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Sébastien Thibaudeau

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COMMUNICATION

Evidence and exploitation of dicationic ammonium-nitrilium superelectrophiles: direct synthesis of unsaturated piperidinones

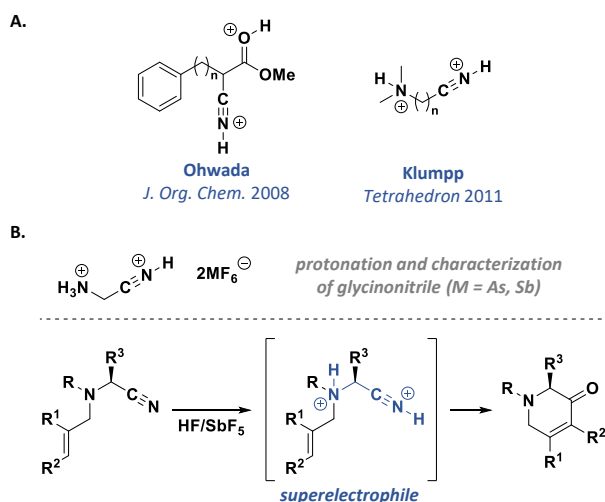
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Exploiting superacid activation, the reactivity of aminonitriles was enhanced through the transient formation of highly reactive ammonium-nitrilium superelectrophiles. Demonstrated by using *in situ* low-temperature NMR experiments and confirmed by X-ray diffraction analysis, these dications can be intramolecularly trapped by non-activated alkenes to generate unsaturated piperidinones, including enantioenriched ones, in a straightforward way.

Implicated in valuable organic reactions known over a hundred years, nitrilium ions¹ are pivotal reactive intermediates in Beckmann rearrangement² and in the Schmidt,³ Ritter,⁴ von Braun,⁵ Bischler-Napieralski⁶ and multi-component Ugi⁷ reactions. In their simplest forms $[\text{HC}\equiv\text{NH}]^+$ and $[\text{CH}_3\text{C}\equiv\text{NH}]^+$, nitrilium ions also play an important role in the chemical evolution process in interstellar clouds,⁸ considered as key intermediates in the synthesis of aminoacids and proteins.⁹ The electrophilic character of nitrilium ions have been especially exploited with success in the synthesis of high valued heterocycles.¹⁰ Commonly generated by *N*-alkylation of nitriles^{11–13} or by Lewis acid-induced chloride abstraction from imidoyl chlorides,¹⁴ nitrilium ions can also be generated by protonation of alkyl and aryl nitriles in HF/MF₅ (M = As, Sb) superacidic solutions.^{15–17} Implicated in Gattermann and Houben-Hoesch reactions, they have been suggested to be activated by subsequent protosolvation in CF₃SO₃H.¹⁸ Klupp showed that a similar effect could be expected by exploiting the proximity of electron-withdrawing fluorine atom(s).¹⁹ Ohwada demonstrated that the proximity of a protonated ester group also activates the nitrilium ion (Scheme 1A).^{20–21} Based on reactivity trends and on NMR data, the involvement of dicationic ammonium-nitrilium superelectrophiles²² has also been suggested to explain the superacid-promoted arylation of aminonitriles.²³ This state of play prompted us to consider that if an ammonium-nitrilium superelectrophilic dication could be generated in superacid, its intramolecular trapping with weak

nucleophiles could be expected. We report here the first isolation of diprotonated glycinonitrile $[\text{NH}_3\text{CH}_2\text{C}\equiv\text{NH}][\text{MF}_6]_2$. Evidenced by X-ray crystallography, low-temperature NMR spectroscopy and DFT calculations, dicationic ammonium-nitrilium superelectrophiles are transformed into functionalized piperidinones after intramolecular addition to alkenes opening new synthetic applications for aminonitriles (Scheme 1B).²⁴



Scheme 1. A. Nitrilium ion containing superelectrophiles; B. This work: generation, characterization and exploitation of ammonium-nitrilium superelectrophiles for the direct synthesis of enantioenriched unsaturated piperidinones.

