ON THE MECHANISM OF THE DIRECT FLUORINATION OF TRIMETHYLSILYL COMPOUNDS

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SUMMARY

In an attempt to elucidate the mechanism of fluorination of silyl compounds, a number of compounds have been fluorinated. Depending on the substrate used the pathway involved may be addition-elimination, cyclic or stepwise.

INTRODUCTION

Fluorine is a very reactive gas with a low bond dissociation energy (37 kcal/mole) and it undergoes many indiscriminate reactions. It is therefore noteworthy that some of its reactions can be moderated by the use of low temperatures and dilution with inert gases. Rozen and coworkers have investigated the fluorination of unactivated tertiary hydrogens and postulate a polar two-electron three center interaction to account for the selectivity [1].

The reaction of fluorine with 2-trimethylsiloxypyridine to form the fluorinating agent, 1-fluoro-2-pyridone, was postulated to proceed by way of a cyclic six-centered transition state [2], eq. 1. Extrapolation of this proposed mechanism has led us to fluorinate many other siloxy compounds for the synthesis of α-fluorocarbonyl compounds [3]. Because of the utility of the reaction, an investigation of the mechanism was undertaken. There are three possible pathways that these reactions might follow: a six-centered transition state, addition-elimination or stepwise reaction.

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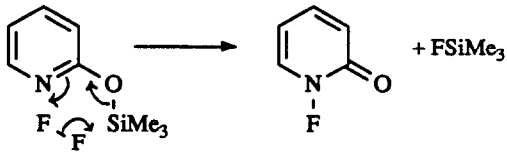
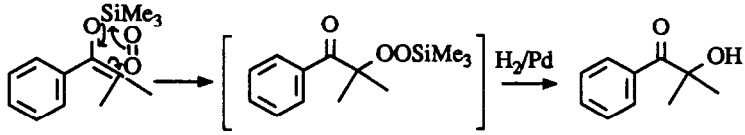


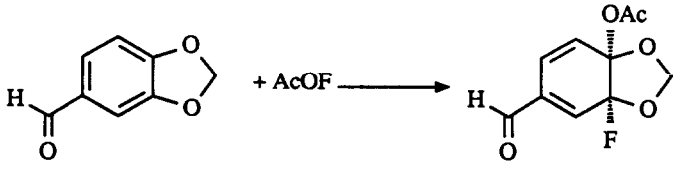
(1)

A concerted cyclic mechanism for the fluorination of enols and phenol was postulated by Misaki and coworkers [4]. The very high ortho selectivity observed in the reaction with phenols supports this mechanism. They rule out a radical pathway because the use of an enol with a p-nitrophenyl group gave the same results as an unnitrated enol. An unusual reaction of singlet oxygen with the silyl enol ether shown in eq. 2 was discovered by Rubottom and Nieves [5]. They rationalized their observations by the cyclic mechanism. Similarly, a ketene bis(trimethylsilyl)ketal gave rise to an α-silyl peroxy ester on photooxidation [6].



(2)

Syn addition of fluorine followed by *anti* elimination of HF is a second mechanistic possibility. Precedent for this type of interaction is found in the reaction of fluorine with uracil [7]. *Syn* addition of fluorine to steroidal olefins was also found by Merritt and Stevens [8]. In a similar vein, Rozen and associates [9] observed *syn* addition of acetyl hypofluorite to piperonal as shown in eq. 3. Elimination of HF is impossible for the observed adduct. They postulate an addition elimination mechanism for the fluorination of aromatic rings activated by alkoxy (OR) or amide (NHCOR) groups [9].



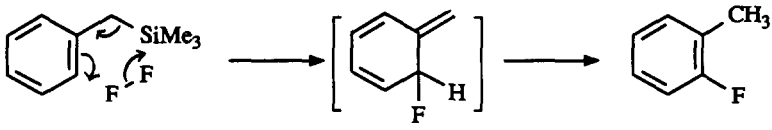
(3)

Addition of fluorine to the double bond followed by loss of trimethylsilyl fluoride should also be considered. Bromination of silyl enol ethers has been postulated to proceed by way of addition of bromine followed by elimination of trimethylsilyl bromide [10].

Many reactions of silyl enol ethers with electrophiles are thought to occur in a stepwise manner [11]. The reaction with N-halosuccinimides has recently been shown to proceed in a non-synchronous fashion [12].

