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On the Inherent Instability of α-Amino α′-Fluoro Ketones. Evidence for Their Transformation to Reactive Oxyvinyliminium Ion Intermediates

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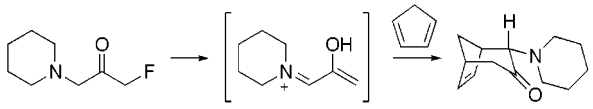
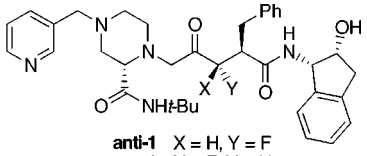
ABSTRACT

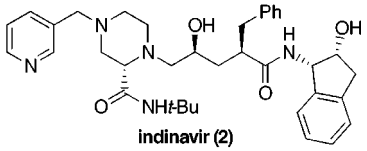


α-Amino α′-fluoro ketones are shown to be inherently unstable intermediates. Evidence is presented that they undergo enolization toward the amino group followed by expulsion of fluoride ion, forming a proposed oxyvinyliminium ion (amino-substituted oxyallyl cation). In protic, nucleophilic media the proposed intermediate is trapped by solvent. In the presence of a reactive diene, [4 + 3] cycloadducts have been isolated. Prior observations concerning fluorinated amino ketones are discussed in light of these findings.

α-Fluorinated ketones have been investigated extensively as inhibitors of proteolytic enzymes.[1] They are proposed to react by the addition of an active-site nucleophile to the electrophilic carbonyl group, generating a stable and tightly enzyme-bound mimic of a tetrahedral species along the pathway for peptide hydrolysis. Fluoro ketone protease inhibitors containing stereogenic fluorinated carbon atoms have been little studied, presumably due to their synthetic inaccessibility.[2] In the context of research directed toward the development of methodology for the asymmetric synthesis of chiral organofluorine compounds, we targeted ketone **anti-1** and its diastereomer **syn-1**, analogues of Merck's HIV-protease inhibitor indinavir[3] (Crixivan, **2**), containing a monofluoro



anti-1 X = H, Y = F
syn-1 X = F, Y = H



indinavir (2)

ketomethylene dipeptide isostere. These were considered targets of obvious interest in light of the synthetic challenge they presented, the importance of indinavir in current HIV therapy, and the fundamental questions they raised concerning enzyme inhibitory activity and its relation to the stereochemistry of the fluorinated center. In the course of studies directed toward the preparation of these compounds, we have learned that α-amino α′-fluoro ketones are inher-

(1) (a) Brodbeck, U.; Schweikert, K.; Gentinetta, R.; Rottenberg, M. *Biochim. Biophys. Acta* **1979**, *567*, 357−369. (b) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813−1817. (c) Imperiali, B.; Abeles, R. H. *Biochemistry* **1986**, *25*, 3760−3767. (d) Mehdi, S. *Bioorg. Chem.* **1993**, *21*, 249−259, and references therein. (e) Sham, H. L. In *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington DC, 1996; pp 184−195, and references therein.

(2) (a) Garrett, G. S.; Emge, T. J.; Lee, S. C.; Fischer, E. M.; Dyehouse, K.; McIver, J. M. *J. Org. Chem.* **1991**, *56*, 4823−4826. (b) Hoffman, R. V.; Saenz, J. E. *Tetrahedron Lett.* **1997**, *38*, 8469−8472. (c) Hoffman, R. V.; Tao, J. *Tetrahedron Lett.* **1998**, *39*, 4195−4198. (d) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1999**, *64*, 126−132.

(3) Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I.-W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1994**, *37*, 3443−3451.

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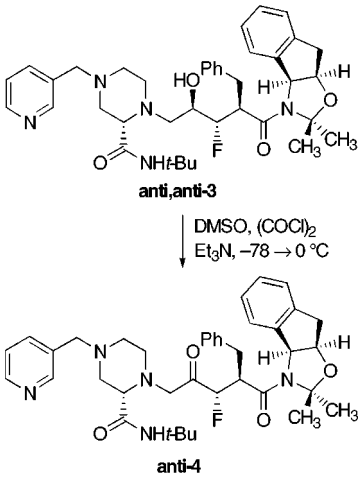
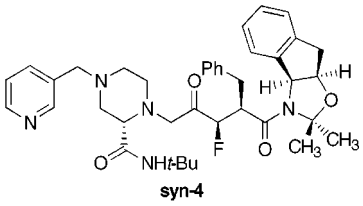
ently unstable structures. They undergo an interesting and unanticipated series of reactions, leading to the formation of a proposed oxyvinyliminium ion, as detailed herein.

