Electronic Effects in Elimination Reactions. VIII. E2 Reaction of 2-Arylethyl Fluorides

Charles H. DePuy* and Arnold L. Schultz

Department of Chemistry, University of Colorado, Boulder, Colorado 80302

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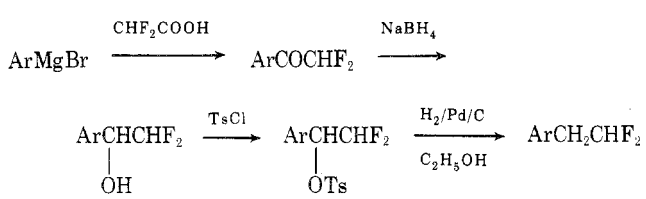
The rates of bimolecular elimination from a series of 1-fluoro-2-arylethanes, 1,1-difluoro-2-arylethanes, and 1,1,1-trifluoro-2-arylethanes have been measured in *tert*-butyl alcohol using potassium *tert*-butoxide as the base. The absolute rate of the reaction and the Hammett ρ value for the elimination both increase with the number of fluorines. Values for the latter are +3.24 for the fluoride, +3.56 for the difluoride, and +4.04 for the trifluoride, indicating that the transition state is highly carbanionic in character, as is also indicated by a relatively low value of k_H/k_D.

Only a relatively few kinetic and mechanistic studies have been performed on organofluorine compounds. Some years ago we measured the rates of elimination of hydrogen fluoride from a series of substituted 2-arylethyl fluorides in sodium ethoxide–ethanol solution.[1] These compounds react slowly as compared to analogs with other halide leaving groups (the relative rates of elimination of 2-phenylethyl halides in sodium ethoxide–ethanol are F:Cl:Br:I = 1:70:4100:26,600), and the elimination reaction of the fluorides has a higher Hammett ρ value (+3.1) as compared to the chlorides (+2.6), bromides (+2.1), or iodides (+2.1). We were interested in investigating elimination reactions of fluorides further, and in this paper we present the results of a study on the elimination of hydrogen fluoride from a series of 1-fluoro-, 1,1-difluoro-, and 1,1,1-trifluoro-2-arylethanes in *tert*-butyl alcohol with potassium *tert*-butoxide as the reacting base.

The synthesis of the requisite fluorides proceeded along straightforward lines. The 1-fluoro-2-arylethanes were prepared as reported previously[1] from the arylacetic acids by reduction to the alcohols, tosylation, and displacement by potassium fluoride in diethylene glycol solution.[2] The 1,1-difluoro-2-arylethanes were prepared as shown in Scheme I, and the 1,1,1-trifluoro-2-arylethanes were prepared analogously using trifluoroacetic acid. The elimination reactions were carried out at 50° in *tert*-butyl alcohol solution containing 0.1 *N* potassium *tert*-butoxide, and the rate of disappearance of base was followed by titration with standard hydrochloric acid solution. The 1-fluoro- and 1,1-difluoroethanes each consumed 1 equiv of base and produced styrenes and a mixture of *cis*- and *trans*-β-fluorostyrenes, respectively. In the case of the 1,1,1-trifluoro-2-arylethanes the elimination reaction was found to occur with the consumption of 2 mol of potassium *tert*-butoxide. If the reaction was carried out in an nmr tube with less than 1 equiv of base, we were able to detect some β,β-difluorostyrene[3] among the products. This initially formed olefin apparently undergoes an addition–elimination reaction analogous to that of trifluorostyrene[4] forming ultimately a cis,trans mixture of 1-(*tert*-butoxy)-1-fluoro-2-arylethylenes (eq 1). The second reaction in this sequence appears to be faster than the first, because initial rate constants were identical with those calculated on the basis of the consumption of 2 mol of *tert*-butoxide for each trifluoroethyl molecule.

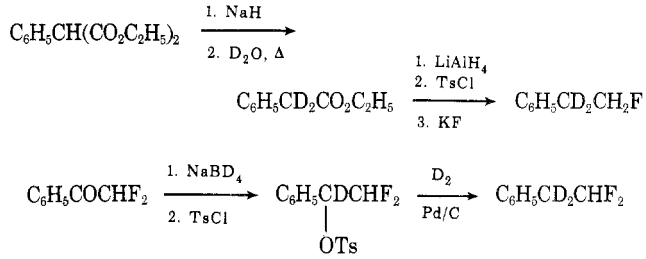
Scheme I



$$ArCH_2CF_3 \xrightarrow{t\text{-}BuO^-} ArCH{=}CF_2 \xrightarrow[t\text{-}BuO^-]{t\text{-}BuOH} ArCH{=}CF(O\text{-}t\text{-}Bu) \quad (1)$$

