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α-FLUORINATION OF β-KETO SULFOXIDES

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SUMMARY

We have developed an efficient new procedure for α-fluorination of β-keto sulfoxide enolate anions which are generated in situ via nucleophilic addition reactions to cyclopentenone sulfoxide 7. Perchloryl fluoride is used as the fluorinating agent. Characterization of the product α-fluoro β-keto sulfoxides includes ^{19}F NMR spectroscopy.

INTRODUCTION

Remarkable enhancement in the biological activity of steroid hormones is observed often upon introduction of a fluorine atom at various sites in the steroid backbone. Furthermore, substitution at steroid position 13 is known to be important for effective contraceptive activity as exemplified by the 13-ethyl estrone, norgestrel. A report by a pharmaceutical company documents an unsuccessful attempt to prepare a 13-fluoro estrone [1]. We envisioned preparation of 13-fluoro dehydroestrone 1 via the intermediate fluoroenolate ion 2. A Michael reaction of enolate 2 with vinyltriphenylphosphonium bromide would generate a phosphonium ylide which would then undergo a spontaneous

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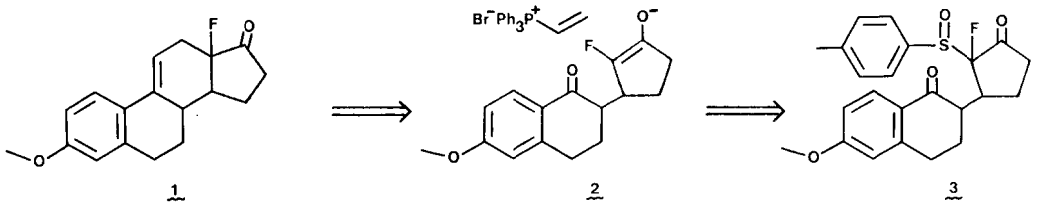
intramolecular Wittig closure (a general reaction sequence we have recently developed) [2]. α-Fluoro β-keto sulfoxide 3 was expected to lead to fluoroenolate ion 2 via reductive cleavage of the carbon-sulfur bond (Scheme I) [3]. In addition, we planned preparation of the 13-fluoro estrone 1' via intramolecular 4+2 cycloaddition of the fluorinated orthoquinodimethane 4 [4]. Intermediate 4 would be formed from fluoro enolate ion 5 generated by reductive removal of the sulfinyl moiety from the α-fluoro β-keto sulfoxide 6 (Scheme II). We report here the successful execution of the first steps of these retrosynthetic schemes: synthesis and ^{19}F NMR characterization of α-fluoro β-keto sulfoxides 3 and 6 via the reactions depicted in equations 1 and 2. Equations 1 and 2 represent efficient, one-pot, tandem β-addition α-fluorination reactions to an α,β-unsaturated ketone (i.e. cyclopentenone sulfoxide 7) and illustrate, for the first time, an effective procedure for α-fluorination of β-keto sulfoxides.

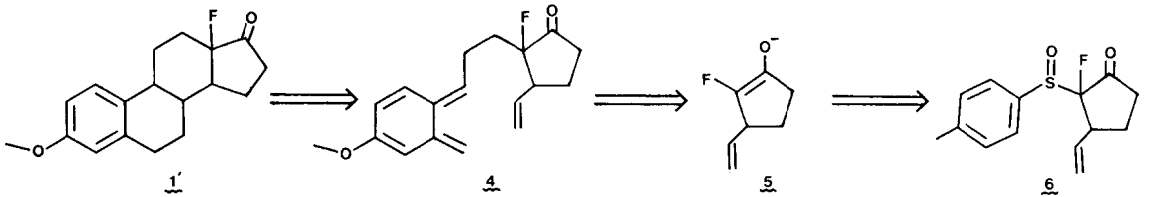
RESULTS AND DISCUSSION

α-Fluoro β-keto sulfoxide 3 was prepared in the following manner (eqn. 1). Cyclopentenone sulfoxide 7 in THF was allowed to react with the enolate ion of 6-methoxytetralone which had been generated by the treatment of 6-methoxytetralone trimethylsilyl enol ether 8 with methyllithium [2]. Perchloryl fluoride* was then added to the resultant enolate ion 9 yielding 3 in 80% chemical yield after chromatography. α-Fluoro β-keto sulfoxide 3 was relatively unstable at room temperature for prolonged periods of time; therefore, the corresponding sulfone 10 was prepared by meta-

