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FURTHER STUDIES ON THE SYNTHESIS OF α-FLUORO CARBONYL COMPOUNDS [1]

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SUMMARY

The trimethylsilyl enol ethers of cycloalkanones and acid esters are converted in high yields (70-90%) to the corresponding α-fluoro carbonyl derivative using XeF_2 in CH_2Cl_2. Non-cyclic α-hydroxy ketones such as ethyl mandelate are efficiently transformed to the α-fluoro product by DAST and by Ishikawa's reagent. Nucleophilic displacement of halogen by fluoride failed in cyclic systems, giving instead, α,β-unsaturated ketones in DMF or CH_3CN (18-crown-6) and 1,2-diones in DMSO, with KF acting as a base. Attempts at DMSO oxidation of I(Br)F adducts failed to give the α-fluoro ketones, but resulted in dehydrohalogenation to the trans-vinyl fluorides.

INTRODUCTION

Despite rapid advances during the past thirty years in new methods for the preparation of fluorine-containing organic compounds, there has been, until recently, a paucity of studies directed toward α-fluoro carbonyl compounds. Within the past few years, a number of methods and reagents for the selective introduction of fluorine into carbonyl compounds have been described. Most of these methods have a common feature, viz., the use of reagents which may be loosely termed 'electrophilic' fluorinating agents, e.g., ClO_3F [3,4], CF_3OF

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[5], CF_3CF_2OF [6], XeF_2 [7,8], $CsSO_4F$ [9,10] and 1-fluoro-2-pyridone [11]. A detailed review of α-fluorination of carbonyl compounds is forthcoming [12].

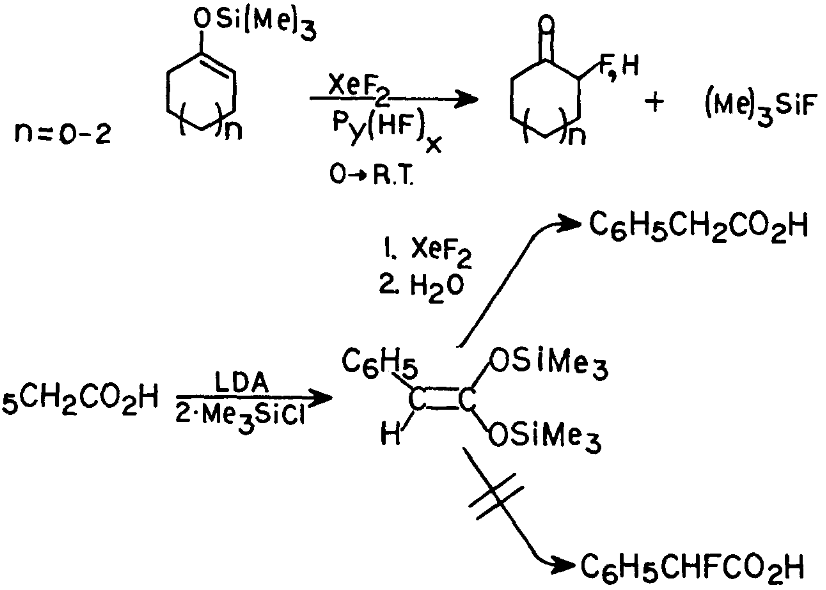
RESULTS AND DISCUSSION

In this study we have focussed our attention on several approaches to α-fluorocycloalkanones and α-fluorobenzeneacetic acid and ethyl ester. The methods examined are adumbrated below:

1. Conversion of $-CH_2C(O)-$ to $-CHFC(O)-$ by reaction of trimethylsilyl enol ethers and xenon difluoride.
2. Conversion of $-CH(OH)C(O)-$ to $-CHFC(O)-$ using DAST and Ishikawa's reagent.
3. Displacement of bromide by fluoride in α-bromo carbonyl compounds.
4. Attempted oxidation of 1-iodo-2-fluoro compounds.