In order to determine kinetic isotope effects and to investigate the possibility of deuterium–hydrogen exchange, 1-fluoro-2-phenylethane-2,2-d_2 and 1,1-difluoro-2-phenylethane-2,2-d_2 were prepared by the methods outlined in Scheme II. The rate constants for these compounds did not increase with time, as they would be expected to do if extensive hydrogen–deuterium exchange were occurring before elimination. As a more sensitive check, one reaction of each deuterium compound was quenched after approximately 1 half-life, and the mass spectrum of the recovered starting material was compared with that of authentic deuterated material. This indicated that no detectable hydrogen deuterium exchange had occurred.

Scheme II



The rate constants that we have determined for the compounds prepared in this study are given in Table I.

In determining Hammett ρ values for these elimination reactions, we found that the σ value for fluorine derived from the acidity of *p*-fluorobenzoic acid would not correlate with that of other substitutents, but that the σ^- value derived from the acidity of *p*-fluorophenol would do so, although less well in the case of the 2-arylethyl fluorides than with the di- and trifluorides. It has previously been observed that the *p*-nitro group also requires the use of a σ^- value for correlation in the elimination reaction of other 2-arylethyl derivatives.[5]

The ρ values found were +3.24 ± 0.05 for the fluoride, +3.56 ± 0.07 for the difluoride, and +4.04 ± 0.30 for the trifluoride.

The results of these measurements indicate that, as might be expected, the eliminations are highly carbanionic. Koch[6] has postulated recently that eliminations of HF from $C_6H_5CHClCF_3$ occurs with reversible formation of the hydrogen-bonded carbanion, a carbanion which has an activation energy for exchange with solvent because of

Table I
Rates of the Elimination Reaction of 2-Arylethyl Fluorides by Potassium *tert*-Butoxide in *tert*-Butyl Alcohol at 50°

Y	Registry no.	$k_{E2} \times 10^4$, l. mol^{-1} sec^{-1}	k_H/k_D
	$YC_6H_4CH_2CH_2F$		
m-CF_3	50512-33-9	46.6 ± 0.36	
H	458-87-7	1.88 ± 0.01	
m-CH_3	50561-90-5	1.21 ± 0.01	
p-F	2343-30-8	1.10 ± 0.01	
p-CH_3	50561-92-7	0.513 ± 0.007	
	$YC_6H_4CD_2CH_2F$		
H	50561-93-8	0.418 ± 0.009	4.50
	$YC_6H_4CH_2CHF_2$		
H	10541-59-0	11.8 ± 0.09	
p-F	50561-95-0	9.62 ± 0.05	
m-CH_3	50561-96-1	6.47 ± 0.03	
p-CH_3	50561-97-2	2.88 ± 0.00	
	$YC_6H_4CD_2CHF_2$		
H	50561-98-3	4.26 ± 0.03	2.77
	$YC_6H_4CH_2CF_3$		
H	21249-93-4	22.8 ± 0.45	
p-F	50561-99-4	16.8 ± 0.30	
m-CH_3	50562-00-0	12.7 ± 0.50	
p-CH_3	50562-01-1	4.45 ± 0.09	

this hydrogen bonding. The ρ value found in that study is, within experimental error, the same as we find for the trifluoro compound. Koch has also suggested that fluoride is a poorer leaving group when it comes from a trifluoromethyl group rather than from a less highly fluorinated group. Our results are thus in agreement with the view that the addition of each fluorine to the methyl group has two effects. On the one hand, it acidifies the hydrogens on the adjacent carbon but at the same time it reduces the leaving ability of the fluorines. As a consequence a larger negative charge is required in the transition state for the elimination from the trifluoro compound than from the di- and monofluoro compounds. We cannot say from our data whether a carbanion is an actual intermediate or not; it may be formed reversibly without exchange in the trifluoro case at least. The low k_H/k_D values also are in agreement with a transition state with a great deal of carbon–hydrogen bond breaking so that the hydrogen is more than half transferred to base.

Experimental Section

Melting points are uncorrected and were taken on a Fisher-Johns melting point apparats. Ir absorption spectra were determined on a Beckman IR-10 spectrometer. All proton nmr spectra were determined on a Varian A-60A spectrometer using TMS as an internal standard. All fluorine nmr spectra were recorded on a Varian HA-100 spectrometer using $FCCl_3$ as an internal standard. Chemical shifts are reported in ppm relative to this standard. Mass spectra were recorded on either a Varian MAT CH-5 or CH-7 spectrometer at 70 eV. Microanalyses were performed by Dr. Alfred Bernhardt Mickroanalytisches Laboratorium, Mülheim, West Germany.