The diastereomeric fluoro ketones **anti-1** and **syn-1** were envisioned to arise by oxidation of fluorohydrin precursors (**3**), followed by acetonide deprotection. The fluorohydrin precursors were prepared as part of another study that led to the development of enantioselective and stereocontrolled synthetic routes to protease inhibitors containing the four stereoisomeric monofluoro hydroxyethylene dipeptide isosteres.[4] Swern oxidation[5] of fluorohydrin **anti,anti-3** efficiently formed the ketone **anti-4** (Scheme 1). Similarly,

Scheme 1

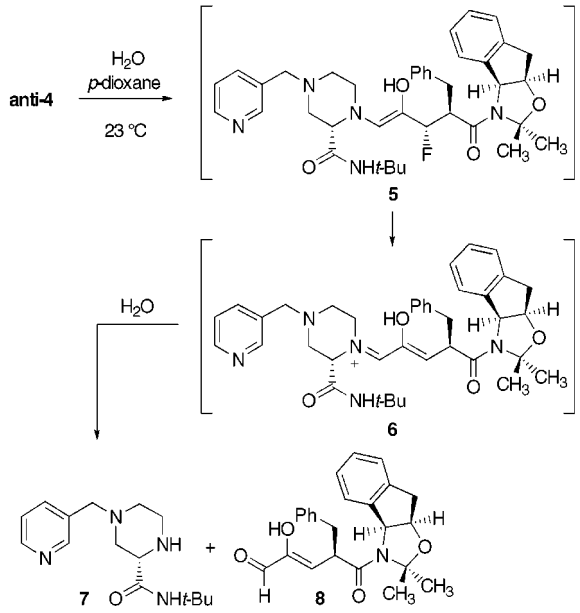


Swern oxidation of fluorohydrin **anti,syn-3** (structure not shown) led to the ketone **syn-4**. Surprisingly, both ketones were observed to fragment when they were subjected to chromatography on silica gel; the piperazine **7**[6] and the aldehyde **8** were identified as the primary products of the fragmentation. Decomposition of ketones **4** also occurred upon attempted acidic hydrolysis of the acetonide groups. The instability of these compounds was clearly associated with the presence of the fluorine atom, for the corresponding nonfluorinated ketone[4] was found to be quite stable and withstood deprotection under acidic conditions (48% yield, unoptimized).



The fragmentation reaction was monitored spectroscopically. Pure samples of the labile ketones **anti-4** and **syn-4** were obtained by gel filtration chromatography (Sephadex LH-20). Incubation of each in D_2O-p-dioxane-d_8 (1:1, v/v) at 23 °C led to smooth fragmentation, affording the piperazine **7** and the aldehyde **8**,[7] as observed by ^{1}H NMR spectroscopy (Scheme 2). The rate of fragmentation was observed to be concentration dependent; at higher initial concentrations of substrate, the fragmentation reaction was faster. This is believed to reflect catalysis of the decomposition reaction by the tertiary amine. Even dilute solutions of the ketones decomposed quickly. For example, **anti-4** was consumed completely within 19 h at 23 °C in a solution initially 16 mM in substrate. The rates of fragmentation of the two diastereomeric ketones **anti-4** and **syn-4** were qualitatively comparable (5 mM initial concentrations: **anti-4**, 42% conversion at 50 h, 23 °C; **syn-4**, 38% conversion at 57 h, 23 °C).

Scheme 2. Proposed Mechanism of Hydrolytic Fragmentation



We propose that the decompositions occur by the mechanism shown in Scheme 2 (for **anti-4**). In this mechanism, enolization of the fluoro ketone forms the γ-fluorinated enamine **5**.[8] Expulsion of fluoride is then proposed to form the oxyvinyliminium ion **6**. Reaction of this intermediate with water leads to the observed products, **7** and **8**. In contrast, incubation of **anti-4** or **syn-4** in methanol-d_4 containing triethylamine (2 equiv) at 23 °C cleanly produced the nonfluorinated methanol adducts **9** (Scheme 3), supporting

(4) Myers, A. G.; Barbay, J. K.; Zhong, B. To be submitted for publication.

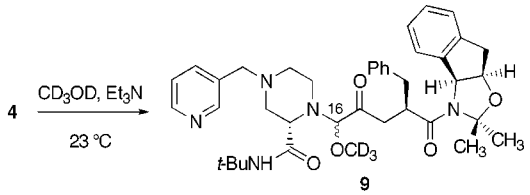
(5) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.

