

Received: October 31, 1988; accepted: December 29, 1988

FLUORINATION OF CYCLOHEXANOLS WITH 4-MORPHOLINOSULFUR TRIFLUORIDE [1]

KEVIN C. MANGE and W. J. MIDDLETON*

Chemistry Department, Ursinus College, Collegeville, Pennsylvania 19426 (U.S.A.)

SUMMARY

In contrast to most simple alcohols, cyclohexanol has proved to be a surprisingly difficult compound to fluorinate with aminosulfur trifluorides. In the reaction of 4-morpholinosulfur trifluoride (morpho-DAST) with cyclohexanol, a correlation was found between the polarity index of the solvent, P' , and the yield of fluorocyclohexane. In solvents of low polarity, there appears to be an uncharged intermediate that leads to fluorocyclohexane. In solvents of higher polarity, there appears to be a charged intermediate that gives fluorocyclohexane. By a study of the fluorination of *cis*- and *trans*-4-*tert*-butylcyclohexanol, conformational effects were shown to be a major factor in hindering the S_N2 attack by fluoride ion on the reactive intermediate(s).

INTRODUCTION

Aminosulfur trifluorides such as DAST (diethylaminosulfur trifluoride) react with most primary, and many secondary and tertiary alcohols to give nearly quantitative yields of the corresponding fluoride in which the hydroxyl group has been replaced with a fluorine atom [2]. However, certain secondary and tertiary alcohols give considerably lower yields of the fluoride due to extensive formation of olefinic by-products. Cyclohexanol is an example of a simple alcohol that fails to give satisfactory yields of the fluoride; the major product of the attempted fluorination is cyclohexene [3]. We have investigated the reaction of cyclohexanol (*Scheme 1*) and *cis* and *trans*-4-*tert*-butylcyclohexanols with morpho-DAST (4-morpholinosulfur trifluoride [4]) to gain a better understanding of this fluorination reaction and of why cyclohexanol gives a low yield of fluorinated product. We chose to do the study with morpho-DAST instead of the more often used fluorinating reagent DAST because our recent studies [3] have shown that yields are higher with this reagent.

* To whom inquiries should be addressed.

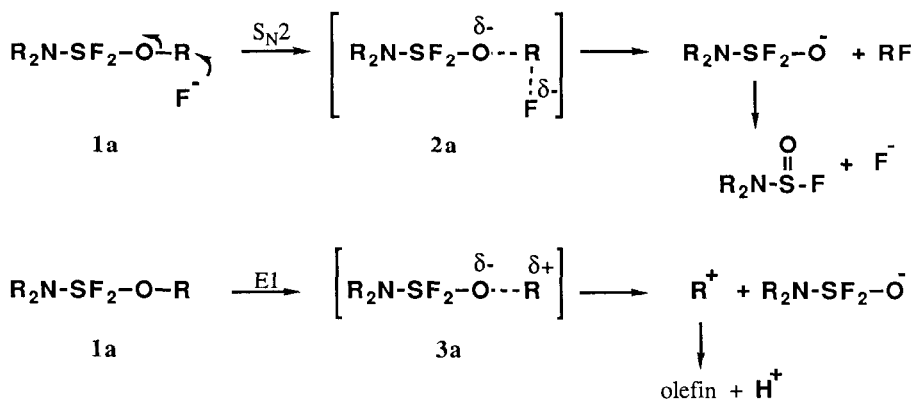


Scheme 1

SOLVENT EFFECTS

Simple alcohols undergo a complete inversion of configuration when fluorinated with aminosulfur trifluorides [4] to give an organic fluoride that has a configuration opposite that of the alcohol. This implies that some intermediate in the reaction undergoes a S_N2 substitution reaction with fluoride ion. This same intermediate also could undergo an E1 elimination reaction to give the observed olefinic by-product. If this is true, then the polarity of the solvent used in the reaction should influence the ratio of fluorinated product to olefin formed in the reaction. *Table I* (in Experimental Section) shows the yield of fluorocyclohexane formed by the reaction of morpho-DAST with cyclohexanol in several solvents with different polarities. The yields of fluorocyclohexane varied, but in all cases the major product formed in these reactions was cyclohexene, which was the only other observed product.