Preparation of 2-Arylethyl Fluorides. All of the 2-arylethanols, with the exception of 2-phenylethanol which is commercially available, were prepared by the reduction of the corresponding arylacetic acid with diborane using the general procedure of Brown and Rao.[7] The arylacetic acids, with the exception of the *m*-trifluoromethylphenylacetic acid, were commercially available. The latter was prepared from *m*-trifluoromethylbenzyl chloride by reaction with magnesium and CO_2.[8] The alcohols were converted into their tosylates by the method of Tipson,[9] and these in turn converted into fluorides by the procedure of Bergman and Shahak.[1,2] **2-*p*-Tolylethanol:** bp 69–74° (0.8–0.6 mm) [lit.[10] bp 117–118° (14 mm)], 85% yield. **2-*m*-Tolylethanol:** bp 69–74° (0.8–0.6 mm) [lit.[11] bp 112° (10 mm)], 86% yield. **2-(*p*-Fluorophenyl)ethanol:** bp 59–61° (0.5 mm) [lit.[12] bp 110° (20 mm)], 87% yield. **2-(*m*-Trifluoromethylphenyl)ethanol:** bp 58–62° (0.5 mm) [lit.[13] bp 85–90° (4 mm)], 72% yield. **2-Phenylethyl *p*-toluenesulfonate:** mp 38.5–39.5° (lit.[14] mp 38.5–39°), 65% yield. **2-*p*-Tolylethyl *p*-toluenesulfonate:** mp 67–68°, 89% yield. **2-*m*-Tolylethyl *p*-toluenesulfonate:** oil, 89% yield. **2-(*p*-Fluorophenyl)ethyl *p*-toluenesulfonate:** mp 35.7–36.2°, 88% yield. **2-(*m*-Trifluoromethylphenyl)ethyl *p*-toluenesulfonate:** oil, 91% yield. **2-Phenylethyl fluoride:** bp 50–51° (9 hm) [lit.[1] bp 55–56° (12 mm)]; 53% yield; ^1H nmr (CCl_4) δ 2.80 (dt, 2 H, $J_{HF,vic}$ = 22.7 Hz, $J_{HH,vic}$ = 6.6 Hz), 4.41 (dt, 2 H, $J_{HF,gem}$ = 47.4 Hz), 7.13 (s, 5 H); ^{19}F nmr ($FCCl_3$) 215.3 ppm (tt). **2-*p*-Tolylethyl fluoride:** bp 74–76° (18 mm), 61% yield. *Anal.* Calcd for $C_9H_{11}F$: C, 78.23; H, 8.02; F, 13.75. Found: C, 78.12; H, 7.86; F, 13.90. **2-*m*-Tolylethyl fluoride:** bp 74–78° (18 mm), 63% yield. *Anal.* Calcd for $C_9H_{11}F$: C, 78.23; H, 8.02; F, 13.75. Found: C, 78.11; H, 7.90; F, 13.94. **2-(*p*-Fluorophenyl)ethyl fluoride:** bp 53.5–54° (10 mm), 63% yield. *Anal.* Calcd for $C_8H_8F_2$: C, 67.60; H, 5.67; F, 26.73. Found: C, 67.79; H, 5.81; F, 26.68. **2-(*m*-Trifluoromethylphenyl)ethyl fluoride:** bp 56–58° (10 mm), 50% yield. *Anal.* Calcd for $C_9H_8F_4$: C, 56.26; H, 4.21; F, 39.55. Found: C, 56.32; H, 4.34; F, 39.76.

Preparation of α,α-Difluoroacetophenones. The ketones were prepared by reaction of the appropriate aryl Grignard reagent with difluoroacetic acid according to the procedure of Dishart and Levine[15] using the modification described by Bergmann, Pelchowicz, and Shani.[16] **α,α-Difluoroacetophenone:** bp 60–62° (10 mm) [lit.[17] bp 83–85° (20 mm)]; 51% yield; nmr (CCl_4) δ 6.18 (t, 1 H, $J_{HF,gem}$ = 53.8 Hz), 7.53 (m, 3 H), 8.03 (m, 2 H). ***p*-Methyl-α,α-difluoroacetophenone:** bp 80–82° (13–14 mm), mp 47–49°, 51% yield. ***m*-Methyl-α,α-difluoroacetophenone:** bp 78–79° (11 mm), 44% yield. ***p*-Fluoro-α,α-difluoroacetophenone:** bp 62–64° (13 mm), 55.5% yield. ***m*-Trifluoromethyl-α,α-difluoroacetophenone:** bp 61–64° (10 mm), 67% yield.

