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REACTION OF EPOXIDES WITH DIETHYLAMINOSULFUR TRIFLUORIDE

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SUMMARY

Diethylaminosulfur trifluoride (DAST) reacts with epoxides (oxiranes) to form geminal difluorides, vicinal difluorides, and bis(2-fluoroalkyl) ethers. Thus cyclopentene oxide gave cis-1,2-difluorocyclopentane and bis(2-fluorocyclopentyl) ether; cyclohexene oxide gave cis-1,2-difluorocyclohexane and bis(2-fluorocyclohexyl) ether; styrene oxide gave 1,1-difluoroethylbenzene and 1,2-difluoroethylbenzene; and cis- and trans-stilbene oxides gave mixtures of meso- and racemic 1,2-difluoro-1,2-diphenylethanes together with 1,1-difluoro-2,2-diphenylethane resulting from a rearrangement. Cyclooctene oxide and cyclohexene sulfide do not react appreciably under the same conditions.

INTRODUCTION

Diethylaminosulfur trifluoride (DAST) and analogous fluorosulfuranes have been used for the replacement of a hydroxyl group by fluorine [1], of a carbonyl oxygen by two fluorines [1,2,3], and for a few more instances of introduction of fluorine into organic molecules [1,2,4]. Thus far, no mention has been found of a reaction of DAST with epoxides (oxiranes) and thiiranes.

Epoxides can be expected to react in several ways. After the cleavage of the carbon-oxygen bond in a nucleophilic attack by oxygen at the sulfur atom of DAST, one fluorine of DAST could be transferred to the carbon of the oxirane ring to form an intermediate from which diethylaminosulfinyl fluoride could be eliminated with simultaneous attachment of fluorine to the second carbon of the original oxirane ring.

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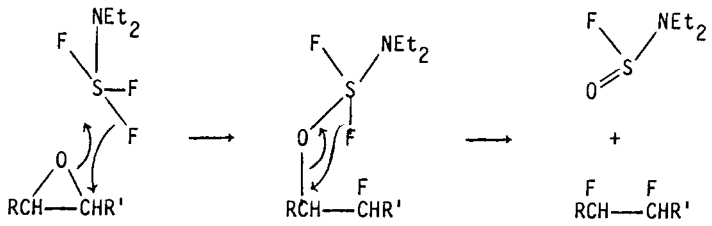
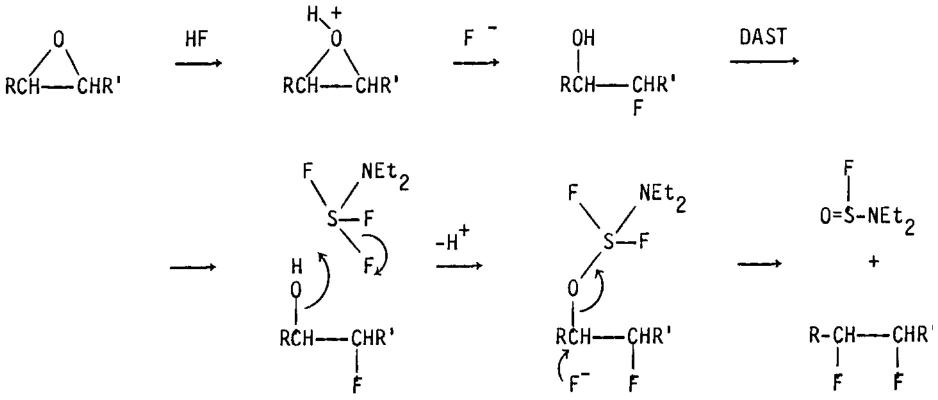
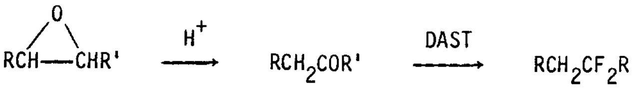


Alternatively, in the presence of moisture, hydrogen fluoride formed from water and DAST could cleave the oxirane ring and give a fluorohydrin. This could react with DAST to form a vicinal difluoride in the conventional way. Since the opening of the oxirane ring occurs in the anti-mode, and so does the replacement of the hydroxyl in the fluorohydrin, the overall stereochemical outcome would be syn-addition of two fluorines to form a vicinal difluoride.



