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SYNTHESIS AND INTRAMOLECULAR CYCLISATION OF ortho-HYDROXY--2,3,3,3-TETRAFLUOROPROPIOPHENONE. FORMATION OF 3-FLUORO--4-HYDROXYCOUMARIN

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SUMMARY

Acidic hydrolysis of 1-(o-methoxyphenyl)pentafluoropropene 1 gave o-hydroxy-2,3,3,3-tetrafluoropropiophenone 2 and o-methoxy-2,3,3,3-tetrafluoropropiophenone 3. Compound 2 when treated with aqueous potassium hydroxide or methanolic sodium methoxide gave 3-fluoro-4-hydroxycoumarin 4. Structure of 4 has been established by spectral means and some chemical reactions. The cyclisation mechanism of 2 is discussed.

INTRODUCTION

Recently, an improved synthesis of 1-phenylpentafluoropropene and a number of its para- and ortho-substituted derivatives has been reported [1] . Acidic hydrolysis of 1-(o-methoxyphenyl)pentafluoropropene 1 expected to give the corresponding o-hydroxyphenyl alkene failed but an interesting compound, viz. o-hydroxy-2,3,3,3-tetrafluoropropiophenone 2 was obtained instead. This paper sets out to describe the unusual cyclisation of compound 2.

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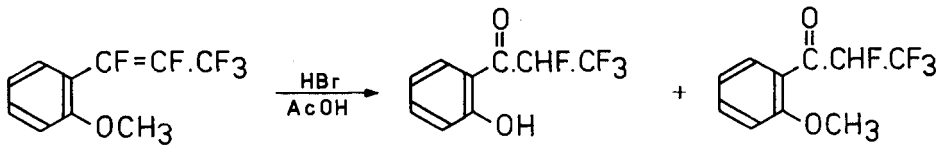
RESULTS AND DISCUSSION

Treatment of 1-(o-methoxyphenyl)pentafluoropropene 1 [1] with a mixture of hydrobromic and acetic acids at 100° gave a mixture of o-hydroxy-2,3,3,3-tetrafluoropropiophenone 2 and o-methoxy-2,3,3,3-tetrafluoropropiophenone 3 in the 1 : 2.25 ratio, but at 140° compound 2 was obtained as the only product, in high yield.



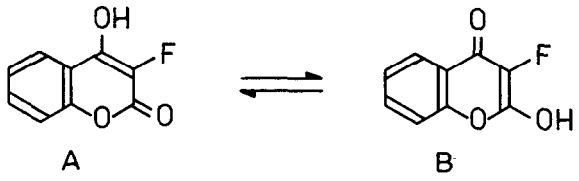
1 2 3

at 100°: 2 (22 %) and 3 (49 %)
at 140°: only 2 (86 %)

These results have shown that under acidic conditions the vinylic α-fluorine in 1 hydrolyses more readily than does the methoxy group. An easy loss of α-fluorine from 1 could be attributed to the resonance effect of an electron-donating substituent on the benzene ring, which increases the electron density at the α-carbon of the olefinic part of the molecule. It has been reported [2] that 1-(p-aminophenyl)pentafluoropropene was hydrolysed readily in an acidic medium to give the corresponding tetrafluoropropiophenone, while hydrolysis of the α-fluorine of unsubstituted 1-phenylpentafluoropropene requires much more drastic conditions.

o-Hydroxy-2,3,3,3-tetrafluoropropiophenone 2, when dissolved in an equimolar amount of aqueous potassium hydroxide or methanolic sodium methoxide, forms yellow solutions of its sodium salt from which compound 2 may be fully recovered after acidification. However, when an excess of the base was added,

