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REACTIONS OF CYCLOOCTENE COMPOUNDS WITH FLUORINATING AGENTS

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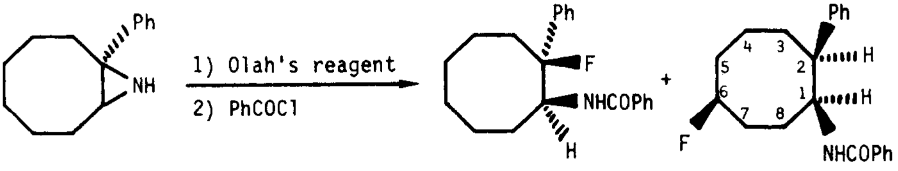
SUMMARY

A comparative study of the reactivity of 9-oxabicyclo[6.1.0]non-4-ene compared to the corresponding aziridine shows trans-opening of the epoxide with the almost neutral fluorinating reagent (Et_3N, 3HF) but no reaction with the aziridine. With Olah's reagent double bond participation is observed in the reaction of the epoxide while a stereoselective addition of HF to the double bond without participation of the aziridine ring takes place with 9-azabicyclo[6.1.0]non-4-ene under the same conditions.

INTRODUCTION

The formation of cationic centers in the course of electrophilic reactions of medium sized rings usually results in rearrangements, namely transannular participation [1]. Recently we showed [2] that the ring opening of 1-phenyl-9-azabicyclo[6.1.0]nonane <u>1</u> with Olah's reagent (10 HF/pyridine) followed by acylation gave a 76:24 mixture of **cis**-2-fluoro-2-phenylcyclooctylamide <u>2</u> and c-6-fluoro-c-2-phenylcyclooctyl-r-1-amide <u>3</u> - both likely derived from an intermediate 'μ-hydrido-bridged' [3] cation.



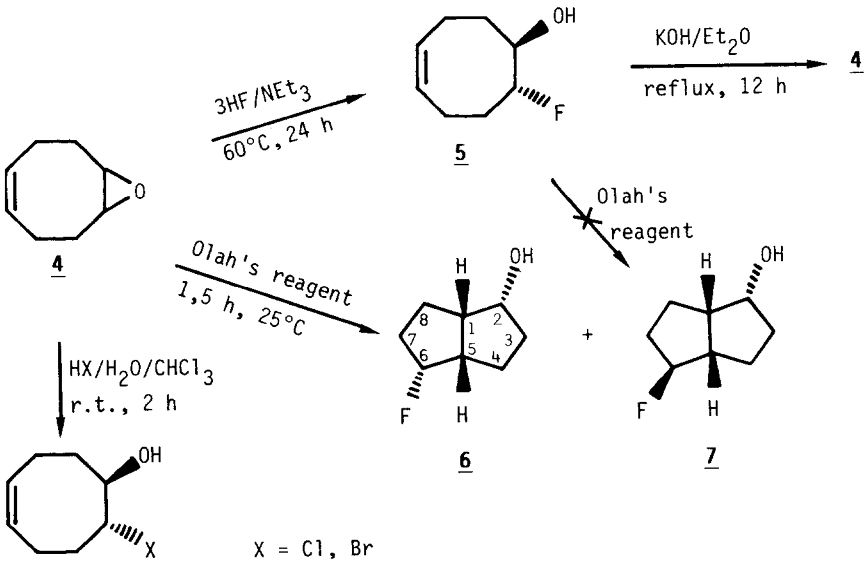
<u>1</u> <u>2</u> <u>3</u>

0022-1139/86/$3.50

Continuing our investigations on the opening of three membered heterocyclic rings [2,4] as well as studies on transannular reactions of unsaturated eight membered rings [5,6], we wish now to describe the reactions of 9-oxa and 9-azabicyclo[6.1.0]nonenes 4 and 8 with Olah's reagent or a modified reagent [7], respectively.