(6) The structure of this compound was confirmed by independent synthesis; see the Supporting Information for details.

(7) The aldehyde **8** was slowly converted to the corresponding keto aldehyde hydrate under these conditions.

(8) Fluoro ketones **4** do not epimerize under the conditions of fragmentation, nor is deuterium incorporated at the fluorinated position, suggesting that enolization is regiospecific (away from fluorine). We have previously noted that tertiary amides of pseudoephedrine with an "epimerizable" α-fluorinated center can be hydrolyzed under basic conditions without isomerization (Myers, A. G.; McKinstry, L.; Barbay, J. K.; Gleason, J. L. *Tetrahedron Lett.* **1998**, *39*, 1335−1338). This apparent kinetic barrier to enolization likely reflects a preference for fluorine to form a bond to carbon with maximal p-character (sp^3 versus sp^2), and perhaps also repulsion between the base and fluorine atom in the disfavored enolization reaction.

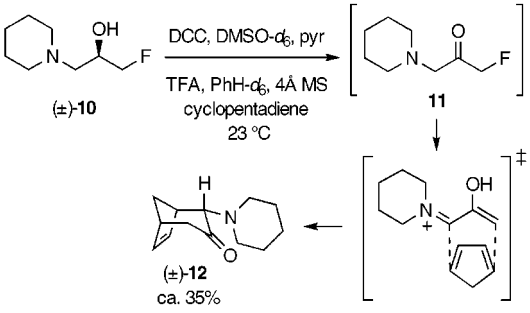
Scheme 3



the assertion that fluoride loss occurs prior to scission of the carbon−nitrogen bond. Both ketones **anti-4** and **syn-4** produced the same ratio of diastereomeric *N*,*O*-acetals **9** (2:1 mixture, >75% yield, isolation by chromatography on Sephadex LH-20). The acetal proton (C_{16}H) in each product was clearly resolved in the ^{1}H NMR spectrum of the methanolysis reactions, allowing assessment of deuterium incorporation at this position. No deuterium incorporation was detected, suggesting that enolization of ketones **4** is not rapid and reversible and may be the rate-limiting step.[9]

To investigate the generality of our observations and to further probe the chemistry of α-amino α′-fluoro ketones, a simpler system was studied (Scheme 4). Whereas Swern

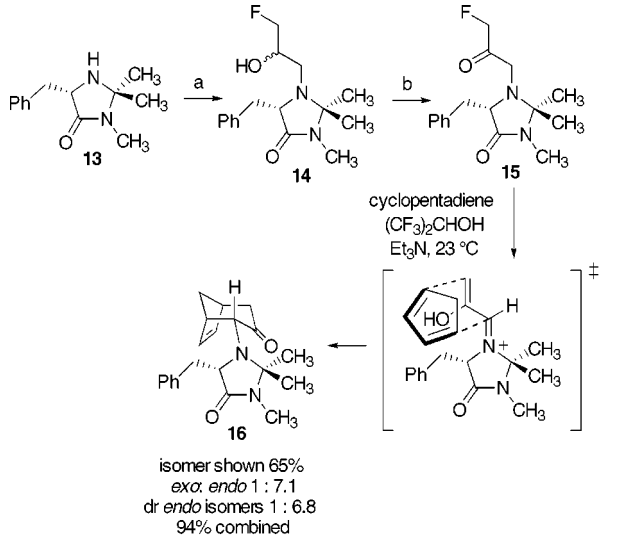
Scheme 4



oxidation of 1-fluoro-3-piperidin-1-yl-propan-2-ol (**10**)[10] resulted in nonspecific decomposition (with complete loss of fluoride, as determined by ^{19}F NMR), under less basic oxidation conditions (DCC, DMSO-d_6, PhH-d_6, TFA, pyr, 4 Å MS)[11] the labile ketone **11** was observed by ^{1}H NMR spectroscopy. When the oxidation was conducted in the presence of cyclopentadiene (5 equiv), it was possible to trap the proposed oxyvinyliminium ion by cycloaddition (∼35% yield).[12,13] The *endo* cycloadduct (**12**) was produced as a single diastereomer; this product is believed to arise by cycloaddition of the proposed intermediate (in the illustrated *s*-trans conformation) through a compact (endo-like) transition state.[14] Oxyallyl cations related to the proposed oxyvinyliminium intermediate, including oxygen-, sulfur-, and amido-substituted variants, are an important class of substrates in [4 + 3] cycloaddition reactions; however, cycloadditions involving amino-substituted oxyallylic cations have not been previously reported.[15]