An alkoxyaminosulfur difluoride, **1a**, has been proposed [2] as an intermediate in the reaction of an aminosulfur trifluoride with an alcohol. If this intermediate were to undergo a S_N2 substitution reaction with fluoride ion and a competitive E1 elimination reaction, as shown in *Scheme 2*, then increasing the polarity of the solvent should increase the activation energy for the S_N2 reaction (the reactant, F^- , would be more highly solvated than the charge-diffused transition state **2a**) and decrease the activation energy for the E1 reaction (the uncharged reactant would be less solvated than the partially-charged transition state **3a**). Consequently, increasing the polarity of the solvent should lead to an increase in the ratio of olefin to alkyl fluoride with the result that a lower yield of the alkyl fluoride would be obtained. The data in *Table I* indicate that this is true for solvents of very low polarity and very high polarity, when the polarity index, P' [5], is used as a measure of the polarity of the solvent. However, increasing the polarity of the solvent from a P' of 2.2 to 3.5 actually decreases the ratio of olefin to fluoride and gives higher yields of the fluoride. In fact, the best yields of fluorocyclohexane were obtained in 1,2-dichloroethane (P' , 3.5) and methylene chloride (P' , 3.1). Apparently, the proposed mechanism in *Scheme 2* will have to be modified to account for the results in these most useful solvents.

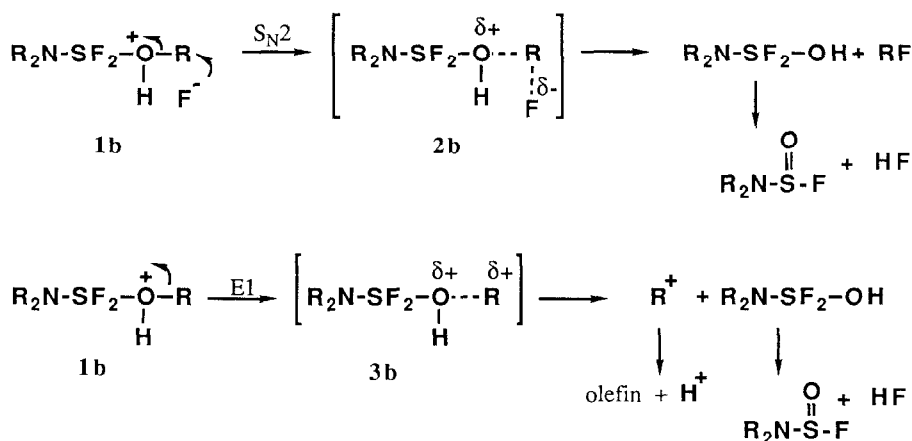


Scheme 2

The observed correlation of yields with solvent polarity in the range of P' from 1.6 to 3.5 can be accommodated better by assuming that the intermediate in the reaction is the protonated alkoxyaminosulfur difluoride **1b**. Logically, this intermediate is formed first in the reaction of an alcohol with an aminosulfur trifluoride, and could exist in equilibrium with the unprotonated form, **1a**. If **1b** were the intermediate in the displacement reaction, increasing the solvent polarity should increase the activation energy for both the $\text{S}_\text{N}2$ reaction and the competing $\text{E}1$ reaction, as shown in *Scheme 3*, since the charge of the transition states in both cases (**2b** and **3b**) would be more diffuse than the charge of the reactants. From these considerations, it is not clear what effect this would have on the ratio of products, but it seems at least possible that the ratio of organic fluoride to olefin could be increased as the solvent polarity is increased, and consequently, the yield of the organic fluoride would be increased. Of course, if the polarity of the solvent becomes too great, as was observed with acetone and acetonitrile, the activation energy for the $\text{S}_\text{N}2$ reaction would become too large for the reaction to proceed (because the fluoride ion would lose its nucleophilicity by being complexed too tightly by the solvent), and no fluorination product would be formed.

EFFECTS OF CATALYST

Acids and bases were added to the reaction mixture in an attempt to catalyze the reaction. However, both had a deleterious effect on the yield of fluorocyclohexane. Bases, such as pyridine, triethylamine, and dimethyl formamide, may have deprotonated the intermediate **3b**, giving a poorer leaving group. Acids, such as hydrofluoric acid and trifluoromethanesulfonic acid may have partially destroyed the fluorinating reagent or sequestered the fluoride ion.