This work needed to face two important challenges: 1) the ability to generate an ammonium-nitrilium dication and the evaluation of its superelectrophilic character; 2) the deactivation of the unsaturation after protonation of amine and nitrile functions, which could prevent substrate from any cyclization. To address these issues, the reactivity of the model *N*-allylic aminonitrile **1a** was evaluated (Table 1). Initial attempts to cyclize substrate **1a** in sulfuric acid failed, and no improvement was noted by performing the reaction in neat triflic acid or hydrogen fluoride (Table 1, entries 1–3). The absence of reactivity of aminonitrile **1a** in these conditions confirmed the challenge associated with this transformation, only one radical-based similar cyclization from unsaturated 2-aminobenzonitrile being reported to date.²⁵ On this basis, the reaction was attempted in the strongest superacidic solutions known yet, HF/SbF₅. Using a 7/1 (v/v) solution of HF/SbF₅, the

^a T. Cantin, Dr. A. Mingot, Prof. S. Thibaudeau Université de Poitiers, IC2MP UMR CNRS 7285 / Superacid Group – Organic Synthesis Team / 4 rue Michel Brunet 86073 Poitiers cedex 9, France ; E-mail: sebastien.thibaudeau@univ-poitiers.fr

^b Dr. Y. Morgenstern, Prof. A. Kornath Department of Chemistry Ludwig-Maximilian University of Munich; Butenandtstr. 5–13, D-81377 München, Germany; E-mail: akoch@cp.uni-muenchen.de

† Footnotes relating to the title and/or authors should appear here.

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substrate was cleanly converted to **3a_F** after hydrofluorination of the alkene moiety²⁶ (Table 1, entry 4). Gratifyingly, increasing the acidity by increasing the SbF₅ amount²⁷ allowed the formation of the desired piperidinone **2a** albeit in poor yield (Table 1, entry 5). By increasing the temperature and reaction time, the substrate **1a** was fully converted to the piperidinone **2a** (Table 1, entries 6–7).

Table 1. Superacid-promoted hydrofluorination and cyclization of unsaturated aminonitrile.

Entry	Acid	Reaction conditions	Yield (%) ^a
1	H ₂ SO ₄	20 °C, 2 h	- ^b
2	CF ₃ SO ₃ H	20 °C, 2 h	- ^b
3	HF	0 °C, 2 h	- ^b
4	HF/SbF ₅ (7/1) ^c	-20 °C, 10 min	-
5	HF/SbF ₅ (1/1) ^c	-20 °C, 10 min	2a (8) ^e 3a_F (81) ^e
6	HF/SbF ₅ (1/1) ^c	0 °C, 10 min	2a 48 3a_F 42
7	HF/SbF ₅ (1/1) ^c	0 °C, 2 h	2a 71 ^d -

[a] Isolated yield; [b] No reaction; [c] Volumic ratio; [d] Full conversion; [e] NMR ratio determined by ¹H-NMR analysis of the reaction crude / Traces of starting material remaining.

