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Primary Cycloalkylimines†

Jean-Claude Guillemin,[a,*] Wafa Nasraoui,[a] Houda Gazzeh[a]

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Primary cycloalkylimines with a 4 to 8-membered ring have been synthesized by dehydrocyanation of the corresponding α-aminonitrile on solid potassium hydroxyde in a vacuum gas-solid reaction. Imine-enamine tautomerism has been demonstrated at room temperature for the kinetically most stable derivatives.

The simplest imine, methanimine $H_2C{=}NH$,[1] ethanimine $CH_3CH{=}NH$,[2] and then E- and Z-cyanomethanimine NC-CH=NH[3,4] were detected in the interstellar medium, generating for several decades a permanent interest for kinetically unstable imines. In the laboratory, the challenging synthesis of most of these simplest imines has been solved by particular experimental procedures. The flash vacuum thermolysis involving retro-ene reactions,[5] retro-Diels-Alder reactions,[6] decomposition of azides[7,8] or some other precursors[8] allowed the synthesis of many imines including the simplest one, the methanimine.[6] In vacuum gas-solid reactions, the vaporization of monochloramines or α-aminonitriles on a solid base is a general and efficient approach to aldimines,[9] methylenamines[9] and cyclic imines with 4 to 6-membered ring.[10] However, cycloalkylimines such as cyclopentanimine or cyclohexanimine, which have been sometimes proposed as intermediates,[11-16] do not have any reported experimental procedure or spectroscopic characterization. Such N-H imines are potential precursors of many compounds including biomolecules as, for example, histrionicotoxin and isodihydrohis-trionicotoxin,[17] marine natural products pinnaic acid or tauropinnaic acid.[18] However, even the preparation of N-unsubstituted and acyclic ketenimines is not easy, the dehydrochlorination of a primary N-chlorodialkylamine leading to a mixture of the expected ketenimine with an N-substituted derivative. The opening of the oxaziridine with a Lewis base[19] or the decomposition of nitrile-Grignard reagent complexes by anhydrous methanol[20] are difficult approaches to these compounds. The reaction of an α-aminonitrile with dicyclohexylcarbodiimide at 110°C, performed on some examples, gives a more convenient approach.[21] The isolated dimethylketimine is stable several days at 0°C. We report here a general approach to the simplest cycloalkylimines **1b**-**1f** with a 4- to 8–membered ring (Chart 1). The particular case of the cyclopropyl derivative 1a will be discussed.

As already described,[9,22] the approach based on the reaction of N-chlorocycloalkylamines on a solid base (KOH or t-BuOK heated at 60-90°C) failed in the synthesis of cycloalkylimines but led to the corresponding cyclic imines by a ring expansion (Scheme 1) .

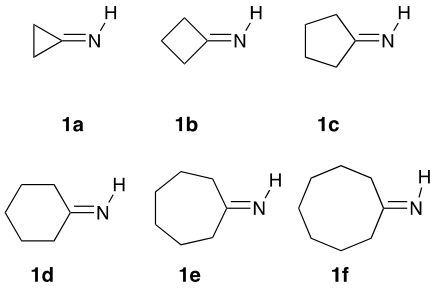
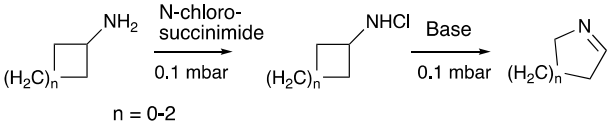


Chart 1 Cycloalkylimines **1a**-**1f**



Scheme 1 Dehydrochlorination of N-chlorocycloalkylamines

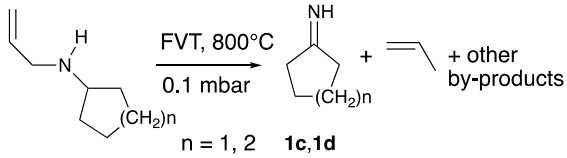
Reinvesting this study using a 400 MHz ^{1}H NMR spectrometer to analyze the products led to the same conclusions: dehydrochlorination on a solid base led to azetine starting from N-chlorocyclopropylamine, 1-pyrroline from N-chlorocyclobutylamine, and 2,3,4,5-tetrahydropyridine from N-chlorocyclopentylamine. Several by-products were also observed but the expected ^{1}H and

