authors were invited to comment on the other paper.

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Supplementary Material Available: Tables of atomic positional parameters, bond distances and angles, thermal parameters, useful least-squares planes, and general temperature-factor expressions (5 pages). Ordering information is given on any current masthead page.

Stereospecific Transannular Cyclization of Mesocyclic Homoallylic Sulfides. 2. (*Z*)- and (*E*)-Thiacyclonon-4-enes. Synthesis, Carbon-13 Nuclear Magnetic Resonance, and Conformation of Methyl-Substituted *cis*-1-Thioniabicyclo[4.3.0]nonane Salts[1]

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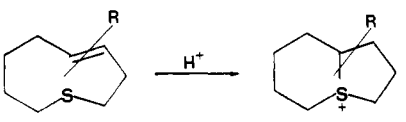
Bicyclic bridgehead [4.3.0] sulfonium salts are obtained from nine-membered cyclic homoallylic sulfides (thiacyclonon-4-enes) by the action of acids. Independently of the geometry, *Z* or *E*, of the starting olefin, cis-ring-joined products are obtained which, while formed under kinetic control, also appear to be thermodynamically favored. The reaction is stereospecific: thus the noninterconverting diastereomeric conformers of (*E*)-2,4,5-trimethylthiacyclononene (**2h'** and **2h''**) give rise to endo/exo C_9 CH_3 epimers (**18** and **19**) without crossover. Several methyl-substituted *cis*-1-thioniabicyclo[4.3.0]nonane salts have been prepared in this way (**4–11**, **14–19**) while two more (**12** and **13**) were obtained by alkylation of the ylide from the parent system, **4**. The ^{13}C spectra of the bicyclic salts have been recorded and elucidated with the aid of a number of regiospecific deuteration methods, thus permitting their unambiguous configurational and conformational assignment.

Transannular interactions are commonplace in medium-size rings (eight to ten membered) where the spatial relationship between the 1,5-functionalities gives rise to unusual reaction patterns, unknown to either smaller or larger rings or to acyclic analogues. This matter has been recently reviewed extensively by Leonard,[2] while Musker has reviewed his work on the transannular reactivity of 1,5-dithiacyclooctane.[3]

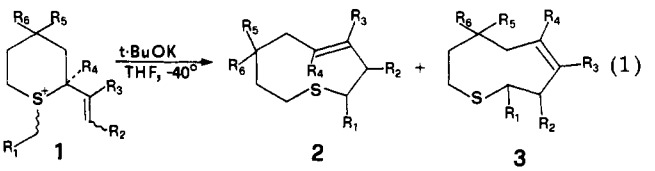
The recently developed ring enlargement by [2,3] sigmatropic rearrangement of sulfonium ylides[4] provides facile access to homoallylic mesocyclic sulfides (thiacycloalk-4-enes) which are expected to be expecially prone to interactions between the S atom and the transannular double bond. Indeed, in a recent report we have given an account of the transannular cyclization of substituted (*Z*)- and (*E*)-thiacyclooct-4-enes to *cis*-1-thioniabicyclo[3.3.0]-octanes promoted by H^+ or Lewis acids, focussing especially on stereochemical aspects.[1] In this paper we report and discuss along similar lines the acid-promoted cyclization of the higher homologues, thiacyclonon-4-enes, to *cis*-1-thioniabicyclo[4.3.0]nonanes.



The ^{13}C NMR spectra of these salts, while unequivocally establishing their configurations, provide considerable insight in to the conformational properties of these bicyclic [4.3.0] bridgehead sulfonium cations.

Results and Discussion

The methyl-substituted thiacyclonon-4-ene precursors have been prepared via ring expansion by [2,3] sigmatropic rearrangement of the appropriately substituted 2-vinylthianium alkylides obtained by in situ deprotonation of the corresponding sulfonium salts (eq 1) as previously reported.[4b,d,5-7]



(1)

all R's = H unless otherwise specified: a, all R's = H; b, $R_1 = CH_3$; c, $R_2 = CH_3$; d, $R_4 = CH_3$; e, $R_5 = CH_3$; f, $R_3 = R_4 = CH_3$; g, $R_5 = R_6 = CH_3$; h, $R_1 = R_3 = R_4 = CH_3$

This synthesis is known to largely afford *E* homoallylic sulfides,[4b,e,5] the *Z* isomers being obtained only in special cases where, because of steric reasons, the transoid transition-state energy is raised substantially.[7] Thus, nine homoallylic sulfides were prepared which have the *E* configuration [**2a–g**, plus the two diastereoisomers of **2h**

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(2) Leonard, N. J. *Acc. Chem. Res.* **1979**, *12*, 423.
(3) Musker, W. K. *Acc. Chem. Res.* **1980**, *13*, 200.
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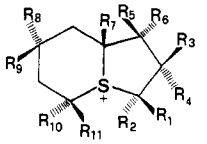
Table I. ^{13}C NMR Spectral Data of Substituted 1-Thioniabicyclo[4.3.0]nonane Salts in D_2O[a]

compd	chemical shift, ppm									predominant conformation
	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	CH_3	
4	36.0	22.2	18.0	24.1	54.5	31.5	27.6	45.2		A
5	35.6	22.2	18.0	24.3	53.7	32.6	36.9	61.9	18.9	A
6	27.0	21.0	17.7	24.7	54.4	30.5	34.3	56.2	13.7	A
7	35.0	21.3	19.9	24.1	52.1	38.8	35.7	50.5	17.7	A + B
8	37.7	22.6	18.1	24.2	54.1	38.8	37.8	51.1	17.8	A
9	37.5	21.9	19.2	33.1	65.3	37.0	25.7	42.9	26.3	A
10	33.0	25.6	26.8	32.4	54.3	34.9	25.5	40.2	22.0	B
11	36.6	30.7	24.7	b	55.3	31.9	27.8	45.3	21.8	A
12	43.8	25.2	19.6	23.4	54.0	33.3	24.4	32.3	18.0	B
13	47.6	31.6	19.2	24.0	56.5	32.0	28.0	43.7	18.2	A
14	33.3	17.1	17.7	26.8	65.0	48.4	31.7	35.0	11.7 (R_6), 21.3 (R_7)	B
15	38.1	22.3	18.8	31.5	65.6	39.8	33.1	40.1	11.7 (R_5), 21.0 (R_7)	A
16	32.0	31.6	27.9	36.8	51.8	34.5	26.2	41.6	27.7 (R_8), 29.7 (R_9)	B
17	29.3	21.8	18.8	31.7	67.1	39.7	40.9	49.8	14.6 (R_2), 12.3 (R_5), 21.1 (R_7)	A
18	28.2	17.3	16.1	26.4	68.3	48.4	42.6	51.9	14.0 (R_2), 11.8 (R_6), 23.9 (R_7)	B
19	32.4	17.5	17.9	27.0	65.9	48.4	39.8	47.3	19.1 (R_1), 11.7 (R_6), 21.4 (R_7)	B

[a] Dioxane was used as an internal reference. The shieldings have been converted to the Me_4Si scale by using $\delta_{dioxane}$ 67.18. [b] One signal is missing, most likely hidden by one of signals of the major isomer (10).