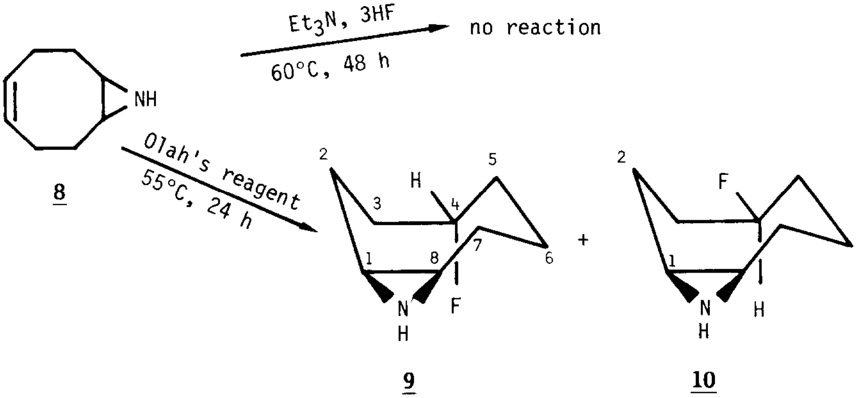
RESULTS AND DISCUSSION

The reaction of 4 with 3 HF/Et$_3$N at 60°C for 24 h gave quantitatively **trans**-2-fluorocyclooct-5-en-1-ol 5, while no reaction took place at room temperature even after 120 h. We also observed simple trans ring opening by stirring 4 with concentrated HCl or HBr in CHCl$_3$ at room temperature for 2 hours [8], while partial π-participation was obtained in formolysis [9]. The structure of 5 was established by spectroscopic methods [8] as well as by reaction with KOH in ether [10] which resulted in the reformation of the epoxide 4 ; from the **cis** isomer cyclooct-4-enone would have been obtained [11].



The reaction of the epoxide 4 with Olah's reagent for 24 h at 20°C on the other hand gave two isomeric bicyclic fluoro alcohols in consequence of transannular π-cyclization of the intermediary cation. The main isomer (65 %) was separated by column chromatography and identified as the **exo-endo**-6-fluorobicyclo[3.3.0]octan-2-ol 7 [8]. The second isomer could not be separated in pure form but should be the C_6 epimer 6. In this reaction 5 is not an intermediate. The reaction of this fluoro alcohol with Olah's reagent under the same conditions gave another fluoro compound, but not 6 or 7, respectively.

In contrast, with the 9-azabicyclo[6.1.0]non-4-ene 8 and Et_3N, 3HF, no reaction occured, even at 60°C for 48 h. With Olah's reagent at room temperature also no reaction was observed whilst the addition was complete after 24 h at 55°C. Two fluoro compounds 9 and 10 with no ethylenic bonds were found in a ratio of 65:35. The product mixture was separated by column chromatography.



The structure of the minor compound 10 was confirmed principally by n.m.r. data which are very similar to that of the former [2] synthesized compound 3 (cf. Table). The smaller coupling constant for 10 [$^3J(C_2\text{-}F) = 9{,}6$ Hz] than for 9 [$^3J(C_2\text{-}F) = 14{,}6$ Hz] is in accord with a fluorine in the equatorial position in compound 10.

TABLE

Chemical shifts (δ, $CDCl_3$ [ppm] and coupling constants J(C-F) and J(H-F) [Hz] in ^1H-, ^{13}C- and ^{19}F- n.m.r. spectra

Compound	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	CHF or CHX	CHN or CHO	ϕ ^{19}F
5	72.2 ^2J=18.6	97.0 ^1J=165	30.3 ^2J=22.8	22.9 ^3J=8.95	128.7^x	128.6^x	22.8	31.1 ^3J=6.7	4.58 J=47.5	4.06	180.4
5 X=Cl	72.5	67.3	32.2*	22.8$^+$	127.9^x	125.2^x	22.4$^+$	30.8*	3.76	4.45	
5 X=Br	72.6	62.8	32.8*	23.8$^+$	127.9^x	124.8^x	22.3$^+$	30.0*	3.96	4.45	
7	39.2	69.9	38.5	20.8	40.8 ^2J=16.2	99.7 ^1J=182.0	29.4 ^2J=19.5	25.8 ^3J=12.0	4.15 J=47.5	3.90	182.5
9	32.9^x	24.3* ^3J=14.6	34.2$^+$ ^2J=24.0	95.4 ^1J=164.8	34.1$^+$ ^2J=23.4	23.4* ^3J=10.3	25.2	32.6^x	4.30 J=46	1.4-1.0	154.3
10	33.4^x	24.9* ^3J=9.6	32.6$^+$ ^2J=22.5	95.6 ^1J=163.9	35.4^x ^2J=24.1	22.8* ^3J=13.2	29.6	32.7^x	4.73 J=48	1.4-1.0	158.7
3 ref.[2]	47.1^x	27.4 ^3J=7.7	31.8* ^2J=23.6	93.3 ^1J=164.8	35.6* ^2J=22.8	20.7 ^3J=12.2	29.8	49.0^x	4.97 J=45.5	4.59	160.1
Fluorocyclooctane ref.[12]	(C_1) (C_4)	(C_8) ^3J=8.8 (C_3)	(C_7) ^2J=22.0 (C_2)	(C_6) ^1J=164.8 (C_1)	(C_5) ^2J=22.0 (C_8)	(C_4) ^3J=8.8 (C_7)	(C_3) (C_6)	(C_2) (C_5)	4.60 J=46.5		160.2

