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Mechanism of the Acid-Mediated Thermal Fragmentation of 5-Spirocyclobutane-isoxazolidines

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Dedicated to Professor Gianfranco Scorrano on the occasion of his 72nd birthday

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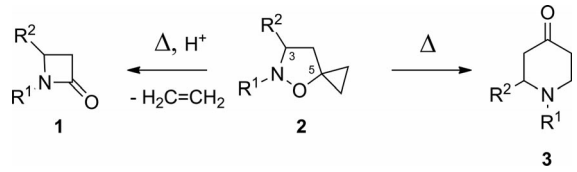
Protonation at the nitrogen of 5-spirocyclopropane-isoxazolidines induces clean thermal rearrangement/fragmentation to β-lactams and ethylene. Under the same conditions, homologous 5-spirocyclobutane-isoxazolidines undergo unselective fragmentation to give cyclobutyl derivatives through a completely different mechanism. Experimental data and DFT calculations show that the process is initiated with less-favored protonation at the isoxazolidine oxygen rather than nitrogen. Highly energetic *O*-protonated isoxazolidines undergo N–O cleavage with concomitant endo- or exocyclic deprotonation to give iminium ions that, in the presence of trifluoroacetate, evolve into 2-(1-hydroxycyclobutyl)ethanones and *N*-[2-(1-hydroxycyclobutyl)ethyl]trifluoroacetamides, respectively. DFT data validate protonation at oxygen of 5-spirocyclobutane-isoxazolidines, which requires higher energy than protonation at nitrogen, but can trigger the proposed process without any energy barrier. The *N*-protonated derivatives could rearrange to give oxazaspirooctane, with enlargement of the spirocyclobutane ring, but this process, owing to its high energy barrier, cannot compete with the reaction channel promoted by oxygen protonation and, in fact, is not experimentally observed. Being independent of the presence of a strained spirofused ring, acid-catalyzed fragmentation was also demonstrated to occur in normal isoxazolidines, such as those derived from cycloaddition of C–Ph–N–Me-nitrone to norbornene, suggesting that isoxazolidines, widely used in organic synthesis, should not be heated in the presence of protic acids.

Special Section

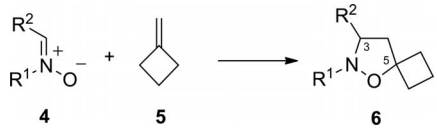
Introduction

The thermal rearrangement of 5-spirocyclopropane-isoxazolidines **2** and -isoxazolines (Brandi–Guarna rearrangement) has revealed its potency in the synthesis of diverse azaheterocyclic ring systems.[1] The synthetic diversity has been further expanded by the simple modification of running the thermal rearrangement in the presence of a protic acid, leading to β-lactams **1** (Scheme 1).[2–4]

Homologous 5-spirocyclobutane-isoxazolidines **6**, obtained by 1,3-dipolar cycloadditions of nitrones **4** to methylenecyclobutane (**5**) (Scheme 2), undergo thermal rearrangement under harsher conditions,[5] as validated by a recent computational study.[6] In particular, the activation energy for the rate-determining step of the rearrangement,



Scheme 1. Thermal rearrangement of 5-spirocyclopropane-isoxazolidines under acidic and neutral conditions.



Scheme 2. Synthesis of 5-spirocyclobutane-isoxazolidines **6**.

that is, cleavage of the N–O bond, was estimated to be around 13 kcal mol^{-1} higher in compounds **6** than in **2**.

The rearrangement of **6** occurs only under flash vacuum thermolysis (FVT) conditions (500 °C, 0.2 Torr) and affords, apart from the expected azepinones **7**, open-chain isomers **8**, which are derived from diradical intermediates **I** by 1,6-hydrogen shift, and, when the *N*-substituent is a phenyl group, benzo-fused heterocycles **9**, which are derived

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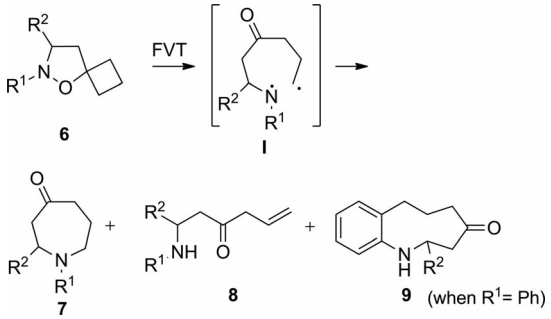
from the delocalization of the radical on the N-aromatic ring in **I** (Scheme 3). Other products formed by hydrogen shift of the intermediates were isolated by starting from 5-spirocyclobutane-4-spirocyclopropane-isoxazolidines.[7]



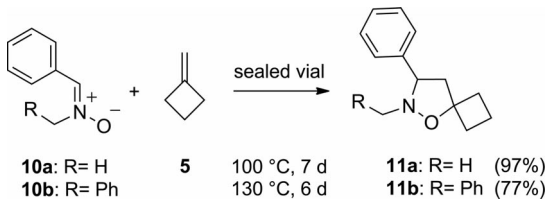
Scheme 3. Thermal rearrangement of 5-spirocyclobutane-isoxazolidines **6**.

In the light of the divergent behavior of **2** under neutral and acidic conditions (see Scheme 1), we also wished to test the behavior of **6** when submitted to heating in the presence of a protic acid.

The synthesis and characterization of 5-spirocyclobutane-isoxazolidines **11** and **27** and the experimental and DFT computational study of the reactivity of these model 5-spirocyclobutane-isoxazolidines in the presence of trifluoroacetic acid (TFA) are reported herein.

Results and Discussion

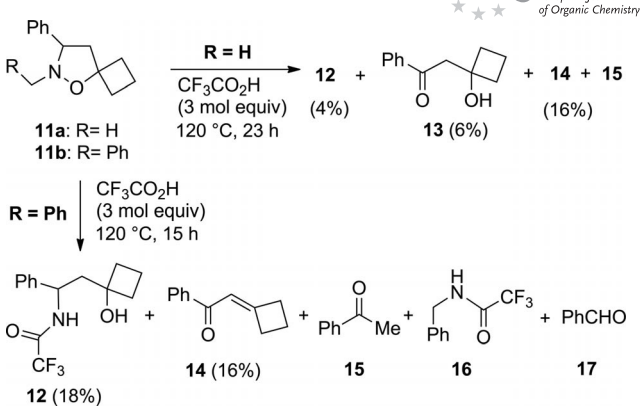
The cycloaddition of an excess of nitrones **10a** and **10b** (2 equiv.) with **5** was carried out in a sealed vial without solvent at 100 °C, for nitrone **10a**, and at 130 °C for nitrone **10b**, for several days to give isoxazolidines **11a** and **11b** in 97 and 77% yield, respectively (Scheme 4).



Scheme 4. Synthesis of isoxazolidines **11**.

The acid-catalyzed thermal reaction was carried out by treating solutions of **11a** and **11b** in toluene with TFA (3 equiv.) at 0 °C for 10 min, then heating the protonated isoxazolidines at 120 °C in a Sovirel tube.