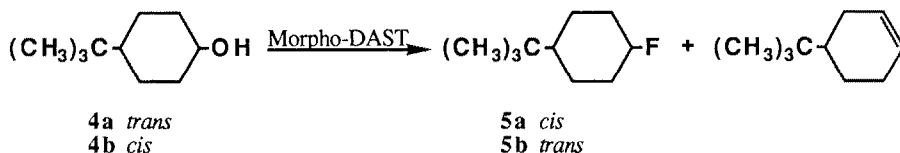
Scheme 3

COMFORMATIONAL EFFECTS

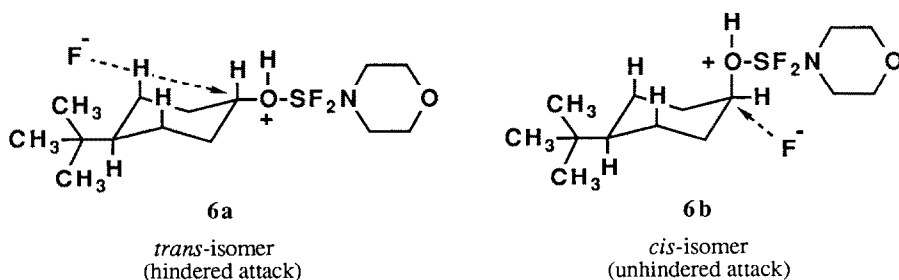
Cyclohexanol gives only low yields of fluorinated product when treated with 4-morpholinosulfur trifluoride, whereas many other secondary alcohols such as 1-phenethanol give almost quantitative yields, even though the carbocation derived from these alcohols may be more stable than the cyclohexyl carbocation. An explanation could be that steric factors are involved in the reaction with cyclohexanol. If an intermediate such as **1a** or **1b** is required for the reaction, the large bulky leaving group $\text{R}_2\text{N-SF}_2\text{O}^-$ or $\text{R}_2\text{N-SF}_2\text{OH}$ would be primarily in the preferred equatorial position of the chair conformation of the six membered ring. In this conformation, the axial hydrogens in the 3 and 5 positions would block the back-side approach of the solvated fluoride ion. Much less steric blocking would occur if the leaving group were in the axial position.

The fluorination reaction of both *cis*- and *trans*-4-*tert*-butylcyclohexanols with 4-morpholinosulfur trifluoride (scheme 4) was examined to determine if conformational effects are important. The bulky *tert*-butyl substituent was chosen as a locking group because it is particularly prone to occupy an equatorial position. In this reaction, the *cis* alcohol **4b** gave the *trans* fluoride **5b**, and the *trans* alcohol **4a** gave the *cis* fluoride **5a**. Scheme 5 represents the most favored conformation of the protonated intermediate of the *cis* alcohol, **6b**, and of the *trans* alcohol, **6a**, with the *tert*-butyl group in the equatorial position in both cases. Back side attack

of fluoride ion on the *cis* intermediate is relatively unhindered, whereas attack on the *trans* intermediate is hindered by the 3 and 5 hydrogens. Thus, one would expect a higher yield of 4-*tert*-butylcyclohexyl fluoride from the *cis* alcohol than from the *trans* alcohol. When the reaction was carried out at -15°C in methylene chloride, the *cis*-alcohol **4b** gave a 72.4% yield of the *trans*-fluoride **5b**, and the *trans*-alcohol **4a** gave only a 36.6% yield of the *cis*-fluoride **5a**, consistent with the theory that conformational factors are important in this reaction. When the reaction was conducted at higher temperature, the difference in yield was less pronounced, as would be expected from lower populations of the preferred conformations of **6a** and **6b**.