Preparation of 1-Aryl-2,2-difluoroethanols and Their Tosylates. The alcohols were prepared by reduction of the acetophenones with sodium borohydride in 90% aqueous dioxane. To a solution of 0.15 mol of the α,α-difluoroacetophenone in 80 ml of 90% aqueous dioxane contained in a 250-ml erlenmeyer flask equipped with a magnetic stirrer was added in small portions with stirring 1.81 g (0.048 mol) of sodium borohydride. Gas evolution was observed with each addition, being more vigorous with the initial ones. Intermittent cooling of the reaction mixture was necessary. After stirring overnight, the reaction mixture was cooled in an ice bath and the excess borohydride was destroyed by the cautious addition of cold, 3 *N* hydrochloric acid. The solution was extracted with ether (4 × 50 ml); the combined extracts were washed with water until the washings were neutral to indicator paper and then dried over anhydrous magnesium sulfate. The solvent was removed and the product distilled. The tosylate was prepared in the usual way, but rather long reaction times (several days in some cases) were required for reaction. **1-Phenyl-2,2-difluoroethanol:** bp 58–61° (1 mm) [lit.[18] bp 107–108° (20 mm)]; 87% yield; nmr (CCl_4) δ 3.45 (s, 1 H), 4.57 (m, 1 H), 5.57 (td, 1 H, $J_{HF,gem}$ = 55.5 Hz, $J_{HH,vic}$ = 4.5 Hz), 7.28 (s, 5 H). **Tosylate:** mp 96.0–96.5°; 77% yield; nmr ($CDCl_3$) δ 2.35 (s, 3 H), 5.55 (td, 1 H, $J_{HF,vic}$ = 10.2 Hz, $J_{HH,vic}$ = 4.0 Hz), 5.91 (td, 1 H, $J_{HF,gem}$ = 55.0 Hz), 7.18 (d, 2 H), 7.30 (s, 5 H), 7.85 (d, 2 H). **1-(*p*-Tolyl)-2,2-difluoroethanol:** bp 60–62° (0.5–0.6 mm), 87% yield. **Tosylate:** mp 65.0–65.5°, 66% yield. **1-(*m*-Tolyl)-2,2-difluoroethanol:** bp 58–61° (0.5 mm), 78% yield. **1-(*p*-Fluorophenyl)-2,2-difluoroethanol:** bp 92–96° (11 mm), 78% yield. **Tosylate:** mp 54–57°, 73% yield. **1-(*m*-Trifluoromethylphenyl)-2,2-difluoroethanol:** bp 50–52° (0.4–0.5 mm), 90% yield. **Tosylate:** mp 42–43°, 58% yield.

Preparation of 1,1-Difluoro-2-arylethanes. Hydrogenolysis of the corresponding tosylates over 5% palladium-on-carbon catalyst in 95% ethanol, at room temperature and atmospheric pressure, gave rise to the desired 1,1-difluoro-2-arylethanes. The hydrogenations were conducted in an apparatus essentially the same as that described by Wiberg.[19] The products were distilled through a 7 × 5/8 in. column packed with glass beads, and the distillation was monitored by glpc. Fractions of the highest purity, usually greater than 99% pure, were used in the kinetic runs. **1,1-Difluoro-2-phenylethane:** bp 68–69° (32 mm); 79% yield; nuclear magnetic resonance (CCl_4) δ 2.85 (td, 2 H, $J_{HF,vic}$ = 17.0 Hz, $J_{HH,vic}$ = 4.5 Hz), 5.75 (tt, 1 H, $J_{HF,gem}$ = 56.5 Hz), 7.20 (s, 5 H). *Anal.* Calcd for $C_8H_8F_2$: C, 67.60; H, 5.67; F, 26.73. Found: C, 67.76; H, 5.74; F, 26.75. **1-Difluoro-2-(*p*-tolyl)ethane:** bp 69° (13 mm), 81% yield. *Anal.* Calcd for $C_9H_{10}F_2$: C, 69.22; H, 6.45; F, 24.33. Found: C, 69.12; H, 6.56; F, 24.29. **1,1-Difluoro-2-(*m*-tolyl)ethane:** bp 61–62° (10 mm), 78% yield. *Anal.* Calcd for