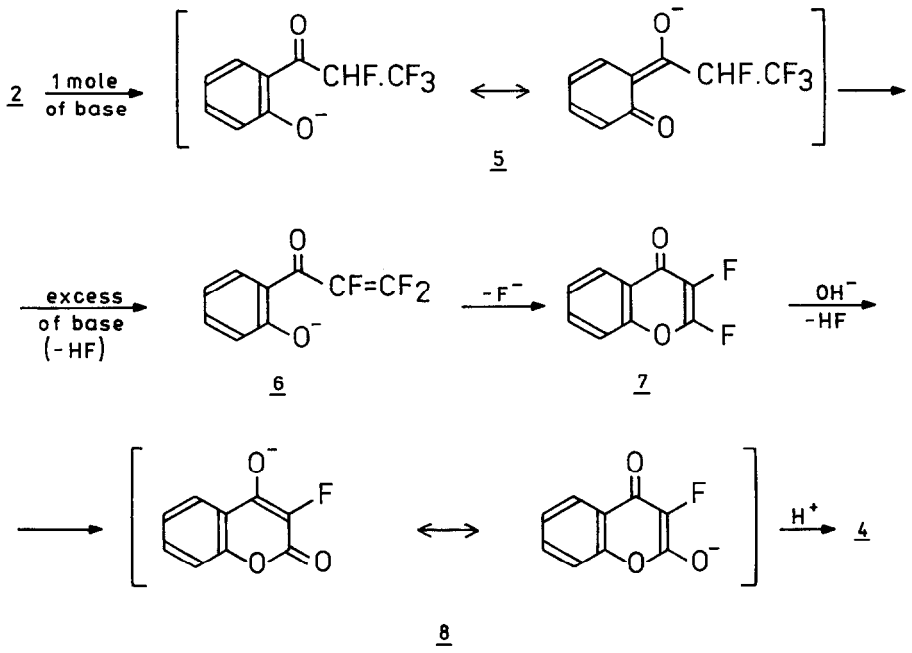
the solutions turned purple (in water) or green (in methanol), and after acidification a white precipitate was formed; this precipitate was identified as 3-fluoro-4-hydroxycoumarin 4 .



4

The structure of compound 4 has been confirmed on the basis of spectral data. The mass spectrum showed an $[M]^{+\cdot}$ ion of very high intensity and very intense ions $[C_7H_5O_2]^+$ and $[C_7H_4O_2]^+$ formed by elimination of C_2FO and C_2FHO fragments respectively. The IR spectrum in the solid state showed very broad absorption of a strongly hydrogen-bonded OH groups, centered at ca.3050 cm^{-1}. In diluted solutions (0.5% in $CHCl_3$ or CS_2) a sharp band of the free OH group appeared at 3580 cm^{-1}. The IR spectra of 4 in the solid state and in solutions also differ significantly in the regions of carbonyl and heterocyclic skeleton vibrations. By analogy to the spectra of 4-hydroxycoumarin [3,4,5] it may be assumed that compound 4 exists in two tautomeric forms A and B. ^1H NMR spectrum at 20° did not show the OH group signal, but at 60° a broad signal appeared at 2.1 ppm ; this signal sharpened with the increased temperature, which points out to the existence of a slowly established equilibrium between the A and B forms of compound 4 . ^{19}F NMR spectrum exhibited a singlet at 167-169 ppm, which slightly varied with a solvent used.

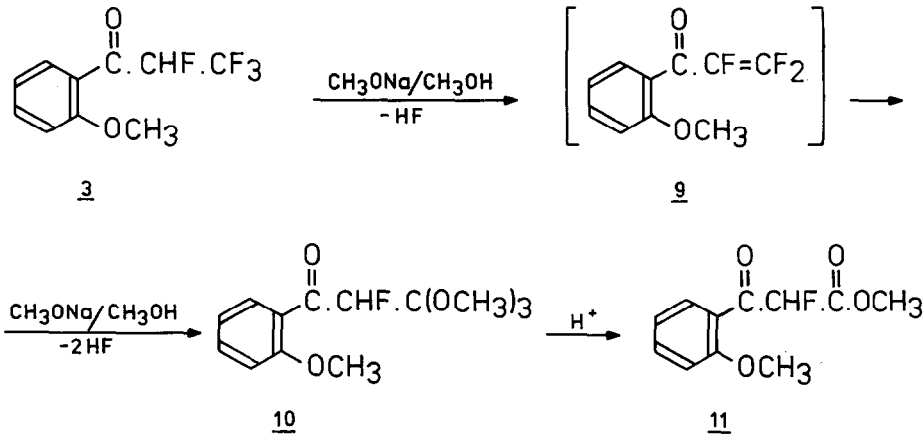
Cyclisation of o-hydroxytetrafluoropropiophenone 2 to form the fluorocoumarin 4 must be a multistep process, which results in total defluorination of the CF_3 group. The following reaction pathway may be considered:



The reaction pathway is difficult to follow because any intermediates are more reactive than is the substrate so, under a variety of the base concentrations, only final product and unreacted substrate were isolated. Nevertheless, there is evidence that the $COCHCF_3$ group when treated with a base is dehydrofluorinated to form an intermediate of the type 6, which is readily attacked by an excess of a base. Thus, o-methoxytetrafluoropropiophenone 3 reacted with methanolic sodium methoxide to give orthoester 10 ; this reaction must involve intermediate vinyl ketone 9*. Compound 10 is stable in alkaline and neutral media, but hydrolyses rapidly in diluted acids to give methyl o-methoxybenzoylfluoroacetate 11 .

Formation of an orthoester from 6 would not lead to any cyclic product, so it seems reasonable that carbanion 6 cyclises prior to the attack by the hydroxide or methoxide ion,

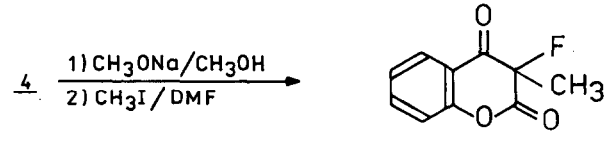
* Vinyl ketones were suggested by Ishikawa et al. as intermediates in dehydrofluorination of $PhCOCHFCF_3$ and $PhCOCHFCClF_2$ [6] .



3 9 10 11

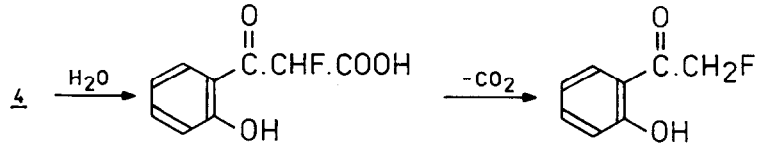
although no evidence has been obtained for the formation of the cyclic intermediate 7 . Carbanions 5 and 8 were observed in the reaction mixture by the ^{19}F NMR spectroscopy. The spectrum of an equimolar methanolic solution of compound 2 and sodium methoxide was identical with that of neat 2 with the CHF group signal being slightly shifted upfield. When an excess of the base was added the spectrum showed only a singlet at 186.4 ppm, identical with a signal of methanolic solution of the sodium salt of 3-fluoro-4-hydroxycoumarin.

The sodium salt of 3-fluoro-4-hydroxycoumarin, prepared by evaporation of an equimolar methanolic solution of coumarin 4 and sodium methoxide, was methylated with methyl iodide in dimethylformamide; C-methylation took place exclusively to give 3-fluoro-3-methyl-benzo-2,4-pyrandione 12 . ^{19}F and ^{1}H NMR spectra of 12 showed a coupling between the fluorine atom and the CH_3 group with a coupling constant value of 6.2 Hz. The IR spectrum showed two strong bands in regions typical for carbonyl groups of ketones and lactones.



12

Coumarin 4, when refluxed with water undergoes hydrolytic ring opening and decarboxylation to give o-hydroxy-fluoroacetophenone 14, probably via β-ketoacid 13 .



13 14

Formation of compounds 12 and 14 gave additional evidence for the structure of 3-fluoro-4-hydroxycoumarin 4 .

