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Simple and versatile synthesis of 1-pyrroline derivatives through thermal rearrangement of *N*-cyclopropylimines

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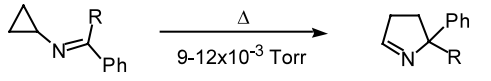
Abstract—*N*-Cyclopropylimines rearrange under thermal conditions to give 1-pyrrolines. The effect of imine and cyclopropane substitution is explored. This methodology allows the presence of different substituents (alkyl, alkenyl, aryl) and the reaction proceeds regiospecifically. © 2002 Elsevier Science Ltd. All rights reserved.

Neureiter reported the first example of isomerization of vinylcyclopropane to cyclopentene in 1959.[1] Following the discovery of the reaction there was an explosive research of vinylcyclopropane rearrangements, including kinetic studies and synthetic scope and applications.[2] As a consequence, this rearrangement is now an established basis for retrosynthetic analyses.[3] However, despite the fact that almost any of the five atoms in the vinylcyclopropane system may be replaced with an heteroatom (Si, P, S, O), the use of N within the system has been mainly limited to vinylaziridines[4] and the effects of heteroatom substitution on the rearrangement of *C*-cyclopropylmethyleneamines.[5] To the best of our knowledge, just one example for this kind of reaction has been described for *N*-cyclopropylimines.[6] Despite the mechanistical interest of that work, the synthetic applicability and scope of the reaction have never been tested. Trying to fill this gap, we published in a recent paper[7] the first examples of photochemically driven rearrangements of *N*-cyclopropylimines to 1-pyrrolines.[8] In that paper, it was also indicated that the assayed imines did not lead to the corresponding 1-pyrrolines when refluxed in toluene for 3 days. The lack of a systematic research of thermal examples and the interest of the products obtained encouraged us to find a thermal way to perform the rearrangement reaction of *N*-cyclopropylimines. We report here the results obtained in this field.

First, we carried out the pyrolysis of the imine derived from cyclopropylamine and benzaldehyde (**1a**)[9] at 250°C under reduced pressure but the starting product was recovered unchanged. At this point, we decided to work at a higher temperature. Thus, when **1a** was pyrolyzed for 4 hours between 0.009 and 0.012 Torr at 400°C we obtained the 1-pyrroline **2a** (Scheme 1), together with some amount of starting product. The rearranged product **2a** was obtained in a 58% yield. This result prompted us to optimize the yield for the 1-pyrroline formation as a function of the reaction temperature. In order to do this, we carried out a series of pyrolyses at different temperatures. The results obtained are shown in Table 1.



1a R = H
1b R = Me
1c R = Ph

2a 67 %
2b 55 %
2c 35 %

Scheme 1.

Table 1. Temperature dependence for the formation of **2a**

T (°C)	Yield (%)[a]	Product
250	0	–
350	67[b]	**2a**
400	58[b]	**2a**
500	51	γ-Phenylbutyronitrile

[a] Yield referred to the obtained crude.
[b] The main side-product is the unreacted imine **1a**. Traces of decomposition products were also detected.

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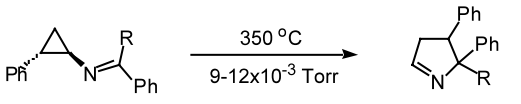
As shown in Table 1, the reaction for **1a** only proceeds successfully within a range of temperatures. The formation of the 1-pyrroline **2a** takes place in a synthetically useful way only between 350 and 400 °C,[10] but these temperatures are significantly below the values needed for the rearrangement on the all-carbon systems, which means a wider applicability in a synthetic sense. The upper limit is due to the pyrroline ring opening once formed, which yields the γ-butyronitrile formation.

On the other hand, we performed the pyrolysis of **1b** and **1c** at 350°C but these imines did not react at this temperature. In these two cases, the explanation for the absence of reactivity could come from the higher steric hindrance due to the two substituents on the iminic carbon, which would make more difficult the ring enlargement. These steric effects could be overcome increasing the pyrolysis temperature. Thus, we carried out the pyrolysis of both imines **1b** and **1c** at higher temperatures. Neither compound **1b** nor **1c** did react at 400°C. However, increasing the temperature to 430°C, the 1-pyrrolines **2b** (40%) and **2c** (24%) could be detected. Furthermore, the pyrolysis of both imines at 450°C yielded the five-membered rings in a higher yield (55 and 35%, respectively, Scheme 1). The increase of the yield at higher temperatures seems to be a rather general feature of these reactions, due to the rate constant dependence of temperature.[11]

Once the feasibility of this method checked, we aimed to survey the scope of the pyrroline formation. Thus, we assayed the reaction using a set of *N*-cyclopropylimines substituted at the cyclopropyl 2-position. We carried out the pyrolysis of these compounds using the temperature optimized for the imine **1a**, namely 350°C. Scheme 2 contains the results obtained.

