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Synthesis and Properties of *gem*-(Difluorocyclopropyl)amine Derivatives of Bicyclo[*n*.1.0]alkanes

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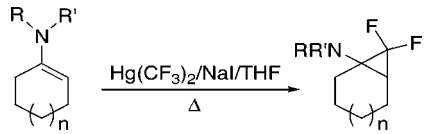
ABSTRACT



R, R' = alkyl, aryl; n = 1–3

Generation of difluorocarbene(carbenoid) in the presence of enamines derived from cyclic ketones results in overall insertion of CF_2 to produce bicyclic difluorocyclopropylamines. These adducts are very weakly basic, and their thermal stabilities vary markedly with their structures.

gem-Dihalocyclopropanes are distinctive intermediates for synthetic organic chemistry.[1] They can serve as rigid lipophilic structural components, and they are valuable substrates for the preparation of other types of molecules. Difluorocyclopropanes deserve special mention because a fluorine substituent can exert profound and unique effects on the properties, reactivity, structure, and stability of compounds.[2] Addition of dichlorocarbene to enamines has given rather unstable *gem*-(dichlorocyclopropyl)amines.[3] However, addition of difluorocarbene to enamines does not appear to have been investigated. Products of such additions might undergo ring cleavage (by analogy to tertiary cyclopropylamines) and function as synthetic equivalents of homologous fluorinated enamines.[4] In contrast with other dihaloocyclopropanes, the fluorine atoms might have markedly enhanced stability during reductive dehalogenation and halogen−metal exchange reactions.[1]

We are interested in enzyme−substrate interactions, which are biological examples of template−ligand binding. Such interactions can be altered markedly by conformational as well as constitutional and stereochemical structure features. Replacement of hydrogen by fluorine can change alternative substrate−enzyme binding by both structural and (stereo)-electronic effects on ligand−protein interactions. Furanosyl rings of nucleic acid components undergo dynamic pseudorotational equilibria. The two-state approximation, and modifications, originally developed by Altona and Sundaralingam[5] provide a basis for evaluation of furanosyl conformer populations. Marquez and others have popularized syntheses and binding studies with bicyclo[3.1.0]hexane analogues of C-nucleosides (cyclopropyl-fused cyclopentyl derivatives of nucleobases).[6]

We have prepared cyclopropyl-fused derivatives of naturally occurring furanosyl nucleosides, and biological activity was observed with certain of these compounds.[7] Our interest has been stimulated in synthesis and biological evaluation

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(4) (a) Lee, J.; Jong, S. U.; Blackstock, S. C.; Cha, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 10241−10242. (b) Lee, H. B.; Sung, M. J.; Blackstock, S. C.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 11322−11324.
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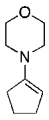
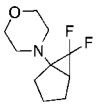
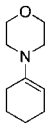
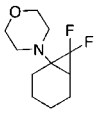
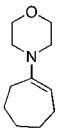
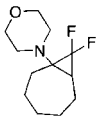
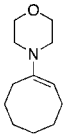
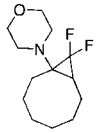
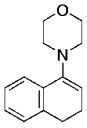
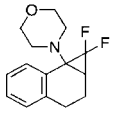
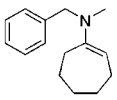
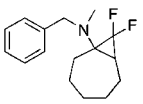
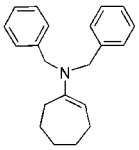
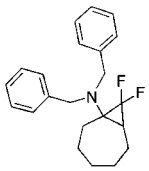
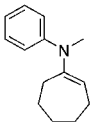
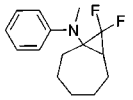
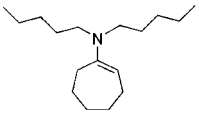
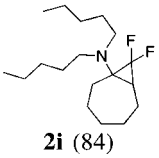
of the *gem*-difluorocyclopropyl analogues of these spiro- and bicyclic-fused systems. We recently reported the protection of the amino group of adenine nucleosides by its elaboration into a 2,5-dimethylpyrrol-1-yl moiety, which satisfied the demands for a base-stable amino-masking function that was removed readily under mildly acidic conditions.[8] We now report studies on generation of difluorocarbene (difluorocarbenoid) species that undergo insertion into the electron-rich double bond of enamines. Nucleoside systems that contain electron-rich vinyl ether units are readily accessible.

