

N-Cyclopropylimine-1-pyrroline Rearrangement. A Novel Photochemical Reaction

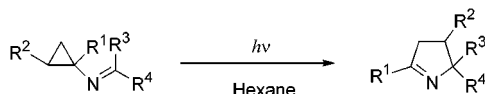
Pedro J. Campos,* Alberto Soldevilla, Diego Sampedro, and Miguel A. Rodríguez*

Departamento de Química, Universidad de La Rioja, Grupo de Síntesis Química de La Rioja, Unidad Asociada al C.S.I.C., Madre de Dios, 51, E-26006 Logroño, Spain

pedro.campos@dq.unirioja.es

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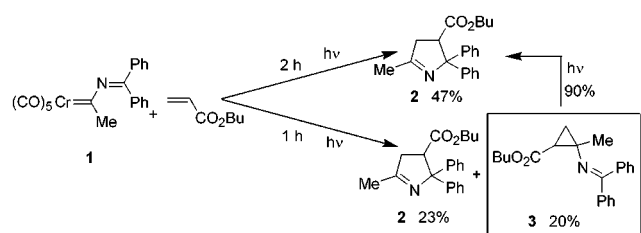
ABSTRACT



A novel aza-(vinylcyclopropane-cyclopentene) photochemical rearrangement is reported. 1-Pyrrolines are easily synthesized in good yields from *N*-cyclopropylimines. Hydrogen, alkyl, and aryl groups can be placed anywhere within the system, and the reaction proceeds regiospecifically.

During the study of the photochemical behavior of group VI Fischer-type imine-carbene complexes to yield 2*H*-pyrroles and 1-pyrrolines,¹ we detected different product distributions depending on the irradiation times (Scheme 1).

Scheme 1



Irradiation until total consumption of carbene complexes yielded the 1-pyrroline **2**. However, with shorter irradiation times, the *N*-cyclopropylimine **3** was isolated as well. When we irradiated the *N*-cyclopropylimine **3**, we detected the corresponding 1-pyrroline **2**. As far as we know, this is the first example of a photochemically induced aza-(vinylcyclopropane-cyclopentene) rearrangement where a nitrogen atom is placed in the α position in relation to the three-

membered ring. Moreover, we have not found any thermal example in the literature.

The rearrangement of vinylcyclopropane was first reported by Neuretier in 1959.² Since then, it has found a wide application in organic synthesis³ as a result of its potentially limitless permutations. Any of the five atoms in the vinylcyclopropyl system may be replaced with almost any other atom (Si, P, S, O, etc.), and the formation of five-membered rings still takes place. Despite its synthetic utility, the use of N in the system has been limited mainly to vinylaziridines⁴ and the effects of heteroatom substitution on the rearrangements of *C*-cyclopropylmethyleamines.⁵ We report here a brand new reactivity involving the photochemically driven rearrangement of *N*-cyclopropylimines to 1-pyrrolines. The 1-pyrroline ring system is found in natural products, especially hydroporphyrins,⁶ and constitutes an adequate substrate for the synthesis of pyrroles.⁷ Besides, much attention is still being paid to the synthesis of 1-pyrroline derivatives.⁸

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(3) For different reviews see: (a) Baldwin, J. E. *J. Comput. Chem.* **1998**, *19*, 222. (b) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlický, T. *Chem. Rev.* **1989**, *89*, 165. (c) Hudlický, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247. (d) Hudlický, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 899.

(4) Schultz, A. G.; Dittami, J. P.; Myong, S. O.; Sha, C.-K. *J. Am. Chem. Soc.* **1983**, *105*, 3273.

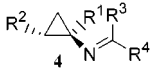
(5) Wasserman, H. H.; Dion, R. P. *Tetrahedron Lett.* **1983**, *24*, 3409.

(6) Montforts, F.-P.; Gerlach, B.; Höper, F. *Chem. Rev.* **1994**, *94*, 327 and references therein.

(1) Campos, P. J.; Sampedro, D.; Rodríguez, M. A. *Organometallics* **2000**, *19*, 3082.

To survey the synthetic applicability of this new reaction, we first synthesized a set of *N*-cyclopropylimines with different substitution patterns. Table 1 shows the results obtained.

Table 1. *N*-Cyclopropylimines **4** Synthesized

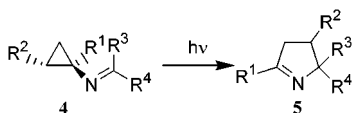


imine	R ¹	R ²	R ³	R ⁴	yield (%)
4a	H	H	H	Ph	98
4b	H	H	Me	Ph	90
4c	H	H	Ph	Ph	94
4d	H	Ph	H	Ph	96
4e	H	Ph	Me	Ph	95
4f	H	Ph	Ph	Ph	90
4g	Ph	H	H	Ph	98
4h	Ph	H	Me	Ph	72
4i	Ph	H	Ph	Ph	90
4j	Ph	H	H	<i>trans</i> -CH=CHPh	94

All of these compounds were synthesized by a condensation reaction between the corresponding amines⁹ and carboxylic compounds.¹⁰ The *anti*-isomer was the only product detected for the imines derived from aldehydes. This was confirmed by NOE experiments for compound **4a**. For acetophenone imines **4b**, **4e**, and **4h** the two isomers were detected by ¹H NMR (1:10).