Monitoring the reactions by TLC showed that compounds **11a** and **11b** were completely consumed after heating for 23 and 15 h, respectively. In both cases, only fragmentation products were formed (Scheme 5), of which some were isolated by flash chromatography, and completely analytically and spectroscopically characterized, and some were only detected by GC–MS and ^{1}H NMR spectroscopic analysis of the crude mixture.



Scheme 5. Acid-catalyzed thermal rearrangement of isoxazolidines **11**.

Compound **12** was isolated in 4 and 18% yield from isoxazolidines **11a** and **11b**, respectively. Its structure was assigned by HRMS and diagnostic signals in NMR spectra, such as the downfield CHPh chemical shift (δ = 5.10 ppm), the resonances of the six cyclobutane protons in the δ = 2.2–1.5 ppm region, and of the fluorine at δ = –77.1 ppm. The presence of the *N*-trifluoroacetate group was confirmed by the ^{13}C NMR signals of the group [δ_{CO} = 156.4 (q, $J_{C,F}$ = 36.8 Hz) and δ_{CF3} = 115.5 (q, $J_{C,F}$ = 287.7 Hz) ppm].

Hydroxyketone **13** was isolated from the reaction of isoxazolidine **11a** in 6% yield and was clearly the precursor of the α,β-unsaturated ketone **14** isolated in 16% from both the reactions of **11a** and **11b**. The diagnostic NMR spectroscopy resonances recorded for the structural assignment of **13** were the methylene moiety (singlet at δ = 3.34 ppm), the six cyclobutane protons in the range of δ = 2.3–1.6 ppm, and the carbonyl group (δ =201 ppm), whereas **14** showed an olefinic proton (quintet at δ = 6.75 ppm), a symmetric cyclobutane ring (3.2–2.2 ppm), and an α,β-unsaturated carbonyl group (δ =190 ppm). The formation of compound **13** was previously observed in the [Mo(CO)$_6$]-mediated ring opening of 3-phenyl-5-spirocyclobutane-2-isoxazoline.[8]

Acetophenone (**15**) was easily detected by GC–MS [120 (28) [M]$^+$, 105 (90) [PhCO]$^+$, base signal 77 (100) [Ph]$^+$] and by the singlet at δ = 2.6 ppm for the methyl group in the ^{1}H NMR spectrum.

Trifluoroacetamide **16**[9] was detected by GC–MS [203 (65) [M]$^+$, 134 (32) [BnNHCO]$^+$, base signal 91 (100) [C_7H_7]$^+$], and by the resonance of the methylene moiety at δ = 4.54 ppm (d, J = 5.8 Hz) in the ^{1}H NMR spectrum. The formation of benzaldehyde (**17**) from **11b** was evident from the GC–MS spectrum and ^{1}H NMR signal at δ = 10.02 ppm. Methyl trifluoroacetamide and formaldehyde, corresponding to **16** and **17**, respectively, were not detected in the reaction mixture of **11a**, probably as a result of their volatility.

The results show that the two isoxazolidines **11** undergo a similar rearrangement/fragmentation process, which appears to be independent of the *N*-substituent. This substituent affects exclusively the volatility and, therefore, the possibility of detecting fragmented compounds containing it.

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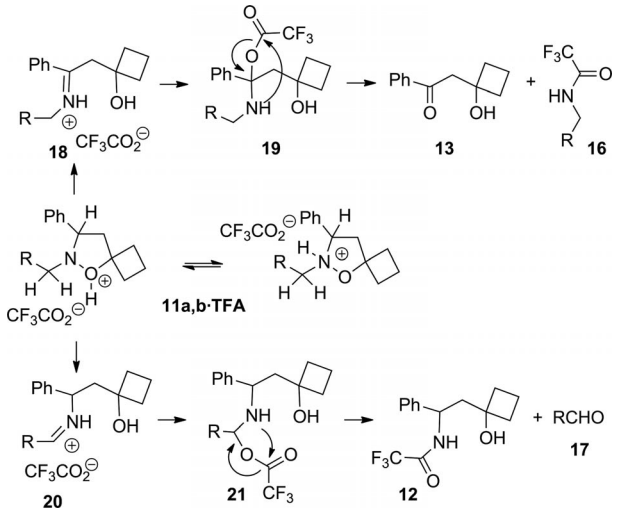
The isolation of compound **13** only in the reaction of **11a** is likely to depend on the fragmentation mechanism (see below).

The difference in the outcome of the acid-mediated thermal rearrangement of 5-spirocyclopropane- and 5-spirocyclobutane-isoxazolidines is rather striking. The 5-spirocyclobutane-isoxazolidines undergo a completely unselective reaction that can be ascribed to the rather different nature of the cyclopropane and the cyclobutane rings. The unselective reaction observed can, however, be easily rationalized.

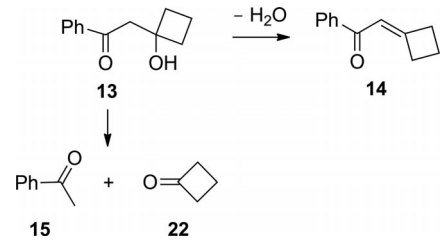
The selective rearrangement of 5-spirocyclopropane-isoxazolidines is attributed to the weakening of one or both spirocyclopropane C–C bonds under nitrogen protonation.[10] On the other hand, the well-known chemistry of isoxazolidinium ions indicates that the 5-H proton of the isoxazolidinium ring becomes more acidic and can be easily deprotonated by a base to yield an aminoketone with N–O bond cleavage.[11,12] If we consider *O*-protonation of the isoxazolidine ring, the acidity induced can now be experienced by the protons on the carbon atoms linked to nitrogen, the C-3 of the isoxazolidine ring, and the *N*-substituent carbon. The result is the formation of the two iminium ions **18** and **20**, originating from 3-H and NCH_2R proton extraction from protonated isoxazolidines **11a**,**b**·**TFA** (Scheme 6).



Scheme 6. Proposed mechanism for the acid-catalyzed thermal rearrangement of **11**.

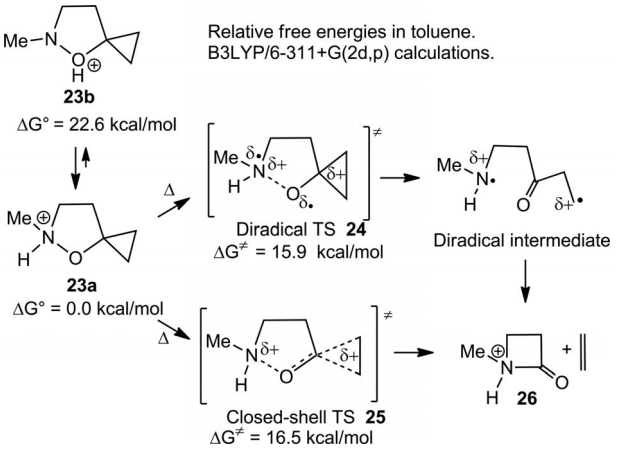
The formation of the iminium ions could not be directly detected, but these intermediates could be chemically correlated with the observed products. In particular, compounds **18** and **20** can undergo hydrolysis to the corresponding carbonyl derivatives **13** and **17** and/or react with the trifluoroacetate anion to form aminals **19** and **21** (Scheme 6) that can evolve into ketone **13** and trifluoroacetamide **16**, and aldehyde **17** and trifluoroacetamide **12**, respectively, by rearrangement with trifluoroacetyl shift.