Finally, the epoxide could rearrange to a carbonyl compound in the presence of strong acids such as hydrogen fluoride or DAST. The aldehyde or ketone thus formed could react with DAST to form a geminal difluoride in the conventional way.



In the subsequent paragraphs, reactions of DAST with six epoxides and one thiirane will be described and the reaction products will be characterized.

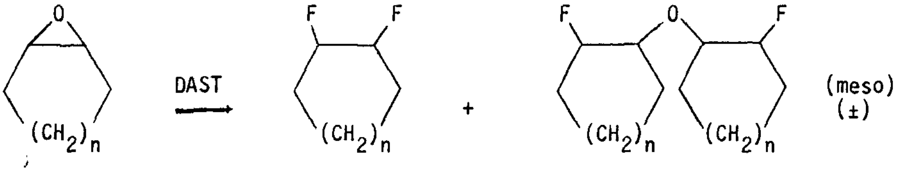
RESULTS AND DISCUSSION

Both types of products, vicinal difluorides and geminal difluorides, anticipated for the reaction of DAST with epoxides were obtained. In addition, products of partial fluorination and partial intermolecular dehydration, bis(2-fluoroalkyl) ethers, were obtained from cyclic epoxides, and products of skeletal rearrangements of 1,2-diphenylethane to 1,1-diphenylethane derivatives were found in the reaction with stilbene oxides. Small amounts of vinylic fluorides were formed by dehydrofluorination. A survey of the results and the yields of the products is shown in Scheme I.

Cyclopentene oxide (Ia) and DAST gave a mixture of four compounds, according to ^{19}F NMR. A fraction distilling at 90-102°/710 mm consisted of two compounds which could not be separated by gas-liquid chromatography on Carbowax 20 M at 120°. The major compound (88%) showed a multiplet at -201.0 ppm and is undoubtedly cis-1,2-difluorocyclopentane (Ib) although its chemical shift differs from that in the literature (-190.0 ppm) [5]. The minor compound (-171.3 ppm) was not identified but is probably trans-1,2-difluorocyclopentane. The higher boiling fraction showed a multiplet at -180.0 ppm and was found to be bis(2-fluorocyclopentyl) ether (Ic). The fourth component (3%) of the crude product showed a multiplet at -196.2 ppm and was not identified.

Most experiments were done with cyclohexene oxide (IIa). At room temperature in a solution in dichloromethane, DAST converted cyclohexene oxide to equal parts of cis-1,2-difluorocyclohexane (IIb) and a diastereomeric mixture of bis(2-fluorocyclohexyl) ethers (IIc). Higher yields of the difluoride IIb were obtained when the reaction was carried out without solvents at 55-60°. Thus the ratio of IIb to IIc was raised to 2:1. Lewis acids as catalysts did not have much effect. Fuming sulfuric acid just increased the amounts of polymeric by-products. Boron trifluoride etherate increased the relative amounts of IIc over IIb. A reaction of cyclohexene oxide with DAST in the presence of an excess of Olah's reagent (70% anhydrous hydrogen fluoride and 30% of pyridine) [6] at room temperature gave essentially the same results as the reaction of DAST with neat IIa at 55-60°.