A mixture of *cis* and *trans* isomers was obtained in the reaction of imines **1d** and **1e**. When the pyrolysis of **1d** was carried out at 350°C, both products *trans* and *cis* were detected in the reaction crude in a 51% combined yield and a 1:2.7 ratio, determined by ^{1}H NMR.

The yield could be increased to 70% at 450°C, but the selectivity decreased to a 1:1.3 ratio, still favorable to the *cis* isomer. The decrease of the selectivity at higher temperatures fits the proposal of mechanism usually invoked to explain this rearrangement.[12] This selectivity on the pyrroline formation decreased with a lower difference in the steric hindrance of the iminic carbon substituents since the pyrolysis of imine **1e** yielded the *cis* and *trans* pyrrolines in a 1:1 ratio.



1d	R = H	**2d**	51 %
1e	R = Me	**2e**	55 %
1f	R = Ph	**2f**	62 %

Scheme 2.

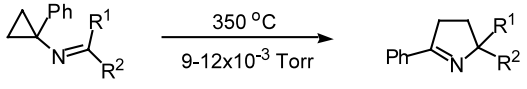
Next, we performed the pyrolysis of imines derived from 1-phenylcyclopropylamine. As shown in Scheme 3, the formation of 1-pyrrolines is quite general and occurs with moderate to good yields.

Comparing the pyrolyses of imines **1b** and **1e** or **1c** and **1f**, it derives that steric effects, should not play a major role in the rearrangement, as far as they can be bypassed by increasing the reaction temperature or by introducing substituents which lower the activation energy for the rearrangement. All four imines have similar steric hindrance, but **1e** and **1f** react at lower temperatures due to the activating effect of substitution on the cyclopropane ring.[13]

The activating effect for this rearrangement can greatly decrease the temperature needed to overcome the activation barrier. While imine **1c** does not react at 350°C, both imines **1f** and **1h** successfully rearranged at that temperature to the corresponding 1-pyrrolines, due to the activating effect of the phenyl substitution on position 2 or 1 of the cyclopropane ring. Although this has been explored through comprehensive studies, most of them were centered on the influence of ring substitution, and less attention has been paid to the substitution on the unsaturated part of the system. However, in this case the activation could also come from the substitution on the imine moiety.

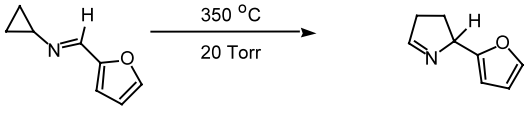
The substitution on the ring has also another effect. It facilitates the reaction by lowering the activation energy for the bond breakage[14] of one of the two possible cyclopropane bonds. Due to this, the reaction becomes regiospecific. This was clearly observed on the reaction of imines **1d–f**, were only one of the two possible regioisomeric pyrrolines was formed.

Finally, the reaction is useful for the preparation of 1-pyrrolines bearing a heteroaromatic ring. Thus, we have synthesized the furan derivative **2j** (Scheme 4) and the nornicotine precursor **2k** (Scheme 5). In both cases, the best yields were obtained under a moderate vacuum since the starting imines are very volatile.



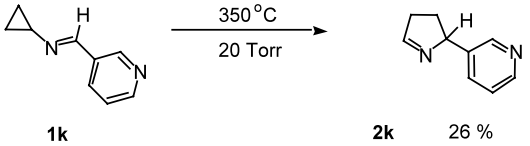
1g	R^1 = H	R^2 = Ph	**2g**	48 %
1h	R^1 = Ph	R^2 = Ph	**2h**	74 %
1i	R^1 = H	R^2 = *trans*-CH=CHPh	**2i**	68 %

Scheme 3.



1j **2j** 32 %

Scheme 4.



1k 2k 26 %

Scheme 5.

Experimental section

The substrates (ca. 100 mg) were distilled under reduced pressure (between 0.009 and 0.012 Torr) into the empty horizontal silica furnace tube (35×2 cm), which was maintained at the appropriate temperature by an electric furnace. The temperatures given are referred to the furnace, and the pressures are measured on the tube's exit point. The inlet temperatures used were between 40°C (for the lighter imines) to 130°C. Products were quenched in a trap cooled with liquid nitrogen located at the exit point of the furnace. At the end of the pyrolysis (usually after 4 h) the products were removed from the trap with solvent, which was subsequently removed in vacuo. The crude products were then purified by column chromatography (silica gel, hexane/ether 8:2) or distillation. Compounds **1a-1i** and **2a-2i** were described on Ref. 7.