EXPERIMENTAL

Melting and boiling points are uncorrected. NMR spectra were recorded with a JEOL JNM-4H-100 spectrometer; chemical shifts are in ppm from internal CCl_3F for ^{19}F spectra (positive upfield) and from internal TMS for ^{1}H spectra (positive downfield). Mass spectra were obtained with an Analytical GCMS System LKB-2091 and IR spectra were recorded on a Beckmann IR 4240 spectrometer. GLC analyses were performed with a Chromatron GCHF.18.3.4 instrument (GDR) using a 3.5 m x 4 mm column packed with Chromosorb G coated with 3 % silicon oil SE-52.

1-(o-Methoxyphenyl)pentafluoropropene 1 was prepared according to the technique developed in this Laboratory [1] .

o-Hydroxy-2,3,3,3-tetrafluoropropiophenone 2 (nc)

Reactions were run in a 300 ml capacity pressure glass tube fitted with a 'Rotaflo' valve.
a) 1-(o-Methoxyphenyl)pentafluoropropene 1 (27 g, 0.113 mole), acetic acid (80 ml), and 40 % hydrobromic acid (60 ml) were placed in the reaction tube, the tube was wrapped with flexible heating tape and shaken mechanically at 100° for 36 hours. After the reaction had run to completion, the tube was allowed

to cool to ambient temperature and the reaction mixture was diluted with two volumes of water, and extracted twice with chloroform. The combined extracts were dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was shown by GLC to consist of three components, which were later identified by comparison of their retention times with those of authentic samples as unreacted 1 (29%), o-hydroxy-2,3,3,3--tetrafluoropropiophenone 2 (22%), and o-methoxy-2,3,3,3--tetrafluoropropiophenone 3 (49%).

b) Compound 1 (45 g, 0.155 mole), acetic acid (120 ml), and 40% hydrobromic acid (100 ml) were reacted at 140° for 30 hours and worked up as above. The crude reaction product, after removal of the solvent, was shown by GLC to consist practically of a single compound. Vacuum distillation gave 30 g (yield 86%) of a yellowish liquid with typical phenolic smell. The compound was identified as o-hydroxy-2,3,3,3-tetrafluoropropiophenone 2. GLC purity was better than 96%. B.p. = 104-108°(16 mmHg). Calculated for $C_9H_6F_4O_2$: C, 48.7; H, 2.7; F, 34.2%. Found: C, 48.8; H, 2.8; F, 34.1%. ^1H and ^{19}F NMR (neat): δ (OH) = 11.4 ppm (s), δ (C$\underline{H}$F) = 6.05 ppm (dq), $\phi(CF_3)$ = 74.7 ppm (dd), ϕ(CH$\underline{F}$) = 201.4 ppm (dq), $^2J(HF)$ = 45.5 Hz, $^3J(HF)$ = 6.3 Hz, $^3J(FF)$ = 12.6 Hz. IR (film): ν(OH) = 3290 cm^{-1}(br), ν(CO) = = 1660 cm^{-1}(vs) (1665 and 1646 cm^{-1} as 0.5% solution in CCl_4).

The OH group stretching frequency is practically independent of concentration indicating strong internal hydrogen bonding to the carbonyl group.

Synthesis of o-methoxy-2,3,3,3-tetrafluoropropiophenone 3 (nc)

Compound 3 was obtained from 1-(o-methoxyphenyl)pentafluoropropene 1 (20 g, 0.084 mole) *via* reaction with ethanolic sodium ethoxide and subsequent treatment of the resulting mixture of 1-ethoxy and 2-ethoxy-substituted alkenes with concentrated hydrochloric acid at 20°. Distillation of the final mixture of products gave, besides 2-ethoxy-1-(o-methoxyphenyl)-1,3,3,3-tetrafluoropropene, o-methoxy-2,3,3,3-tetrafluoropropiophenone 3 in a 25.2% yield. M.p. = 29-30°. Calculated for $C_9H_8F_4O_2$: C, 50.7; H, 3,3; F, 32.4 %. Found: C, 50.8; H, 3.3; F, 32.3 %. ^1H and ^{19}F NMR (in CCl_4): δ (OCH_3) = 3.88 ppm (s), δ (C$\underline{H}$F) = 6.37 ppm (dq), $\phi(CF_3)$ = 74.7 ppm (dd), ϕ(CH$\underline{F}$) =

203.7 ppm (dq), $^{2}J(HF)$ = 45.4 Hz, $^{3}J(HF)$ = 6.75 Hz, $^{3}J(FF)$ = 11.5 Hz. IR(film): ν(CO) = 1700 cm^{-1}(vs).