Products **14** and **15** are likely to originate from ketone **13** by β-elimination and a retro-aldol process, respectively (Scheme 7). The second product of the retro-aldol reaction, cyclobutanone **22**, however, could not be detected due to its volatility.



Scheme 7. Products derived from **13**.

The mechanistic aspects of the above acid-catalyzed reactions were addressed by careful DFT computational studies [mostly B3LYP/6-311+G(2d,p) calculations in toluene][13,14] with the aim, in particular, to explain different behavior of 5-spirocyclopropane and 5-spirocyclobutane-isoxazolidines. In fact, the formation of β-lactams from 5-spirocyclopropane-isoxazolidines has been recently fully rationalized.[10] The computational study has shown that protonation of the isoxazolidine nitrogen, energetically much more favored than *O*-protonation, induced cleavage of the N–O bond with concomitant rupture of one, or both, C–C bonds of the cyclopropane ring. Actually, a small difference of less than 1 kcal mol^{-1} was evaluated for free energies of the transition states (TSs) **24** and **25**, that is, for a diradical two-step and a closed-shell one-step fragmentation process, respectively (Scheme 8).[15] The most relevant difference between diradical TS **24** and the closed-shell counterpart **25** is that the bond rupture of the spirocyclopropane bonds is more advanced in the latter TS than in the former one, as overemphasized in Scheme 8.



Scheme 8. Mechanism of the acid-catalyzed thermal rearrangement/fragmentation of 5-spirocyclopropane-isoxazolidines according to DFT calculations.

The TS free energy of around 16–17 kcal mol^{-1} justifies the easy reaction path towards the β-lactam formation and, what is more relevant here, the rearrangement/fragmentation process from *N*-protonated derivative **23a** should overcome any decomposition route starting from the *O*-proton-

ated form **23b**, since the latter compound resides at significantly higher energy than both TSs **24** and **25**.

With regard to 5-spirocyclobutane-isoxazolidines, in acidic toluene they are involved in equilibriums between complexes of isoxazolidine–CF_3COOH and isoxazolidinium cation–trifluoroacetate anion. According to calculations, complexes of isoxazolidine–CF_3COOH (**27a**–CF_3COOH) and isoxazolidinium cation–trifluoroacetate anion (**28a**–CF_3COO^-) exhibit similar stability and are more stable than solvent-separated isoxazolidine + CF_3COOH and much more stable than solvent-separated isoxazolidinium + CF_3COO^- ions (Figure 1).

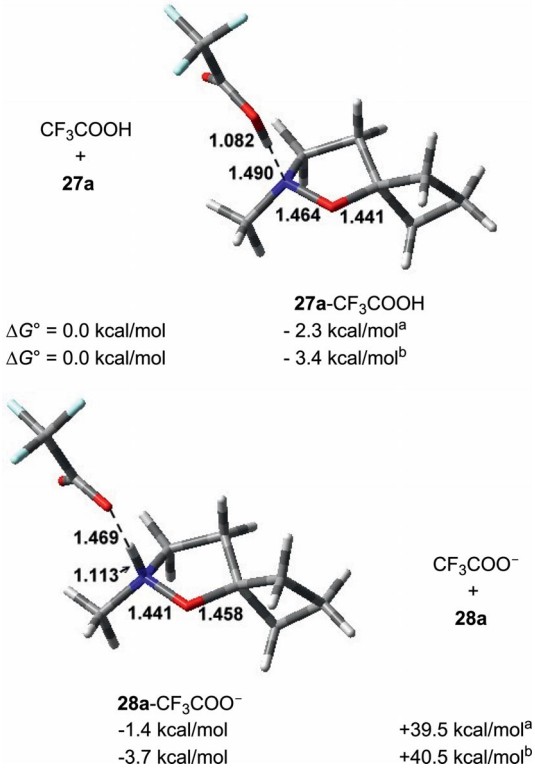
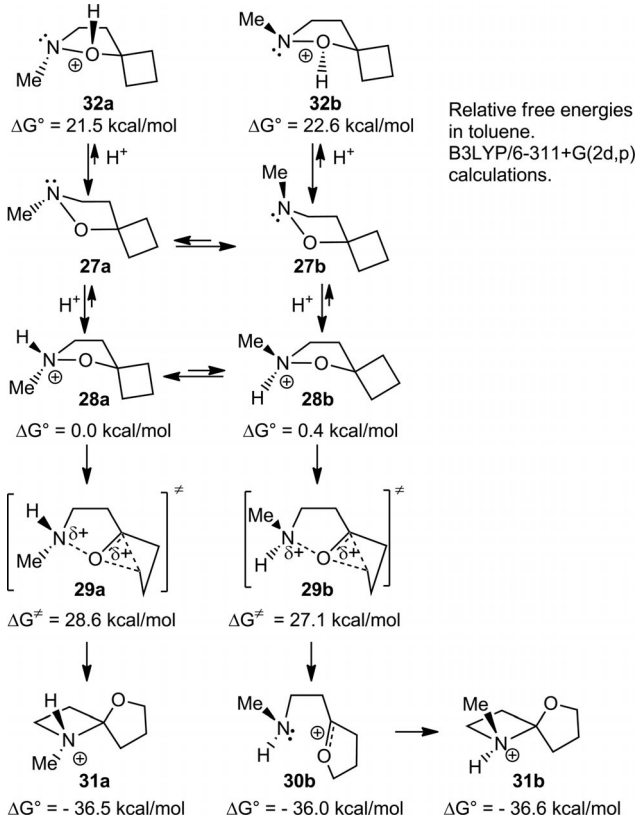


Figure 1. Relative free energies of species involved in the *N*-protonation of isoxazolidines [[a] B3LYP/6-311+G(2d,p) in toluene, [b] PBE1PBE/6-311+G(2d,p) in toluene].

For sake of simplicity, we performed computational modeling on the naked protonated isoxazolidines, while neglecting the trifluoroacetate counteranion on the assumption that its solvating effect was similar for the species in competition.[16] Switching to competition reactions, protonation at the nitrogen atom is again much more favored than that at the oxygen atom by a similar amount (ca. 22 kcal mol^{-1}; Schemes 8 and 9) to that observed for spirocyclopropane-isoxazolidines. Calculations also clearly suggest that protonation at the nitrogen atom in 5-spirocyclobutane-isoxazolidines can trigger, upon heating, an interesting cationic rearrangement that starts with heterolytic fragmentation of the N–O bond and simultaneous breakdown of a C–C bond of the cyclobutane ring to give closed-shell TSs (i.e., **29a** and **29b**). IRC analysis showed that TS **29b** was connected, on the product side, to a carbocationic intermediate (**30b**) that can easily be transformed into an oxazaspirooctane derivative (**31b**) (Scheme 9) as a final product.[17] TS **29a** collapses directly to **31a**.