[a] Univ Rennes, Ecole Nationale Supérieure de Chimie de Rennes, CNRS, ISCR – UMR6226, F-35000 Rennes, France. E-mail: jean-claude.guillemin@ensc-rennes.fr

†Electronic Supplementary Information (ESI) available: Synthesis of imines **1b**-**1f** and compound **3b,** ^{1}H and ^{13}C NMR spectra of imines **1b**-**1f** and infrared spectra of **1b**-**1e**, ^{1}H and ^{13}C NMR spectra of tetradeutero imines **1e**,**1f**. .See DOI: 10.1039/x0xx00000x

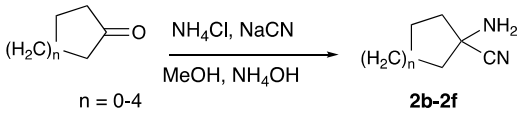
^{13}C NMR signals of cycloalkylimines **1a**-**1d** have never been detected. These results are consistent with an α-elimination of HCl from N-chloroalkylamines and a complete lack of β-elimination.[23] Thus, the reported characterization by photoelectron spectroscopy of **1a** by this approach[22] without high level theoretical calculations to confirm the spectroscopic data is at least questionable.

We then studied retro-ene reactions starting from N-allylcyclopentyl- and allylcyclohexylamine.[14] By flash vacuum pyrolysis at 800°C, small amounts of compounds attributable to cyclopentanimine **1c** and cyclohexanimine **1d** were obtained in the presence of propene and several other by-products (Scheme 2). However, imine **1b** was not observed in the thermolysis products of the corresponding N-allyl derivative.

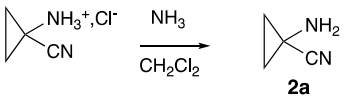


Scheme 2 Flash vacuum thermolysis of N-allylcycloalkylamines

The dehydrocyanation of 2-aminocycloalkylcarbonitriles was then studied. The α-aminonitrile precursors with a 4-8 membered ring **2b**-**2f**[24,25] were easily prepared in good yields in a Strecker reaction (Scheme 3). The 1-amino-1-cyclopropylcarbonitrile hydrochloride is commercially available and the free system was easily obtained by bubbling ammonia in a suspension of the salt in dichloromethane (Scheme 4).