Conversion of $-CH_2C(O)-$ to $-CHFC(O)-$

The trimethylsilyl enol ether of cyclohexanone in dichloromethane reacts with elemental fluorine to regenerate cyclohexanone exclusively. With CF_3OF, 2-fluorocyclohexanone is obtained in high yield, as reported previously [5]. We have now found that xenon difluoride in dry CH_2Cl_2, in the presence of a trace of pyridinium poly(hydrogen fluoride), reacts rapidly at 0-5°C with the trimethylsilyl enol ethers of cyclopentanone, cyclohexanone and 1-indanone to provide 70-90% yields of the corresponding 2-fluorocycloalkanone (Scheme I). As reported previously by Zupan [8], formation of 2-fluorocycloheptanone is accompanied by a substantial yield of cycloheptanone, generated, presumably, by XeF_2 cleavage of the silyl enol ether. We find that the reactivity of the silyl enol ethers toward XeF_2 is greater than the reactivities of the corresponding enamines and enol acetates [8]. Similarly, the silyl enol ether of ethyl benzeneacetate is smoothly converted to $C_6H_5CHFC(O)_2Et$ [5] in 75% yield. However, in contrast to CF_3OF [5] the reaction of XeF_2 with bis(trimethylsilyl)ketene acetal derived from benzeneacetic acid does not afford α-fluorobenzeneacetic acid. Instead, cleavage of the O-silyl group occurs to give benzeneacetic acid.