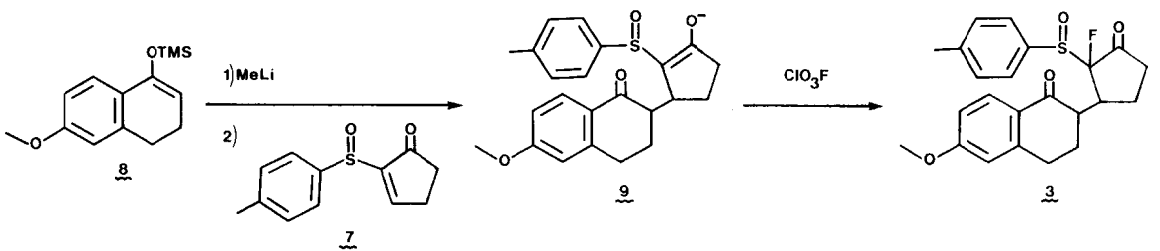
*Perchloryl fluoride is potentially very dangerous. Before undertaking any reactions using this reagent, handling and safety information should be obtained from the distributor!



SCHEME I



SCHEME II

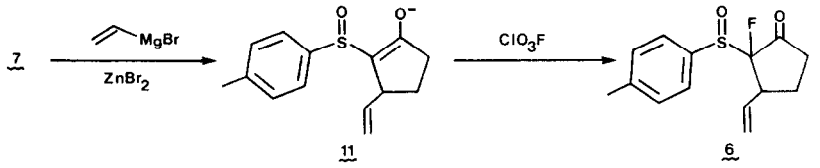


(1)

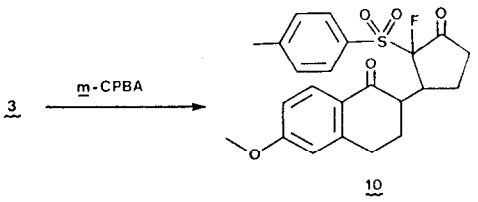
chloroperoxybenzoic acid oxidation [1] (eqn. 3) in 87% yield. The ^{19}F NMR spectrum of 10 showed a doublet (δ 152.750, J = 18.311 Hz) which collapsed to a singlet upon irradiation of the proton region.

α-Fluoro β-keto sulfoxide 6 was prepared in a manner similar to that of 3 (eqn. 2). Divalent zinc-coordinated cyclopentenone sulfoxide 7 was treated with vinylmagnesium bromide. The resultant enolate ion 11 was treated with perchloryl fluoride giving the fluoro sulfoxide 6 in 39% yield after chromatography. A singlet was observed in the proton decoupled ^{19}F NMR spectrum, while the undecoupled spectrum showed a doublet (δ 161.412, J = 18.311 Hz). The ^{13}C-^{19}F coupling constant of 6 was found to be 246.6 Hz. The resonance attributed to the carbon with the attached fluorine atom was verified by gated decoupling experiments.

α-Fluoro ketones exhibit an α-polar group effect in their infrared spectra; the carbonyl absorption for the α-fluoro compound is observed at a higher wavenumber than that for the α-proton species. In the cases of α-fluoro ketones 3 and 6, a higher wavenumber shift was indeed observed for both the carbonyl and the sulfoxide absorptions (Table 1).



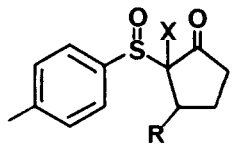
(2)

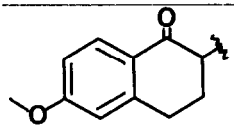


(3)

TABLE 1

Polar Group Effect in the IR



R	X=H	X=F
	1736 cm^{-1} (C=O) 1020 cm^{-1} (S=O)	1758 cm^{-1} (C=O) 1040 cm^{-1} (S=O)
vinyl	1740 cm^{-1} (C=O) 1040 cm^{-1} (S=O)	1750 cm^{-1} (C=O) 1050 cm^{-1} (S=O)

Generation of enolate ions 2 and 5 via reductive cleavage of the carbon-sulfur bonds of α-fluoro β-keto sulfur compounds 3, 6, and 10 is currently under study in our laboratories.