Scheme 9. Protonation equilibria of *N*-methyl-5-spirocyclobutane-isoxazolidine conformers and rearrangement of the *N*-protonated derivatives as disclosed by DFT calculations.

However, oxazaspirooctane derivatives of the type **31** have never been observed in product mixtures of acid-induced decomposition of spirocyclobutane-isoxazolidines. It is gratifying that, consistent with this experimental finding, calculations demonstrate that now, in contrast to the behavior of spirocyclopropane-isoxazolidine systems, protonation at the oxygen atom is much easier than the a priori viable cationic rearrangement of the *N*-protonated derivatives (Scheme 9), that is, TSs **29** are significantly less stable than compounds **32**.[18]

Moreover, *O*-protonation certainly paves the way to a very easy, apparently without any energy barrier, base (CF_3COO^-)-assisted ring-opening reaction. In fact, geometry data clearly show that *O*-protonation significantly weakens the two ring σ bonds that involve the oxygen atom, as clearly testified by the substantial bond lengthening of the N–O bond in compounds **32** (e.g., **32b** in Figure 2) relative to the N–O bond in compounds **28** (e.g., **28b** in Figure 2; see also **28a**–CF_3COO^- in Figure 1).[19]

In accordance with the fragility of compounds **32**, any attempt to locate a TS for the trifluoroacetate anion assisted ring opening of these compounds, both by attack at position 3 or at the NCH_3 group, failed and the system

Special Section

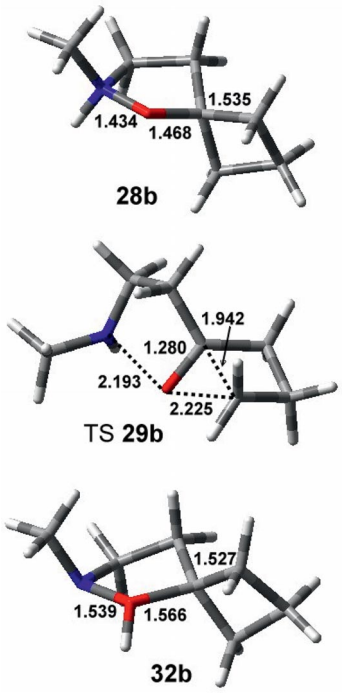
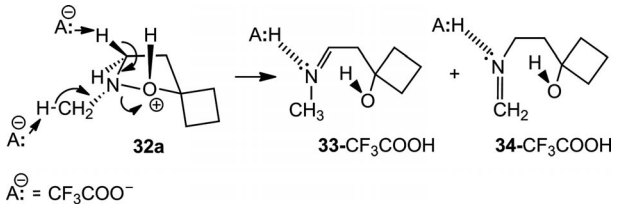


Figure 2. B3LYP/6-311+G(2d,p)-optimized geometries (toluene, bond lengths in Å) for *N*-protonated isoxazolidine **28b**, TS **29b**, and *O*-protonated isoxazolidine **32b**.

always collapsed directly to the final products (i.e., imine–CF_3COOH complexes **33**–CF_3COOH and **34**–CF_3COOH, Scheme 10).[20,21]

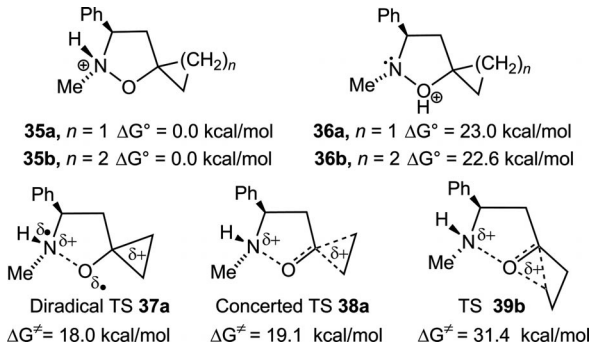


Scheme 10. Ring opening of *O*-protonated isoxazolidine **32a** according to DFT calculations.

Thus, calculations predict clear-cut dominance of imine derivatives, and products formed thereof, over the possible, but kinetically disfavored, formation of oxazaspirooctanes.

In conclusion, computational data on simple derivatives seem to offer a convincing mechanistic rationale for the different reactivity behavior of protonated isoxazolidines 5-spirocyclobutane and 5-spirocyclopropane.

It was then investigated whether phenyl substitution on the isoxazolidine ring, for example, at position 3, significantly changed the scenery depicted for the unsubstituted derivatives. Scheme 11, which reports free energies differences in toluene,[22] clearly shows that all reactivity features of the unsubstituted terms are maintained by the 3-phenyl derivatives.

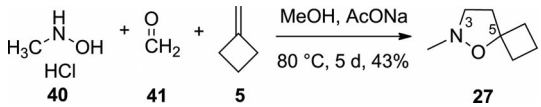


Scheme 11. Relative free energies [R(U)B3LYP/6-311+G(2d,p) calculations in toluene] of protonated, spirofused 3-phenyl-isoxazolidines and of the corresponding rearrangement TSs.

In particular, the diradical and concerted TSs, **37a** and **38a**, for the fragmentation/rearrangement process of the *N*-protonated 5-spirocyclopropane derivative **35a**, exhibit substantially lower free energy than the *O*-protonated isoxazolidine **36a**, whereas the rearrangement TS **39b**, from the *N*-protonated 5-spirocyclobutane isoxazolidine **35b**, is much less stable than the *O*-protonated form, **36b**.

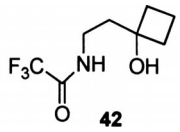
However, it must also be noted that here a weakness in the computational data emerges. The data correctly predict similar selectivity for protonated 3-phenyl-substituted and unsubstituted 5-spirocyclobutane-oxazolidines, respectively, but they also suggest that reaction rates of acid-induced fragmentations should be similar for the two kinds of compounds (i.e., protonation at the oxygen atom, which is the rate-determining step, to give compound **36b** is almost as difficult[23] as that to give compounds **32**). This prediction was not corroborated by experimental data that indicate significantly higher reactivity for the 3-phenyl derivatives.

To test this aspect, unsubstituted isoxazolidine **27** was synthesized by the multicomponent reaction conditions shown in Scheme 12 and submitted to thermal reaction under the usual conditions.



Scheme 12. Synthesis of isoxazolidine 27.

In contrast with computational data, isoxazolidine **27** was more stable than the substituted analogues, since it was essentially unaltered after being heated for 15 h at 120 °C. After further heating for 15 h at 120 °C, only traces of fragmentation products, apart from the unchanged starting isoxazolidine, could be observed by GC–MS and ^1H NMR spectroscopy. The only product identified by GC–MS [183 (14) $[M - 28]^+$, 140 (16) $[CF_3CONHCH_2CH_2]^+$, 126 (16) $[CF_3CONHCH_2]^+$, base signal 70 (100)] was the trifluoroacetamide **42**, which was derived from deprotonation of the *N*-methyl group.



