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Reactivity and Regiochemical Behavior of the 2,2-Difluorocyclopropylcarbinyl Cation: A New and Improved Mechanistic Probe To Distinguish Radical and Carbocation Intermediates

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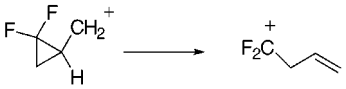
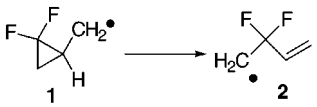
ABSTRACT



Acetolysis of 2,2-difluorocyclopropylcarbinyl tosylate (5) yields products derived from both S_N1 and S_N2 processes. Product identification and kinetic data indicated, as had been predicted computationally, that the cyclopropylcarbinyl–allylcarbinyl cationic rearrangement of 5 occurs simultaneously with its ionization and with regiospecific proximal bond cleavage to give products that formally derive from the 1,1-difluoro-3-butenyl cation with a rate constant that is 8.3×10^4 smaller than that of the parent cyclopropylcarbinyl tosylate and 1.8 times larger than isobutyl tosylate at 96.6 °C.

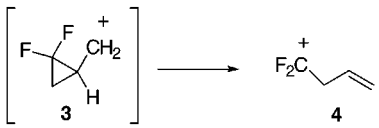
The 2,2-difluorocyclopropylcarbinyl radical, **1**, undergoes an extraordinarily fast, regiospecific unimolecular ring opening distal to the geminal fluorine substituents to form the 2,2-difluoro-3-butenyl radical, **2**[1] (Scheme 1). Its calculated activation barrier of 1.9 kcal/mol and estimated rate constant of 1.5×10^{11} s^{-1} at 25 °C qualifies this system as a "hypersensitive" probe of reactions involving radicals as intermediates.[2] As demonstrated by the extensive work of Newcomb,[3] a radical probe is made much more valuable if it can, by virtue of differences in regiochemistry, distinguish between a radical and a carbocation intermediate.

Scheme 1



Because β-fluorine substituents destabilize carbocations, whereas α-fluorines are stabilizing, it appeared likely to us that reactions involving the 2,2-difluorocyclopropylcarbinyl cation, **3**, would undergo rearrangement via regiospecific cleavage of the *proximal* bond to form the1,1-difluorobut-3-enyl cation, **4**.[4−6] This intuitive prediction received support from our recent DFT calculations that indicated a regiospecific conversion of **3** to a homoallylic, stabilized version of **4** with virtually no activation barrier (Scheme 2). At this time, we report experimental corroboration of these predictions.

Scheme 2



(1) Tian, F.; Bartberger, M. D.; Dolbier, W. R., Jr. *J. Org. Chem.* **1999**, *64*, 540−546.

(2) Rate constant calculated using conventional transition-state theory, using computed values of 1.6 kcal/mol and −2 cal/mol K for activation enthalpy and entropy, respectively.[1]

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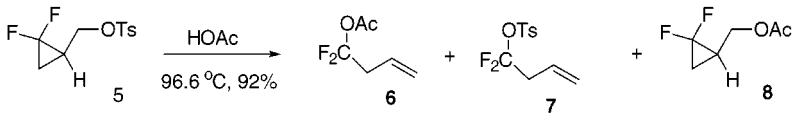
Scheme 3



6 : **7** : **8** = 39 : 4.4 : 56.5

The solvolysis of 2,2-difluorocyclopropylcarbinyl tosylate, **5**, in glacial acetic acid at 96.6 °C led to the formation of both ring-opened (**6** and **7**) and non-ring-opened products (**8**),[7] with **6** and **7** reflecting exclusively the regiochemistry of ring opening that had been predicted computationally[1] (Scheme 3).

Assuming that the ring-opened and ring-closed products derived from competing S_N1 and S_N2 processes, respectively, the partial rate factors for the two processes could be calculated. Thus, the S_N1 process, in which tosylate **5** undergoes heterolytic cleavage to (presumably) form ring-opened cation **4**, which then is trapped by either HOAc or TsO^- to give products **6** and **7**, was assigned a first-order rate constant (k_Δ) of $(4.4 \pm 0.1) \times 10^{-6}$ s^{-1}, and the process involving solvent participation, which led to ring-closed product **8**, was assigned a pseudo-first-order rate constant (k_S) of $(5.8 \pm 0.1) \times 10^{-6}$ s^{-1}.