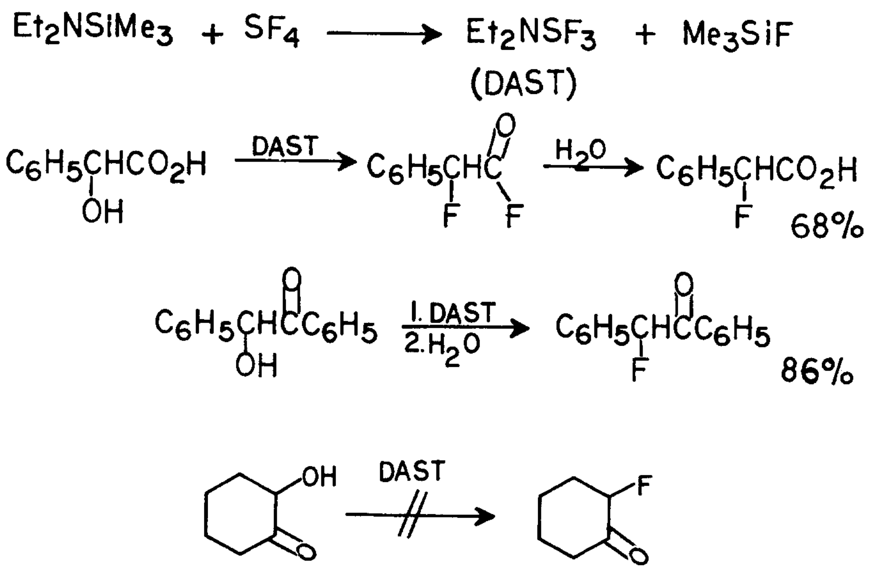


Scheme I

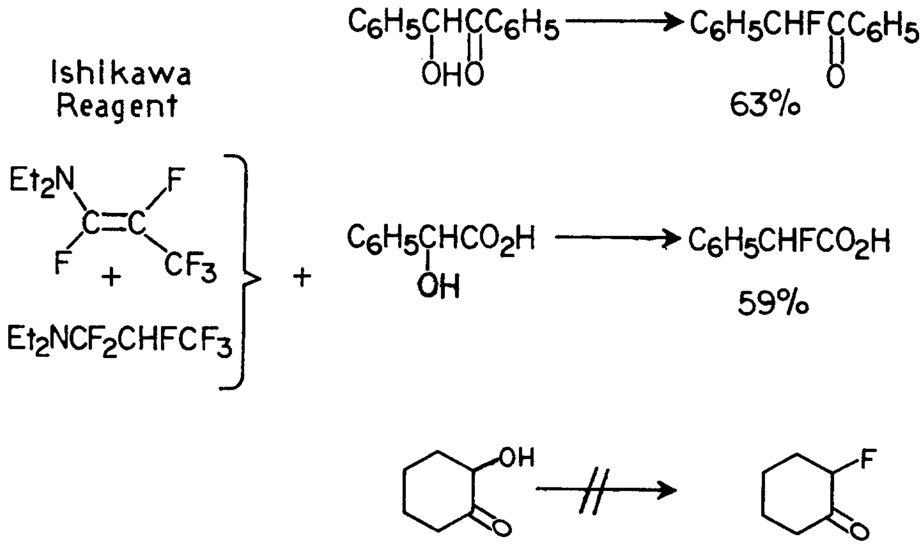
Conversion of -CH(OH)C(O)- to -CHFC(O)-

(Diethylamino)sulfur trifluoride (DAST), $(Et)_2NSF_3$, reacts with both hydroxyl [13] and carbonyl [13,14] groups, but more readily with the hydroxyl. 2-Hydroxycyclohexanone (adipoin) failed to give the fluoro ketone with DAST, but mandelic acid reacted readily to give α-fluorobenzeneacetic acid [5] in 68% yield. Benzoin similarly gives an 86% yield of $C_6H_5C(O)CHFC_6H_5$[5] (Scheme II).

In order to obviate the high cost, the lack of complete structural specificity and the safety factor in the use of DAST, we examined the reaction of α-hydroxy carbonyls with Ishikawa's reagent [15] (Scheme III), which appears to be superior to the fluoroalkylamine (FAR [16,17], Yarovenko [18]) reagent.



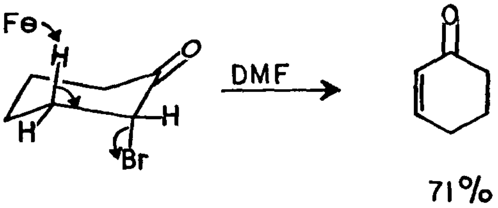
Scheme II



Scheme III

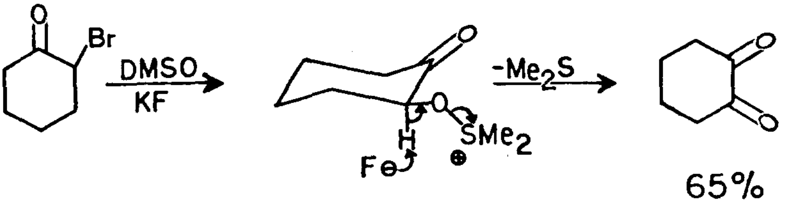
Nucleophilic Displacement of Fluoride in α-Substituted Carbonyl Compounds

In preliminary studies, we attempted to convert 2-bromocyclohexanone to 2-fluorocyclohexanone using KF in dimethylformamide or 'naked' (18-crown-6) fluoride [19] in acetonitrile. The sole product isolated, in good yield, is the elimination product, 2-cyclohexen-1-one, with fluoride behaving as a strong base [20] (Scheme IV). Both the five- and seven-membered analogues react similarly to give the α,β-unsaturated ketones. There is no evidence of a competing displacement reaction. We were surprised, therefore, to note the report [19] that 2-chloro-2-methylcyclohexanone reacted with 'naked' fluoride to yield 2-methylcyclohexen-1-one and 2-fluoro-2-methylcyclohexanone in a 2:1 ratio. We have repeated the experiment and found **no evidence of the fluoro product.** Severe steric restrictions should preclude displacement of a tertiary chloride. If, indeed, the fluoro compound is formed, an electrophile assisted ionization process would be required.



Scheme IV

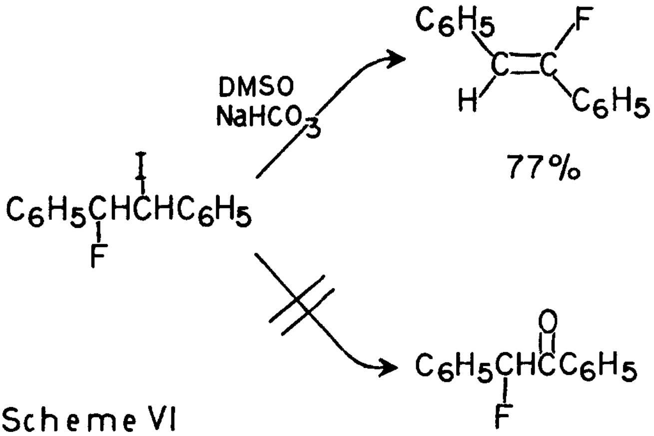
In dimethylsulfoxide, fluoride-mediated oxidation of 2-bromocyclohexanone (Scheme V) leads to a high yield (65%) of 1,2-cyclohexanedione, an excellent new approach to this compound. This behavior is an extension of a previously reported study [21].