(vide infra)] and three which have the *Z* configuration (**3f–h**).

The bridgehead sulfonium salts **4–11** and **14–19** were obtained from the corresponding sulfides by acid-promoted (CF_3SO_3H in CH_2Cl_2) transannular cyclization. From 2-methyl-, 3-methyl-, and 7-methylthiacyclonon-4-ene were obtained mixtures of exo–endo epimers (the **5–6**, **7–8**, and **10–11** pairs, respectively. The **12–13** epimeric pair was obtained, again as a mixture, by methylation of the ylide from the parent cation **4**. The ^{13}C NMR spectra of the



all R's = H unless otherwise specified: **4**, all R's = H; **5**, $R_1 = CH_3$; **6**, $R_2 = CH_3$; **7**, $R_3 = CH_3$; **8**, $R_4 = CH_3$; **9**, $R_7 = CH_3$; **10**, $R_8 = CH_3$; **11**, $R_9 = CH_3$; **12**, $R_{10} = CH_3$; **13**, $R_{11} = CH_3$; **14**, $R_6 = R_7 = CH_3$; **15**, $R_5 = R_7 = CH_3$; **16**, $R_8 = R_9 = CH_3$; **17**, $R_2 = R_5 = R_7 = CH_3$; **18**, $R_2 = R_6 = R_7 = CH_3$; **19**, $R_1 = R_6 = R_7 = CH_3$

bridgehead cations are recorded in Table I. The assignments have been based on (1) the chemical shift effects of methyl substituents in comparison with those known for thianium[8] and thiolanium[9] salts, (2) off-resonance decoupling experiments, and (3) regiospecific deuteration. The latter was used whenever the first two criteria left any ambiguity and was achieved by application of one or more of the following methods. (i) Base-catalyzed H–D exchange at the α-positions (C_2 and C_9) of the bicyclic sulfonium salt[10] allowed the assignment of C_2 and C_9 (intensity decrease due to broadening from fast deuterium quadrupole relaxation) as well as C_3 and C_8 (from the 0.1–0.2-ppm upfield shifts with respect to undeuterated samples).[11] (ii) Cyclization of homoallylic sulfides deuterium labeled at C_2, in turn obtained by rearrangement of S–CD_2 thianium methylides, allows for specific deuteration of C_9 and was used to distinguish (see i above) C_9 from C_2 and C_8 from C_3. (As our understanding of these systems increased, however, it was realized that a simpler distinction between C_2 and C_9 could be based on the relative rate of deuteration. Although no quantitative rate measurements were carried out, the protons at C_2 were invariably found to exchange more rapidly than those at C_9.) (iii) Cyclization with deuterium-labeled sulfuric acid, allowing for the assignment of C_7 and its adjacent carbons (see i above), was also used. It is noteworthy that these deuteration methods permit the direct assignment of all carbons of the bicyclic cations except C_4 and C_5 which, however, can be unambigously assigned by exclusion and/or by applying the first two criteria.

Stereochemistry. All the bicyclic salts obtained appear to have the same cis stereochemistry of the ring junction, irrespective of the configuration of the starting olefin or the substituent pattern. For example, the same product, **16**, was obtained from **2g** and **3g** which are a pair of *E–Z* isomers. Since cyclization occurs rapidly at ambient temperature, that is, under conditions where pyramidal inversion at sulfur is negligible,[12] **16** is the kinetically controlled product. However, **16** also appears to be the thermodynamically more stable isomer since on prolonged heating (100 °C, H_2O, 26 h) it failed to undergo any detectable (^{13}C NMR) isomerization. Since the product arising from the *Z* olefin can only have a cis ring junction, **16** must necessarily be *cis*-4,4-dimethyl-1-thioniabicyclo[4.3.0]nonane (triflate). None of the bicyclic sulfonium salts synthetized (**4–19**) showed any propensity for epimerization at sulfur under conditions of facile pyramidal inversion,[8] while their ^{13}C NMR spectra are fully consistent with the cis assignment, as will be shown below.

The comparison of the ^{13}C shifts of **4** with those of *cis*- and *trans*-1,2-dimethylthianium[8b,d] and *cis*- and *trans*-1,2-dimethylthiolanium[9] shows that the ^{13}C shifts of **4** fit

(8) (a) Barbarella, G.; Dembech, P.; Garbesi, A.; Fava, A. *Org. Magn. Reson.* **1976**, *8*, 108. (b) *Ibid.* **1976**, *8*, 469. (c) Eliel, E. L.; Willer, R. L. *J. Am. Chem. Soc.* **1977**, *99*, 1936. (d) Willer, R. L.; Eliel, E. L. *Org. Magn. Reson.* **1977**, *9*, 285.

(9) Barbarella, G.; Dembech, P. *Ibid.* **1981**, *14*, 72.

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(12) (a) Darwish, D.; Tourigny, G. *J. Am. Chem. Soc.* **1966**, *88*, 4303. (b) Scartazzini, R.; Mislow, K. *Tetrahedron Lett.* **1967**, 2719. (c) Garbesi, A.; Corsi, N.; Fava, A. *Helv. Chim. Acta* **1970**, *53*, 1499. (d) Roush, D. M.; Price, E. M.; Templeton, L. K.; Templeton, D. H.; Heathcock, C. H. *J. Am. Chem. Soc.* **1979**, *101*, 2971.