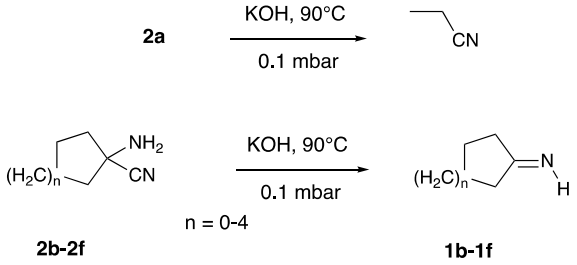


Scheme 3 Synthesis of α-aminonitriles **2b**-**2f**

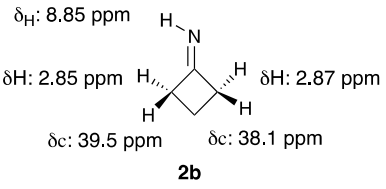


Scheme 4 Preparation of α-aminonitrile **2a**

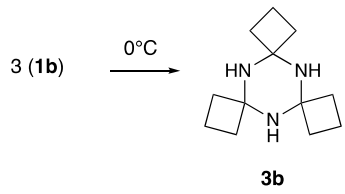
The vaporization of α-aminonitriles **2b**-**2f** on KOH in powder heated to 90°C in a vacuum line gave the expected imines in good yields except **1b** which was obtained in a 51 % yield in the presence of an isomer, the butanenitrile, formed in a 7 % yield. The reaction of the cyclopropyl derivative **2a** on the solid base led to an isomer of imine **1a**, the propanenitrile, observed with an important amount of residual precursor (Scheme 5). Imines **1b**-**1f** were easily characterized by ^{1}H NMR spectroscopy with the chemical shift of the H on the nitrogen atom which appears between 8.5 and 8.9 ppm at up-field of those of simple aldimines observed around 10 ppm.[9] The structures were confirmed by ^{13}C NMR spectroscopy with the chemical shift of the carbon of the C=N bond around 184 ppm at down-field of the one of simple N-H aldimine observed between 164 and 175 ppm.[9] The recording of ^{13}C NMR spectra of imines **1b**-**1f** cooled at 180-193 K allowed to differentiate the two sp^3 carbon atoms connected to the sp^2 carbon. On the basis of the chemical shifts reported for ethanimine,[9,23] the carbon on the same side than the hydrogen on the nitrogen is at down-field, and the carbon on the side of the lone pair at up-field (Scheme 6), with a difference in the chemical shifts of 1 to 4 ppm for **1b**-**1f**. On heating at 193-243 K, at a temperature depending on the size of the cycle, coalescence led to a large signal corresponding to both carbon atoms, giving then a thin signal at room temperature (see ESI). At the opposite, the chemical shift of the hydrogen on the nitrogen atom was broader on heating up to be very large at room temperature.



Scheme 5 Deshydrocyanation of α-aminonitriles **2a-2f**



Scheme 6 ^{1}H and ^{13}C NMR data of imine **2b**



Scheme 7 Trimerisation of **1b**

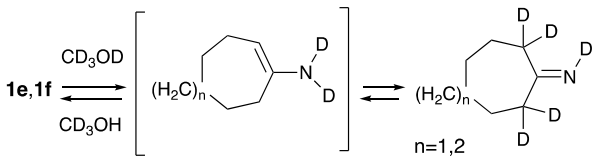
The infrared spectrum of **1c-1f** showed characteristic $\nu_{C=N}$ absorptions between 1634 and 1703 cm^{-1}. These value are comparable to those observed for methanimine ($\nu_{C=N}$: 1635 cm^{-1}) or ethanimine ($\nu_{C=N}$: 1642 cm^{-1})[9] for the larger cycles but are blue-shifted for the smaller cycles[26] as similarly observed for the $\nu_{C=O}$ of the corresponding cyclic ketones. ‡

A few hundred milligrams of imines **1b**-**1f** can be condensed in a trap immersed in a liquid nitrogen bath and then vaporized without loss of product. Compound **1b** diluted at 5% in CD_2Cl_2 is stable at 193 K but decomposes very rapidly at 273K. In similar conditions, the half-the of imines **1c**,**1d** is of about one hour at room temperature but no decomposition was observed after a week for 7- and 8-membered ring derivatives **1e**,**1f**. We attributed this dramatic difference to steric constraints in compounds **1b**-**1d**. §

Reactive imines decompose on heating with the formation of trimeric or oligomeric compounds.[9,10,23,27] On heating at room temperature, cycloalkylimines **1d**-**1e** diluted in a solvent formed

small amounts of trimers **3d**-**3e** among several unidentified oligomeric compounds while only **1b** gave the corresponding trimer in a good yield (Scheme 7). The chemical shift around 70-75 ppm is characteristic of the bridgehead carbon connected to two nitrogen atoms. The corresponding trimer of **1c** has never been observed in the spectra of decomposition products. For **1d**, the trimeric compound was also obtained when the corresponding ketone, a saturated solution of ammonia in methanol and molecular sieves were stirred for one day at room temperature. In similar conditions, only small amounts of imine **1e**,**1f** and the corresponding ketone were observed after one day starting from cycloheptanone and cyclooctanone, respectively. The trimer 3**d** diluted in methanol with potassium cyanide and trimethylamine hydrochloride (to generate HCN in situ) gave the aminonitrile **2d** in a 30% yield demonstrating the reversibility of the trimerisation. However, trimers **3b**, **3d** thermolyzed at 800°C gave only traces of **1b**, **1d**, respectively, and thereby, they cannot be considered as efficient precursors of the corresponding imine in these conditions.