3-Fluoro-4-hydroxycoumarin 4 (nc)

a) A solution of sodium methoxide prepared from 2.3 g (0.1 mole) of sodium metal and 30 ml of methanol was slowly added to a stirred solution of o-hydroxy-2,3,3,3-tetrafluoropropiophenone 2 (4.44 g, 0.02 mole) in 20 ml of methanol. The reaction mixture was stirred at ambient tenperature for 2 hrs and then most of the methanol was removed under vacuum. the residue was dissolved in 100 ml of water, filtered to remove the fine precipitate of sodium fluoride, and the fitrate was acidified with hydrochloric acid. A white precipitate of 3-fluoro-4-hydroxycoumarin 4 was filtered off, washed with cold water and dried over P_2O_5 (yield 3.1 g, 85 %). The product was recrystallised from CH_3OH-H_2O (1:1). M.p. = 203-204°. Calculated for $C_9H_5FO_3$: C, 60.0; H, 2.8; F, 10.6 %. Found: C, 59.9; H, 2.7; F, 10.7 %. MS: 180(92.5%)$[M]^{+\cdot}$, 121(100%)$[C_7H_5O_2]^{+}$, 120(36%)$[C_7H_4O_2]^{+}$, 104(10%)$[C_7H_4O]^{+}$, 93(19.5%)$[C_6H_5O]^{+}$, 92(10.5%)$[C_6H_4O]^{+}$. ^{19}F NMR: ϕ(F) = 167.3 ppm (s) in CD_3NO_2, 168.8 ppm (s) in $(CD_3)_2CO$.IR; in the solid state: ν(OH) = 3050 cm^{-1}(br), ν(CO and C=C) = 1695 cm^{-1}, 1650 cm^{-1}, and 1625 cm^{-1}(vs); 0.5 % in CCl_4: ν(OH) = 3580 cm^{-1}, ν(CO and C=C) = 1746 cm^{-1}, 1720 cm^{-1}, 1650cm^{-1} (vs), and 1620 cm^{-1}(m).

b) A solution of 5.6 g (0.1 mole) of potassium hydroxide in 50 ml of water was added portionwise to a vigorously agitated suspension of compound 2 (4.44 g, 0.02 mole) in 30 ml of water. The reaction mixture was stirred at ambient temperature for 3 hours and then acidified with hydrochloric acid. A brownish precipitate of crude 3-fluoro-4-hydroxycoumarin 4 (2.2 g,0.012 mole) was purified by repeated crystallisations from methanol--water. The yield of the crude product was 61 %.

Reaction of o-methoxy -2,3,3,3-tetrafluoropropiophenone 3 with sodium methoxide

Compound 3 (3.7 g, 0.016 mole) was slowly added to a solution of sodium metal (2 g, 0.087 mole) in methanol (15 ml). The reaction mixture warmed up as a consequence of an exothermic

reaction and was agitated at ambient temperature for 3 hours and then diluted with water. A white precipitate of the orthoester 10 was filtered off, washed with water and purified by dissolving in methanol, filtering off a fine precipitate of sodium fluoride and evaporating to dryness. The yield was 3 g (68%). M.p. = 73-75°. Calculated for $C_{13}H_{17}FO_5$: C, 57.3; H, 6.3; F, 7.0 %. Found: C,57.1; H, 6.2; F, 7.1 %. ^1H and ^{19}F NMR (in CCl_4): δ (OCH_3) = 3.30 ppm (s) and 3.95 ppm (s), δ (C<u>H</u>F) = 5.98 ppm (d) relative intensities being as 9:3:1, ϕ(C<u>H</u>F) = 202.3 ppm (d), $^2J(HF)$ = 48.0 Hz. IR (in CCl_4): ν(CO) = 1700 cm^{-1}(vs).

