Regioselective Conversions of 1-Phenyl-Substituted Acetylenes to α,α-Difluoro Ketones with "F-TEDA-BF_4"

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Studies of electrophilic additions to acetylenic systems have been few in comparison to the studies of olefinic systems. In spite of the obvious structural analogies between double and triple carbon–carbon bonds, triple bonds are less reactive toward electrophilic reagents than double bonds by as much as a factor 10^5. This is due to the differential ease of formation of carbonium ions and vinyl cations under the conditions of electrophilic addition.[1] It has been observed that the structure of the fluorinating agent plays an important role in the "electrophilic" fluorination of acetylenes and has a particular striking effect with diphenylacetylene. The low-temperature reaction of diphenylacetylene with fluoroxytrifluoromethane led to 1,2,2-trifluoro-1,2-diphenyl-1-(trifluoromethoxy)ethane,[2] while low-temperature fluorination with fluorine in methanol[3] produced 1,1,2-trifluoro-2-methoxy-1,2-diphenylethane, 1,1,2,2-tetrafluoro-1,2-diphenylethane, and a small percentage of 1,1-difluoro-2,2-dimethoxy-1,2-diphenylethane. Reaction with trifluoroacetyl hypofluorite gave 2-fluoro-1,2-diphenylethanone and benzil,[4] while reaction with acetyl hypofluorite failed under identical conditions. Reaction with xenon difluoride depends on the catalyst used and in the presence of hydrogen fluoride led to 1,1,2,2-tetrafluoro-1,2-diphenylethane in high yield, while with trifluoroacetic acid a reaction mixture with up to six products was formed.[5]

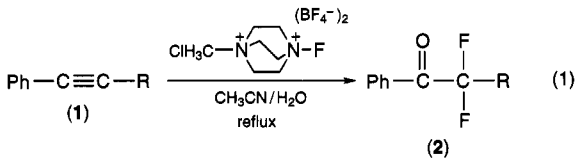
The regioselectivity of fluorination of mono-phenylacetylenes in methanol at room temperature with cesium fluoroxysulfate depends on the other acetylene substituent. The parent 1-phenylacetylene and the 1-phenyl-2-*tert*-butyl analogue displayed Markovnikov's type of regioselectivity. However 1-phenyl-1-propyne and 1-phenyl-1-pentyne underwent anti-Markovnikov type of addition.[6]

Recently, a variety of types of *N*-fluoro compounds have been found to be appropriate sources for the mild introduction of fluorine into organic molecules.[7] As such, an important breakthrough was achieved by Banks and co-workers[8] in the preparation of 1-alkly-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts, which are easy to handle and, now, commercially available.[9] The tetrafluoroborate salt, known as F-TEDA-BF_4, is the subject of the present report.

We initially studied the reaction of F-TEDA-BF_4 with diphenylacetylene in acetonitrile under reflux for 24 h, and only a small amount of fluorinated product was indicated by the ^{19}F NMR spectra of the crude reaction mixture. Conversion of the acetylene increased when methanol was present in the reactiom mixture, and 2,2-difluoro-1,2-diphenylethan-1-one and 1,1-dimethoxy-2,2-difluoro-1,2-diphenylethane were formed. Similar conditions, but with the presence of water, gave 1,1-difluoro-1,2-diphenylethanone in high yield, as the sole product.

We studied the regioselectivity of fluorine addition to substituted phenylacetylenes and found that all three (alkyl)phenylacetylenes (**1**) followed Markovnikov regioselectivity, thus forming α,α-difluoro ketones (**2a–c**) as sole products. All crude reaction mixtures were analyzed by ^{19}F and ^1H NMR spectroscopy and more than 90% conversions of starting acetylene had occurred. The use of octafluoronaphthalene as an internal standard revealed that the crude reaction mixtures contained 50–80% of fluoro-substituted products, based on starting acetylene. Further loss of products could be ascribed to the isolation procedure.

Finally, we examined the effect of the phenylacetylene substituent on the relative rate of fluorine addition and found that the substitution of hydrogen (**1a**) with a methyl substituent (**1b**) greatly increased the reactivity. No transformation of phenylacetylene in a mixture with phenylpropyne was observed, which means that phenylacetylene is at least 100 times less reactive.[10,11] However, substitution of the methyl group with a larger *tert*-butyl (**1c**) or phenyl group (**1d**) decreased the reactivity somewhat, as shon in eq 1and Table 1. A similar substituent



effect on fluorination with F-TEDA-BF_4 was previously observed in reactions of phenyl-substituted olefins, wherein substitution of hydrogen by a methyl group increased the reactivity of 1,1-diphenyl-1-propene to 8.6 times that of 1,1-diphenylethene.[12] Substitution of methyl with phenyl (triphenylethene) decreased the reactivity three times.