The generality of the oxyvinyliminium ion formation outlined above was further investigated with the chiral substrate **15**, with a view toward corroborating the proposed cycloaddition model, here in the context of the well-defined imidazolidinone iminium ion system of MacMillan and coworkers.[16] The cycloaddition substrate **15** was prepared by ytterbium triflate-catalyzed opening of epifluorohydrin with amine **13**[16a] followed by Swern oxidation of the resultant diastereomeric mixture of alcohols **14** (1:1, Scheme 5). In

Scheme 5[a]



[a] (a) Epifluorohydrin, Yb(OTf)$_3$, CH_2Cl_2, 23 °C, 70%; (b) DMSO, $(COCl)_2$, Et_3N, −78 → 0 °C, 81%.

marked contrast to the α-fluoro α′-amino ketones described thus far, **15** was found to be stable to chromatography on silica gel. Although cycloaddition between ketone **15** and

(9) Rate-limiting proton abstraction followed by rapid halide expulsion has been observed in the Favorskii rearrangement of certain α-bromo and α-chloro ketones, see: Bordwell, F. G.; Frame, R. R.; Scamehorn, R. G.; Strong, J. G.; Meyerson, S. *J. Am. Chem. Soc.* **1967**, *89*, 6704−6711, and references therein.

(10) Rozen, S.; Shahak, I.; Bergmann, E. D. *Synthesis* **1971**, 646−647.

(11) (a) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661−5670. (b) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5670−5679.

(12) Isolation of cycloadduct **12** is complicated by its instability to silica gel chromatography. Two-dimensional TLC suggests that this compound undergoes a reversible reaction upon exposure to silica gel; the product is tentatively assigned as the hydrate.

(13) Attempts to trap the proposed oxyvinyliminium ion **6** with cyclopentadiene were unsuccessful, presumably due to steric factors.

(14) The stereochemistry of cycloadduct **12** was confirmed by a NOESY experiment.

(15) For reviews of cycloaddition reactions involving oxyallyl cations, see: (a) Rigby, J. H.; Pigge, F. C. *Org. React.* **1997**, *51*, 351−478. (b) Hosomi, A.; Tominga, Y. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 5.1, pp 593−615. (c) Mann, J. *Tetrahedron* **1986**, *42*, 4611−4659. (d) Hoffman, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1−88. For the specific case of amido-substituted oxyallyl cations, see: (e) Walters, M. A.; Arcand, H. R. *J. Org. Chem.* **1996**, *61*, 1478−1486. (f) Walters, M. A.; Arcand, H. R.; Lawrie, D. J. *Tetrahedron Lett.* **1995**, *36*, 23−26.

(16) (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243−4244. (b) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874−9875.

cyclopentadiene proceeded poorly or not at all in CH_3CN, DMSO, CH_2Cl_2, THF, 2-propanol, or neat cyclopentadiene as solvent (each containing 2 equiv of Et_3N), use of 2,2,2-trifluoroethanol (TFE) as solvent led to the formation of a mixture of cycloadducts and solvolysis products, the latter predominating (2.9:1 mixture).[17] Use of the polar, nonnucleophilic solvent hexafluoro-2-propanol, by contrast, afforded a mixture of four diastereomeric cycloaddition products in 94% combined yield (*endo*:*exo* products = 7.1:1; *endo* diastereomers = 6.8:1).[18] The major cycloadduct (**16**) was isolated as a single stereoisomer in 65% yield by column chromatography. The stereochemistry of this product was confirmed by X-ray structure determination (see Supporting Information) and is consistent with preferred cycloaddition of the proposed oxyvinyliminium ion from the less hindered *Re*-face, in accord with the MacMillan model,[16] in a compact (endo-like) transition state.

It is interesting to compare the reactivity of the fluorinated ketones described herein with literature reports regarding other α-amino α′-fluoro ketones. There are at least two reports of the hydrolytic fragmentation of α-amino α′-(tri)-fluoro ketones. In 1990, Peet and co-workers reported that attempted acidic hydrolysis (concentrated hydrochloric acid, reflux) of α-amido α′-trifluoromethyl ketones **17** led to the formation of α-hydroxy ketones **18** rather than the anticipated products of amide hydrolysis (Figure 1a).[19] Subsequently, a series of α-dialkylamino α′-trifluoromethyl ketones (see structure **19**) were reported to be unstable toward chromatographic purification on silica gel; fragmentation to a mixture of α-hydroxy ketones **20** and **21** was observed (Figure 1b).[20] These results can be rationalized by a simple tautomerization−hydrolysis mechanism. In these cases, neither expulsion of fluoride ion nor elimination of HF occurs, likely a result of the energetic cost associated with conversion of a trifluoromethyl group to a divinyl fluoride.[21] An important counterpoint and prior example of the preparation of α-amino α′-monofluoro ketones is the synthesis of the series of *N*-(triphenylmethyl)amines **22** (Figure 1c) by Hoffman and co-workers. These compounds evidently did not display unexpected reactivity and could be purified by chromatography on silica gel without decomposition, factors which may be attributable to the bulky amino group.[2d,22] Finally, it should be noted that *N*-acyl α-amino α′-fluoro ketones and ammonium salts of α-amino α′-fluoro ketones[23] have been frequently employed as inhibitors of proteolytic enzymes and as synthetic intermediates, suggesting that the availability of the nitrogen lone pair is central to the instability of α-amino α′-fluoro ketones.