$C_9H_{10}F_2$: C, 69.22; H, 6.45; F, 24.33. Found: C, 69.04; H, 6.27; F, 24.18. **1,1-Difluoro-2-(*p*-fluorophenyl)ethane:** bp 77° (37 mm), 82% yield. *Anal.* Calcd for $C_8H_7F_3$: C, 60.00; H, 4.41; F, 35.59. Found: C, 59.86; H, 4.34; F, 35.32. **1,1-Difluoro-2-(*m*-trifluoromethylphenyl)ethane:** bp 80–81° (30 mm), 81% yield. *Anal.* Calcd for $C_9H_7F_5$: C, 51.44; H, 3.36; F, 45.20. Found: C, 51.24; H, 3.19; F, 45.51.

Preparation of α,α,α-Trifluoroacetophenones. All of α,α,α-trifluoroacetophenones were prepared by reaction of the appropriate aryl Grignard reagent with trifluoroacetic acid in a manner analogous to that described above for the preparation of the α,α-difluoroacetophenones. **α,α,α-Trifluoroacetophenone:** bp 143.5–144° (lit.[20] bp 152°), 71% yield. ***p*-Methyl-α,α,α-trifluoroacetophenone:** bp 66–68° (13 mm) [lit.[21] bp 81–82.5° (22 mm)], 67% yield, ***m*-Methyl-α,α,α-trifluoroacetophenone:** bp 62–64° (14–20 mm) [lit.[22] bp 79° (24 mm)]; 61% yield; nmr (CCl_4) δ 2.38 (s, 3 H), 7.42 (m, 2 H), 7.83 (m, 2 H). ***p*-Fluoro-α,α,α-trifluoroacetophenone:** bp 58–60° (24 mm) [lit.[23] bp 66–67° (34 mm)]; 69% yield; nmr (CCl_4) δ 7.23 (m, 2 H), 8.13 (m, 2 H). ***m*-Trifluoromethyl-α,α,α-trifluoroacetophenone:** bp 52–54° (14 mm) [lit.[24] bp 65.0–67.5° (24 mm)], 75% yield.

Preparation of 1-Aryl-2,2,2-trifluoroethanols and Their Tosylates. The 1-aryl-2,2,2-trifluoroethanols were prepared by reduction of the corresponding α,α,α-trifluoroacetophonones in a manner analogous to that described above for the preparation of the 1-aryl-2,2-difluoroethanols. The tosylates were prepared in an analogous manner to that described above for the preparation of the 1-aryl-2,2-difluoroethyl *p*-tolunenesulfonates. **1-Phenyl-2,2,2-trifluoroethanol:** bp 90–91° (18 mm) [lit.[25] bp 64–65° (5 mm)]; ^1H nmr (CCl_4) δ 3.86 (s, 1 H), 4.73 (q, 1 H, $J_{HF,vic}$ = 6.8 Hz), 7.27 (s, 5 H); ^{19}F nmr ($FCCl_3$) 78.5 ppm (d, $J_{HF,vic}$ = 6.9 Hz). **Tosylate:** mp 115–116°; 63% yield; ^1H nmr ($CDCl_3$) δ 2.37 (s, 3 H), 5.68 (q, 1 H), 7.27 (d, 2 H), 7.32 (s, 5 H), 7.63 (d, 2 H); ^{19}F nmr ($FCCl_3$) 76.8 ppm (d, $J_{HF,vic}$ = 6.4 Hz). **1-(*p*-Tolyl)-2,2,2-trifluoroethanol:** bp 50° (0.75 mm) [lit.[24] bp 74.5–75° (2.5 mm)], 90% yield. **1-(*m*-Tolyl)-2,2,2-trifluoroethanol:** bp 54° (0.55 mm) [lit.[22] bp 95–97° (24 mm)], 90% yield. **Tosylate:** mp 75–78°, 82% yield. **1-(*p*-Fluorophenyl)-2,2,2-trifluoroethanol:** bp 88–90° (17 mm), 92% yield. **Tosylate:** mp 78.0–78.5°, 80% yield. **1-(*m*-Trifluoromethylphenyl)-2,2,2-trifluoroethanol:** bp 76–78° (10 mm) [lit.[24] bp 95–97° (24 mm)], 93% yield. **Tosylate:** mp 51.5–52.5°, 68% yield.