***E*-Cyclopropyl-(2-furanyl)methyleneamine (1j)**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (m, 2H), 0.98 (m, 2H), 2.94 (m, 1H), 6.45 (m, 1H), 6.58 (m, 1H), 7.46 (m, 1H), 8.24 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.0, 42.1, 111.4, 112.9, 144.1, 147.1, 151.6. GC-MS: 135(M, 37), 134(25), 108(95), 107(87), 106(46), 94(25), 81(20), 80(100), 79(34). MS-ES(+): 136 (M+1). Anal. calcd for C_8H_9NO: C, 71,09; H, 6,71; N, 10,36; O, 11,84. Found: C, 71.00; H, 6.65; N, 10.31.

***E*-Cyclopropyl-(3-pyridinyl)methyleneamine (1k)**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (m, 4H), 3.06 (m, 1H), 7.30 (dd, J=3,10 Hz, 1H), 8.03 (dd, J=10,10 Hz, 1H), 8.46 (s, 1H), 8.60 (dd, J=10,10 Hz,1H), 8.81 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.1, 42.2, 123.5, 131.9, 133.8, 149.5, 150.8, 155.1. GC-MS: 146(M, 2), 145(12), 118(100), 91(39). MS-ES(+): 147 (M+1). Anal. calcd for $C_9H_{10}N_2$: C, 73,94; H, 6,89; N, 19,16. Found: C, 73.99; H, 6.71; N, 19.30.

5-(2-Furanyl)-1-pyrroline (2j). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.96 (m, 1H), 2.22 (m, 1H), 2.66 (m, 1H), 2.76 (m, 1H), 5.16 (m, 1H), 6.18 (m, 1H), 6.32 (m, 1H), 7.36 (m, 1H), 7.73 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.3, 37.2, 69.8, 105.4, 110.1, 141.8, 155.8, 168.0. GC-MS: 135(M, 85), 134 (18), 108 (100), 107 (83), 106 (45), 94 (17), 81 (37), 80 (89), 79 (70). MS-ES(+): 136 (M+1). Anal. calcd for C_8H_9NO: C, 71,09; H, 6,71; N, 10,36; O, 11,84. Found: C, 71.23; H, 6.83; N, 10.28.

5-(3-Pyridinyl)-1-pyrroline (2k). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65 (m, 1H), 2.45 (m, 1H), 2.69 (m, 1H), 2.76 (m, 1H), 5.13 (m, 1H), 7.26 (dd, J=3,10 Hz, 1H), 7.58 (dd, J=10,10 Hz, 1H), 7.86 (m, 1H), 8.52 (dd, J=3,10 Hz, 1H), 8.62 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.1, 37.5, 73.5, 130.1, 136.4, 148.2, 149.6, 154.8, 168.2. GC-MS: 146(M, 4), 145 (11), 118 (100), 91 (19). MS-ES(+): 147 (M+1). Anal. calcd for $C_9H_{10}N_2$: C, 73,94; H, 6,89; N, 19,16. Found: C, 74.00; H, 6.95; N, 19.05.

Acknowledgements

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8. The importance of 1-pyrrolines has greatly increased with the recent discovery of pyrrolysine, a new genetically encoded amino acid with such structure. See: Hao, B.; Gong, W.; Ferguson, T. K.; James, C. M.; Krzyckl, J. A.; Chan, M. K. *Science* **2002**, *296*, 1462.
9. For the preparation of imines **1** see Ref. 7 and references cited therein.
10. The required temperatures in this case are lower than in the all-carbon system due to the activating effect of the N. Values for the temperature in other cases are between 400 and 500°C for the all-C systems. These values can be reduced by ring substitution to 300–400°C. See Ref. 2.
11. This accelerating effect only takes place at relatively low temperatures. Increasing the temperature over 500–600°C has a little effect on the rate constant and product distribution. See for example: Doubleday, C. *J. Phys. Chem. A*, **2001**, *105*, 6533.
12. For a synopsis of work on the mechanistic aspects of the vinyilcyclopropane-cyclopentene rearrangement see Ref. 2d.
13. The activating effect of cyclopropyl substitution is a well-known feature of these rearrangements. See for example: McGaffin, G.; Grimm, B.; Heinecke, U.; Michaelsen, H.; de Meijere, A.; Walsh, R. *Eur. J. Org. Chem.* **2001**, 3559.
14. See for example Ref. 2c.