Scheme 4



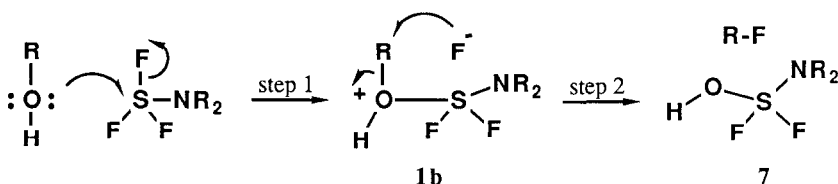
Scheme 5

CONCLUSIONS

Both solvent and conformational effects are pronounced in the fluorination of cyclohexanols with 4-morpholinosulfur trifluoride. There is a bimodal correlation between solvent polarity and yield of fluorocyclohexanes. In solvents of very low polarity, the reaction is believed to proceed by way of an uncharged alkoxyaminosulfur difluoride intermediate **1a**, but in solvents of higher polarity, the charged intermediate **1b** is more important. In solvents of very high polarity, such as acetone (P' 5.1) and acetonitrile (P' 5.8), no fluorination occurs, probably because the nucleophilic fluoride ion is deactivated by being tightly complexed with the solvent. Of the solvents studied, dichloromethane (P' 3.1) and 1,2-dichloroethane (P' 3.5) gave the

highest yields. Attempts to catalyze the reaction by both acids and bases had a deleterious effect on the yields of fluorinated products.

Based on this limited study, we propose the mechanism shown in *Scheme 6* for the fluorodehydroxylation of an alcohol with an aminosulfur trifluoride in solvents such as dichloromethane and 1,2-dichloroethane. In the first, rate determining step, a fluorine is displaced from the sulfur by a nucleophilic attack of the alcohol to give the protonated intermediate **1b** and a fluoride ion. While **1b** and F^- are still in the same solvent cage (and therefore the fluoride ion is relatively unsolvated and very reactive), a second nucleophilic reaction occurs with the fluoride ion displacing the R_2N-SF_2OH leaving group (**7**) to give the alkyl fluoride.



Scheme 6

The low yields of cyclohexyl fluoride that result from the fluorination of cyclohexanol with aminosulfur trifluorides are believed to be due to conformational effects. The most stable conformation of the intermediate in the reaction blocks the attack of fluoride ion.

EXPERIMENTAL

Gas Chromatographic Analyses.

All reaction mixtures containing solvent, organic fluoride, and olefin were analyzed with a Perkin Elmer gas chromatograph using a 3' or 6' 1/8" column packed with 5% SP-2100 (dimethylpolysilane) on 100/120 Supelcoport or 5% Carbowax PEG 20M on 100/120 Supelcoport. Authentic samples of the expected products, either purchased or prepared by the literature procedures cited, were used for calibration purposes.

Reactions of Cyclohexanol with 4-Morpholin sulfur Trifluoride (Table I).

A solution of 100 mg (1 mmol) of dry cyclohexanol in 4 mL of solvent at 25° C was mixed with 350 mg (2 mmol) of 4-morpholin sulfur trifluoride [6] contained in a glass vial. After 5 to 10 minutes, the reaction mixture was poured into an equal volume of aqueous 5% sodium bicarbonate solution and shaken. The organic layer was separated (for solvents miscible with water, 4 mL of methylene chloride was added), washed with water, dried (MgSO₄), and then analyzed by gas chromatography.

Reactions of *cis* and *trans*-4-*tert*-butylcyclohexanol with 4-Morpholin sulfur Trifluoride.

The *cis* and *trans* isomers of 4-*tert*-butylcyclohexanol were separated by the method of Pike and Schank [7]. A solution of 3.12 g of 98% *cis*-4-*tert*-butylcyclohexanol in 40 mL of methylene chloride was cooled to -15°, and 7.0 g of 4-morpholin sulfur trifluoride was added dropwise. The reaction mixture was warmed to room temperature, and then poured into aqueous 5% sodium bicarbonate. The organic layer was separated, washed with water, and dried (MgSO₄). Enough bromine was added to react with the olefins formed in the reaction (monitored by gc), and then the reaction mixture was shaken with a few drops of mercury to remove excess bromine and distilled to give 1.80 g (57 % yield) of *trans*-1-fluoro-4-*tert*-butylcyclohexane (containing about 1% of the *cis* isomer, as indicated by gc analysis), bp. 59-60° (10 mm) [8]. Similar reactions at one-tenth this scale, analyzed by gc before losses were encountered in the isolation steps, indicated that *cis*-4-*tert*-butylcyclohexanol gave *trans*-1-fluoro-4-*tert*-butylcyclohexane [8] in 72.4% yield, and *trans*-4-*tert*-butylcyclohexanol gave *cis*-1-fluoro-4-*tert*-butylcyclohexane [8] in 36.6% yield.

Reaction of 1-Phenethanol with 4-Morpholin sulfur Trifluoride.