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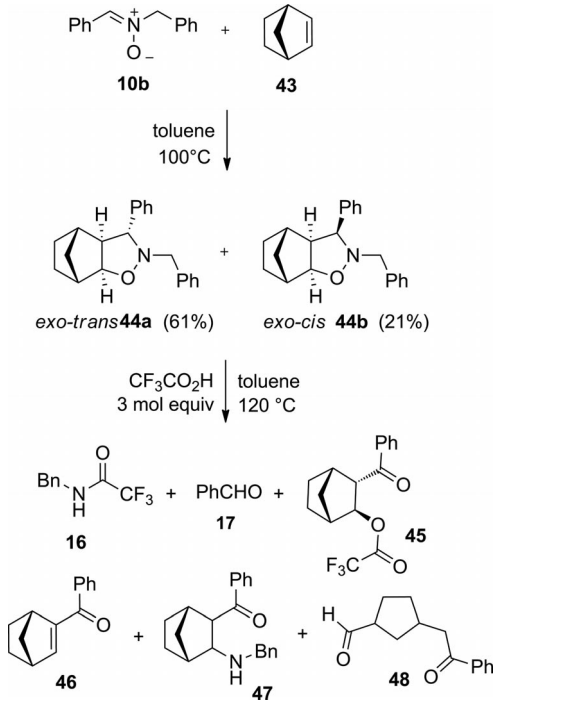
However, it must be emphasized that it was not possible to detect any trace of deprotonated oxazaspirooctane **31**, which would be derived from the calculated rearrangement process shown Scheme 9; this is the product of the more difficult of the two possible pathways.

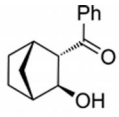
The study of the thermal reactions of 5-spirocyclobutane-isoxazolidines in the presence of TFA, both experimentally and computationally, indicates that the isoxazolidine ring undergoes *O*-protonation, followed by N–O bond cleavage, and deprotonation of C-3 or the *N*-alkyl substituent to form iminium ions that are trapped by the acid-conjugated base. The strained 5-spirocyclobutane is not directly involved in the observed acid-catalyzed reaction and its presence does not even promote this process. Experimental data clearly suggest that phenyl substituents at position 3 or at the *N*-alkyl moiety are more effective at inducing this reaction.

To prove that the 5-spirocyclobutane ring was not necessary for the observed rearrangement/fragmentation process, the same chemistry was studied for common isoxazolidines. To this end, a symmetrical, reactive, unfunctionalized dipolarophile was chosen to produce model isoxazolidines. The diastereomeric cycloadducts **44a**,**b** were synthesized from *C*-phenyl-*N*-methyl-nitrone (**10b**) and norbornene (**43**), and submitted to the standard reaction conditions (Scheme 13).



Scheme 13. Synthesis and rearrangement of isoxazolidines **44**.

The major isomer **44a** was heated in toluene at 120 °C with TFA (3 equiv.) for 15 h. Analysis of the resulting complex reaction mixture by GC–MS and ^{1}H NMR spectroscopy showed the presence of compounds **16**, **17**, **45**, **46**,[24] **47**, and **48**.[25,26] Chromatographic separation on silica gel afforded a mixture of **45** and **46** and enriched fractions of **47**, **48**, and hydroxy ketone **49**,[27] the presence of which in the crude mixture was not observed. By using minor isomer **44b** under the same conditions, analogous results were obtained.



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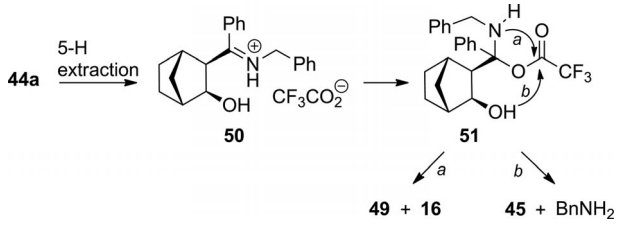
Benzyltrifluoroacetamide (**16**) and benzaldehyde (**17**) are the same products formed from isoxazolidine **11b**. Compounds **46**, **48**, and **49**, which are analogous to compounds **14**, **15**, and **13**, were derived from the endocyclic iminium formation (5-H extraction from **44**). Products **45** and **47**, however, have no analogous products in the rearrangement/fragmentation of spirocyclobutane isoxazolidines. Compounds **45** and **49** are likely to undergo inversion of the orientation of the benzoyl group to avoid eclipsing interactions. In the case of ketoalcohol **49**, structural assignment was possible by comparison of literature data of both the diastereomers.[27] Trifluoroacetyl ester **45** is likely to originate from aminal intermediate **51** through migration of the trifluoroacetyl moiety to the hydroxy group, which is suitably oriented to attack the activated carbonyl group (path b, Scheme 14). Compounds **46** and **48** are derived from **49** by H_2O elimination and a retro-aldol reaction, respectively. Finally, benzylamine **47** is the aza-Michael adduct of benzylamine and α,β-unsaturated ketone **46**.



Scheme 14. Proposed mechanism for the rearrangement of **44a**.

These experiments confirm that isoxazolidines lacking the 5-spirocyclobutane substituent also undergo a thermal reaction under acidic conditions to produce fragmentation of the isoxazolidine ring initiated by protonation at the oxygen atom, followed by deprotonation in the ring or out of the ring (N substituent) to form iminium ions. This observation, unprecedented in the literature, could be of interest to the wider scientific community involved in the synthesis of isoxazolidine derivatives and their use as synthetic intermediates.

Conclusions

The acid-mediated reaction of 5-spirocyclobutane-isoxazolidines, although not synthetically useful, is interesting

from a mechanistic point of view. The reaction can be rationalized in terms of less-favored oxygen protonation evolving into the observed products with no activation barrier, according to DFT computational data. Experimental results showed that 3-phenyl-substituted isoxazolidines were more reactive than unsubstituted derivatives, which was in contrast with computational data. The spirocyclobutane moiety was not required for the observed rearrangement/fragmentation, which could, in fact, be extended to simple isoxazolidines. Further studies are necessary to determine if an appropriate choice of the substituents can lead to synthetically useful, acid-induced fragmentation of these useful class of heterocycles.

Experimental Section

General Remarks: R_f values refer to TLC on 0.25 mm silica gel plates. $CDCl_3$ was used as solvent in NMR and IR analyses. NMR spectroscopic data are reported in δ (ppm) from tetramethylsilane (TMS) at 25 °C.