EXPERIMENTAL

Melting points were determined using a Mel-Temp melting point apparatus; melting points are uncorrected. IR spectra were recorded on a Perkin Elmer 599B spectrometer. ^{1}H NMR were obtained using a Varian CFT-20 or a Bruker 300 spectrometer at 80 or 300 MHz, respectively. ^{19}F NMR spectra were recorded using a Bruker 300 spectrometer. ^{19}F Chemical shifts (δ) are reported in ppm downfield from $CFCl_3$. ^{13}C NMR spectra were obtained using a Varian XL-400 spectrometer at 100 MHz. Mass spectra were obtained by the Middle Atlantic Regional Facility, The Johns Hopkins University, Baltimore, Maryland.

Medium pressure liquid chromatography (MPLC) was performed using an apparatus described by Meyers [5]. Analytical thin layer chromatography (TLC) was performed on Machery-Nagel Polygram Silica G/UV 254 pre-coated plastic sheets.

The following reagents were purchased from Aldrich Chemical Company and were distilled or recrystallized prior to use: 6-methoxytetralone, diisopropylamine, trimethylsilyl chloride, and vinyl bromide. m-Chloroperoxybenzoic acid, n-butyllithium, and low-halide methyllithium were purchased from Aldrich Chemical Company and used as received. Perchloryl fluoride was obtained from Ozark-Mahoning, Inc. Zinc dibromide was purchased from Alfa-Ventron, Inc. and used as received.

The vinylmagnesium bromide was titrated with sec-butanol in xylenes using 1,10-phenanthroline as the indicator. The methyllithium was titrated using diphenylacetic acid as the indicator. The zinc dibromide was dissolved in anhydrous THF and used as a solution of known concentration. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl.

2-Fluoro-2-(p-tolylsulfinyl)-3-(6-methoxytetralonyl)cyclopentanone 3

An oven and flame dried 100 mL 1-necked round bottomed flask equipped with a magnetic stirring bar, a septum, and a gas-needle inlet was charged with freshly Kugelrohr distilled (90°C/0.05 mm Hg) 6-methoxytetralone trimethylsilyl enol ether 8 [2] (0.86 g, 3.45 mmol), flushed with argon, dissolved in 25 mL dry THF, and cooled to 0°C. Methyllithium (2.5 mL, 1.5 M, 1.52 mmol) was added slowly dropwise. This solution was stirred at 0°C for 30 min, allowed to warm to room temperature and stirred for 1 hour, and then cooled to -78°C. A -78°C THF solution (40 mL) of (S)-(+)-2-(p-tolylsulfinyl)-2-cyclopentenone 7 [6] (0.54 g; 2.46 mmol) was added dropwise to the above enolate ion via a cannula and the solution was stirred at -78°C for 2.5 hours. The mixture was warmed to -20°C and diluted with 10 mL dry THF.

Perchloryl fluoride was then bubbled through the solution for 10 min. and the entire apparatus flushed well with argon. Aqueous saturated NaH_2PO_4 solution was added and the mixture allowed to warm to room temperature. The THF was removed by rotary evaporation and the residues extracted well with diethyl ether. The combined ether layers were dried with anhydrous $MgSO_4$ and filtered. Rotary evaporation and MPLC purification (SiO_2, 25 x 300 mm column, 5% acetone in benzene, R_f 0.18) gave 0.817 g (80%) of 3 as a pale yellow crystalline solid: mp 119.5-120.0°C (decomp.); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.955 (d, J = 8.456 Hz, 1H), 7.44 (dd, J = 8.089 and 63.976 Hz, 4H), 6.90-6.68 (m, 2H), 3.855 (s, 3H), 3.45-3.57 (m, 1H), 3.20-2.05 (m, 12H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ 152.750 (d, J = 18.260 Hz); IR ($CHCl_3$, cm^{-1}) 3100-2820 (m), 1758 (s), 1671 (s), 1600 (s), 1495 (m), 1452 (m), 1405 (m), 1350 (m), 1310 (m), 1300-1180 (s), 932 (m), 890 (M), 842 (m), 812 (m), 630 (m); Mass Spec. (70 eV, m/e) 414 (M^+), 91 (base, p-tolyl$^+$).