Tautomerism between such enolizable cycloalkylimines and the corresponding enamines was easily evidenced recording the NMR spectra of the kinetically stable **1e**-**1f** in CD_3OD. At room temperature, the 2,2,7,7- or 2,2,8,8-tetradeutero derivative, respectively, was slowly formed (**1e-d$_4$**: δ_{C2} = 39.0 ppm (q), J_{CD} = 19.6 Hz, **1f-d$_4$**: δ_{C2} = 37.3 ppm (q), J_{CD} = 21.2 Hz) (Scheme 8). The exchange can be accelerated by the presence of a base (DBU). Such a tautomerism between an imine and the corresponding enamine is usually challenging to demonstrate with N-H derivatives. At room temperature in methanol, the decomposition of imines **1b**-**1d** was faster than tautomerism.



Scheme 8 Imine-enamine tautomerism of imines **1e,1f** demonstrated by deuteration

To summarize, unsubstituted cycloalkylimines with a 4 to 8 membered ring have been prepared on gram scale through the dehydrocyanation of cyclic α-aminonitriles. The kinetic stability of these imines is strongly dependent on the size of the ring. The use of these imines in chemistry and particularly in the preparation of polycyclic compounds is currently under progress in our lab.

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Conflicts of interest

There are no conflicts to declare.

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Notes and references

‡ https://chem.pg.edu.pl/documents/175230/54717567/8.%20IR.pdf. $\nu_{C=O}$: C_4: 1785, C_5: 1748, C_6: 1715, C_7: 1705, C_8: 1700 cm^{-1}.

§ **Cyclobutanimine 1b**. $\tau_{1/2}$ = 10 min (248 K, 5% in CD_2Cl_2). Yield: 51% in the presence of butyronitrile (7%). Removing of butyronitrile by selective trapping of **1b** at -43°C under 0 .1 mbar is difficult and leads to an important loss of product even on an analytical sample. ^{1}H NMR (CD_2Cl_2, 400 MHz, 183 K) δ 1.85 (quint, 2H, $^3J_{HH}$ = 8.2 Hz, CH_2) ; 2.85 (t, 2H, $^3J_{HH}$ = 8.2 Hz, CH_2) ; 2.87 (td, 2H, $^3J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 2.6 Hz, CH_2) ; 8.85 (s brd, 1H, NH). ^{13}C NMR (CD_2Cl_2, 100 MHz, 183 K) δ 11.7 ($^1J_{CH}$ = 139.3 Hz (t), CH_2) ; 38.1 ($^1J_{CH}$ = 135.4 Hz (t), CH_2) ; 39.5 ($^1J_{CH}$ = 135.2 Hz (t), CH_2) ; 185.7 (s, C=N). Coalescence was observed around 213 K. ^{13}C NMR spectrum at 243K: δ 11.7; 38.6; 185.1. IR (ν cm^{-1}, film): 3137 (m, ν_{NH}), 2980 (s), 2961(s), 2923 (s), 1703 (m, $\nu_{C=N}$), 1353 (s), 1019(s).

Cyclopentanimine 1c. $\tau_{1/2}$ = 1h (296 K, 5% in CD_2Cl_2). Yield: 80 %.^{1}H NMR (CD_2Cl_2, 400 MHz, 183 K) δ 1.72 (m, 4H, CH_2C=N) ; 2.19 (m, 4H, CH_2CH_2CN) ; 8.94 (s brd, 1H, NH). ^{13}C NMR (CD_2Cl_2, 100 MHz, 183 K) δ 25.5 ($^1J_{CH}$ = 131.6 Hz (t), $\underline{C}H_2CH_2CN$) ; 35.2 ($^1J_{CH}$ ≈ 130.0 Hz (t), $\underline{C}H_2CN$), 37.0 ($^1J_{CH}$ ≈ 130.0 Hz (t), $\underline{C}H_2CN$) ; 185.7 (s, C=N). Coalescence was observed around 190 K. ^{13}C NMR spectrum at 296 K: δ 25.5, 36.4 ($^1J_{CH}$ = 128.7 Hz (t), $\underline{C}H_2CN$), 185.7 (C=N). IR (ν cm^{-1}, film): 3180 (m, ν_{NH}), 2957(s), 2869(s), 1675 (m, $\nu_{C=N}$), 1418(m), 1182 (m), 952.