x, *, +, or reverse

From our former study it is known that the fluoride ion in the $Et_3N/3HF$ reagent is a nucleophile [13] which attacks immediately with trans opening of the epoxide ring [14] in **4**. On the other hand this reagent is not able to open the aziridine ring in 9-azabicyclo[6.1.0]non-4-ene **8**. Further, Olah's reagent itself could not open this unactivated ring, which we have already observed in the related reaction of the saturated analogue [2].

In contrast, in the reaction of **4** with this more acidic reagent the opening of the epoxide ring occurs at even lower temperatures. The transannular double bond competes successfully with the fluoride ion, which is weaker in Olah's reagent than in the $Et_3N/3HF$ reagent [13] during the reaction on the epoxidonium ion.

Thus, first a transannular π-cyclisation leads to a 6-hydroxybicyclo[3.3.0]oct-2-yl carbenium ion which is then attacked by the fluoride from one or the other side leading to the epimeric fluoro alcohols **6** and **7**. So, by a proper choice of the fluorinating agent, we can direct specifically the reaction of 9-oxabicyclo[6.1.0]non-4-ene either toward the epoxide's ring opening or the participation of the π-system of the double bond to form bicyclic fluoro-alcohols.

EXPERIMENTAL

IR spectra are recorded in solution ($CHCl_3$) on a PERKIN-ELMER 297 spectrophotometer. Absorption values are given in cm^{-1}.

^1H n.m.r. spectra are recorded in $CDCl_3$ solution on a VARIAN EM 360 spectrometer. Signals are described in δ values (ppm) related to TMS as internal reference, with the following abreviations : s, singlet ; d, doublet ;

t, triplet ; q, quadruplet ; m, multiplet and dm, doublet of multiplet. J coupling constants are given in Hz.

^{19}F n.m.r. spectra are recorded in $CDCl_3$ solution on a VARIAN XL 100 or BRUCKER spectrometer. Signals are described in ϕ values (ppm) related to $CFCl_3$ as internal reference.

^{13}C n.m.r. spectra are recorded in $CDCl_3$ solution on a VARIAN XL 100 spectrometer. Signals are described in δ values related to TMS as internal reference.

Mass spectra are recorded on a VARIAN MAT CH5 spectrometer with a 70 eV ionisation energy.

All new compounds have been fully characterized by spectrometric analyses (including mass spectrometry, ^{13}C and ^{19}F n.m.r.).

Starting materials

9-oxabicyclo[6.1.0]non-4-ene **4** synthesis has already been reported [15].

9-azabicyclo[6.1.0]non-4-ene **8** was prepared by $LiAlH_4$ reduction of 5-azido-6-iodo-cyclooctene [16] according to HASSNER's procedure [17]. All physical and spectroscopic data for **8** are in good agreement with those already reported by BARRELLE *et al*. [18].

I - Reactions of 9-oxabicyclo[6.1.0]non-4-ene 4

With $Et_3N/3HF$

A mixture of 3.1 g (25 mmol) of 9-oxabicyclo[6.1.0]non-4-ene **4** and 24.3 g (30 ml) of $Et_3N/3HF$ is heated at 60°C for 24 h. The reaction mixture is poured on ice, neutralized with 28 % ammonia, extracted 3 times with Et_2O, dried over $MgSO_4$ and concentrated under vacuum. The crude is purified by distillation (Kugelrohr) to give **5** almost quantitatively (b.p.$_{0.2}$ = 46°C).

