imines.

Keywords: phosphazenes, ketenimines, cycloadditions, benzimidazo-isoquinolines.

The participation of ketenimines as the 4π-electron component in [4 + 2] cycloaddition reactions was first studied by Ghosez almost thirty years ago.[1] Since then, only a few research teams have taken advantage of that synthetic methodology, either inter- or intramolecularly, for the construction of isolated or fused six-membered rings, respectively.



These reactions may be classified into two main groups: i) *N*-vinyl (or aryl) ketenimines as 2-azadienes; and ii) *C*-vinyl (or aryl) ketenimines as all-carbon dienes.

The pioneering work of Ghosez[1] as well as some[2] of our previous reports on this theme fall into the first group. Further reports by Ghosez's group,[3] and others by Dondoni,[4] Molina,[5] Lee,[6] Schmittel,[7] and Wang[8] can be included in the second group of the above classification. In all these reactions, double[2,5] and triple[1,3,7,8] carbon-carbon bonds have been usually employed as dienophiles, whereas heterodienophiles, such as thiocarbonyl[4] and hydrazono[6] double bonds, have been rarely used.

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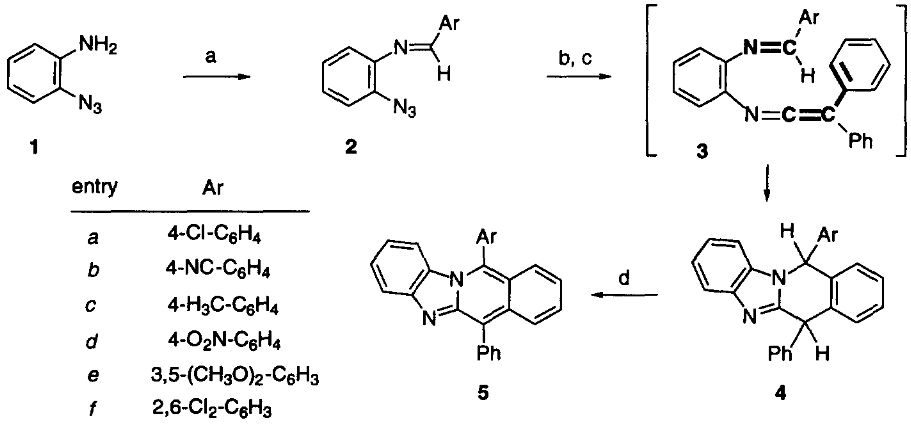
Herein we describe the successful [4 + 2] intramolecular cycloaddition of *C*-aryl ketenimines as all-carbon dienes with the imino C=N bond when both functional groups are linked by a rigid two-atom tether connecting the ketenimino and imino nitrogen atoms.

The reaction of 2-azidoaniline **1**[9] with aromatic aldehydes under standard conditions gave *N*-(2-azidophenyl)imines **2**. Staudinger reaction[10] of **2** with one equivalent of a 1 M toluene solution of trimethylphosphane (N_2 evolution) led to red solutions of the respective trimethylphosphazenes,[11] which were not isolated but treated in the same flask with one equivalent of diphenylketene. The colour of the reaction mixture immediately faded to pale yellow. After 30 minutes the mixture was chromatographed (silica gel column, hexane/ethyl acetate 1:1) and the corresponding 11-aryl-6-phenyl-6,11-dihydrobenzimidazo[1,2-*b*]isoquinolines **4** were isolated in excellent yields (84-92%) (Scheme 1).



entry	Ar
a	4-Cl-C_6H_4
b	4-NC-C_6H_4
c	4-H_3C-C_6H_4
d	4-O_2N-C_6H_4
e	3,5-$(CH_3O)_2$-C_6H_3
f	2,6-Cl_2-C_6H_3

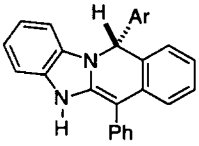
***Reagents and conditions*:** (a) ArCHO, EtOH, cat. AcOH, reflux, 30 min; (b) PMe_3, toluene, r.t., 10 min; (c) $Ph_2C=C=O$, toluene, r.t., 30 min; (d) Pd/C, toluene, reflux, 16 h.