Distillation of the reaction mixture gave two fractions. The lower boiling fraction was cis-1,2-difluorocyclohexane with a ^{19}F NMR signal appearing as a multiplet at -193.9 ppm. The structure and stereochemistry of this compound was confirmed by elemental analysis as well as by proton and fluorine NMR. The chemical shift agrees well with the literature value of -192.8 [5]. Moreover, at a temperature of 215 K (-58°C) the fluorine



n = 1	Ia	Ib	Ic
		36-47%* (15-16%)**	45-50% (25-34%)
n = 2	IIa	IIb	IIc
		23-79% (19-29%)	24-72% (13-19%)
n = 4	IIIa	—	—

$$\text{PhCR}\overset{O}{-}\text{CHR'} \xrightarrow{\text{DAST}} \text{PhCHRCR'F}_2 + \text{PhCRFCHR'F} + \text{PhCHR'CHRF}_2 + \text{PhCR'=CHF(cis)}$$

R = R' = H IVa	IVb	IVc		IVd
	33-42% (15%)	40-67% (23-27%)		Trace
R = H,R' = Ph Va		Vc (meso)	Ve	Vf
cis (Z)		42-29%	24-29%	5-6%
R = H,R' = Ph Vb		Vd (±)		
trans (E)		21-24%		

* Numbers indicate contents in the crude product based on ^{19}F NMR.

** Numbers in parentheses indicate isolated yields.

Scheme I

spectrum in fluorotrichloromethane gave signals at -182.7 and -207.0 ppm, respectively. These values agree with those obtained at -78° in hexadeuterioacetone (-179.8 and -204.3 ppm) or in carbon disulfide (-180.5 and -204.8), respectively [7].

The higher boiling fraction was a mixture of two diastereomers of IIc showing doublets of multiplets at -181.4 and -183.2 ppm in varying ratios, the average being 2:1, respectively.

In addition to these three major components, a small amount (3-5% of the crude mixture) of an unknown compound was found as a by-product (-196.2 ppm). It is neither 1,1-difluorocyclohexane (-96.1 ppm) nor 1-fluorocyclohexene (-100.6 ppm).

Cyclooctene oxide (IIIa) and DAST did not react appreciably at 55-60° after 24 hours. In addition to 54.3% of recovered IIIa, small amounts of two fluorinated compounds showed signals in the ^{19}F NMR spectrum at -1.2 and -151.7 ppm in a ratio of 1:2. Because of the minute quantities, no attempts were made to isolate or identify them.

Styrene oxide (IVa) on treatment with DAST at 55-60° afforded a mixture of 2,2-difluoroethylbenzene (IVb) and 1,2-difluoroethylbenzene (IVc) in ratios of 1:2 on the average. The proximity of the boiling points of these two isomers did not allow for their separation by distillation. However both compounds were isolated in the pure state by preparative gas-liquid chromatography at 120° on Carbowax 20 M. Their NMR spectra agree with the literature [5,8]. A small amount of a fluorinated by-product (less than 5% of the crude mixture) is cis-β-fluorostyrene (IVd), for both the chemical shift (-125.8 ppm) and the pattern of the signal agree with the literature [9,10].

Both cis- and trans-stilbene oxides (Va and Vb, respectively) reacted sluggishly and incompletely, even with an excess of DAST, whether at 55-60° or at 80°. Even after 24 hours at 55-60°, 56% of crystalline Vb was recovered. The mother liquor contained, according to the ^{19}F NMR spectrum, meso- (Vc) and racemic (Vd) 1,2-difluoro-1,2-diphenylethanes in an average ratio of 1:2. Both stilbene oxides Va and Vb gave the same products in approximately the same ratios. The fluorine chemical shifts (-187.5 ppm for Vc and -184.9 ppm for Vd) as well as the AA'XX' pattern agree with the literature [11,12].

In addition to these two diastereomers, two more fluorinated compounds were found in the reaction mixture. The major compound showed a doublet of doublets at -118.9 ppm and was identified as 1,1-difluoro-2,2-diphenylethane (Ve) (-118.6 ppm) [8]. This compound is a product of skeletal rearrangement very common in the diphenylethane and diphenylethylene systems in fluorination reactions [13,14,15]. A negligible peak at -127 ppm belongs to 1-fluoro-2,2-diphenylethylene (Vf) formed by dehydrofluorination of Ve (-126.4 ppm) [13].