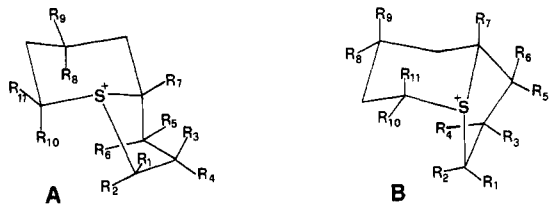
much better those of the cis isomers **20** and **22**. Particularly significant are the shifts of C_2–C_5, in the six-membered moiety of **4**, which appear to match very closely those of the corresponding carbons in **20**, with one important difference, however. That difference is that the more shielded carbons in **20** (C_5) and in **4** (C_4) bear a different relation with respect to the heteroatom. This discrepancy may be simply resolved, however, by assuming that **20** and the six-membered ring of **4** populate different chair conformations. Consider the two chair conformers of *cis*-1,2-dimethylthianium, **20A** and **20B**. The chemical

shift parameters developed by Eliel and Willer[8d] allow the computation of the ^{13}C NMR shifts of the individual conformers, as written. Of the two carbons C_4 and C_5, respectively δ and γ with respect to sulfur, the more shielded is that which is γ with respect to a axial CH_3, i.e., C_4 and C_5 in **20A** and **20B**, respectively. The monocyclic salt appears to largely populate the *S*-CH_3 axial conformer, **20B**[8b-d] (about 94% according to Eliel),[8c] and consistently C_5 (the unsubstituted γ-carbon) is more shielded than C_4. Our present finding that the δ-carbon (C_4) is more shielded than the unsubstituted γ-carbon (C_3) requires that **4**, unlike **20**, largely adopt the type A rather than the type B

conformation.[13] Why the sizeable preference (~1.6 kcal/mol)[8c] for the B conformer in the monocyclic system is reversed in the bicyclic case is not completely clear. One factor, however, could be the steric compression between the *endo*-H's at C_5 and C_8 in **4B**, which models suggest to be considerably more pronounced than the corresponding interaction between the endo H's at C_4 and C_7 in **4A**. A second and probably more important factor may be the inhibition of the S–CH_2 axial bond in **4B** to bend outward to the extent it does in S–CH_3 axial thianium salts.[14] From X-ray structural studies of epimeric *cis*- and *trans*-4-*tert*-butyl-1-methylthianium salts,[14] this outward displacement is known to obtain through a flattening of the sulfur vertex of the thianium chair, permitting the axial S–CH_3 group to release the repulsion by the syn-axial H's and to reduce its conformational energy. In **20B** this flattening appears to be somewhat resisted by the adjacent equatorial S–CH_3,causing a buttressing effect which raises the conformational energy of the axial S–CH_3 by ~0.4 kcal/mol.[8c] The resistence to flattening of the S vertex may well increase when the substituents at S and C_α are joined in a five-membered ring as in **4**, since any change of the dihedral angle at the S–C_α bond would cause some additional torsional strain in the five-membered ring.

In examining the substituted bicyclics **5**–**19**, it will be assumed that, independently of substituents, they all populate only type A or/and type B conformers and that conformational arguments may be applied based only on the six-membered ring. In other words, the conformation will be assumed to depend primarily on the geometrical requirements of the six-membered ring. This is a reasonable first approximation, however, since conformational barriers and conformational energies of substituents are much larger for six- than for five-membered rings.

It will be useful to start this analysis with those compounds that, because of their substitution pattern, may be expected to populate exclusively, or nearly exclusively, one of the two conformers, A or B. One such case is



offered by cation **16** (R_8 = R_9 = CH_3): because of the *gem*-Me_2 grouping at C_4, conformation A cannot be populated due to the syn-diaxial relation between C_7 and the *endo*-Me group. Thus **16** may be expected to populate conformer B exclusively where *endo*-CH_3 and C_7 are 1,3-diequatorial.

This conformational change (with respect to the parent system (**4**) shows up in the shifts of C_9 (upfield 3.7 ppm) and C_7 (downfield 3.0 ppm). Both variations are expected for an A ⇌ B conformational change since, viewed as substituents of the six-membered moiety, C_9 switches from equatorial to axial and C_7 from axial to equatorial.[20] Thus the shifts of C_9 and C_7 provide an additional conformational criterion which may be useful for compounds having substituents at positions C_2–C_5, for which the criterion based on the shifts of both C_3 and C_4 may be ambiguous. A case in point is that of the 4-Me epimers, **10** and **11**, obtained as a 3:1 mixture from **2e**. The very nearly equal CH_3 shifts, 22.0 and 21.8 ppm, typical of equatorial 4-CH_3 groups in thianium cations,[8b,d] indicate that the methyl group is equatorial in both isomers, which must therefore populate different conformations. Since the endo isomer **10**, like **16**, necessarily adopts the B conformation, the exo isomer **11** should adopt the A conformation. Indeed, this change in conformation shows up dramatically in the shifts of C_9 (40.9 and 45.2 ppm and C_7 (34.9 and 31.9 ppm in **10** and **11**, respectively, in accord with C_9 switching from axial

(13) It may be noted that in either form, **4A** or **4B**, the chair conformation of the six-membered ring is compatible with a twist-chair conformation of the five-membered ring, with maximum torsion at the bond facing the heteroatom, which is known to be the most stable conformation for both the thiolane[14,15] and thiolanium cations.[9,16] This is likely to be a major factor contributing to the greater stability (>2 kcal/mol) of the cis form, unlike the homobicyclic system (hydrindane) where the trans isomer is known to be more stabe (~1.0 kcal/mol).[17,18]

(14) Nahlovska, Z.; Nahlovsky, B.; Seip, H. M. *Acta Chem. Scand.* **1969**, *23*, 3534.

(15) Barbarella, G.; Dembech, P. *Org. Magn. Reson.* **1980**, *13*, 282.

(16) Barbarella, G.; Garbesi, A.; Fava, A. *J. Am. Chem. Soc.* **1975**, *97*, 5853.

(17) Stull, D. R.; Westrum, E. F., Jr.; Sinke, G. C. "The Chemical Thermodynamics of Organic Compounds"; Wiley: New York, 1969; Chapter 14.

(18) Allinger, N. L.; Tribble, M. T.; Miller, M. A.; Wertz, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 1637.

(19) Eliel, E. L.; Willer, R. L.; McPhail, A. T.; Onan, K. D. *J. Am. Chem. Soc.* **1976**, *98*, 3021.

(20) Axial carbon substituents in a thiane ring are, like in cyclohexanes,[21] more shielded than equatorial ones.[8b,d]

(21) Dalling, D. K.; Grant, D. M. *J. Am. Chem. Soc.* **1972**, *94*, 5318.

to equatorial and C_7 from equatorial to axial with changing of the stereochemistry at C_4 from endo to exo.