The sodium iodide-induced in situ decomposition of bis(trifluoromethyl)mercury[9] at 70 °C (*CAUTION*, see Supporting Information) was used to generate difluorocarbene in the presence of an enamine in THF. The enamine concentration was maintained at ~0.5 M to minimize formation of insoluble resins and other unidentified byproducts that were formed in major amounts with higher enamine concentrations (≥3 M). The crude reaction mixtures were monitored by ^{19}F NMR to follow the disappearance of the carbene precursor and formation of the cyclopropane products **2** (Table 1). Decomposition of the carbene precursor was complete within 80 min at 70 °C in all cases.

A homologous series of morpholine enamines derived from five- to eight-membered cyclic ketones was subjected to the general reaction conditions (entries 1−4). Only the reaction with 1-(morpholin-4-yl)cycloheptene (**1c**) gave the adduct, 8,8-difluoro-1-(morpholin-4-yl)bicyclo[5.1.0]octane (**2c**), in high yield. A complex mixture of difluorocyclopropane compounds and extensive polymerization was observed (^{19}F NMR) with the six-membered analogue **1b**. A decrease in the ratio of $Hg(CF_3)_2$ (0.5 equiv) resulted in formation of the desired product **2b** in low yield (18%). It is noteworthy that enamine **1e**, which has the six-membered cyclohexene fused with a benzene ring, gave **2e** in high yield (93%). Treatment of the enamine **1a**, derived from cyclopentanone, under standard conditions resulted in extensive charring, and none of the difluorocyclopropane product **2a** was detected. Analogous treatment of 1-(morpholin-4-yl)cyclooctene (**1d**) gave a low yield of **2d** plus extensive polymerization. The product **2d** was formed in moderate yield (57%) upon limiting the reaction time to 1 h. It was evident that ring size has a profound effect on the outcome of this addition. The seven-membered morpholine-containing cycloheptene ring was clearly preferred over five-, six-, or eight-membered homologues. Variation of the amino substituent was next examined. Enamine **1f**, with a benzyl and a methyl group, and **1g**, with two benzyl groups on nitrogen, gave the respective adducts **2f** and **2g** in yields comparable to that from **1c**. The increase of steric hindrance by introduction of a second benzyl group was inconsequential to the outcome of the carbene addition. Enamine **1i**, with two *N*-pentyl groups, and **1h**, which has the nitrogen atom conjugated with an aromatic ring, gave the expected products **2i** and **2h**, respectively, in high yields. Attempted syntheses of more sterically hindered or conjugated enamines (from branched

Table 1. Addition of Difluorocarbene to Enamines **1** to Give Bicyclic Difluorocyclopropylamines **2**[a]

entry	**1**	**2** (%)
1	 **1a**	 **2a** (0)
2	 **1b**	 **2b** (18)
3	 **1c**	 **2c** (89)
4[b]	 **1d**	 **2d** (57)
5	 **1e**	 **2e** (93)
6	 **1f**	 **2f** (89)
7	 **1g**	 **2g** (91)
8	 **1h**	 **2h** (88)
9	 **1i**	 **2i** (84)

[a] General procedure used for all reactions except entry 4. [b] Reaction time was 60 min.