In our efforts to gain information about the mechanism of fluorination, we observed that the reaction of phenyl

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Table 1. The Effect of Substituents on the Relative Rates of Formation of α,α-Difluoro Ketones Formation from Acetylenes with F-TEDA-BF_4

compd	R	k_{rel}
1a	H	<0.01
1b	CH_3	1
1c	$C(CH_3)_3$	0.63
1d	Ph	0.56

ethyl ketone with F-TEDA, under the same conditions employed for 1-phenylpropyne, produced no fluorinated products. The same was observed in the reaction of 2-fluoro-1-phenylpropanone, which had been prepared from enol acetate by F-TEDA fluorination. In contrast to phenylacetylenes, no fluorinated products were obtained with 1-decyne under similar conditions.

Experimental Section

Materials. 1-(Chloromethyl)-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4)[9] and the acetylenes were obtained from commercial sources, 1-phenyl-2-*tert*-butylacetylene was synthesized.[13] Methylene chloride and acetonitrile were purified by distillation and stored over molecular sieves. ^1H and ^{19}F NMR spectra were recorded with a Varian EM 360L spectrometer with Me_4Si or CCl_3F as internal standard.

Fluorination of Phenyl-Substituted Acetylenes with F-TEDA-BF_4. In a typical experiment 1 mmol of (alkyl)-phenylacetylene was diluted in 10 mL of acetonitrile and 20 mmol of water, and 2.2 mmol of F-TEDA-BF_4 was added and heated under reflux for 10–20 h (consumption of fluorinating reagent was followed by KI starch paper). The reaction mixture was poured into water and extracted with 30 mL of methylene chloride, the organic phases were washed with water and dried over Na_2SO_4, and the solvent was evaporated in vacuo. The crude reaction mixture was analyzed by TLC and by ^{19}F and ^1H NMR spectroscopy, while pure products were isolated by column chromatography (SiO_2, $CHCl_3$).

2,2-Difluoro-1-phenylethan-1-one (2a):[3,6] 100 mg of crude product, 60 mg (36%) of pure oily product was isolated; NMR δ (F) −124.2 ppm (d, J = 54 Hz); δ (H) 6.37 ppm (t, J = 54 Hz, 1H), 7.2–8.4 ppm (m, 5H).

2,2-Difluoro-1-phenylpropan-1-one (2b):[3,6] 102 mg of crude product, 88 mg (51%) of pure oily product was isolated; NMR δ (F) −94.3 ppm (q, J = 20 Hz); δ (H) 1.87 ppm (t, J = 20 Hz, 3H), 7.3–8.4 ppm (m 5H).

2,2-Difluoro-1-phenyl-2-*tert*-butylethan-1-one (2c):[3,6] 120 mg of crude product, 96 mg (48%) of pure oily product was isolated; NMR δ (F) −110.7 ppm (s), δ (H) = 1.17 ppm (s, 9H), 7.2–8.3 ppm (m, 5H).

1,1-Difluoro-1,2-diphenylethanone (2d):[3,6] 180 mg of crude product, 120 mg (51%) of pure oily product was isolated; NMR δ (F) −99.3 ppm (s); δ (H) = 7.2–8.3 ppm (m).

Determination of Relative Rate Factors of Phenylacetylenes. To a stirred solution of 0.5 mmol of 1-phenyl-1-propyne and 0.5 mmol of substituted phenylacetylene in 5 mL of acetonitrile was added 1.0 mmol F-TEDA-BF_4 and the reaction mixture heated at 76 °C for 10–20 h (consumption followed by KI starch paper). The mixture was poured into water and extracted with methylene chloride, the organic phases were washed with water and dried (Na_2SO_4), and the solvent was evaporated in vacuo. The amount of products was calculated from ^{19}F and ^1H NMR spectra. Relative rate factors were calculated from the equation[10] $k_{rel} = k_A/k_B = \log[(A-X)/A]/\log[(B-Y)/B]$, which was derived from the Ingold–Shaw relation,[11] where A and B are the amounts of starting material and X and Y are the amounts of fluorinated products derived from them.

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