2-fluorocyclooct-5-en-1-ol **5**

IR : 3600, 3430 (OH) ; 1650 (C=C).

^{1}H n.m.r. : 1.35 to 2.65 (m, 9H) ; 2.91 (s, 1H) ; 4.06 (m, 1H, C<u>H</u>OH) ; 4.58 [dm, 1H, ^{2}J(H-F) = 47.5] ; 5.60 [t, 2H, ^{3}J(H-H) = 2].

^{19}F n.m.r. and ^{13}C n.m.r. : see Table in the text.

Mass m/z (%) : 144 ($M^{+\cdot}$, 7.2), 116 (34.7), 97 (18.5), 85 (64.5), 83 (100), 68 (19.3), 54 (31.5), 47 (25.8).

By refluxing the fluoro-alcohol **5** for 12 h over powdered potassium hydroxyde in ether according to KNUNYANT'S method [10] the compound **4** is obtained in a 83 % yield.

With Olah's reagent

A mixture of 3 g (24.2 mmol) of 9-oxabicyclo[6.1.0]non-4-ene **4** and 30 ml of Olah's reagent is stirred at 25°C for 1.5 h. The reaction mixture is poured on ice, neutralized with 28 % ammonia, extracted 3 times with Et_2O, dried over $MgSO_4$ and concentrated under vacuum. The ^{19}F n.m.r. of the crude reaction mixture shows the presence of two fluorinated compounds in the ratio 65:35. The crude is purified by column chromatography (silica gel, eluant : ether-light/pet. ether, 20:80).

exo,endo-6-fluoro-cis-bicyclo[3.3.0]octan-2-ol **7**

IR : 3600, 3410 (OH).

^{1}H n.m.r. : 1.0 to 2.7 (m, 11H) ; 3.82 (m, 1H, C<u>H</u>OH) ; 4.15 [m, 1H, C<u>H</u>F, ^{2}J(H-F) = 47.5].

^{19}F n.m.r. and ^{13}C n.m.r. : see Table in the text.

Mass m/z (%) : 144 ($M^{+\cdot}$, 12), 124 (27), 109 (66), 107 (100), 67 (45).

With concentrated aqueous HCl or HBr

A solution of 0.62 g (5 mmol) of **4** in 15 ml of $CHCl_3$ is treated with 5 ml of 35 % aq. HCl (or 48 % aq. HBr) and stirred vigorously for 2 h at 20°C. Work up of the reaction mixture [5] leads to the pure trans-2-halo-cyclooct-4-enes in 95 % or 92 % isolated yield [8].

II - Reaction of 9-azabicyclo[6.1.0]non-4-ene 8 with Olah's reagent

A mixture of 1 g (8.2 mmol) of 9-azabicyclo[6.1.0]non-4-ene **8** and 15 ml of Olah's reagent is heated at 55°C for 24 h. The reaction mixture is poured on ice, neutralized with 28 % ammonia, extracted 3 times with Et_2O, dried over $MgSO_4$ and concentrated under vacuum. The ^{19}F n.m.r. of the crude reaction mixture shows the presence of two fluorinated compounds in the ratio 65:35. The crude is purified by column chromatography (silica gel, eluant : ether).

cis- and **trans**-4-fluoro-9-azabicyclo[6.1.0]nonane **9** and **10**

IR : 3310 (NH).

The two isomers **9** and **10** are separated by preparative TLC.

9 - ^{1}H n.m.r. : 0.82 (s, 1H, NH) ; 1.0-1.4 (m, 2H, C$\underline{H}$, C$\underline{H}$, aziridine ring) ; 1.5 to 2.5 (m, 10H) ; 4.30 [dm, 1H, $^{2}J(H\text{-}F)$ = 46].

Mass m/z (%) : 143 ($M^{+\cdot}$, 3.5), 83 (100), 82 (50), 56 (39).

10 - ^{1}H n.m.r. : 0.9 (s, 1H, NH) ; 1.0 to 1.4 (m, 2H, CH, CH, aziridine ring) ; 1.5 to 2.5 (m, 10H) ; 4.73 [dm, 1H, ^{2}J(H-F) = 48].

^{19}F n.m.r. and ^{13}C n.m.r. : see Table in the text.

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