2-Fluoro-2-(p-tolylsulfinyl)-3-vinylcyclopentanone (6)

An oven and flame dried 50 mL 2-necked round bottomed flask with a magnetic stirring bar, a septum, a stopcock-gas outlet, and a gas-needle inlet (for ClO_3F) was charged with 7 (0.10 g, 0.47 mmol) and flushed with argon. A THF solution of zinc dibromide (0.24 mL, 2.0 M, 0.47 mmol) was added, the resultant solution was stirred at room temperature for 10 min., diluted with 6 mL dry THF, and cooled to -78°C. Vinylmagnesium bromide (0.35 mL, 1.5 M, 0.50 mmol) was added slowly dropwise and the mixture stirred at -78°C for 1.5 hours. The reaction was then warmed to -20°C and perchloryl fluoride was bubbled through the solution for 5 min.; saturated aqueous NaH_2PO_4 solution was added and the reaction warmed to 0°C. The THF was removed by rotary evaporation at 0°C and the residues extracted well with 0°C diethyl ether. The combined diethyl ether layers were dried with anhydrous $MgSO_4$. Filtra-

tion, rotary evaporation, and MPLC purification (SiO_2, 25 x 300 mm column, 2:1:1 hexane:diethyl ether:methylene chloride, R_f 0.42) gave 48.2 mg (39%) of 6 as a white crystalline solid: mp 77.0-77.5°C, ^1H NMR ($CDCl_3$, 300 MHz) δ 7.47-7.27 (m, 4H), 6.51-6.39 (m, 1H), 5.55-5.48 (m, 2H), 3.36-3.33 (m, 1H), 2.53-1.25 (m, 7H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ 161.412 (d, J = 18.311 Hz); ^{13}C NMR ($CDCl_3$, 100 MH_3) δ 142.95, 134.06, 132.69, 129.42, 125.58, 120.56, 105.09 (d, J = 246.6 Hz), 47.73, 35.41, 21.48, 21.34; IR ($CHCl_3$, cm^{-1}) 3100-2820 (m), 1700 (s), 1640 (m), 1595 (m), 1480 (m), 1456 (m), 1396 (m), 1285 (m), 1082 (s), 1050 (s), 1019 (s), 995 (m), 935 (m), 810 (m); Mass Spec. (70 eV, m/e) 266 (M^+), 246 (20% M^+-HF), 139 (base, p-tolylSO$^+$.), 91 (70%, p-tolyl$^+$); HRMS (70 eV, m/e) 266.0774 (calc. 266.0776).

2-Fluoro-2-(p-tolylsulfonyl)-3-(6-methoxytetralonyl)cyclopentanone 10.

A 25 mL 2-necked round bottomed flask was charged with 3 (0.599 g, 1.4 mmol) and vacuum dried (0.05 mm Hg) for 30 min, and opened under argon. Methylene chloride was added via syringe. This solution was transferred dropwise via a cannula to a briskly stirred solution of m-chloroperoxybenzoic acid (4.94 g, 71%, 2.03 mmol) in 30 mL dry CH_2Cl_2 under argon. The resultant mixture was stirred at room temperature for 3 hours 20 min. Aqueous saturated $NaHCO_3$ solution was added, the CH_2Cl_2 layer removed and washed well with aqueous saturated $NaHCO_3$ solution. The combined $NaHCO_3$ layers were back extracted with CH_2Cl_2 and the combined organic layers dried with anhydrous $MgSO_4$. Filtration, rotary evaporation, and MPLC purification (SiO_2, 25 x 300 mm column, 5% acetone in benzene, R_f 0.33) gave 0.529 g (87%) of 10 as a white crystalline solid: mp 180.0-181.0°C; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.94 (d, J = 8.5 Hz, 1H), 7.53 (dd, J = 7.9 and 26.8 Hz, 4H), 6.89-6.68 (m, 2H), 3.85 (s, 3H), 3.73-3.12 (m, 1H), 3.09-2.16 (m, 13H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ 152.750 (d, J = 18.311 Hz); IR ($CHCl_3$, cm^{-1}) 3100-2820 (m), 1763 (s), 1678 (s), 1601

(s), 1495 (m), 1460 (m), 1403 (w), 1333 (s), 1280-1200 (s), 1153 (s), 1080 (m), 1020 (m), 932 (m), 586 (m); Mass Spec. (70 eV, m/e) 430 (M^+), 275 (32%, M^+-p-tolylSO$_2^+$), 176 (base, 6-methoxytetralone), 69 (68%); HRMS (70 eV) 430.1243 (calcd. 430.1250).

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