6-Methyl-7-phenyl-5-oxa-6-azaspiro[3.4]octane (11a): A mixture of nitrone **10a** (478 mg, 3.54 mmol) and **5** (120 mg, 1.77 mmol) was heated at 100 °C in a sealed tube for 7 d. The crude product was purified by chromatography on silica gel (petroleum ether/AcOEt, 10:1) to give **11a** (350 mg, 1.72 mmol, 97% yield) as a colorless oil. R_f = 0.67 (petroleum ether/AcOEt, 5:1). ^{1}H NMR (400 MHz): δ = 7.41–7.24 (m, 5 H), 3.66–3.50 (m, 1 H), 2.71 (dd, J = 12.3, 7.0 Hz, 1 H), 2.60 (s, 3 H), 2.51–2.42 (m, 2 H), 2.46 (dd, J = 12.3, 9.8 Hz, 1 H), 2.41–2.31 (m, 1 H), 2.24–2.05 (m, 1 H), 1.74 (dtt, J = 11.0, 9.8, 3.1 Hz, 1 H), 1.63–1.49 (m, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 139.3 (s), 128.5 (d, 2 C), 127.7 (d), 127.6 (d, 2 C), 81.4 (s), 73.2 (d), 51.3 (t), 44.2 (q), 37.3 (t), 36.9 (t), 12.5 (t) ppm. IR: $\tilde{\nu}$ = 3065, 3030, 2987, 2872, 2849, 2777, 1603, 1494, 1454, 1436, 1361, 1252, 1164, 1020 cm^{-1}. MS (EI): m/z (%) = 203 (24) [M$^+$], 175 (25), 160 (21), 146 (8), 133 (30), 132 (83), 118 (30), 104 (14), 91 (35), 77 (28), 42 (100). $C_{13}H_{17}NO$ (203.28): calcd. C 76.81, H 8.43, N 6.89; found C 76.86, H 8.05, N 6.88.

6-Benzyl-7-phenyl-5-oxa-6-azaspiro[3.4]octane (11b): A mixture of nitrone **10b** (832 mg, 3.94 mmol) and **5** (134 mg, 1.97 mmol) was heated at 130 °C in a sealed tube for 6 d. The crude product was purified by chromatography on silica gel (petroleum ether/AcOEt, 15:1) to give **11b** (423 mg, 1.52 mmol, 77% yield) as a pale yellow solid; m.p. 59–61 °C; R_f = 0.7 (EP/AcOEt, 5:1). ^{1}H NMR (400 MHz): δ = 7.45–7.40 (m, 2 H), 7.36–7.18 (m, 8 H), 3.97 (A part of an AB system, J = 14.2 Hz, 1 H), 3.92 (dd, J = 9.1, 7.0 Hz, 1 H), 3.80 (B part of an AB system, J = 14.2 Hz, 1 H), 2.71 (dd, J = 12.2, 7.0 Hz, 1 H), 2.48–2.31 (m, 2 H), 2.44 (dd, J = 12.2, 9.1 Hz, 1 H), 2.17–2.04 (m, 2 H), 1.71 (dtt, J = 11.0, 9.9, 3.1 Hz, 1 H), 1.61–1.48 (m, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 140.1 (s), 137.9 (s), 128.8 (d, 2 C), 128.5 (d, 2 C), 128.1 (d, 2 C), 127.6 (d, 2 C), 127.7 (d), 126.9 (d), 81.8 (s), 69.9 (d), 61.0 (t), 50.5 (t), 37.2 (t), 36.6 (t), 12.6 (t) ppm. IR: $\tilde{\nu}$ = 3087, 3065, 3030, 2986, 2936, 2870, 1603, 1495, 1454, 1369, 1300, 1253, 1119, 1028 cm^{-1}. MS (EI): m/z (%) = 279 (16) [M$^+$], 251 (5), 208 (12), 194 (4), 129 (11), 104 (26), 91 (100). $C_{19}H_{21}NO$ (279.38): calcd. C 81.68, H 7.58, N 5.01; found C 81.29, H 7.59, N 5.00.

Acidic Thermal Rearrangement of 11a: A solution of adduct **11a** (102 mg, 0.50 mmol) in toluene (8.4 mL) was treated with TFA (0.116 mL, 1.5 mmol) at 0 °C for 10 min, then was heated at 120 °C for 23 h. The reaction mixture was concentrated under reduced pressure, and the crude residue was purified by chromatography on silica gel (petroleum ether/AcOEt from 20:1 to 7:1) to give **12** (6 mg, 0.02 mmol, 4% yield), **13**[8] (5.6 mg, 0.03 mmol, 6% yield), and **14** (12 mg, 0.07 mmol, 16% yield).

Acid-Catalyzed Thermal Rearrangement of 11b: A solution of adduct **11b** (100 mg, 0.36 mmol) in toluene (6 mL) was treated with TFA (0.083 mL, 1.07 mmol) at 0 °C for 10 min, then was heated at 120 °C for 15 h. The reaction mixture was concentrated under reduced pressure, and the crude residue was purified by chromatography on silica gel (petroleum ether/AcOEt from 20:1 to 5:1) to give **12** (18.4 mg, 0.06 mmol, 18% yield) and **14** (10 mg, 0.06 mmol, 16% yield).

2,2,2-Trifluoro-*N*-[2-(1-hydroxycyclobutyl)-1-phenylethyl]acetamide (12): Yellow oil. R_f = 0.23 (petroleum ether/AcOEt, 5:1). ^{1}H NMR (400 MHz): δ = 8.03 (br. s, 1 H), 7.38–7.25 (m, 5 H), 5.10 (dt, J = 8.6, 5.5 Hz, 1 H), 2.45 (br. s, 1 H), 2.21–2.09 (m, 3 H), 2.10–2.01 (dt, J = 12.1, 9.1 Hz, 1 H), 1.92–1.71 (m, 3 H), 1.52 (d quintet, J = 11.4, 8.6 Hz, 1 H) ppm. ^{13}C NMR (50 MHz): δ = 156.6 (q, $J_{C\text{-}F}$ = 36.8 Hz), 140.6 (s), 128.7 (d, 2 C), 127.6 (d), 126.0 (d, 2 C), 115.8 (q, $J_{C\text{-}F}$ = 287.7 Hz), 75.5 (s), 52.5 (d), 43.7 (t), 37.7 (t), 36.1 (t), 12.3 (t) ppm. ^{19}F NMR (188 MHz): δ = –77.1 ppm. IR: $\tilde{\nu}$ = 3609, 3348, 3089, 3067, 3033, 2987, 2966, 2935, 1720, 1540, 1495, 1455, 1329, 1210, 1174 cm^{-1}. MS (EI): m/z (%) = 287 (3) [M$^+$], 259 (3), 244 (5), 216 (7), 202 (100), 190 (10), 174 (11), 146 (42), 131 (23), 104 (53), 79 (50), 69 (30). HRMS: calcd. for $C_{14}H_{17}F_3NO_2^+$ [M + H]$^+$ 288.12059, found 288.12142.

2-Cyclobutylidene-1-phenylethanone (14): Yellow oil. R_f = 0.7 (petroleum ether/AcOEt, 5:1). ^{1}H NMR (400 MHz): δ = 7.94–7.89 (m, 2 H), 7.55–7.50 (m, 1 H), 7.47–7.42 (m, 2 H), 6.76 (pseudo quintet, J = 2.2 Hz, 1 H), 3.29–3.22 (m, 2 H), 2.99–2.91 (m, 2 H), 2.18 (pseudo quintet, J = 7.8 Hz, 2 H) ppm. ^{13}C NMR (50 MHz): δ = 190.0 (s), 169.6 (s), 138.7 (s), 132.1 (d), 128.3 (d, 2 C), 127.9 (d, 2 C), 116.1 (d), 35.2 (t), 33.3 (t), 18.6 (t) ppm. IR: $\tilde{\nu}$ = 3061, 3028, 2989, 2960, 2923, 1676, 1621, 1578, 1447, 1359, 1252 1228, 1215, 1036 cm^{-1}. MS (EI): m/z (%) = 172 (45) [M$^+$], 157 (50), 144 (10), 129 (19), 115 (11), 105 (77), 77 (100), 51 (73), 39 (36). HRMS: calcd. for $C_{12}H_{13}O^+$ [M + H]$^+$ 173.09609, found 173.09654.