Hydrolysis of the orthoester 10

Compound 10 (1 g, 0.0037 mole) was added to 5 ml of diluted (1:1) hydrochloric acid, the mixture was stirred at 20° for 10 minutes and then extracted with chloroform. The extract was dried over silica-gel and the solvent was removed under vacuum to give an oily material (0.8 g, 0.0035 mole), which was identified as methyl o-methoxybenzoylfluoroacetate 11. The yield was 95.7 %. Calculated for $C_{11}H_{11}FO_4$: C, 58.4; H, 4.9; F, 8.4 %. Found: C, 58.2; H, 5.0; F, 8.3 %. ^1H and ^{19}F NMR (in CCl_4): δ (OCH_3) = 3.75 ppm (s) and 3.87 ppm (s), δ (C<u>H</u>F) = 5.95 ppm (d) relative intensities being as 3:3:1, ϕ(C<u>H</u>F) = 193.1 ppm (d), $^2J(HF)$ = 47.2 Hz.

Methylation of 3-fluoro-4-hydroxycoumarin 4

Coumarin 4 (1.8 g, 0.01 mole) was dissolved in methanol containing an equimolar amount of sodium methoxide and the solution was evaporated to dryness under vacuum. The resulting yellow sodium salt, 10 ml of dry dimethylformamide, and 3 g (0.02 mole) of methyl iodide were stirred together at 40° for 10 hours. During that time a crystalline precipitate was formed. An excess of methyl iodide was removed under vacuum. Addition of water to the reaction mixture caused precipitation of more of the crystalline product. The product was filtered off, washed with water and recrystallised from methanol-water (1:1) to give 0.5 g (0.0026 mole) of 3-fluoro-3-methyl-benzo-2,4-pyrandione 12. M.p. = 123-124°. Calculated for $C_{10}H_7FO_3$: C, 61.9; H, 3.6; F, 9.8 %. Found: C, 61.5; H, 3.6; F, 9.8 %. MS: 194(100%)$[M]^{+\cdot}$, 166(11%)$[C_9H_7FO_2]^+$, 151(42%)$[C_8H_4FO_2]^+$, 123(21%)$[C_7H_4FO]^+$,

95(24%)$[C_6H_4F]^+$. ^1H and ^{19}F NMR (in $(CD_3)_2CO$): $\delta(CH_3)$ = 4.43 ppm (d), $\phi(F)$ = 162.6 ppm (q), $^3J(HF)$ = 6.2 Hz. IR (in KBr): $\nu(CO)$ = 1715 and 1642 cm^{-1}(vs).

Decarboxylation of 3-fluoro-4-hydroxycoumarin 4

A suspension of coumarin 4 (1.5 g, 0.008 mole) in 100 ml of water was refluxed for 4 hours. The unreacted 4 was filtered off and the filtrate was left overnight in a refrigerator. Crystals of o-hydroxyfluoroacetophenone 14 were separated and dried over P_2O_5. Yield 0.4 g (32.5%). M.p. = 67-69°. Calculated for $C_8H_7FO_2$: C, 62.3; H, 4.6; F, 12.3 %. Found: C, 62.3; H, 4.6; F, 12.6 %. MS: 154(27%)$[M]^{+\cdot}$, 121(100%)$[C_7H_5O_2]^+$, 92(20%) $[C_6H_5O]^+$, 65(27%)$[C_5H_5]^+$. ^1H and ^{19}F NMR (in CCl_4): $\delta(CH_2F)$ = 5.38 ppm (d), $\delta(OH)$ = 11.4 ppm (s), $\phi(F)$ = 231.0 ppm (t), $^2J(HF)$ = 47.1 Hz. IR (in CCl_4): $\nu(OH)$ = 3200-3040 cm^{-1} and 3580 cm^{-1}, $\nu(CO)$ = 1670 and 1645 cm^{-1}.

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