Scheme V

Attempted Conversion of Alkenes to 2-Fluoro Ketones *via* 1-Halo-2-fluoro Compounds

The iodide-catalyzed oxidation of 2-bromo ketones by dimethylsulfoxide [21] led us to examine the possibility of oxidizing 1-iodo-2-fluoro-1,2-diphenylethane to the fluoro ketone. Instead of oxidation, the major reaction pathway is dehydrohalogenation to the *trans*-vinyl fluoride (Scheme VI).



Scheme VI

EXPERIMENTAL

General

^{1}H NMR spectra were taken on a Varian T-60 at 60 MHz with tetramethylsilane (δ 0.0) as the internal standard. ^{19}F-NMR spectra were recorded on a JEOL FX-90Q spectrometer at 84.6 MHz in $CDCl_3$ solution with $CFCl_3$ (ϕ 0.0) as the internal reference. The infrared spectra of neat liquids or solids (KBr) were recorded on a Pye-Unicam 3-300 spectrophotometer calibrated with polystyrene. Melting points (uncorrected) were determined with a Melt-Temp capillary apparatus. Microanalyses were carried out by Micro-Tech Laboratory of Skokie, Illinois. XeF_2 was supplied from PCR and other reagents were purchased from Aldrich Chemical Company. Silica Gel G(Type 60) purchased from EM Reagents was used in chromatography. Dry dichloromethane was obtained by distilling under N_2 over calcium hydride. Dry THF was distilled from potassium-benzophenone under N_2. DMF was distilled under reduced pressure from CaH_2 and stored over dried molecular sieves (4Å, 10-16 mesh). Acetonitrile, HPLC grade, and DMSO, reagent grade, were dried over molecular sieves. The KF used in this study was commercial anhydrous which was additionally dried (180°C, 0.05 mm Hg) for 8 h prior to use.

The following experiments exemplify each category of reaction.

2-Fluoroindanone

The previously reported trimethylsilyl enol ether of 1-indanone [22] was prepared by the method of House [23]. To a polyethylene bottle containing a 5 ml solution of XeF_2 and a catalytic amount of pyridinium poly(hydrogen fluoride) in dry dichloromethane, was added the silyl enol ether (0.66 g, 3.2 mmol) in 2 ml of dichloromethane. The reaction mixture was maintained at 0-5°C for a period of 2 h and allowed to warm to room temperature over a one hour period. At the end of this time, the mixture was poured into a saturated solution of $NaHCO_3$ and extracted. The dichloromethane layer was extracted with 10 ml of water and dried over $MgSO_4$. After filtration, the dichloromethane was removed under reduced pressure. The resultant light yellow oil was chromatographed on silica gel using hexanes as eluent. The major fraction collected was sublimed at room temperature (0.5 mm Hg) to give a crystalline solid. Upon recrystallization from 95% ethanol, α-fluoroindanone (0.47 g, 2.8 mmol) was collected and identified by its m.p. (59°C), spectral characteristics [24] and analysis (Calculated for C_9H_7FO: C, 72.00; H, 4.70; F, 12.65. Found: C, 71.70; H, 4.66; F, 12.74.).

α-Fluorobenzeneacetic acid

A solution of 2-hydroxybenzeneacetic acid (1.40 g, 9.21 mmol) in 3 ml of dichloromethane was slowly added to a stirred solution of DAST (Aldrich) (3.0 g, 19 mmol) in 6 ml of dichloromethane contained in a polyethylene bottle under N_2 at -78°C. Once the addition was complete, the solution was allowed to warm to room temperature. The reaction mixture was added to 50 ml of cold water, stirred several hours, extracted (2x10 ml of water), and then dried over $MgSO_4$. The volatile components were removed under reduced pressure. From the remaining yellow oil, an off-white solid was sublimed (rt, 0.1 mm Hg). Recrystallization from 95% ethanol gave α-fluorobenzeneacetic acid (0.98 g, 6.3 mmol), m.p. 74-76°C (m.p. 75-77°C [5]) for a 68% yield.