RESULTS AND DISCUSSION

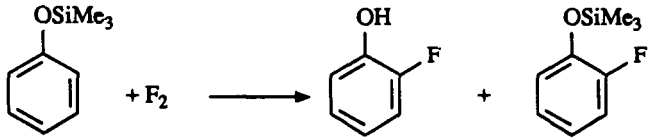
We have undertaken a number of reactions to try to elucidate the mechanism of the reaction of fluorine with silyl enol ethers. The fluorination of benzyltrimethylsilane with 5% fluorine in nitrogen produced 2-fluorotoluene. Clearly, a cyclic pathway is indicated as envisioned in eq. 4. The product was identified by ^{19}F NMR, gas chromatographic comparison with a known sample and mass spectrometry. In order to show that the



(4)

reaction is not stepwise and initiated by adventitious fluoride, benzyltrimethylsilane was treated with methyl iodide in the presence of fluoride. Ethyl benzene was the only product. Thus, had fluoride initiated the reaction with fluorine, the expected product would have been benzyl fluoride.

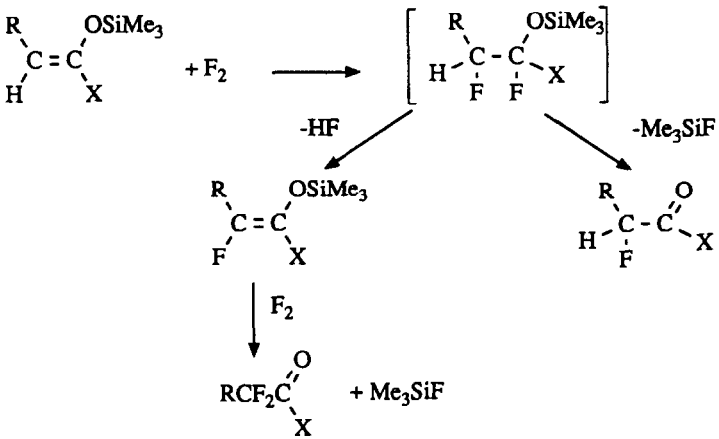
However, the cyclic mechanism for fluorination of silyl enol ethers is not necessarily the only one involved. This was clearly demonstrated by the fluorination of phenoxytrimethylsilane, a special silyl enol ether where the double bond is part of the aromatic system. o-Fluorophenol and o-fluorophenoxytrimethylsilane were the major products of the reaction shown in eq. 5. The o-fluorophenol is thought to arise by way of the cyclic transition state while the o-fluorophenoxytrimethylsilane is formed by addition of fluorine across the electron-rich double bond followed by elimination of HF. The



(5)

absence of phenol in the product mixture is particularly noteworthy as it provides evidence that under the reaction conditions fluoride promoted cleavage of the phenoxide does not occur. This result is not surprising because any hydrogen fluoride formed is rapidly purged from the system. The absence of phenol is also indicative that the o-fluorophenol does not result from cleavage of o-fluorophenoxytrimethylsilane. A blank experiment where phenoxytrimethylsilane was treated with aqueous HF did not result in cleavage of oxygen-silicon bond. While studying the hydrolysis of triphenylmethyl fluoride, Badley and Ford also noted that HF produced in the reaction did not react with silica supports of the catalysts used [13]. In an attempt to simulate the non-aqueous reaction conditions, HF was generated by treatment of KHF_2 with p-toluenesulfonic acid in CD_3CN. After addition of o-fluorophenoxytrimethylsilane, the ^{19}F NMR signal of the silane was unaffected.

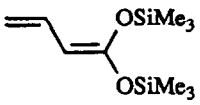
Our observations that α,α-difluorocarbonyl compounds are by-products in the fluorination of silyl enol ethers [3a] and silyl ketene acetals [3c] also can be accounted for by way of addition to the electron rich double bond as shown in Scheme I. Loss of HF followed by addition of a second molecule of fluorine results in the difluoro species.



Scheme I.

In the case of ketene bis(trimethylsilyl)acetals where X=$OSiMe_3$, only monofluoro-carboxylic acids are formed. If fluorine adds to the double bond, loss of trimethylsilyl fluoride rather than HF is necessary. Alternately, the fluorine may react by way of a cyclic transition state when the trimethylsiloxy groups are geminal.

Finally, we investigated the ketene bis(trimethylsilyl)acetal of crotonic acid. As shown in eq. 6 only δ-fluorination was observed. This rather unusual result is most likely due to a stepwise reaction as Fleming and coworkers observed with other electrophiles [14].



$$+ F_2 \xrightarrow[H_3O^+]{\text{then}} CH_2FCH{=}CHCO_2H \qquad (6)$$

In conclusion, fluorine has been shown to add to silylated compounds by a variety of different mechanisms depending on the substrate.

EXPERIMENTAL

The ^1H NMR (90 MHz) and ^{19}F NMR (90MHz) were obtained on a Varian EM-390 spectrometer. Chemical shifts are reported in ppm down field relative to external Me_4Si for ^1H NMR and internal $CFCl_3$ for ^{19}F NMR with $CDCl_3$ as the solvent in both cases. Capillary GC analyses were accomplished on a Hewlett Packard 5890 gas chromatograph, equipped with a split/splitless injection and an FID detector. All analyses were carried out on an SE-30, 25m fused silica column using an HP 3392A integrator.