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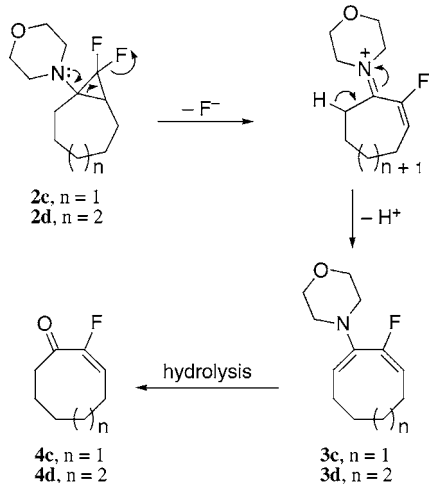
(9) Knunyants, I. L.; Komissarov, Y. F.; Dyatkin, B. L.; Lantseva, L. T. *Izv. Acad. Nauk SSSR, Ser. Khim.* **1973**, 943−944.

secondary amines or diarylamines) by the standard procedures were unsuccessful. Other approaches were not investigated.

Dihalocyclopropanes are known to decompose thermally. Relief of strain, relative stabilities of possible intermediate ions, and anchimeric assistance by heteroatoms are factors that can influence their stabilities. The reaction mixtures of entries 2 and 4 (Table 1) were heated for an extended time period. Gradual disappearance of **2b** and **2d**, respectively, was observed with concomitant formation of products. Complete decomposition of **2b** (140 °C, 24 h), **2c** (170 °C, 24 h), and **2d** (100 °C, 1 h) occurred upon heating. The ^{1}H, ^{13}C, and ^{19}F NMR spectra of crude decomposition mixtures from amines **2c** and **2d** indicated loss of one fluorine, formation of the ring-expanded dienamines **3**, and minor generation of the ketones **4**[10] (Scheme 1). The ^{13}C NMR

Scheme 1. Thermal Decomposition of **2c** and **2d**



spectra of **3** had four vinylic signals; one had $^{1}J_{CF}$ ~250 Hz, two had $^{2}J_{CF}$ ~20 Hz, and one had $^{3}J_{CF}$ ~0−6 Hz. Acid-catalyzed hydrolysis of these decomposition mixtures gave the volatile and somewhat unstable fluoroketones **4** plus resinous material.

Reports have appeared on the preparation of α-halo-α-ethylenic analogues by thermal or (acid or base)-catalyzed decomposition of dichlorocyclopropylamines,[11] chlorofluorocyclopropanols,[12] and ethers of dichloro-[13] and difluorocyclopropanols.[14] A mechanism for formation of the dienamines includes loss of a fluoride anion with participation of the electron pair on nitrogen and cyclopropyl ring opening to give an imminium species that loses a proton to produce **3**. Analogous rearrangements of cyclopropyl to allyl cations are used for the preparation of allylic compounds from halogenocyclopropanes.[15] Decomposition of **2b** also produced a dienamine (^{1}H, ^{13}C, and ^{19}F NMR), which underwent rapid transformation into a number of other products. These experiments indicated that the isolation of purified **2b** and **2d** in lower yields resulted from their decomposition under the reactions conditions. Presumably, transient generation of **2a** is followed by its immediate decomposition.

The difluorocyclopropylamines **2** are colorless, volatile liquids or solids that are quite stable to air and light, with the exception of the aryl-substituted amine **2h**. They are unreactive with methyl iodide, and characterization was performed with the free amines and/or their air-stable HCl or HBr salts. The weakly basic amines **2b**, **2d**, and **2e** formed hydrogen halide salts reversibly, and they readily lost HCl or HBr upon moderate heating, storage under vacuum, or upon heating their solutions in water, alcohols, or THF. Addition of water to **2d**·HBr and heating resulted in separation of the free amine from aqueous HBr. This was reversed by addition of concentrated HBr/H_2O. Amine **2h** failed to form stable salts with either HCl(HBr) or H_2SO_4.