To provide some insights into the mechanism of this reaction, efforts were made to capture any ammonium-nitrilium dicationic intermediates. 2-Aminoacetonitrile (NH₂CH₂C≡N; glycinonitrile) was submitted to superacidic systems HF/AsF₅ and HF/SbF₅ (Figure 1). Satisfyingly, the salts of the ammonium-nitrilium dications [NH₃CH₂C≡NH][AsF₆]₂ **A₁** and [NH₃CH₂C≡NH][SbF₆]₂·HF **A₂** were formed (see SI). The bond lengths and angles of the dication [NH₃CH₂C≡NH]²⁺ do not differ significantly from the bond lengths and angles of the monocation [NH₃CH₂C≡N]⁺ generated in less acidic conditions. The slightly distorted anion [SbF₆]⁻ has regular Sb–F bond lengths between 1.860(3) and 1.889(3) Å which are in the regular range of typical Sb–F bond distances.^{28–31} The ions are connected by a three dimensional network of N⋯H and H⋯F hydrogen bonds (Figure 1A). The calculated geometric parameters of the dication are in good agreement with the one experimentally found in the crystal structure (Figure 1B).³² The Infrared and Raman spectra of [NH₃CH₂C≡NH]²⁺ salts **A₁** and **A₂** and of the isotopomer [ND₃CH₂C≡ND][AsF₆]₂ **A_{1D}** (generated in DF) and the Raman spectrum of glycinonitrile hydrochloride are shown in Figure 1C. For the dication, 24 fundamental vibrations are expected which are all Raman and Infrared active. Compared to the monocation [NA₃CH₂C≡N]⁺ the experimental spectra of [NA₃CH₂C≡N][AsF₆]₂ (A = H for **A₁**, A = D for **A_{1D}**), and [NH₃CH₂C≡NH][SbF₆]₂ **A₂** show no significant differences except of the C≡N stretching vibration and an additional N–H stretching vibration at 3554 cm⁻¹ (IR, **A₁**). The spectra of the deuterated species [ND₃CH₂C≡ND]²⁺ show a corresponding, red-shifted N–D stretching vibration at 2519 (IR, **A_{1D}**) and 2525 cm⁻¹ (Ra, **A_{1D}**) which is in good agreement with the Teller-Redlich rule for an H/D isotropic effect. Compared to glycinonitrile (2194 cm⁻¹),³³ the C≡N stretching vibration in the monocation [NH₃CH₂C≡N]⁺ is

blue-shifted to 2270 (IR) and 2272 (Raman) and after protonation at the nitrogen of the C≡N group in [NH₃CH₂C≡NH]²⁺, the C≡N stretching vibration shows a splitting in the spectra (**A₁**: 2244, 2214 cm⁻¹ (IR) and 2246, 2218 cm⁻¹ (Ra); **A₂**: 2251, 2215 cm⁻¹ (IR), 2269, 2221 cm⁻¹ (Ra)) and appears red-shifted, compared to the monocation, as a medium strong band in the infrared spectrum and a weak line in the Raman spectrum.

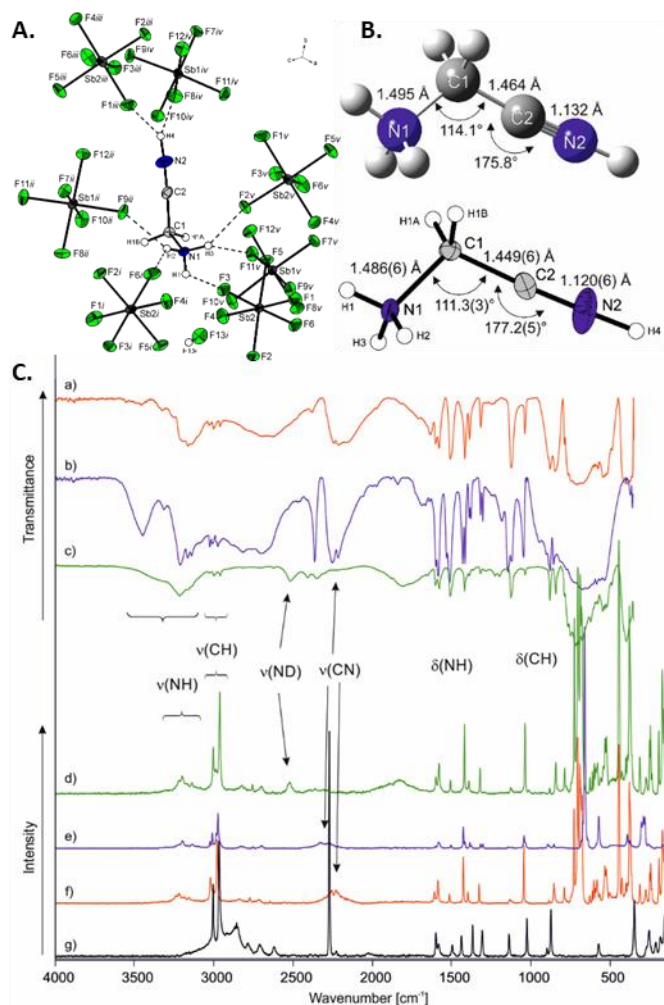
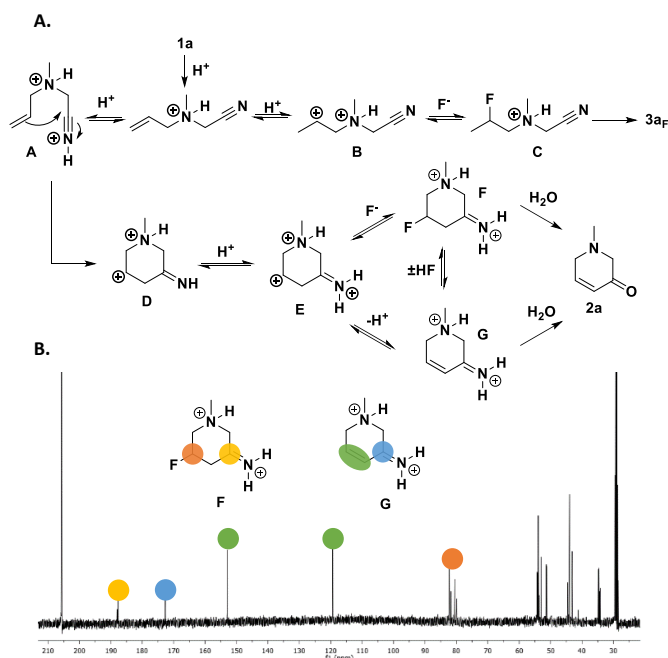