To confirm that competitive unimolecular and bimolecular reactions were involved and that all three products do not derive from the common intermediate carbocation **3**, additional acetolysis experiments were carried out in 0.200 and 0.400 M NaOAc/HOAc solutions. The results are given in Table 1.

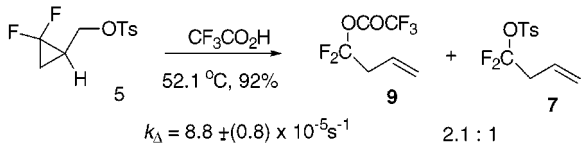
Table 1. Kinetic Results for Solvolyses of 2,2-Difluorocyclopropylcarbinyl Tosylate in NaOAc/HOAc Solutions at 96.6 °C

conditions	k_{obs} (10^{-5} s^{-1})	mass balance (%)	ratio **8**/(**6** + **7**)	k_S (10^{-6} s^{-1})	k_Δ (10^{-6} s^{-1})
pure HOAc	1.0 ± 0.1	92	57:43	5.8	4.4
0.200 M NaOAc	2.87 ± 0.07	92	84:16	24	4.6
0.400 RM NaOAc	4.7 ± 0.3	90	90:10	42	4.7

Correcting k_S by subtracting the background k_S(HOAc) (which is the k_S in pure HOAc), one can obtain the pseudo-first-order rate constants $k_S(^-OAc)$ that reflect the rates of nucleophilic attack by acetate ion. The values for $k_S(^-OAc)$, (1.8 ± 0.1) and $(3.6 \pm 0.4) \times 10^{-5}$ s^{-1} for 0.200 and 0.400 M [$^-$OAc], respectively, clearly demonstrate the dependence on [$^-$OAc], hence the S_N2 nature of the process that leads to non-ring-opened product **8**. On the other hand, the values of k_Δ for the three reactions increase only slightly, consistent with the influence of a small salt effect on the ionization process.

These results do not completely rule out the possibility that some of **8** might be formed via the S_N1 process. However, when the solvolysis was carried out in trifluoroacetic acid, a solvent of high ionizing power but poor nucleophilicity, only ring-opened products were formed (Scheme 4), under conditions where the potential ring-closed

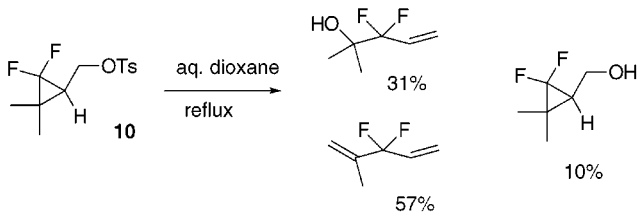
Scheme 4



product, 2,2-difluorocyclopropylcarbinyl trifluoroacetate, was demonstrated to be stable to the solvolytic conditions.

The above solvolytic results are completely consistent with the ionization of **5** proceeding directly and regiospecifically to the homoallylic carbocation **4**, as had been predicted computationally.[1] Our results would appear to be at odds with an earlier report by Schlosser, indicating that solvolysis of 2,2-difluoro-3,3-dimethylcyclopropylcarbinyl tosylate, **10**, proceeds with regiospecific *distal* ring opening[6] (Scheme 5).

Scheme 5



However, further calculations (HF/6-31G*) indicate that even a *single* methyl group on the cyclopropane ring is apparently sufficient to alter the regiochemistry in favor of distal ring opening. This simply indicates, of course, that the stabiliza-

(3) (a) Newcomb, M.; Chestney, D. L. *J. Am. Chem. Soc.* **1994**, *116*, 9753−9754. (b) Toy, P. H.; Newcomb, M.; Hollenberg, P. F. *J. Am. Chem. Soc.* **1998**, *120*, 7719−7729 and references therein.