When cyclohexene sulfide was treated with DAST, no reaction took place after 7 hours at 55-60°. After 24 hours at the same temperature, all the DAST reacted. The product was a very viscous brown mass which contained a small amount of a fluorinated material. The position of the ^{19}F NMR signals at -171 and -172 ppm, respectively, and the shapes of the spectra resemble those of bis(2-fluorocyclohexyl) ether (-181.4 ppm and -183.2 ppm, respectively). This indicates the possibility of formation of bis(2-fluorocyclohexyl) sulfide. However, no attempts were made to isolate the compound.

The yields of the products are shown in Scheme I, physical constants and elemental analyses are given in the Experimental section, and the NMR data are displayed in Tables 1 and 2.

EXPERIMENTAL

Starting materials were commercial products of reagent grade. Diethylaminosulfur trifluoride (DAST) was the product of Aldrich Chemical Company and of Alfa Products. cis-Stilbene oxide was prepared from trans-stilbene oxide according to the literature [16]. Cyclohexene sulfide was prepared from cyclohexene oxide and potassium thiocyanate according to the literature [17].

Gas-liquid chromatography was carried out on a Gow-Mac chromatograph series 150 with a thermal conductivity detector using column of Carbowax 20 M and helium as a carrier gas at a flow rate of approximately 100 ml/min. ^{1}H and ^{19}F NMR spectra were taken on a Varian EM 390 spectrometer at 90 MHz and 84.6 MHz, respectively, using carbon tetrachloride and/or deuteriochloroform as the solvents and TMS, fluorotrichloromethane (F11) and hexafluorobenzene (HBF) as internal standards. ^{1}H NMR spectra were also taken on a Bruker WP 270 SY spectrometer at 270 MHz, and ^{19}F NMR on a Bruker WP 200 SY at 188.3 MHz. ^{19}F NMR values are negative upfield (east) from F11.

TABLE 1
^{1}H NMR Spectra

Compound	∂ Arom	∂ ppm	J_{HFgem} Hz	J_{HFvic} Hz	J_{HH} Hz	∂ ppm	J_{HFgem} Hz	J_{HFvic} Hz	J_{HH} Hz	∂ ppm	Ref.
Ib		4.91(dm)	59			1.98(m)					Exptl
		4.76	52.5	12, 18[a]		1.90				1.70	5
Ib[b]		5.19(m)	56							1.80(m)	Exptl
Ic[c]		4.91(dm)	53.6			3.99(dm)		16.4		1.90(m), 1.66(m)	Exptl
IIb		4.67(ddd)	50.2	18.9, 8.5[a]		1.69(m)[d]				1.44(m)[d]	Exptl
		4.55	48	18, 13.5[a]		1.75				1.50	5
IIc[c]		4.38(dm)	50			3.50(m)				1.69[e]	Exptl
IV[b]	7.29(m)	5.90(tt)	58.1		4.8	3.13(td)		17.8	4.9		Exptl
	7.2	5.8	58.0		5.0	3.1		17	5.0		18
IV[c]	7.38(m)	5.67(ddd)	49.8	15.9	3.0	4.62(dm)					Exptl
		5.54	48	16.5		4.44	46.5[f]	23.8[f]			5
Vc	7.28(m)	5.65	AA'XX'	Identical with the literature							Exptl
			45.4	14.9	4.0						12
Vd	7.28(m)	5.59	AA'XX'	Identical with the literature							Exptl
			46.5	14.5	6.40						12
Ve	7.28(m)	6.28(td)	56.7		4.6	4.38(td)		16.1	4.4		Exptl
	7.2	5.5	56.2[f]			3.2		17.1[f]			19
Vf	7.28(m)	7.05	84.8[f]								Exptl
	7.3	6.8	81								15

See footnotes on page 381.