Preparation of 1,1,1-Trifluoro-2-arylethanes. The 1,1,1-trifluoro-2-arylethanes were prepared by the hydrogenolysis of the corresponding 1-aryl-2,2,2-trifluoroethyl *p*-toluenesulfonates in a manner analogous to that described above for the preparation of the 1,1-difluoro-2-arylethanes. **1,1,1-Trifluoro-2-phenylethane:** bp 124–126°; 81% yield; nmr (CCl_4) δ 3.17 (q, 2 H, $J_{HF,vic}$ = 11.0 Hz), 7.18 (s, 5 H). *Anal.* Calcd for $C_8H_7F_3$: C, 60.00; H, 4.41; F, 35.59. Found: C, 60.20; H, 4.45; F, 35.83. **1,1,1-Trifluoro-2-(*p*-tolyl)ethane:** mp 43.5–43.7° (sublimed), 84% yield. *Anal.* Calcd for $C_9H_9F_3$: C, 62.07; H, 5.21; F, 32.72. Found: C, 61.99; H, 5.10; F, 32.88. **1,1,1-Trifluoro-2-(*m*-tolyl)ethane:** bp 45.0–45.7° (11 mm), 88% yield. *Anal.* Calcd for $C_9H_9F_3$: C, 62.07; H, 5.21; F, 32.72. Found: C, 62.22; H, 5.24; F, 32.81. **1,1,1-Trifluoro-2-(*p*-fluorophenyl)ethane:** bp 58° (34 mm), 78% yield. *Anal.* Calcd for $C_8H_6F_4$: C, 53.94; H, 3.40; F, 42.66. Found: C, 54.23; H, 3.16; F, 42.74. **1,1,1-Trifluoro-2-(*m*-trifluoromethylphenyl)ethane:** bp 37–38° (8 mm), 82% yield. *Anal.* Calcd for $C_9H_6F_6$: C, 47.38; H, 2.65; F, 49.97. Found: C, 47.48; H, 2.81; F, 49.83.

Preparation of Deuterio Compounds. 2-Phenylethyl-2,2-d_2 fluoride was prepared by a scheme analogous to that used to prepare 2-phenylethyl fluoride with the exception that 2-phenylethanol-2,2-d_2, which was prepared from ethyl phenylacetate-2,2-d_2, was the starting material in this sequence. **Ethyl phenylacetate-2,2-d_2:** bp 45–46° (0.1 mm) [lit.[26] bp 73–74° (0.5 mm)]; 11% yield; nmr (CCl_4) δ 2.13 (t, 3 H), 4.08 (q, 2 H), 7.25 (s, 5 H). **2-Phenylethanol-2,2-d_2:** bp 73–74° (2.0 mm) [lit.[26] bp 110° (20 mm)], 82% yield. **2-Phenylethyl-2,2-d_2 *p*-toluenesulfonate:** oil (lit.[27] mp 37.5–38.2°), 90% yield. **2-Phenylethyl-2,2-d_2 fluoride:** bp 51° (2 mm); 38% yield; nmr (CCl_4) δ 4.45 (dd, 2 H, $J_{HF,gem}$ = 47.8 Hz), 7.15 (s, 2 H). (Comparison of *m/e* 92 and 91 in the deuterio compound with 90 and 89 in the undeuterated compound indicated a minimum of 1.87 atoms of D/molecule in the former.)

Reduction of α,α-difluoroacetophenone with sodium borodeuteride in deuterium oxide–dioxane in a manner analogous to that described above for the preparation of the 2,2-difluoro-1-arylethanols gave rise to 2,2-difluoro-1-phenylethanol-1-d_1. Hydrogenolysis of the tosylate, prepared from this alcohol in the usual manner, with deuterium following the procedure described above for the preparation of 2,2-difluoro-1-arylethanes, with the exception that the catalyst was prereduced with deuterium before the tosylate was introduced, yielded 2,2-difluoro-1-phenylethane-1,1-d_2. **2,2-Difluoro-1-phenylethanol-1-d_1:** bp 63–64° (0.3 mm); 86% yield; nmr (CCl_4) δ 3.42 (s, 1 H), 5.57 (t, 1 H, $J_{HF,gem}$ = 56.0 Hz), 7.27 (s, 5 H). **Tosylate:** mp 93–95°; 85% yield; nmr ($CDCl_3$) δ 2.37 (s, 3 H), 5.92 (t, 1 H, $J_{HF,gem}$ = 55.0 Hz), 7.20 (d, 2 H), 7.30 (s, 5 H), 7.85 (d, 2 H). **2,2-Difluoro-1-phenylethane-1,1-d_2:** bp 69.5–70.0° (33 mm); 73% yield; nmr (CCl_4) δ 5.75 (t, 1 H, $J_{HF,gem}$ = 57.0 Hz), 7.18 (s, 5 H). (Comparison of *m/e* 144 and 143 in the deuterio compound with 142 and 141 in the undeuterated compound indicated a minimum of 1.93 atoms of D/molecule in the former.)