6-Methyl-5-oxa-6-azaspiro[3.4]octane (27): A solution of hydroxylamine hydrochloride (589 mg, 7.06 mmol), paraformaldehyde (212 mg, 7.06 mmol), **5** (160 mg, 2.35 mmol) and NaOAc (579 mg, 7.06 mmol) in MeOH (2 mL) was heated at 80 °C in a sealed tube for 5 d. The reaction mixture was diluted with CH_2Cl_2 and concentrated under reduced pressure. The resulting residue was redissolved in a 1:1 mixture of water and pentane (20 mL + 20 mL). The aqueous phase was separated and extracted with pentane (15 mL × 3). The combined organic layers were washed with brine and dried with Na_2SO_4. The pentane was removed by distilled at ordinary pressure to give **27** (127 mg, 1.00 mmol, 43% yield) as a pale yellow oil.

27: R_f = 0.43 (CH_2Cl_2/MeOH, 20:1). ^{1}H NMR (400 MHz): δ = 3.36–3.19 (m, 1 H), 2.67 (s, 3 H), 2.64–2.52 (m, 1 H), 2.40–2.27 (m, 4 H), 2.12–1.99 (m, 2 H), 1.71 (dtt, J = 11.0, 9.8, 3.0 Hz, 1 H), 1.56 (dtt, J = 11.0, 9.8, 8.3 Hz, 1 H) ppm. ^{13}C NMR (50 MHz): δ = 82.1 (s), 56.7 (t), 46.4 (t), 40.6 (q), 37.1 (t), 37.0 (t), 12.7 (t) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2959, 2931, 2872, 2779, 1458, 1379, 1304, 1269, 1253, 1163, 1144, 1120 cm^{-1}. MS (EI): m/z (%) = 127 (35) [M$^+$], 126 (10), 99 (100), 84 (11), 81 (18), 79 (20), 60 (78), 57 (87). HRMS: calcd. for $C_7H_{14}NO^+$ [M + H]$^+$ 128.10699, found 128.10718.

(1*R,2*S**,5*R**,6*S**,7*S**)-4-Benzyl-5-phenyl-3-oxa-4-azatricyclo[5.2.1.0^{2,6}]decane (44a) and (1*R**,2*S**,5*S**,6*S**,7*S**)-4-Benzyl-5-phenyl-3-oxa-4-azatricyclo[5.2.1.0^{2,6}]decane (44b):** A mixture of

nitrone **10b** (112 mg, 0.53 mmol) and norbornene (75 mg, 0.79 mmol) in toluene (0.25 mL) was heated at 100–110 °C in a Sovirel tube for 4 d. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by flash chromatography on silica gel (petroleum ether/ CH_2Cl_2, 1:1) to give **44a** (99 mg, 0.324 mmol 61% yield) and **44b** (34 mg, 0.111 mmol, 21% yield) as colorless crystalline solids. The relative *trans* and *cis* orientation of hydrogen atoms 5-H/6-H in adducts **44** was determined by NOESY1D NMR spectroscopy.

44a: M.p. 66–68 °C (*i*Pr_2O); R_f = 0.32 (CH_2Cl_2/petroleum ether, 1:1). ^{1}H NMR (400 MHz): δ = 7.46–7.42 (m, 2 H), 7.38–7.18 (m, 8 H), 4.08 (d, J = 6.6 Hz, 1 H), 3.90 (A part of an AB system, J = 14.5 Hz, 1 H), 3.62 (B part of an AB system, J = 14.5 Hz, 1 H), 3.21 (br. d, J = 7.2 Hz, 1 H), 2.34–2.53 (m, 2 H), 2.22 (br. s, 1 H), 1.82 (d, J = 10.2 Hz, 1 H), 1.57–1.39 (m, 2 H), 1.09 (d, J = 10.2 Hz, 1 H), 1.02–0.91 (m, 2 H) ppm. ^{13}C NMR (50 MHz): δ = 140.1 (s), 137.8 (s), 128.5 (d, 4C), 127.9 (d, 2C), 127.7 (d, 2C), 127.5 (d), 126.8 (d), 83.9 (d), 75.6 (d), 61.9 (d), 59.1 (t), 39.4 (d), 38.1 (d), 32.5 (t), 27.7 (t), 23.2 (t) ppm. IR: $\tilde{\nu}$ = 3065, 3031, 2959, 2876, 1603, 1496, 1454, 1369, 1342, 1230, 1141, 1078, 1043, 1027 cm^{-1}. MS (EI): *m*/*z* (%) = 305 (37) [M$^+$], 228 (18), 214 (7), 91 (100). $C_{21}H_{23}NO$ (305.41): calcd. C 82.58, H 7.59, N 4.59; found C 82.20, H 7.69, N 4.26.

44b: M.p. 116–118 °C (Et_2O); R_f = 0.55 (CH_2Cl_2/petroleum ether, 1:1). ^{1}H NMR (400 MHz): δ = 7.42–7.18 (m, 10 H), 4.20 (d, J = 6.4 Hz, 1 H), 4.05 (A part of an AB system, J = 14.8 Hz, 1 H), 3.95 (d, J = 7.8 Hz, 1 H), 3.61 (B part of an AB system, J = 14.8 Hz, 1 H), 2.58 (dd, J = 7.8, 6.4 Hz, 1 H), 2.42–2.36 (m, 2 H), 1.72 (br. d, J = 3.1 Hz, 1 H), 1.45–1.23 (m, 2 H), 1.04–0.88 (m, 3 H) ppm. ^{13}C NMR (50 MHz): δ = 138.2 (s), 138.0 (s), 128.2 (d, 2 C), 128.0 (d, 4 C), 127.8 (d, 2 C), 127.0 (d), 126.6 (d), 84.7 (d), 73.0 (d), 60.7 (t), 57.4 (d), 42.1 (d), 36.9 (d), 34.6 (t), 28.5 (t), 23.9 (t) ppm. IR: $\tilde{\nu}$ = 3065, 3030, 2958, 2874, 1602, 1496, 1473, 1453, 1373, 1333, 1318, 1259, 1165, 1072, 1026 cm^{-1}. MS (EI): *m*/*z* (%) = 305 (33) [M$^+$], 228 (1), 214 (21), 91 (100). $C_{21}H_{23}NO$ (305.41): calcd. C 82.58, H 7.59, N 4.59; found C 82.19, H 7.98, N 4.47.