The 5% F_2 in N_2 was supplied by Air Products. Crotonic acid and tetrahydrofuran (THF) were supplied by Fisher Scientific Company. Fluorotrichloromethane was purchased from Flura Corporation. Benzyltrimethylsilane was supplied by Petrarch Systems Inc. o-Fluorophenol was supplied by Alfa Products. All other materials came from Aldrich Chemical Co.

THF was distilled from sodium benzophenone ketyl prior to use. Chlorotrimethylsilane and 1,1,1,3,3,3-hexamethyldisilazane were distilled from CaH_2 under N_2 prior to use. Crotonic acid was recrystallized from pentane and stored under nitrogen. All glassware was oven dried and flame dried. The reactions were done under N_2 with rigorous exclusion of moisture. The synthesis of the ketene bis(trimethylsilyl)acetal of crotonic acid was done with minor modifications of standard procedures reported earlier[15]. ^1H NMR δ 0.2(s,18H); 4.2(d,1H); 5.1(d,1H); 5.7(m,2H).

Fluorinations

Fluorinations were done following standard procedures reported earlier [3]. All fluorinations were done in $FCCl_3$ at -78 C. The reaction vessel was purged with N_2 prior to addition of 5% fluorine in nitrogen and after addition was completed. A sodium iodide trap was used as a scrubber for removal of HF. Potassium iodide traps were used to destroy unreacted fluorine eluting from the reaction vessel and to determine when the reaction was completed. The addition of fluorine was stopped when the second potassium iodide trap began to change color.

4-Fluorocrotonic acid

The ketene bis(trimethylsilyl)acetal of crotonic acid (1.0 g) was dissolved in approximately 25 mL $FCCl_3$ and fluorinated as described above. The reaction mixture was washed with water and extracted with 20% sodium hydroxide. The water layer was acidified with 10% H_2SO_4 and extracted with diethyl ether. The ether layer was dried with $MgSO_4$, filtered, and the solvent evaporated to yield 0.34g of 4-fluorocrotonic acid, 75% yield. ^{19}F NMR δ-228.6 (m), m.p. 86-87°C; lit. 88-89°C [16].

2-Fluorotoluene

Benzyltrimethylsilane (1.0g) was dissolved in $FCCl_3$ and fluorinated as above. The concentrated product mixture was dissolved in diethyl ether and washed with water. The ether layer was dried over $MgSO_4$, filtered, and the solvent removed. The product was found to co-elute with an authentic sample of 2-fluorotoluene. ^{19}F NMR δ-118.1 (s), lit. -118.1 [17]. MS mass calc. 110g/mol; mass found 110g/mol.

o-Fluorophenoxytrimethylsilane

o-Fluorophenol (1.12 g, 1.00 mmol), bis(trimethylsilyl)acetamide (2.50g, 1.23 mmol) and dry acetonitrile (25 mL) were heated under N_2 for 2h. The solvent and

byproduct were removed by rotary evaporation. Vacuum distillation (103°C/24 mmHg) gave 1.36g (84.7%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 0.38 (s,9H); 7.1-6.8 (m, 4H), ^{19}F NMR ($CDCl_3$) δ-133 ppm. This product was also observed in the fluorination of phenoxytrimethylsilane. o-Fluorophenol could also be silylated with hexamethyldisilazane.

Treatment of Phenoxytrimethylsilane with HF

Phenoxytrimethylsilane (1.2g, 7.2 mmole) in CH_2Cl_2 (40 mL) was mixed with 48% HF (2.5 mL in 50 mL H_2O). The two solutions were stirred vigorously for 15 min. The organic layer was separated, dried over $MgSO_4$ and the solvent was evaporated. The starting material (1.1g, 92%) was recovered as shown by the ^{1}H NMR: δ 0.18 (s,9H); 7.7-6.6 (m, 5H).

In an NMR tube containing KHF_2, p-toluenesulfonic acid in CD_3CN was added. A ^{19}F NMR signal was observed at δ-180 ppm. Upon addition of o-fluorophenoxy-trimethylsilane, the HF signal shifted to δ-160 ppm, but the signal for o-fluoro-phenoxytrimethylsilane was unaffected.

Ethylbenzene

Benzyltrimethylsilane (1.00 g, 6.09 mmol) was added to a 50 mL round bottom flask followed by methyl iodide (4.0 mL, 64.3 mmol). The solution was stirred 5 min. and tetrabutylammonium fluoride (8.0 mL, 8.0 mmol) was added. The solution was stirred 10 hours. Diethyl ether (15 mL) was added and the solution was washed with water. The ether layer was dried over $MgSO_4$, filtered and the solvent removed. Simple distillation gave 0.360 g (51.8%) of ethylbenzene which eluted on gas chromatography with an authentic sample. ^{1}H NMR δ 1.25 (t, 3H); 2.65 (q,2H); 7.10 (m, 5H).

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