Kinetic Procedures. Anhydrous *tert*-Butyl Alcohol. Reagent grade *tert*-butyl alcohol was distilled from Na (5 g of sodium/l. of alcohol) three times and then from potassium once. The purified alcohol was stored under nitrogen.

0.2 *N* Potassium *tert*-Butoxide. A clean, dry 5-g ampoule of pure potassium metal (99.95%, Alfa Inorganics) was broken into 640 ml of anhydrous *tert*-butyl alcohol under a nitrogen atmosphere. The flask was protected from moisture and carbon dioxide by means of a drying tube containing anhydrous calcium sulfate and Ascarite until the metal had all reacted. The flask was then fitted with a siphon device which allowed removal of portions of the solution under a slight positive pressure of nitrogen.

Kinetic Runs. All kinetic runs were preformed at 50.00 ± 0.03°. Reactions for which the second-order rate constant for elimination was less than 10^{-3} l. mol^{-1} sec^{-1} were run in sealed ampoules. The fluoride sample, approximately 2.5 mmol, was accurately weighed into a 50-ml volumetric flask and diluted with 25 ml of anhydrous *tert*-butyl alcohol. The flask was then filled to the mark with 0.2 *N* potassium *tert*-butoxide, and the reagents were mixed thoroughly. Nine 5-ml aliquots were pipetted, from automatic zeroing pipets that had been calibrated at 26° with *tert*-butyl alcohol [density (at 26°) 0.779 g/ml], into 15 × 125 mm test tubes which were then sealed and placed in the reaction bath. When the ampoules had equilibrated at the reaction temperature, one was withdrawn and the timer started. The ampoule was opened and the reaction quenched in 50 ml of distilled water. The ampoule was washed out with a 1:1 solution of *tert*-butyl alcohol–distilled water. Two drops of 0.25% phenolphthalein solution in 1:1 ethyl alcohol–water were added, and the sample was titrated with standard hydrochloric acid. The ampoules were withdrawn at appropriate intervals and the samples titrated.

Reactions for which the second-order rate constant for elimination was greater than 10^{-3} l. mol^{-1} sec^{-1} were run directly in the volumetric flask. The fluoride sample was accurately weighed into a 50-ml volumetric flask and diluted with 25 ml of anhydrous *tert*-butyl alcohol. The flask was stoppered and placed in the reaction bath. When the solution had equilibrated at the reaction temperature 0.2 *N* potassium *tert*-butoxide that had been equilibrated at the reaction temperature was added to the mark, and the reagents were thoroughly mixed. A 5-ml aliquot was pipetted directly from the volumetric flask and the timer started as the reaction mixture started to drain. The sample was quenched and titrated. Aliquots were withdrawn and titrated at appropriate intervals.

The second-order rate constant, k_2, was calculated for each kinetic point. An average rate constant was calculated for each run. For reactions run in sealed ampoules a correction factor of a 3% increase in measured rate constant was made to account for the thermal expansion of the solvent.[28]

Measured infinity points were generally less than, but within 3% of, those calculated because some substrate reacted before the zero point could be taken.

An unweighted least-squares statistical analysis computer program was employed to calculate the rate constants. The computer rate constants varied slightly from the numerical average due to the emphasis on the zero and infinity points in calculating the best least-squares slope.

Registry No.—Deuterium, 7782-39-0; 2-*p*-tolylethyl *p*-toluenesulfonate, 14503-40-3; 2-(*p*-fluorophenyl)ethyl *p*-toluenesulfonate, 50562-02-2; α,α-difluoroacetophenone, 395-01-7; *p*-methyl-α,α-difluoroacetophenone, 704-36-9; *m*-methyl-α,α-difluoroacetophenone, 50562-05-5; *p*-fluoro-α,α-difluoroacetophenone, 50562-06-6; *m*-trifluoromethyl-α,α-difluoroacetophenone, 50562-07-7; 1-phenyl-2,2-difluoroethanol, 345-64-2, 50562-09-9 (tosylate); 1-(*p*-tolyl)-2,2-difluoroethanol, 50562-10-2, 50562-11-3 (tosylate); 1-(*m*-tolyl)-2,2-difluoroethanol, 50562-12-4; 1-(*p*-fluorophenyl)-2,2-difluoroethanol, 2546-44-3, 50562-14-6 (tosylate); 1-(*m*-trifluoromethylphenyl)-2,2-difluoroethanol, 50562-15-7, 50562-16-8 (tosylate);