For the sake of comparison, the shifts of **11** may be computed from the shifts of the parent system, **4**, and the chemical shift parameters for methyl substituents in thianium salts.[8d] The following values are obtained for C_2–C_9, respectively: 36.4, 30.0, 25.2, 32.1, 54.4, 31.5, 27.6, 45.2 ppm. The excellent agreement with the observed values (Table I) validates the assumption that the six-membered moiety of the bicyclic system can be treated as if it were a monocyclic thianium cation.

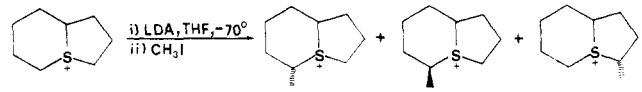
The criteria developed above have been applied for assigning the conformation of the other cations. Naturally such assignment presupposes that the configuration, endo or exo, of the substituent(s) be known. This, however, is a straightforward matter, as will be seen in the following.

Two 9-CH_3-substituted isomers were obtained as a 4:1 mixture from (*E*)-2-methylthiacyclonon-4-ene. The major (**5**; δ_{CH_3} 18.9, δ_{C_2} 35.6) and minor isomers (**6**: δ_{CH_3} 13.7, δ_{C_2} 37.0) can be unambigously assigned exo and endo stereochemistry, respectively.[22] The differential γ shift is exceptionally large (8.6 and 5.2 ppm for C_2 and CH_3, respectively),[23] indicating a highly congested system. Indeed, the shifts of C_3 and C_4 indicate that both isomers largely adopt the same conformation (A); consequently, the methyl group is quasi-equatorial in the exo but quasi-axial in the endo isomer, consistent with the unusually large shielding effect in the latter.

The exo–endo pair of 8-methyl-1-thioniabicyclo [4.3.0]nonane salts, **7** and **8**, were obtained from **2c** as a 4:1 mixture. Their relative configurations have been assigned on the basis of the shift of the single carbon atom C_6, which is γ with respect to the Me substituent. Thus **7** (δ_{C_6} 52.1) is assigned the exo configuration where CH_3 and C_6 are very nearly gauche to one another, while **8** (δ_{C_6} 54.1) is assigned the endo configuration, where CH_3 and C_6 are very nearly anti. Although the differential shift of C_6 may appear small (2.00 ppm), it is in the correct range since the carbon concerned (C_6) is tertiary,[26] and the Me group is located on a (relatively flat) five-member ring.[27] The shifts of C_3 and C_4 of the endo epimer **8** are essentially the same as in the parent system, **4**, indicating that it largely populates the A conformer. In the exo epimer, on the other hand, C_3 and C_4 are shifted significantly (at high and low field, respectively), suggesting the B conformer is also substantially populated.

Since the parent system **4** populates conformation A (see above), with the bridgehead H equatorial, the substitution of a CH_3 group for the bridgehead H should not change the conformation. In accord with this view, the ^{13}C spectrum of **9**, the 6-CH_3 derivative, compared to that of **4** shows only minor deshielding effects on the γ-carbons located in the six-membered moiety (in keeping with the deshielding γ effect of a *gem*-Me_2 grouping relative to an axial CH_3).[8d,21] On the other hand, C_9, the γ-carbon on the five-membered ring, experiences a 2.3-ppm shielding effect, i.e., of the same magnitude as that experienced by C_5 in going from 1,2-*cis*-dimethyl- to 1,2,2-trimethylthiolanium.[9]

***exo*- and *endo*-2-Methyl-*cis*-1-thioniabicyclo-[4.3.0]nonanes (12 and 13).** Methylation (CH_3I) of the ylide obtained by in situ LDA deprotonation of **4** in THF at −70 °C gave three monomethylated products in a 9:3:1 ratio, the minor of which was identified as **6**, the product



4 12 (70%) 13 (23%) 6 (7%)

of endo methylation at C_9. The major and intermediate products can be identified from the shifts of C_9 to be the *endo*- and *exo*-2-Me epimers. Thus the alkylation is 12:1 regioselective in favor of the six-membered ring and 4:1 stereoselective in favor of the endo side. The preference for six-membered-ring alkylation finds a parallel in the greater kinetic acidity (see above) of the six- with respect to the five-membered-ring α-protons. However, one does not know whether the equilibrium between the six- and five-membered ylides is rapid with respect to methylation; if it is, the product distribution would be solely determined by the relative alkylation rate of the two ylides. As to the stereochemistry, although the preference for the endo side may seem surprising on the basis of steric hindrance considerations, it is not unprecedented insofar as highly preferential endo alkylation has been previously reported also for *cis*-1-thioniabicyclo[4.4.0]decane.[28] At the present time no fully satisfactory theory is available that may explain the stereochemistry of sulfonium ylide alkylation.[29] Theoretical[31c] as well as experimental work is being pursued in this laboratory, and the results will be reported in due time; a full discussion of the matter will be deferred until then.

The endo isomer **12** is expected to populate conformer B, where CH_3 and C_7 are 1,3-diequatorial. For the exo

(22) That the cyclization affords two isomers is consistent with the notion that the precursor olefin also exists as unequally populated diastereomeric conformers.[6] If the product is kinetically controlled and arises from a twist conformation analogous to that of (*E*)-cyclononene,[23] the endo and exo isomers would originate from the 2*S*,4*S*, 2*R*,4*R* and 2*R*,4*S*, 2*S*,4*R* diastereoisomers, respectively, as depicted below:

(23) Ermer, O.; Lifson, S. *J. Am. Chem. Soc.* **1973**, *95*, 4121.

(24) These γ shieldings are among the largest ever recorded, larger than those observed in seemingly analogous systems. Thus in the bridgehead [3.3.0] sulfonium salt the corresponding (exo–endo) shifts are 6.6 and 4.0 ppm for C_8 and CH_3,[1] and for 2-methylnorbornane they are 7.7 and 4.9 ppm for C_6 and CH_3.[25]

(25) Grutzner, J. B.; Jautelat, M.; Dence, J. B.; Smith, J. A.; Roberts, J. D. *J. Am. Chem. Soc.* **1970**, *92*, 7107.

(26) Reference 11, p 42.

(27) The 2.0-ppm differential shift of C_6 compares well with that (1.7 ppm) of 1,*cis*-2,*trans*-4- and 1,*cis*-2,*cis*-4-trimethylthiolanium salts,[9] which are the monocyclic analogues of **7** and **8**.