Scheme 1

Although ketenimines **3** could be neither isolated nor detected in the reaction mixture,[12] they must be, reasonably, transient precursors of compounds **4**, resulting from the aza-Wittig reaction of the ketene with the phosphazene derived from **2**.[13] Ketenimines **3** converted into **4** by a new type of formal [4 + 2] intramolecular cycloaddition followed by H shift. Compounds **4** so obtained are new examples of a little known fused tetracyclic system.[14]

The analytical and spectroscopic data[15] of compounds **4** were unequivocal in assigning their structures. The appearance of two singlets in the region $5.6 < \delta < 6.8$ of their ^{1}H NMR spectra, correlated with methine carbons in their respective ^{13}C NMR spectra, is due to protons H6 and H11. Moreover, one of the two equivalent phenyl groups of the reactant $Ph_2C{=}C{=}O$ appeared in **4** as an *ortho*-disubstituted benzene ring, whereas the Ar group of **2** remained as such. The partially saturated compounds **4** were oxidized in the presence of Pd/C to give the fully aromatic compounds **5** in moderate yields (45-67%).

Compounds **4** were obtained as mixtures of *cis* and *trans* isomers. Integration of the signals assigned to H6 and H11 in the ^{1}H NMR (300 MHz) spectra of the mixtures revealed their similar composition, showing isomeric ratios close to 3:2 (except for entry *f*, ratio 9:1). The isomeric mixtures could not be resolved into their components by preparative column or thin-layer chromatography. However, the different solubility of both isomers in diethyl ether allowed us to separate, in entries *a* and *e*, the most insoluble one in pure form; in both cases, this compound was the minor component of the mixture. Chemical shift differences and nOe experiments did not show features allowing us to assign *cis* and *trans* stereochemistry to the mixture components. Attempts to obtain crystals of any isomer of **4** suitable for X-ray structure determination have been unsuccessful to date.



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When the ^{1}H NMR spectra of the pure minor isomers were recorded after a few hours in $CDCl_3$ solution, low intensity signals corresponding to the major isomers were clearly perceptible, and the equilibrium ratio (~3:2) was reached after 3-4 days. Most probably, the equilibrium between *cis*- and *trans*-**4** is established through the intermediacy of the enamino tautomer **6**, which contains only one stereogenic carbon atom.

Ab initio RHF/6-31G* and B3LYP/6-31G* calculations on the 6,11-dimethyl simplified system predicted that both isomers would adopt a boat conformation and the *cis* isomer to be more stable than the *trans* [-762.0116701 a.u. (ZPE 0.285734) at RHF/6-31G* level and -766.9821949 a.u. at B3LYP/6-31G* level for the *cis* isomer, and -762.0100666 a.u. (ZPE 0.285847) at RHF/6-31G* level and -766.9809042 a.u. at B3LYP/6-31G* level for the *trans* isomer].

Acknowledgements

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11. ^{31}P-NMR (121.4 MHz, $CDCl_3$) δ: 2-(4-Cl-C_6H_4-CH=N-)C_6H_4-N=PMe_3 8.62 ppm; 2-(4-O_2N-C_6H_4-CH=N-)C_6H_4-N=PMe_3 8.20 ppm.
12. IR spectra of the reaction mixtures recorded immediately after the addition of diphenylketene did not show absorptions in the region 1900-2100 cm^{-1}.
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15. Satisfactory ^{1}H, ^{13}C-NMR, mass spectra and elemental analyses were obtained for all new compounds. Compound **4a** (Ar = 4-Cl-C_6H_4) *major isomer*: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.78 (s, 1H), 6.48 (s, 1H), 6.92 (d, 2H, J = 8.4 Hz), 7.05-7.25 (m, 10H), 7.29-7.37 (m, 3H), 7.43-7.46 (m, 1H), 7.79 (d, 1H, J = 8.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 44.94, 60.12, 110.13, 119.66, 122.49, 122.71, 127.11, 127.51, 127.71, 128.00, 128.25, 128.44, 128.63, 128.98, 130.77, 132.87 (s), 133.84 (s), 133.92 (s), 134.23 (s), 138.61 (s), 141.06 (s), 143.48 (s), 152.52 (s); *minor isomer*: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.67 (s, 1H), 6.64 (s, 1H), 7.07-7.40 (m, 16H), 7.73 (d, 1H, J = 7.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 45.76, 60.32, 110.65, 119.96, 122.29, 122.54, 127.36, 127.44, 127.49, 128.20, 128.40, 129.01, 129.47, 129.53, 129.84, 133.57 (s), 134.33 (s), 134.45 (s), 139.40 (s), 141.70 (s), 143.76 (s), 152.87 (s), one quaternary carbon was not observed.