1,1-difluoro-2-(*m*-trifluoromethylphenyl)ethane, 50562-17-9; *p*-fluoro-α,α,α-trifluoroacetophenone, 655-32-3; 1-phenyl-2,2,2-trifluoroethanol, 340-04-5; 1-(*m*-tolyl)-2,2,2-trifluoroethanol tosylate, 655-32-3; 1-(*p*-fluorophenyl)-2,2,2-trifluoroethanol, 50562-19-1, 50562-20-4 (tosylate); 1-(*m*-trifluoromethylphenyl)-2,2,2-trifluoroethanol tosylate, 50562-21-5; 1,1,1-trifluoro-2-(*m*-trifluoromethylphenyl)ethane, 50562-22-6; 2,2-difluoro-1-phenylethanol-*1*-d_1, 50562-23-7, 50562-24-8 (tosylate).

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Steric and Electronic Factors Which Effect the Thermal Cyclization of Meta-Substituted Aryl Propargyl Ethers. Synthesis of 5- and 7-Substituted 3-Chromenes[1]

Wayne K. Anderson,* Edmond J. LaVoie, and Peter G. Whitkop

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214

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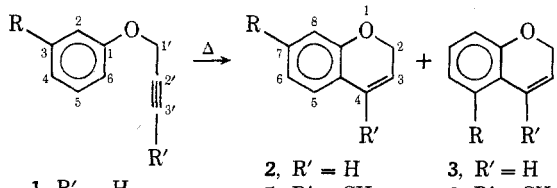
The thermal cyclization of meta-substituted phenyl propargyl ethers (**1** and **4**) proceeded to yield a mixture of 5- and 7-substituted 3-chromenes. The ratio of chromene isomers was somewhat dependent upon the nature of the starting materials. Thus, terminal acetylenes (**1**) gave a mixture of **2** and **3** (resulting from para and ortho cyclization, respectively) with the latter product usually in slight excess. Nonterminal acetylenes (**4**) also gave a mixture of ortho- and para-cyclized products (**6** and **5**, respectively); however, para cyclization was found to be favored. Regioselective cyclization was greatest for **4d**, which gave a mixture of 4,7- and 4,5-dimethyl-3-chromene in a ratio of 2:1. The cyclization of 3-(3-methoxyphenyloxy)-3-methylbutyne (**16**) also proceeded with little regioselectivity to give a mixture of **17** and **18**. The effects of electron-donating and electron-withdrawing meta substituents were also studied.

In our initial studies[2] on the thermal cyclization of aryl propargyl ethers we found that the cyclization of **1a** did not proceed in the regioselective manner previously reported.[3] Instead, the cyclization of **1a** led to the formation of both **2a** and **3a** where, in fact, the previously unreported 5-methoxy isomer (**3a**) was the more abundant product. Our interest in the use of certain substituted chromenes as intermediates in the synthesis of tumor-inhibitory trichothecan mycotoxins[4] prompted us to further examine those factors which influence regioselectivity in this reaction and to study the effects of various substituents on the aromatic ring.



1, R′ = H
4, R′ = CH_3

2, R′ = H
5, R′ = CH_3

3, R′ = H
6, R′ = CH_3

a, R = OCH_3
b, R = $COCH_3$
c, R = $N(C_2H_5)_2$
d, R = CH_3
e, R = $OCOCH_3$

The aryl propargyl ethers used in this study were synthesized by a Williamson reaction using the appropriately substituted phenols and propargyl bromides.[2] The cyclization of the aryl propargyl ethers was carried out in *N,N*-diethylaniline at 210–215°;[2] the isolated yield of the cyclized products, boiling points, reaction times, and product ratios are given in Table I.

The structures of the various chromene isomers were determined by comparison of nmr spectra. Typical 1,2,3- and 1,2,4-trisubstituted benzene patterns were generally evident in the nmr spectra of the 5 and 7 isomers ($J_o \cong 8$ and $J_m \cong 2$ Hz).

In the nmr spectra of the various chromenes the C-2 protons always appeared at slightly higher field in the 5-substituted isomer compared to the 7-substituted isomer. Similarly, the C-3 proton appeared at slightly lower field in the 5 isomer compared to the 7 isomer. The C-4 proton (or the C-4′ methyl protons) generally appeared at lower field in the nmr spectra of the 5-substituted compound compared to the 7 isomer. One exception to this latter