(28) Roush, D. M.; Price, E. M.; Templeton, L. K.; Templeton, D. H.; Heathcock, C. H. *J. Am. Chem. Soc.* **1979**, *101*, 2971.

(29) Heathcock and co-workers have suggested that the stereochemistry of sulfonium ylide alkylation may be predicted on the basis of the relative stability of the (pyramidal) diastereomeric ylides which may arise by removal of one or the other of a pair of diastereotopic protons.[28] In turn, such relative stability would be simply assessed from the angle formed by the directions of the one pairs on the adjacent carbon and sulfur atoms.[28] While this suggestion is of no help in interpreting the direction of alkylation of flexible ylides (like that under consideration here and all cis bridgehead sulfonium ylides in general) and is difficult to reconcile with some experimental results,[30] the theoretical model on which it is based,[31] i.e., pyramidal ylide geometry, is contraddicted by more recent calculations[32] and experimental results.[33]

(30) Garbesi, A. *Tetrahedron Lett.* **1980**, *547*. However, for a possible explanation of the discrepances see: Graham, S. L.; Heathcock, C. H. *Ibid.* **1980**, 5865.

(31) Graham, S. L.; Heathcock, C. H. *J. Am. Chem. Soc.* **1980**, *102*, 3713.

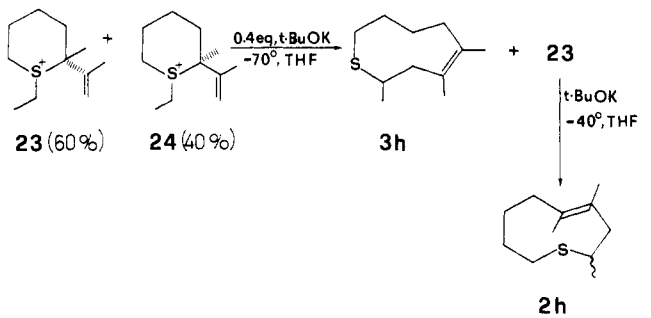
(32) (a) Eades, R. A.; Gassmann, P. G.; Dixon, D. A. *J. Am. Chem. Soc.* **1981**, *103*, 1066. (b) Mitchell, D. J.; Wolfe, S.; Schlegel, H. B. *Can. J. Chem.* **1981**, *59*, 3280. (c) Andreetti, D. A.; Bernardi, F.; Bottoni, A.; Fava, A. *J. Am. Chem. Soc.* **1982**, *104*, 2176.

(33) Barbarella, G.; Dembech, P.; Garbesi, A., submited for publication in *Tetrahedron Lett.* We thank the authors for letting us know of their results before publication.

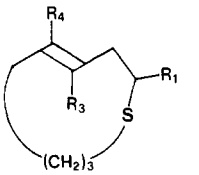
isomer instead, conformation A is expected to prevail as it permits the Me group to stay equatorial. The shifts of C_4 confirm both expectations. That the two isomers populate different conformations explains the exceptionally large (10.4 ppm) differential shift of C_9, only about half of which is a differential γ effect of the CH_3 group, the rest being imputable to the conformational switch.

The remaining di- and trimethyl-substituted derivatives offer a clear-cut picture. The 6,7-dimethyl isomers **14** and **15**, arising from (*E*)- and (*Z*)-4,5-dimethylthiacyclonon-4-ene, respectively, must differ for the stereochemistry at C_7, the endo and exo configuration being expected from the former and the latter, respectively. The ^{13}C data bear out this expectation as indicated by the shifts of C_5, C_9, and CH_3 which are considerably shielded in **14** with respect to those in **15**. From the viewpoint of conformation, the shifts of C_3 and C_4 indicate that the endo and exo isomers largely populate the B and A conformers, respectively. This conformational change is most probably dictated by the requirement of the Me group at C_7 to occupy a quasi-equatorial position. It may be noted in this connection that the Me group has the same shift in both isomers. The differential shift of C_7, amounting to 8.6 ppm, is most striking; however, part of it (3.0 ppm) is accounted for by the conformational change.

Synthesis and Cyclization of (*E*)- (2h) and (*Z*)-2,4,5-Trimethylthiacyclonon-4-ene (3h). Triethyloxonium fluoborate alkylation of 2-methyl-2-(1-methylvinyl)thiane[7] gave a 3:2 mixture of *r*-1-ethyl, *c*-2-methyl- and *r*-1-ethyl,*t*-2-methyl-2-(1-methylvinyl)thianium fluoborates (**23** and **24**). The mixture, subjected to stepwise ring expansion[7] at −70 °C with a 60% deficit of base,[7] gave essentially pure **3h** which could be easily separated from

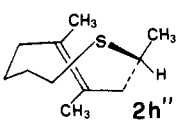


unreacted **23**. The latter, ring expanded at −40 °C, gave a 1.5:1 mixture of *E* diastereoisomers **2h**. The assignment of the double bond geometry follows from previous evidence[7] concerning the ring expansion of the corresponding isomeric *S*-methyl sulfonium salts[7] and is confirmed by the behavior of **2h** in comparison with **3h**. Thus **2h** may be (very slowly) converted to **3h** by heat, the isomerization being suppressed in the presence of a radical scavenger such as 2,6-di-*tert*-butylphenol.[34] That **2h** may exist as diastereoisomers is due to the presence in the molecule of two elements of chirality, a chiral center (carbon 2) and a chiral plane. Interconversion of the two diastereoisomers may occur through configurational inversion of the chiral plane, a process which requires a 180° rotation of the sp^2 plane around the σ bonds adjacent to the π bond and involving the passage of one of the R groups inside out the ring. When $R_3 = R_4 = H$, the energy barrier is two low (16.4 kcal/mol) for the isomers to be separable, although their interconversion may be "frozen" at low temperature and studied by dynamic NMR.[6] For $R_3 = R_4 = CH_3$, the

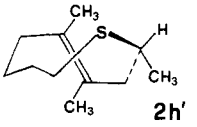


energy barrier is expected to increase enough for the isomers to be separable by ordinary chemical methods,[34] and, in fact, the two isomers of **2h** could be separated by the $HgCl_2$ fractional precipitation method.[7] They appear to be quite stable: heating for 100 hr at 125 °C did not result in any appreciable interconversion, indicating a barrier for chiral inversion in excess of 36 kcal/mol.