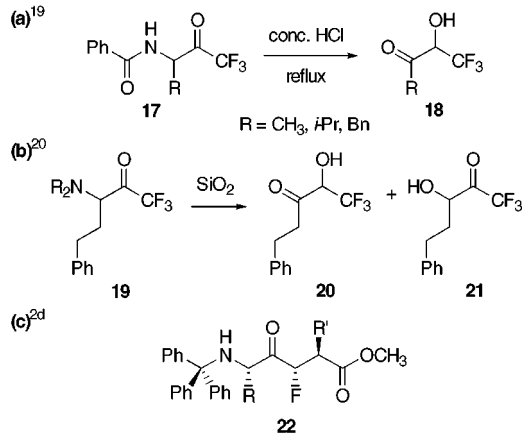


Figure 1. Reported properties of α-amino α′-fluoro ketones. (a) α-Amido α′-trifluoromethyl ketones **17** fragmented under acidic conditions.[19] (b) Ketones **19** fragmented upon purification on SiO_2.[20] (c) α-Amino α′-monofluoro ketones stable to SiO_2 chromatography.[2d]

In conclusion, we have described unexpected reactivity associated with α′-monofluorinated α-amino ketones. The development of an improved understanding of the properties of α-amino α′-fluorinated ketones is of particular significance in light of their role as inhibitors of proteolytic enzymes. It is conceivable, for example, that a new class of "suicide" inhibitors could be derived from such intermediates if they could be delivered to or formed at an enzyme active site. The instability of α-amino α′-fluoro ketones is proposed to result from the formation of an oxyvinyliminium ion intermediate. This intermediate undergoes solvolysis in protic, nucleophilic media and [4 + 3] cycloaddition reactions when generated in the presence of a reactive diene.

Acknowledgment. Financial support from the National Institutes of Health is gratefully acknowledged. We thank Andrew Haidle for obtaining crystallographic data for cycloadduct **16**.

Supporting Information Available: Experimental procedures and characterization data for compounds **4**, **7**−**10**, and **12**−**16** and X-ray crystal data for **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The CF_3CH_2OH/Et_3N system has been previously employed in cycloadditions of oxyallylic cations: Föhlisch, B.; Gehrlach, E.; Herter, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *2*, 137.

(18) The four diastereomeric cycloadducts were separable by silica gel chromatography. The relative stereochemistry of the centers within the bicyclo[3.2.1]octenone ring system in each product was assigned on the basis of observed NOESY cross-peaks.

(19) Peet, N. P.; Burkhart, J. P.; Angelastro, M. R.; Giroux, E. L.; Mehdi, S.; Bey, P.; Kolb, M. K.; Neises, B.; Schirlin, D. *J. Med. Chem.* **1990**, *33*, 394−407.

(20) Bégué, J.-P.; Bonnet-Delpon, D.; Sdassi, H. *Tetrahedron Lett.* **1992**, *33*, 1879−1882.

(21) Smart, B. E. In *Molecular Structure and Energetics*; Liebman, J. F., Greenberg, A., Eds.; VCH: Deerfield Beach, FL, 1986; Vol. 3, pp 141−190.

(22) For another example of a stable α-amino α′-monofluoro ketone, see: Blanco, M.-J.; Sardina, F. J. *J. Org. Chem.* **1996**, *61*, 4748−4755.

(23) See, for example: (a) Angelastro, M. R.; Burkhart, J. P.; Bey, P.; Peet, N. P. *Tetrahedron Lett.* **1992**, *33*, 3265−3268. (b) Dancer, J. E.; Ford, M. J.; Hamilton, K.; Kilkelly, M.; Lindell, S. D.; O'Mahony, M. J.; Saville-Stones, E. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2131−2136.