Acid-Catalyzed Thermal Rearrangement of 44a: A solution of adduct **44a** (66.8 mg, 0.219 mmol) in toluene (3.6 mL) was treated with TFA (0.05 mL, 0.656 mmol) at 0 °C for 10 min, was then heated at 120 °C for 15 h. The reaction mixture was concentrated under reduced pressure. GC–MS and ^{1}H NMR analyses of the crude residue product showed the presence of compounds **16**, **17**, **45**, **46**,[24] **47**, and *cis*-/*trans*-**48**.[25,26] Separation by chromatography on silica gel (petroleum ether/AcOEt from 10:1 to 5:1) gave a mixture of **45** and **46** and enriched fractions of **47**, **48** (*cis*/*trans* mixture), and **49**.[27] Only partial spectroscopic characterization of **45** and **47** was possible.

(2*S,3*S**)-3-Benzoylbicyclo[2.2.1]hept-2-yl Trifluoroacetate (45):** Mixture with **46**. ^{1}H NMR (400 MHz): detectable signals δ = 5.41–5.43 (m, 1 H), 3.73–3.70 (m, 1 H), 2.81–2.75 (m, 1 H), 2.56 (d, J = 5.2 Hz, 1 H), 1.94 (dm, J = 10.3 Hz, 1 H), 1.50 (dm, J = 10.3 Hz, 1 H) ppm. MS (EI): *m*/*z* (%) = 312 (2) [M$^+$], 245 (2), 198 (10), 120 (22), 105 (100), 77 (45), 69 (8).

[3-(Benzylamino)bicyclo[2.2.1]hept-2-yl](phenyl)methanone (47): Enriched fraction. ^{1}H NMR (400 MHz): δ = 8.00–7.96 (m, 2 H), 7.57–7.51 (m, 1 H), 7.48–7.41 (m, 2 H), 7.27–7.16 (m, 5 H), 3.72–3.68 (m, 1 H), 3.70 (A part of an AB system, J = 12.9 Hz, 1 H), 3.59 (A part of an AB system, J = 12.9 Hz, 1 H), 2.82–2.78 (m, 1 H), 2.49–2.44 (m, 1 H), 2.37 (d, J = 4.0 Hz, 1 H), 1.90–1.81 (m, 1 H), 1.69 (tt, J = 12.2, 4.5 Hz, 1 H), 1.63–1.17 (m, 5 H) ppm. IR: $\tilde{\nu}$ = 3065, 3028, 2956, 2872, 1676, 1448, 1211 cm^{-1}. MS (EI): *m*/*z* (%) = 305 (0.5) [M$^+$], 214 (10), 146 (6), 105 (30), 91 (100), 77 (37).

Supporting Information (see footnote on the first page of this article): Calculation parameters and ^{1}H and ^{13}C NMR spectra.

Acknowledgments

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[13] All calculations were carried out by using the Gaussian 03 suite of programs with the B3LYP method. Bulk solvent effects were evaluated with the SCRF theory using the PCM united atom topological model (UAHF radii) as implemented in the C.02 revision of Gaussian 03.[14] For a more detailed description of computational methods, see the Supporting Information. Thermodynamic parameters of compounds **27**–**39** are reported in Tables S1–S4 and geometries in Figures S1–S5 of the Supporting Information.
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Special Section

Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, revision C.02, Gaussian, Inc., Wallingford CT, **2004**.

[15] Free energies (kcal mol^{-1}) reported in Schemes 8 and 9 and Figure 1 were evaluated by R(U)B3LYP/6-311+G(2d,p) full geometry optimizations in toluene. The contribution of molecular motions to free energy were calculated at 25 °C (298.15 K). However, increasing the temperature from 25 to 110–120 °C (the experimental reaction temperatures) did not give rise to any significant change in the calculated free energy differences for compounds given in Schemes 8 and 9, while the temperature increase added about 2.4 kcal mol^{-1} to solvent-separated components (e.g., **27a** + CF_3COOH) with respect to complexes (e.g., **27a**-CF_3COOH) of the equilibrium given in Figure 1 (see Table S3 in the Supporting Information).

[16] We feel that this choice should not cast serious doubt on our conclusions. For example, the calculated energy difference between protonated isoxazolidines **28a** and **32a** in toluene is 21.50 kcal mol^{-1} (Scheme 9) and that between the same compounds (in which the N–H$^+$ and O–H$^+$ bond lengths are frozen) "solvated" by CF_3COO^- in toluene, that is, complexes **28a**-CF_3COO^- and **32a**-CF_3COO^- is 19.7 kcal mol^{-1} at the same theory level.

[17] The very same rearrangement can, in principle, also be operative as a first step in the formation of β-lactams from protonated 5-spirocyclopropane-isoxazolidines. However, it can be confidently rejected on the basis of the computational results (see Scheme S1 in the Supporting Information).

[18] The relative free energy differences among the compounds investigated do not change substantially upon changing the basis set or on going from the gas phase to a solution in toluene (Tables S1 and S2 in the Supporting Information). Moreover, DFT calculations with other functionals [PBE1PBE/6-311+G(2d,p) and MPWB1K/6-31+G(d,p); Table S4 in the Supporting Information] fully confirm the data obtained with the B3LYP methods.

[19] The N–O and O–C bond lengths in *N*-methyl-5-spirocyclobutane-isoxazolidine **27a** (**27b**) are 1.468 (1.449) and 1.425 (1.446) Å, respectively, with the B3LYP/6-311+G(2d,p) method in toluene. Further geometry data of compounds given in Scheme 9 are reported in Figures S1 and S2 in the Supporting Information.

[20] Optimization of the complex CF_3COO^--**28a**, with the CF_3COO^- group properly oriented to attack either H-3 (or H–CH_2N– proton), led directly to complexes CF_3COOH-**33** (or CF_3COOH-**34**) (Scheme 10; see also Scheme S2 and Figure S3 in the Supporting Information).

[21] We also succeeded in locating the TSs for [1,2-H] sigmatropic shifts in **32a** that give the protonated imines (**33**-H$^+$ or **34**-H$^+$) directly without involvement of any base. However, these TSs exhibit activation free energies too high to successfully compete with the cationic rearrangements via TSs of the type **29** (Scheme S3 and Figure S4 in the Supporting Information). Thus, imino alcohols **33** and **34** must be produced by a base-promoted ring opening of **32a**.

[22] Free energies (kcal mol^{-1}) reported in Scheme 11 were evaluated by full geometry optimizations in toluene with the B3LYP/6-31G(d) method followed by single-point energy refinement at the B3LYP/6-311+G(2d,p) level in toluene (Tables S1 and S2 and Figure S5 in the Supporting Information).

[23] The free energy difference between solvent-separated **27a** + CF_3COOH and solvent-separated **32a** + CF_3COO^- ions is 61.0 kcal mol^{-1} and that between solvent-separated **36b** + CF_3COO^- ions and solvent-separated unprotonated isoxazolidine + CF_3COOH is only slightly smaller (i.e., 59.7 kcal mol^{-1}) [in toluene, B3LYP/6-311+G(2d,p) calculations].

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