Cyclohexanimine 1d. $\tau_{1/2}$ = 2h (296 K, 5% in CD_2Cl_2). Yield: 77 %. ^{1}H NMR (CD_2Cl_2, 400 MHz, 193 K) δ 1.50 (m, 2H, CH_2) ; 1.60 (m, 4H, 2 CH_2) ; 2.20 (t, 4H, $^3J_{HH}$ = 6.7 Hz, CH_2CN) ; 8.64 (s brd, 1H, NH). ^{13}C NMR (CD_2Cl_2, 100 MHz, 193 K) δ 25.3 ($^1J_{CH}$ = 128.3 Hz (t), CH_2) ; 27.4 ($^1J_{CH}$ = 129.5 Hz (t), CH_2) ; 37.5 ($^1J_{CH}$ ≈ 127.2 Hz (t), $\underline{C}H_2CN$), 41.5 ($^1J_{CH}$ = 126.8 Hz (t), $\underline{C}H_2CN$) ; 184.4 (s, C=N). Coalescence was observed around 240 K. ^{13}C NMR spectrum at 296 K: δ 25.4, 27.4, 39.6 ($^1J_{CH}$ = 126.4 Hz (t), CH_2), 183.1 (s, C=N). IR (ν cm^{-1}, film): 3182 (m, ν_{NH}), 2930(s), 2852(s), 1660 (m, $\nu_{C=N}$), 1449(m), 1401 (m), 1248 (m), 1178 (m), 1011 (m).

Cycloheptanimine 1e. Yield: 73 %. ^{1}H NMR (CD_2Cl_2, 400 MHz, 183K) δ 1.50 (s brd, 4H, CH_2) ; 1.57 (s brd, 4H, 2 CH_2) ; 2.38 (t, 4H, $^3J_{HH}$ = 6.1 Hz, CH_2CN) ; 8.75 (s brd, 1H, NH). ^{13}C NMR (CD_2Cl_2, 100 MHz, 183 K) δ 26.2 ($^1J_{CH}$ = 128.3 Hz (t), CH_2) ; 30.3 ($^1J_{CH}$ = 126.4 Hz (t), CH_2) ; 39.0 ($^1J_{CH}$ ≈ 127.2 Hz (t), $\underline{C}H_2CN$), 41.7 ($^1J_{CH}$ = 126.8 Hz (t), $\underline{C}H_2CN$) ; 184.4 (s, C=N). Coalescence was observed around 190K. ^{13}C NMR spectrum at 296 K: δ 26.2, 30.3, 40.3 ($^1J_{CH}$ = 126.4 Hz (t), CH_2), 187.5 (s, C=N). IR (ν cm^{-1}, film): 3177 (m, ν_{NH}), 2924(s), 2849(s), 1637 (s, $\nu_{C=N}$), 1453(m), 1390(m), 1135(m), 834(m).

Cyclooctanimine 1f. Yield: 68 %. ^{1}H NMR (CD_2Cl_2, 400 MHz , 183 K) δ 1.32 (s brd, 2H, CH_2) ; 1.42 (s brd, 4H, CH_2) ; 1.67 (s brd, 4H, CH_2) ; 2.24 (s brd, 4H, CH_2CN) ; 8.92 (s brd, 1H, NH). ^{13}C NMR (CD_2Cl_2, 100 MHz, 183 K) δ 24.2 ($^1J_{CH}$ = 126.4 Hz (t), 1 CH_2) ; 26.1 (brd, $^1J_{CH}$ =

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126.0 Hz (t), 2 CH_2) ; 26.8 (brd, $^1J_{CH}$ = 125.2 Hz (t), 2 CH_2) ; 37.8 ($^1J_{CH}$ ≈ 126.8 Hz (t), $\underline{C}H_2CN$), 39.5 ($^1J_{CH}$ = 126.4 Hz (t), $\underline{C}H_2CN$) ; 189.7 (s, C=N). Coalescence was observed around 190K. Spectrum at 296 K: δ 24.9, 26.3, 27.0, 38.8 ($^1J_{CH}$ = 126.2 Hz (t), CH_2), 189.0 (s, C=N). IR (ν cm^{-1}, film): 3176 (m, ν_{NH}), 2926(s), 2848(m), 1634(m, $\nu_{C=N}$), 1449(m), 1392(m).

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