The major (**2h′**) and minor (**2h″**) isomers yielded **18** and **19**, respectively, by acid treatment. The ^{13}C shifts indicate



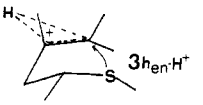
(2*R*,4*R*)

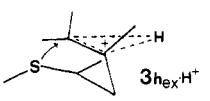


(2*S*,4*R*)

18 to have the endo and **19** the exo configuration at C_9. Both, of course, have the endo configuration at C_7. From the stereospecificity of the cyclization one may assign the (2*S*,4*R*) (2*R*,4*S*) and (2*R*,4*R*) (2*S*,4*S*) configurations to the major and minor isomers, respectively, of the precursor olefins.

Cyclization of the *Z* isomer, **3h**, gave a single bicyclic salt, **17**, which from the shifts of C_2 and of the CH_3 at C_9 may be assigned the *endo*-9-CH_3 configuration. This result, surprising at first sight, may be rationalized on the basis of the diastereomeric protonated *Z* olefin precursors $\mathbf{3h}_{en}$-H^+ and $\mathbf{3h}_{ex}$-H^+. On focussing ones the attention on





the ($-SC_2C_3C_4C_5-$) fragment, it is apparent that $\mathbf{3h}_{ex}$-H^+ suffers a severe steric interaction between the quasi-axial 1,3-methyl groups, while $\mathbf{3h}_{en}$-H^+ does not. That no appreciable *exo*-9-CH_3 product (<2%) is formed would indicate the energy of $\mathbf{3h}_{ex}$-H^+ to be at least 2.5 kcal/mol higher, which is reasonable in view of the postulated interaction.

As to conformation, the shifts of C_3 and C_4 indicate that both **18** and **19** populate the B while **17** populates the A conformation. Apparently the conformational preference in trimethyl derivatives is determined by the stereochemistry, endo or exo, of the C_7 CH_3.

Conclusions

The carbon-13 NMR analysis of the bicyclic [4.3.0] salts formed in the acid-promoted transannular cyclization of Me-substituted (*E*)- or (*Z*)-thiacyclonon-4-enes has allowed the unambiguos stereochemical assignment, exo or endo, of the methyl groups, as well as of the ring junction (invariably cis), and established the stereospecificity of the reaction. With the configuration firmly established, the ^{13}C NMR data have provided information on the conformational properties of this ring system. It has been assumed, as a first approximation, that the conformation depends primarily on the geometrical requirements of the six-membered ring and hence that only two conformations need to be considered, those featuring a chair thianium ring (A and B). On this basis the bicyclic salts **4**–**19** have been assigned a predominant conformation, as reported

(34) Konicek, T. R. "The Synthesis and Absolute Configuration of (*E*)-1,2-Dimethylcyclodecene"; Ph.D. Thesis, Northwestern University, 1980. Quoted by: Marshall, J. A. *Acc. Chem. Res.* **1980**, *13*, 213.

in Table I (last column). It should be realized, however, that this analysis is semiquantitative at best and that the assignment to a predominant conformer may not, in most cases, rule out a small though nonnegligible proportion of the other conformer.

Experimental Section

Proton NMR spectra were recorded at 60 or 100 MHz on Varian EM-360 L and XL-100 instruments, respectively. The latter was used for obtaining proton-noise-decoupled ^{13}C NMR spectra at 25.15 MHz by the FT technique. Single-frequency off-resonance spectra were obtained by irradiation at δ −4 in the proton spectrum. Unless otherwise stated, ^1H shifts are given in parts per million from Me_4Si in $CDCl_3$. The shieldings of ^{13}C NMR spectra in D_2O have been converted to the Me_4Si scale by using $\delta_{dioxane}$ 67.18. GLC analyses were carried out with a Hewlett-Packard 5700 instrument equipped with a flame-ionization detector ($^1/_8$ in. × 3 m column, 10% Xe-60 on Chromosorb W).

Solvents and reagents were obtained dry as follows. Benzene, dichloromethane, *tert*-butyl alcohol, and diisopropylamine were distilled from calcium hydride. Tetrahydrofuran, dried over sodium and distilled, was redistilled from $LiAlH_4$ immediately before use. All reactions involving organolithium reagents were carried out under nitrogen, the reagent being introduced by syringe through a rubber stopper.

The cyclic homoallylic sulfides were synthetized by ring expansion of the appropriate sulfonium hexafluorophosphate salts (soluble in THF at low temperature) by using one of two methods. Method I involved *t*-BuOK as the base in THF/*t*-BuOH (10:1 v/v) at −70 to −40 °C. Method II empolyed lithium diisopropylamide in THF at −70 °C.

Deuterium Labeling. Regiospecific deuteration of the bicyclic [4.3.0] salts was carried out as follows. (i) Deuteration at C_2 and C_9 was achieved by dissolving the salt in 2 N NaOD in D_2O and warming the mixture at 55 °C for 4 h, the salt being recovered by CH_2Cl_2 extraction. By this treatment the replacement of D for H was, normally, nearly complete at C_2 but still incomplete at C_9. (Of course this generalization does not hold for those cations bearing CH_3 groups at either C_2 or C_9.) (ii) Deuteration at C_9 was obtained by cyclization of the pertinent homoallylic sulfide precursors deuterium labeled at C_2. In turn, these have been obtained by ring expansion of the appropriate *S*-CD_3 thianium salt (prepared by CD_3I alkylation of the corresponding thiane. (iii) Monodeuteration at C_7 was obtained by D_2SO_4 cyclization of the homoallylic sulfide precursors, under the conditions described for the CF_3SO_3H cyclization.

***r*-1-Ethyl,*c*-2-methyl- and *r*-1-Ethyl,*t*-2-methyl-2-(1-methylvinyl)thianium Hexafluorophosphates (23 and 24).** Triethyloxonium fluoborate (0.40 g, 2.1 mmol) was added to 2-methyl-2-(1-methylvinyl)thiane[7] (0.31 g, 2.0 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C. After warming at room temperature, stirring was continued for 2 h. The residue, after CH_2Cl_2 evaporation followed by metathesis with aqueous NH_4PF_6, CH_2Cl_2 extraction, and solvent evaporation, gave 0.49 g (74%) of a material which by ^{13}C NMR appears to be a 3:2 mixture of isomers. The ^1H NMR (acetone-d_6) of the mixture shows multiplets at δ 5.37 (2 H, olefinic H), 3.40 (m, 4 H, C_6H_2 and S–CH_2), 1.97 and 2.00 (2 s, 3 H, CH_3C=), 1.75 and 1.80 (2 s, 3 H, C_2CH_3), and 1.52 and 1.47 (2 q, 3 H, CH_3–C–S); the remaining six H's appear as a complex multiplet in the region δ 2.4–1.8 superimposed on the signals for acetone-d_5. No attempt was made to separate the isomers; however, a fairly pure sample of the major isomer (**23**) was obtained by recovering the sulfonium salt left unreacted after ring expansion with a deficit of base (see below): ^{13}C NMR (acetone-d_6) δ 143.4 (>C=), 118.6 (CH_2=), 61.2 (C_2), 34.9, 33.5 (C_6 and C_3, interchangeable), 31.4 (SCH_2CH_3); the remaining five carbons occur at δ 21.5, 19.9, 19.4, 18.3, and 10.1 (SCH_2CH_3).