Figure 1. A. Projection of the interionic contacts in the [NH₃CH₂C≡NH][SbF₆]₂·HF **A₂** crystal (50% probability displacement ellipsoids). Symmetry codes: i = 1/2–x, 1–y, 1/2+z; ii = –x, 1/2+y, 1/2–z; iii = 1/2+x, 3/2–y, –z; iv = x, 1+y, z; v = 1/2–x, 1/2+y, z; B. Calculated structure of the diprotonated glycinonitrile cation [NH₃CH₂C≡NH]²⁺ (up) and the diprotonated glycinonitrile cation of the single-crystal X-ray structure of the dication **A₂** (down); C. Low temperature Infrared spectra of [NH₃CH₂C≡NH][AsF₆]₂ (**A₁**, a), [NH₃CH₂C≡NH][SbF₆]₂ (**A₂**, b), [ND₃CH₂C≡ND][AsF₆]₂ (**A_{1D}**, c), low temperature Raman spectra of [ND₃CH₂C≡ND][AsF₆]₂ (**A_{1D}**, d), [NH₃CH₂C≡NH][SbF₆]₂ (**A₂**, e), [NH₃CH₂C≡NH][AsF₆]₂ (**A₁**, f) and Raman spectrum of glycinonitrile hydrochloride (g).

On this basis, the following mechanism was suggested for the formation of **2a** (Scheme 2A). After protonation of the amine **1a**, a subsequent protonation of the double bond would favour the formation of a dication **B** prone to be fluorinated (precursor of **3a_F**). Protonation occurring on the nitrile function

could generate the ammonium-nitrilium ion **A**.³⁴ The superelectrophilic character of the ion **A** must favour its intramolecular trapping, in spite of the strong electronic deactivation of the double bond, to form a dication **D** (in equilibrium with its iminium analogue **E**). The fluorination of **E** could generate the fluorinated intermediate **F** (probably existing in equilibrium with species **G** obtained after elimination) as a precursor of the cyclic product **2a**. The formation of dications **F** and **G** in superacid was explored by *in situ* NMR spectroscopic analysis. While submitting **1a** to HF/SbF₅ (7/1; v/v) revealed the clean formation of the fluorinated dicationic ammonium-nitrilium diastereomers **C** (see SI), a similar experiment conducted in more acidic conditions at 0 °C showed the formation of ions **F** and **G**. In the clean ¹³C NMR spectrum (Scheme 2B), fluorinated diastereomers **F** are characterized by an iminium ion peak at 188.0 ppm and two doublets (*J* = 178 Hz) at about 81 ppm. The olefinic carbons of ion **G** appears at 153.0 ppm and 119.4 ppm and the conjugated iminium ion at 172.6 ppm.