Combination of the powerful electron-withdrawing effect of two β-fluorine atoms and conjugation of nitrogen with the phenyl ring results in loss of basicity. Although certain β-di- and trifluroethylamines have increased oxidation potentials[16] and lowered proton affinities,[17] they do form stable salts.[18] The remarkably diminished basicities of compounds **2** might result from the steric compression that is apparent from the X-ray-derived distances between the ammonium proton and the exo-oriented fluorine atom (F_{exo}). These short contact distances are 2.40 Å for **2c**·HCl and 2.57 Å for **2e**·HCl (i.e., equal to or less than the sum of the van der Waals radii for hydrogen and fluorine[19]).

An alternative explanation is the preference of fluorine to bond with carbon orbitals with enhanced p-character. This is observed with the calculated F−C−F bond angle of 109.6° in difluorocyclopropane versus the H−C−H bond angle of 114.5° in cyclopropane.[20] Comparison of X-ray structures for **2e** and its HCl salt (Supporting Information) indicates an increase in the F−C−F bond angle from 107.5 to 109.6° upon protonation. Other structural consequences include lengthening of the C1−C2 (0.9%) and C1−C3 (1.0%) bonds and shortening of the distal C2−C3 (0.6%), C1−F_{exo} (1.0%), and C1−F_{endo} (1.2%) bonds. It should be noted that the decrease in the C1−F_{exo} bond length (i.e., increase in the C1−F_{exo} bond strength) argues against an attractive N−H···F interaction (Figure 1).

Two signals in ^{19}F NMR spectra of **2** have characteristic $^{2}J_{F,F}$ coupling constants from 140 to 170 Hz. The signal for one of the fluorine atoms is split into four lines (dd) resulting

(10) Adventitious H_2O for in situ hydrolysis of the dienamines **3** could be supplemented by reaction between the glass surface and HF.

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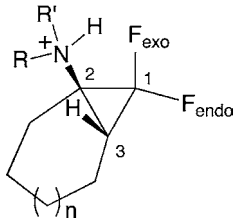

Figure 1. Protonated difluorocyclopropylamines **2**.

from vicinal coupling with a hydrogen atom 15−18 Hz in addition to the geminal fluorine. Protonation of **2** results in significant changes in the ^{19}F NMR spectra. The ^{19}F chemical shifts after protonation are usually downfield for both signals, with the signal for F_{exo} exhibiting a larger downfield shift (Table 2). Changes in geminal coupling constants ($^2J_{F,F}$) also occur upon protonation but do not have an apparent correlation with structure. The hydrohalide salts of the weakly basic amines **2** even underwent equilibration with oxygen-containing NMR solvents to give spectra with broadened peaks and chemical shifts that varied with concentration. Consistent ^{13}C and ^{19}F NMR spectra were obtained in solutions of deuterated dimethyl sulfoxide and concentrated HX/H_2O (9:1), which produced the fully protonated amine salts.

In summary, addition of difluorocarbene to enamines derived from cyclic ketones provides convenient access to bicyclic difluorocyclopropylamines with significantly different stabilities. The seven-membered fused-ring analogues are most stable. These amines have markedly weaker basicities than analogous dichlorocyclopropylamines or acyclic β-difluoroamines. Applications of these model studies for the synthesis of sugar-modified nucleosides are in progress.

Table 2. Changes in the Chemical Shifts of the Fluorine Atoms in **2** upon Protonation of the Nitrogen Atom[a]

compound	$\Delta\delta F_{exo}$[b]	$\Delta\delta F_{endo}$[b]
2b	−4.0	−1.1
2c	−2.6	0.0
2d	−1.2	−0.4
2e	−1.5	−0.4
2f	−5.6	−0.3
2g	−1.6	−0.3
2i	−3.4	0.9

[a] Spectra were determined in DMSO-d_6/concentrated HCl/H_2O (9:1). [b] In parts per million.

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Supporting Information Available: Procedures, spectral data, ^{13}C NMR spectra for compounds **2**, ^{1}H and ^{13}C NMR spectra for the 2,4-dinitrophenylhydrazones of **4c**,**d**, and X-ray crystal structures and data (CIF) for **2e** and salts of **2b**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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