Ring Expansion of 23 and 24 with a Deficit of Base. (*Z*)-, (*RS,SR*)-, and (*RR,SS*)-(*E*)-2,4,5-trimethylthiacyclonon-4-enes (**3h**, **2h′**, and **2h″**) were obtained by the procedure previously described for (*Z*)- and (*E*)-4,5-dimethylthiacyclonon-4-enes.[7] A solution of 1.48 g (4.5 mmol) of the 3:2 mixture of **23** and **24** in 44 mL of THF–*t*-BuOH (10:1 v/v, method I) was treated at −70 °C with *t*-BuOK [0.18 g, 1.6 mmol (65% deficit)]. After 2 h at −70 °C the mixture was quenched with 5 mL of H_2O and extracted with pentane/water. Evaporation of the pentane extract gave 0.25 g (30% based on total salt) of a sulfide which appears to be (*Z*)-2,4,5-trimethylthiacyclonon-4-ene (**3h**): ^{13}C NMR ($CDCl_3$) δ 129.9 and 127.3 (C_4 and C_5, interchangeable), 42.3 (C_3), 39.7 (C_2), 31.3, 26.9, 26.0 24.5 (C_6, C_7, C_8, and C_9, interchangeable), 24.7 (C_2CH_3), 19.3 and 18.3 (C_4CH_3 and C_5CH_3, interchangeable); ^1H NMR δ 2.6 (m, 5 H) 1.71 and 1.67 (2 brs, 3 H each, C_4CH_3 and C_5CH_3 interchangeable), 1.37 (d, 3 H, C_2CH_3); the remaining six H's occur as a multiplet in the δ 2.2–1.3 region.

The aqueous phase, after evaporation of the organic solvents under reduced pressure, was twice extracted with CH_2Cl_2 to recover the unreacted salt (0.99 g, 3.00 mmol). By ^{13}C NMR this appears to largely consist of **23** with only ~5% of **24**, indicating **3h** was formed by reaction of the latter. The unreacted salt was treated a second time with *t*-BuOK [0.05 g, 0.45 mmol (85% deficit)] for 30 min at −40 °C and worked up. The pentane extract was discarded, and the unreacted salt was recovered from the aqueous phase (0.63 g, 1.90 mmol). This proved to be isomerically pure **23** (see above). The salt was finally ring expanded with a slight excess of base (method I) at −40 °C to give 0.27 g (80%) of a crude product consisting of two diastereoisomers, **2h′** and **2h″**, in a 3:2 ratio. The two isomers were separated by fractional precipitation with $HgCl_2$. In practice this was achieved by adding a 0.5-mL portion of 6% (w/v) aqueous $HgCl_2$ to a pentane solution of the crude sulfide mixture (0.24 g of crude sulfide in 24 mL) until GLC monitoring of the supernatant revealed that the minor component had been removed. From the precipitate by treatment with aqueous KI (50% w/v) and pentane extraction was recovered 0.08 g of a mixture enriched (~3:1) in the minor isomer. Evaporation of the solvent left a residue (0.12 g) consisting of the isomerically pure major component. The two diastereomers have the following: ^{13}C NMR ($CDCl_3$; the numbers in parentheses pertain to the minor diastereomer, **2h″**): δ 129.6 and 128.9 (131.8 and 127.0, C_4 and C_5 interchangeable), 46.3 (47.1, C_2), 44.2 (45.0, C_3), 37.5, 34.3, 31.0, and 29.9 (36.7, 34.1, 28.1, and 26.6, C_6, C_7, C_8, and C_9, interchangeable), 25.4 (24.5, C_2CH_3), 22.9 and 19.6 (23.1 and 20.4), C_4CH_3 and C_5CH_3, interchangeable); ^1H NMR (**2h′**) δ 3.0 (m, 4 H, C_3H_2 and C_6H_2), 2.0 and 1.8 (2 brs, 3 H each, C_4CH_3 and C_5CH_3), 1.2 (d, 3 H, C_2CH_3), the remaining seven H appear as a complex multiplet in the δ 2.0–1.4 region; ^1H NMR (**2h″**) δ 2.7 (m, 5 H), 1.9 and 1.8 (2 brs, 3 H each, C_4CH_3 and C_5CH_3), 1.3 (d, 3 H, C_2CH_3), the remaining six H's show up as a complex multiplet in the δ 2.1–1.6 region.

Some isomerization of **2h′** and **2h″** to **3h** was observed upon heating for 4 days at 125 °C in octane. Such isomerization was suppressed, however, in the presence of a radical scavenger such as 2,6-di-*tert*-butylphenol (0.1 equiv). No **2h′** ⇄ **2h″** interconversion could be observed after heating either isomer at 125 °C for 100 h in octane.

All other homoallylic sulfides employed in this work had been reported previously: **2a**,[4d] **2b**,[6] **2e**,[5] **2c**, **2d**, **2g**, **2f**, **3f**, and **3g**.[7]

***cis*-1-Thioniabicyclo[4.3.0]nonane (4) trifluoromethanesulfonate** was prepared, as described for the [3.3.0] analogue[1] from (*E*)-thiacyclonon-4-ene (1 mmol in 2 mL of CH_2Cl_2) and trifluoromethanesulfonic acid (1.03 mmol). After the mixture was stirred for 2 h at room temperature and the solvent removed in vacuo, 0.30 g (100%) of the title compound were obtained as a viscous colorless oil. Methatesis to the picrate was performed by dissolving the oil in the minimum amount of water and adding sodium picrate: yellow crystals; mp 238–239 °C (after crystallization from ethanol). This procedure was also employed for obtaining all the bicyclic salts except **12** and **13** (see below).

Melting points (limited to those salts which could be obtained as single isomers) are collected in Table II.