α-Fluorodeoxybenzoin

Into a stirred solution of benzoin (4.22 g, 19.9 mmol) in 8 ml of dry dichloromethane at 0-5°C, was slowly added Ishikawa's reagent [25] (4.5 g) in 4 ml of dichloromethane. Stirring of the reaction mixture under N_2 was continued at this temperature for 12 h. At the end of this period, the reaction mixture was poured into 25 ml of water and extracted with 2x15 ml of saturated $NaHCO_3$, dried over $MgSO_4$ and filtered. Upon removal of the dichloromethane, a yellow oil remained. Distillation gave N,N-diethyl-2,3,3,3-tetrafluoropropionamide [15] (b.p. 42-45°C, 0.5 mm Hg) in the first fraction. α-Fluorodeoxybenzoin [17] distilled at b.p. 140-143°C (0.5 mm Hg). Flash-chromatography using hexanes as the eluent followed by recrystallizations from 95% ethanol afforded white crystals of the product (2.68 g, 12.6 mmol, 63%), m.p. 60-62°C (m.p.62°C [17]).

2-Cyclohexen-1-one

Potassium fluoride (4.0 g, 69 mmol) was added under N_2 to 25 ml of DMF contained in a 50 ml three-necked flask. The solution was heated to 95°C with 2-bromocyclohexanone (6.07 g, 34.3 mmol) introduced by syringe over a period of 15 min. The reaction was monitored by ^1H NMR at 1 h intervals. After 6 h, the mixture was allowed to cool to room temperature. The solution was slowly poured into a 500 ml beaker containing 100 ml of 2% sulfuric acid and 100 ml Et_2O. After a 4 h period, the remaining ether was extracted and saved. The aqueous layer was extracted with 4x15 ml portions of ether. The combined ether extracts were extracted with 2x20 ml of a saturated NaCl solution and 15 ml of saturated $NaHCO_3$ solution. The ether layer was dried over Na_2SO_4 and evaporated under reduced pressure. The remaining light yellow oil was distilled (b.p. 42-45°C, 5 mm Hg) to give 2-cyclohexen-1-one (2.34 g, 24.4 mmol) identified by comparison of physical and spectral properties with that of a commercial sample. The overall yield from the bromo ketone was 71%.

1,2-Cyclohexanedione

Potassium fluoride (3.5 g, 60.3 mmol) was added to 75 ml of DMSO under N_2. Once the stirred solution was preheated to 85°C, 2-bromocyclohexanone (5.56 g, 31.4 mmol) was added. After stirring for 5 h, the mixture was allowed to cool to room temperature and then poured into 200 ml of an ice-cooled, saturated NaCl solution. The resulting solution was extracted with Et_2O (4x50 ml). The combined ether layers were washed with water (75 ml), $NaHCO_3$ (75 ml), saturated NaCl (75 ml), dried over Na_2SO_4 and filtered. After evaporation of the ether under reduced pressure, a yellow oil remained. The oil was flash-chromatographed on silica gel using hexanes:dichloromethane (2:1) as eluent. and subsequently distilled (b.p. 42-45°C, 2 mm Hg) , to give a clear oil which solidified upon standing, m.p. 33-35°C (m.p. 34°C [26]). Spectral properties were consistent with an authentic sample (Aldrich). 1,2-Cyclohexanedione (2.27 g, 20.3 mmol) was synthesized in 65% overall yield.

Trans-1-fluoro-1,2-diphenylethene

1-Iodo-2-fluoro-1,2-diphenylethene was prepared by the procedure of Olah [27] from *trans*-stilbene. The adduct (3.45 g, 10.6 mmol) was placed into a stirred solution of $NaHCO_3$ (1.26 g) in 15 ml of DMSO heated to 85°C. The solution was stirred for 3 h during which time there was a slow evolution of gas. The reaction mixture underwent a similar workup as with 1,2-cyclohexanedione. Flash-chromatography using hexanes as eluent afforded a white solid. Recrystallization from 95% ethanol gave the product, *trans*-1-fluoro-1,2-diphenylethene, (1.60 g, 8.08 mmol), m.p. 94°C (m.p. 94-95°C [28]), having spectral properties as reported [28]. The yield from the IF adduct was 77%.

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