(4) Previous reports of solvolytic studies of 2,2-difluorocyclopropylcarbinyl systems led to varying regiochemical results.[5,6]

(5) Proximal cleavage: Boger, D. L.; Jenkins, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 8860−8870.

(6) Distal cleavage: (a) Bessard, Y.; Kuhlmann, L.; Schlosser, M. *Tetrahedron* **1990**, *46*, 5230−5236. (b) Kobayashi, Y.; Morikawa, T.; Taguchi, T. *Chem. Pharm. Bull.* **1983**, *31*, 2616.

tion provided by a methyl group is sufficiently greater than that provided by the two fluorine substituents to overcome the *de*stabilization of the β-fluorines.

With the 2,2-difluorocyclopropylcarbinyl radical and cation both undergoing requisite, ultrafast ring opening, but with opposite regiochemistries, the system certainly qualifies as a hypersensitive probe capable of distinguishing between the two types of mechanisms. In evaluating the potential efficacy of such a new probe, it should be remembered that in addition to its ability to differentiate between the intermediacy of a radical and a carbocation, it should ideally play simply the role of an "observer" of the reaction. That is, it should not exert a significant mechanistic influence upon the reaction system it is testing. If the diagnostic probe itself has a steric or electronic bias so as to favor or disfavor one of the possible mechanistic pathways, then the interpretation of the results from use of such a probe may be ambiguous. This is certainly one of the potential flaws of any cyclopropylcarbinyl system that purports to distinguish carbocation from radical intermediate, because although the cyclopropyl group should exert little if any kinetic influence upon a radical-forming process, it is well-recognized to greatly enhance formation of carbocations.[8] Cyclopropylcarbinyl tosylate, for example, undergoes acetolysis with a rate constant more than 100 000 times that of model primary system, isobutyl tosylate.[9,10] Carbocation-stabilizing substituents on the cyclopropane ring, such as phenyl or alkoxy, will only serve to make such enhancements greater. Therefore, experimental results obtained from use of most of the present cyclopropylcarbinyl probes need to be interpreted with care in those cases where a carbocation intermediate is detected.

Considering the acetolysis of **5** in this context, its rate constant (k_Δ) is only 1.8 times greater than that of isobutyl tosylate at 96.6 °C, which means that the two fluorine substituents of **5** have a substantial inductive destabilizing influence on its ionization transition state. The net result of such destabilization is to essentially eliminate the rate-enhancing effect of the cyclopropylcarbinyl moiety relative to a typical primary substrate, such as isobutyl tosylate. Therefore, as a result, the 2,2-difluorocyclopropylcarbinyl system exhibits *no* kinetic bias toward either the radical or the carbocation mechanism.

Steric or stereoelectronic influences should also not pose a problem for the 2,2-difluorocyclopropylcarbinyl system. Therefore, we conclude, on the basis of our kinetic and computational examination of the 2,2-difluorocyclopropylcarbinyl radical and cation systems, that, being sterically and electronically benign, but exhibiting high rearrangement reactivity and regiospecificity, this system should be capable of acting as an ideal, hypersensitive probe of radical and/or carbocation mechanisms.

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Supporting Information Available: Full details regarding the synthesis and characterization of all starting materials and products, procedures for kinetic experiments, and tables of kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990527K

(7) Cyclopropylcarbinyl acetate product **8** was found to be stable to the reaction conditions.

(8) (a) Wiberg, K. B.; Hess, B. A., Jr.; Ashe, A. J., III. In *Carbonium Ions*; Olah, G. A., Schleyer, P. V. R., Eds.; Wiley: New York, 1972; Vol. III, p 1295. (b) Wiberg, K. B.; Shobe, D.; Nelson, G. L. *J. Am. Chem. Soc.* **1993**, *115*, 10645−10652.

(9) Wiberg, K. B.; Ashe, A. J., III. *J. Am. Chem. Soc.* **1984**, *90*, 63−74.

(10) Reich, I. L.; Diaz, A.; Winstein, S. *J. Am. Chem. Soc.* **1969**, *91*, 5635−5637.