Scheme 2. A. Suggested mechanism for the formation of **2a** from **1a**; B. ¹³C NMR of ions **F** and **G** from the reaction of substrate **1a** in HF/SbF₅ (1/1; v/v) at 0 °C.

The reaction scope was then explored. As expected, substrate **1b** did not cyclize to a seven-membered ring and the alcohol **3b_{OH}** (obtained after hydrolysis) and the fluorinated product **3b_F** were generated. Protection of the amine function with an *ortho*-nitrobenzyl group is not detrimental to the process, as shown by the formation of product **2c**. When the double bond was substituted with a methyl group, the reaction led to the cyclic products **2d** and **2e** (Table 2, entries 4-5), the product **2d** being unstable during chromatography purification. To verify whether the chlorine atom substitution of the double bond could favour the process, the substrate **1f** was submitted to cyclization leading to the desired fluorinated product **2f_F** and chlorinated analogue **2f_{Cl}**. Increasing reaction time favoured the formation of the chlorinated product **2f_{Cl}** in 59% yield (Table 2,

entries 6-7). As expected, the cyclization also occurred when employing aryl group as a nucleophile (Table 2, entry 8). One step further in complexity, the synthesis of enantioenriched products was explored following the same strategy from **1h-k**.³⁵ **Table 2.** Superacid-catalyzed cyclization of unsaturated aminonitriles in superacid and synthesis of unsaturated piperidinones.

Entry	Substrate 1	Product / Yield (%) ^a
1 ^b		2a 71 ^c
2		 3b_F 14, X = F 3b_{OH} 20 ^d , X = OH
3 ^e		2c 48 ^c
4		2d / ^{c,f}
5		2e 85 ^c
6		 2f_F 45, X = F 2f_{Cl} 20, X = Cl
7 ^g		 2f_F / ^h 2f_{Cl} 59
8		2g 45 ^c
9 ^b		2h 40 ^c
10 ^b		2i 26 ^c
11 ^b		2j 8 ⁱ
12 ^b		2k 20 ⁱ

[a] Yield obtained after purification by column chromatography; [b] 2 h reaction time at 0 °C; [c] full conversion; [d] traces of γ -hydroxylated analogue was also detected in the crude (see SI); [e] 30 min reaction time; [f] unstable under silica column chromatography; [g] 5 h reaction time; [h] traces detected in the reaction crude; [i] side products formation

In all cases, the superacid-promoted cyclization allowed the synthesis of the corresponding enantioenriched unsaturated piperidinones. Products **2h** and **2i** were quantitatively generated, although obtained in modest yield after purification (Table 2, entries 9-10). Proline-type substrates were found to be more reluctant to cyclize, generating the desired bicyclic enantioenriched products **2j** and **2k** (Table 2, entries 11-12). At this stage, it is important to note that, by using conventional approaches, the non-racemic or halogen-substituted unsaturated piperidin-3-ones **2f-k** could only be generated at

the expense of long multi-step synthetic procedures.³⁶ Furthermore, these molecules can be considered as especially valuable synthetic platforms for natural products³⁷ and bioactive compounds syntheses.^{36b,38}

In conclusion, using single-crystal X-ray diffraction studies, vibrational spectroscopy, and *in situ* low temperature NMR experiments, the formation of ammonium-nitrilium dications in superacid is evidenced. Their intramolecular trapping with poor nucleophilic alkenes is highly dependent on their superelectrophilic character favouring the straightforward synthesis of high valued unsaturated piperidin-3-ones.

Conflicts of interest

There are no conflicts to declare.

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