TABLE 2

^{19}F NMR Spectra

Compound	ϕ Upfield from CCl_3F	Coupling Constants J in Hz (Experimental)	ϕ Upfield from CCl_3F	Coupling Constants J in Hz (Literature)	Ref.
Ib	-171.3[a](m) -201.0(m)		-190	J_{HFgem} 52.5, J_{HFvic} 12, 18[b]	5
Ic	-180.0(m)			New compound	
IIb	-193.9(m)		-192.8	J_{HFgem} 48, J_{HFvic} 18,13.5[b]	5
IIc	-181.4(dm) -183.2(dm)			New Compounds	
IVb	-115.5(dt) -116.1[c]	J_{HFgem} 56.2, J_{HFvic} 17.6	-115.0(dt) -115.0(dt)	J_{HFgem} 57, J_{HFvic} 16 J_{HFgem} 56.5, J_{HFvic} 17.0	8 20
IVc	-187.8(m) -CHF-		-188	J_{HFgem} 50.4, J_{HFvic} 23.8, J_{FF} 15.7	5
IVc	-224.0(tt) $-CH_2F-$	J_{HFgem} 47.9, J_{HFvic} 16.2	-223.8	J_{HFgem} 46.5, J_{HFvic} 16.5, J_{FF} 15.7	5
IVd	-124.0(dm)	J_{HFgem} ~80	-123.0 -122.8	J_{HFgem} 79.5, J_{HFvic} 44.0 J_{HFgem} 82.0, J_{HFvic} 44.7	10 9
Vc	-187.5[d] AA'XX'	Identical to those of the literature	-188.0 AA'XX'	J_{HFgem} 45.4, J_{HFvic}14.9, J_{FF} -17.7	12
Vd	-184.9[d] AA'XX'	Identical to those of the literature	-185.0 AA'XX'	J_{HFgem} 46.5,J_{HFvic}14.5, J_{FF} -16.9	12
Ve	-118.9[d](dd)	J_{HFgem} 57.4, J_{HFvic} 15.0	-118.6(dd) -115.1(td)	J_{HFgem} 57, J_{HFvic} 16 J_{HFgem} 56.2, J_{HFvic} 17.1	8 9
Vf	-127.0[d](d)	J_{HFgem} 84.8	-126.4(d)	J_{HFgem} 81 H_2	15

See footnotes on page 381.

Footnotes to Table 1.

[a] Coupling constant to the proton of the CH_2 group.
[b] An unidentified compound, possibly <u>trans</u>-1,2-difluorocyclopentane.
[c] New compound.
[d] At 270 MHz the spectrum consisted of three multiplets with ∂ 2.05, 1.69 and 1.44 ppm in the ratio of 1:2:1, respectively.
[e] At 270 MHz the spectrum consisted of three multiplets with ∂ 2.05, 1.69 and 1.26 ppm.
[f] Coupling constants determined from ^{19}F NMR spectra [5].

Footnotes to Table 2.

[a] An unidentified compound, possibly <u>trans</u>-1,2-difluorocyclopentane.
[b] Coupling constant to the proton of the $-CH_2$ group.
[c] On Bruker WP 200 SY at 188.28 MHz ϕ was -116.1 ppm.
[d] The values are average chemical shifts of the products obtained from both diastereomers, IVa and IVb.

General Procedure

The epoxide (0.01-0.02 mol) was added all at once to a molar equivalent or 10% excess of DAST in a 25 ml side-arm flask fitted with a magnetic stirring bar, a septum, and a reflux condenser connected to argon. The mixture was stirred and heated in an oil bath at 55-60°, exceptionally at 70° or 80°. Samples were taken to follow the progress of the reaction by ^{19}F NMR spectra (disappearance of the broad peak of DAST at 46.5 ppm and appearance of the peak of diethylaminosulfinyl fluoride at 54.0 ppm.) When all the DAST has reacted (after 2-24 hours), the brown reaction mixture was poured over 5-10 g of crushed ice, diluted with 3-6 ml of dichloromethane, and shaken up in a separatory funnel. The lower layer was separated, washed with a saturated solution of sodium bicarbonate, then with water, and finally dried with absorbent cotton.