A solution of 7.0 g (0.04 mol) of 4-morpholin sulfur trifluoride in 10 mL of methylene chloride was added dropwise to a solution of 2.44 g (0.02 mol) of 1-phenethanol in 40 mL of methylene chloride at 25° C. The reaction mixture was poured into 5 % aqueous sodium bicarbonate, and the organic layer was separated, washed with water, dried (MgSO₄). Analysis by gc of the crude reaction mixture indicated that no styrene was present. Distillation gave 2.13 g (86 % yield) of 1-fluoroethylbenzene, bp 136-138°. An authentic sample prepared by the literature [9] procedure of treating 1-phenethanol with anhydrous hydrogen fluoride at -50° C gave only a 10% yield of 1-fluoroethylbenzene.

TABLE I

Fluorination of cyclohexanol with morpholinosulfur trifluoride^a

Solvent	Polarity Index ^b (P')	Dielectric Constant (20°)	Fluorocyclohexane ^c % Yield
Acetonitrile	5.8	37.5	0.0
Acetone	5.1	20.7 ^d	0.0
Chloroform	4.1	4.81	13.3
Tetrahydrofuran	4.0	7.58 ^d	26.5
1,2-Dichloroethane	3.5	10.36 ^d	43.1
Dichloromethane	3.1	8.93 ^d	39.4
Diethyl Ether	2.8	4.33	17.2
Carbon Tetrachloride ^e	1.6	2.24	1.0
1-Chlorobutane	~1.0	7.39	8.6
Pentane ^e	~0.0	1.84	19.0
1,1,2-Trichlorotrifluoroethane	~0.0	2.41 ^d	23.0

^a All reactions were conducted at 25°. ^b Ref. 5; (~) indicates values that were estimated by L. R. Snyder and reported in the Solvent Guide, Burdick & Jackson Laboratories, Inc., or by private communication to the author. ^c In all examples, the only other major product was cyclohexene. ^d Value at 25°C. ^e Reaction mixture was not homogeneous due to solubility problems.

Effect of Solvent Polarity on Yield

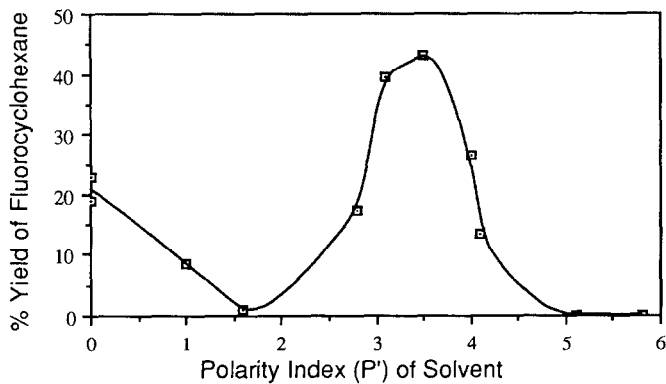


CHART I

ACKNOWLEDGEMENT

Acknowledgement is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

REFERENCES

- 1 Portions of this paper were presented at Intercollegiate Student Chemists Convention, Juniata College, Huntingdon, Pa., April 16, 1988.
- 2 M. Hudlicky, ' Fluorinations with Diethylaminosulfur Trifluoride and Related Aminosulfurans ', in Organic Reactions, Vol. **35**, pp. 513-637, John Wiley & Sons, Inc., New York, 1988.
- 3 P. A. Messina, K. G. Mange and W. J. Middleton, J. Fluorine Chem. **42** (1989) 137.
- 4 J. Leroy, E. Herbert, and C. Wakselman, J. Org. Chem., **44** (1979) 3406.
- 5 L. R. Snyder, J. Chromatogr. Sci., **16** (1978) 223.
- 6 L. N. Markovskii, V. E. Pashinnik, and N. A. Kirsanova, Synthesis, **(1973)** 787.
- 7 R. A. Pike and R. L. Schank, J. Org. Chem., **27** (1962) 2190-92.
- 8 J. San Filippo and L. J. Louis, J. Org. Chem., **40** (1975) 782-7; E. L. Eliel and R. J. L. Martin, J. Am. Chem. Soc., **90** (1968) 682-9.
- 9 K. Wiechert, C. Gruenert, and H. J. Preibish, Z. Chem., **8** (1968) 64-5.