Methylaton of 1-Thioniabicyclo[4.3.0]nonane (Triflate). *endo*-and *exo*-2-Methyl-*cis*-1-thioniabicyclo[4.3.0]nonane (12 and 13). A THF solution of the title compound (3 mmol in 5 mL of THF) was added dropwise at −78 °C to a THF solution of lithium diisopropylamide (LDA), prepared at −78 °C from diisopropylamine in THF (3 mmol in 5 mL) and 1 equiv of BuLi in hexane (1.6 M). After 15 min at −78 °C, CH_3I was added (1.2 equiv in 1 mL of THF). The mixture was stirred for 30 min at −78 °C, allowed to warm to room temperature over a period of 1 h, and filtered. The solid (75%) consisted of a mixture of three (out of four possible) α-methyl-substituted bicyclic sulfonium salts

Table II. Melting Points of Methyl-Substituted *cis*-1-Thioniabicyclo[4.3.0]nonane Picrates

salt[b]	mp,[a] °C	salt[b]	mp,[a] °C
4	238–239	15	229–230
5	170–172	16	142–143
7	135–136	17	194–195
10	137–138	18	182–183
14	241–242	19	198–199

[a] Uncorrected. [b] Satisfactory analytical data (C and H) were found for all the compounds in this table.

in a ~9:3:1 ratio. The minor product appears to be the *endo*-9-CH_3 derivative **6**. The major and intermediate products could be identified from their ^{13}C NMR spectra as the *endo*- and *exo*-2-CH_3 derivatives **12** and **13**, respectively. On the other hand, under the basic conditions leading to H–D exchange of the α-protons, the **12**/**13** ratio was found to decrease (undoubtedly via the ylide), **13** being the thermodynamically more stable epimer. No attempt was made to separate the isomers.

Registry No. (*E*)-**2a**, 68013-79-6; (*E*)-**2b**, 74263-06-2; (*E*)-**2c**, 77743-88-5; (*E*)-**2d**, 71411-37-5; (*E*)-**2e**, 77743-86-3; (*E*)-**2f**, 77743-84-1; (*E*)-**2g**, 77743-85-2; (*E*)-**2h′**, 81643-12-1; (*E*)-**2h″**, 81702-61-6; (*Z*)-**3f**, 77743-81-8; (*Z*)-**3g**, 77743-82-9; (*Z*)-**3h**, 81702-62-7; **4** triflate, 81643-14-3; **4** picrate, 81643-15-4; **5** triflate, 81643-17-6; **5** picrate, 81702-63-8; **6** triflate, 81702-65-0; **7** triflate, 81643-19-8; **7** picrate, 81702-66-1; **8** triflate, 81702-68-3; **9** triflate, 81643-21-2; **10** triflate, 81643-23-4; **10** picrate, 81702-69-4; **11** triflate, 81702-71-8; **12** triflate, 81643-25-6; **13** triflate, 81702-73-0; **14** triflate, 81643-27-8; **14** picrate, 81702-74-1; **15** triflate, 81702-76-3; **15** picrate, 81737-59-9; **16** triflate, 81643-29-0; **16** picrate, 81643-30-3; **17** triflate, 81643-32-5; **17** picrate, 81702-77-4; **18** triflate, 81702-79-6; **18** picrate, 81702-77-4; **19** triflate, 81702-81-0; **19** picrate, 81737-60-2; **23** BF_4, 81643-34-7; **23** PF_6, 81643-35-8; **24** BF_4, 81643-37-0; **24** PF_6, 81643-38-1; 2-methyl-2-(1-methylvinyl)thiane, 77743-97-6.

Photochemical Perfluoroalkylation of Imidazoles

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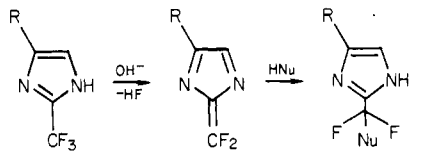
Imidazole and its derivatives undergo facile trifluoromethylation or perfluoroalkylation, in methanol solution at ambient temperature, following radical dissociation of R_FI by γ or UV irradiation. In the case of imidazole, attack occurs preferentially at C-4 with either γ or UV radiation, but the latter method gives consistently higher yields of both C-4 and C-2 isomers. Isolated yields of 4-R_F-imidazoles (R = C_1–C_{10}) ranged from 34% to 61% and those of 2-R_F-imidazoles from 10% to 33%. Trifluoromethylation of substituted imidazoles provided 4-CF_3 isomers in 26–95% yield and 2-CF_3 isomers in 8–46% yield. Small amounts of bis(trifluoromethyl) products are also obtained. The reaction is facilitated by electron-releasing substituents and is retarded by electronegative groups. 1-Alkylimidazoles are trifluoromethylated mainly at C-5 and benzimidazole mainly at C-4. Structural assignments are based on analyses of ^1H and ^{19}F NMR spectra. In the case of 2-R_F-imidazoles (R = C_3–C_{10}), evidence is presented for tautomer stabilization by an intramolecular N–H···F bond.

In continuation of our studies on the chemistry and biochemistry of ring-substituted histamines and histidines,[1] we recently described facile syntheses of the 2-trifluoromethyl derivatives[2] of these biologically essential imidazoles. A general property of ring-trifluoromethylated imidazoles (**1**, and its 4(or 5)-isomer), is the tendency to eliminate hydrogen fluoride under rather mild alkaline conditions to form transient difluorodiazafulvenes (**2**);[3] the



1 **2** **3**

latter species have been found to react rapidly with a variety of nucleophiles (**3**), ultimately providing additional analogues of histamine and histidine.[4] Recognizing the possibility that appropriate difluorodiazafulvenes might serve as covalent affinity labels in biological systems, we have investigated the effects of other ring substituents and of position isomerism on the rate of hydrogen fluoride elimination[5] and found 4-(trifluoromethyl)imidazole to be ca. 10-fold more reactive than the 2-isomer. Since this difference in reactivity might prove important in biological applications, we turned to the problem of general synthetic routes to the 4-trifluoromethyl series. A number of 4-(trifluoromethyl)imidazoles had already been prepared from (trifluoromethyl)glyoxal by classical condensation methods.[6] Syntheses of 4-(trifluoromethyl)histamine and -histidine by analogous procedures would have required laborious sequences and we examined the possibility of direct introduction of the trifluoromethyl group into preformed imidazoles.

Numerous reports describe the copper-catalyzed condensation of aryl[7a] and heteroaryl[7] halides with per-

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