The solution was weighed, its concentration was determined by ^{1}H NMR (the amount of the solvent), and the composition of the product was determined by means of ^{19}F NMR. Isolation of products Ib, Ic, IIb, IIc, IVb, and IVc was carried out by distillation through a short Vigreux adapter, and compounds Ib, IIb, IVb, and IVc were purified by preparative gas-liquid chromatography on Carbowax 20 M at 120°. The contents of the individual compounds in the crude product and the isolated yields (where applicable) are shown in Scheme I. Products of fluorination of both cis- and trans-stilbene oxides, Vc,.Vd, Ve, and Vf, were not isolated because of the very small yields.

Fluorination of Ia (3 experiments, 55-60°, 8-17 hours). Distillation of the crude product gave cis-1,2-difluorocyclopentane Ib at 92-94°/710 mm (lit. [5] 42°/20 mm) and bis(2-fluorocyclopentyl) ether Ic, distilling at 59-85°/20-24 mm. The first fraction, Ib, even after chromatographic purification still contained about 12% of a fluorinated compound (multiplet at -171.3 ppm) which is probably trans-1,2-difluorocyclopentane.

Analysis: Found for Ib 56.47% C, 7.52% H, 35.68% F. Calcd. for $C_5H_8F_2$ (106.11): 56.59% C, 7.60% H, 35.82% F. Found for Ic 62.99% C, 8.52% H, 19.62% F. Calcd. for $C_{10}H_{16}F_2O$ (190.23): 63.13% C, 8.48% H, 19.98% F.

Fluorination of IIa (17 experiments, room temperature or 55-60°, 16-24 hours). Distillation of the crude product gave cis-1,2-difluorocyclohexane IIb distilling at 120-122°/710 mm, (lit. [5] 45°/20 mm), m.p. 35-37°, and a diastereomeric mixture of two bis(2-fluorocyclohexyl) ethers IIc distilling at 133-140°/12-13 mm and giving two separate doublets of multiplets at -181.4 and -183.2.

Analysis: Found for IIb 59.94% C, 8.46% H, 31.55% F. Calcd. for $C_6H_{10}F_2$ (120.14): 59.98% C, 8.39% H, 31.63% F. Found for IIc (nc) 65.87% C, 9.26% H, 17.28% F. Calcd. for $C_{12}H_{20}F_2O$ (218.28): 66.03% C, 9.24% H, 17.41% F.

Fluorination of IVa (3 experiments, 55-60°, 2-4.5 hours). Distillation at 72-76°/16-17 mm gave a mixture from which 2,2-difluoroethylbenzene IVb and 1,2-difluoroethylbenzene IVc were isolated by gas-liquid chromatography on Carbowax 20 M at 120°. The faster fraction, IVb, had a b.p. of 156-158° (lit. [18] 58-59°/18 mm, [20] 68-89°/32 mm); the slower fraction, IVc, had a b.p. of 146-148° (dec.) (lit. [5] 68°/20 mm).

Analysis: Found for IVb, 67.78% C, 5.62% H, 25.81% F. Found for IVc, 67.54% C, 5.84% H, 26.24% F. Calcd. for $C_8H_8F_2$ (142.14), 67.60% C, 5.67% H, 26.73% F.

Fluorination of both Va and Vb (2 experiments each, 55-60°, 18-101 hours, or 80°, 9-15 hours) gave only negligible amounts of fluorinated products. Most of the starting material was recovered, in the case of Vb in crystalline form (over 56%). In the oily mother liquor, four compounds were identified by ^{19}F NMR (see Scheme I and Tables 1 and 2).

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