Next, we irradiated¹¹ the *N*-cyclopropylimines **4** using a Pyrex glass with the imines that showed an absorption above the 290 nm limit in the UVA spectrum. The results are given in Scheme 2 and Table 2.

Scheme 2



As shown in Table 2, no limitations were detected regarding the position or nature of the substituents, as both alkyl and aryl groups and hydrogen can be used without significant influence on the product distribution. The substituents of the imine moiety can be easily modified in the synthesis of the *N*-cyclopropylimines. Aryl and alkyl groups and hydrogen were successfully used. Regarding the cyclo-

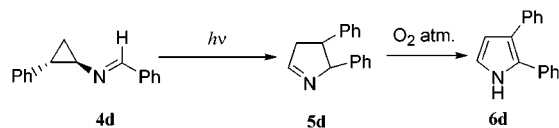
Table 2. Formation of 1-Pyrrolines **5**

pyrroline	R ¹	R ²	R ³	R ⁴	<i>t</i> (h) ^a	yield (%)
5a	H	H	H	Ph	6	70
5b	H	H	Me	Ph	6	65
5c	H	H	Ph	Ph	5	80
5d	H	Ph	H	Ph	5	65 ^{b,c}
5e	H	Ph	Me	Ph	5	60 ^{b,d}
5f	H	Ph	Ph	Ph	4	85 ^b
5g	Ph	H	H	Ph	0.75	70
5h	Ph	H	Me	Ph	0.75	^e
5i	Ph	H	Ph	Ph	0.5	80
5j	Ph	H	H	<i>trans</i> -CH=CHPh	5	50 ^b

^a Time for 1 mmol of imine **4** in 50 mL. ^b Pyrex filtered. ^c Pyrrole **6d** was isolated. ^d Mixture of two stereoisomers in a 1:3 ratio. ^e Only decomposition products were detected.

propyl substituents, hydrogen and phenyl groups were placed in positions 1 and 2 with no significant effect on the overall reaction. Corresponding 1-pyrrolines **5** could be synthesized easily in moderate to good yields. As an exception, 1-pyrroline **5d** detected in the reaction crude¹² was readily oxidized during the workup and only the pyrrole **6d** could be isolated (Scheme 3).

Scheme 3



For the 2-substituted imines **4d–f**, two different regioisomers could be formed. In every case analyzed, the regiochemistry of the rearrangement was directed by the phenyl group in position 2. Therefore, only one of the two possible regioisomers was obtained, and thus the reaction became completely regiospecific.

To ensure the photochemical nature of these reactions, we refluxed several imines **4** in toluene for 3 days. The imines were recovered unchanged with the exception of imines **4g** and **4h**, where some decomposition was observed, but the formation of 1-pyrroline was not detected by ¹H NMR in any case.

(10) An equimolecular solution of the corresponding amine and carbonyl compound was refluxed in toluene for 1–2 days, with occasional addition of molecular sieves. Once the reaction was finished (monitored by TLC), it was filtered and the solvent was removed under vacuum. Most of the imines were then ready to use. Compounds **4c**, **4f**, and **4i** can be purified by column chromatography in silica gel (hexane/ether 1:1). Alternatively, an excess of amine (3–5 equiv) and lower temperatures (ca. 80 °C) must be used for cyclopropylamine derivatives (R₁ = R₂ = H).

(11) One millimole of imines **4** in 50 mL of dry deoxygenated hexane was irradiated (through Pyrex glass when indicated in Table 2) in a quartz reactor with a medium-pressure 400-W mercury lamp. When no more imine was detected by TLC, the solution was filtered through Celite, and the solvent was evaporated. Corresponding 1-pyrrolines **5** could be purified by distillation or column chromatography (silica gel, hexane/ether 8:2).

(12) Two different isomers were detected in the reaction crude by ¹H NMR in a 5:1 ratio. The major product was assigned as the *cis* isomer on the basis of the coupling constants (PhCH–CHPh *cis* *J* = 6 Hz, *trans* *J* = 8 Hz).

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(8) (a) Gagosz, F.; Zard, S. Z. *Synlett* **1999**, 1978. (b) Duncan, D.; Livinghouse, T. *Organometallics* **1999**, 18, 4421. (c) Boivin, J.; Schiano, A.-M.; Zard, S. Z.; Zhang, H. *Tetrahedron Lett.* **1999**, 40, 4531.

(9) For the preparation of 1-phenylcyclopropylamine (imines **4g–j**) by a modified Curtius reaction, see: Kaiser, C.; Weinstock, J. *Org. Synth.* **1971**, 51, 48. *trans*-2-Phenylcyclopropylamine (imines **4d–f**) and cyclopropylamine (imines **4a–c**) are commercially available as a hydrochloride and free amine, respectively.

All of the compounds herein described have been fully characterized on the basis of their spectral data (IR, ^1H and ^{13}C NMR, MS-ES(+) and GC-MS).

Further investigation to explore the synthetic utility and to gain a mechanistic insight into this new reaction is currently underway in our group.

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Supporting Information Available: Characterization data for new compounds and representative UVA spectra for compounds **4**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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