SHORT PAPER

J. Chem. Research (S),
2000, 142–144

Study on the addition of hydrogen fluoride to 2′,2′-difluorostyrenes[†]

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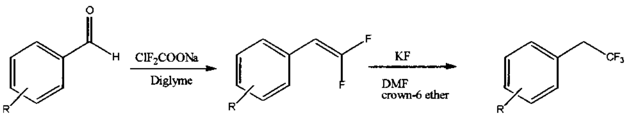
2,2,2-Trifluoroethylarenes were obtained in good yield from the addition of KF to 2′,2′-difluorostyrenes in the presence of crown ether. A linear regression line obtained from correlation between log(reaction rate) and Hammett constants with slope of +4.28 suggested that this addition process is very sensitive to the substituents on the phenyl ring.

There is considerable interest in organofluorine chemistry.[1] Organic fluorine compounds containing a trifluoromethyl group have attracted attention because of their biological activity.[2] The unique properties of the trifluoromethyl group, *e.g.* high electronegativity,[3] stability[4] and lipophilicity,[5] have ensured it an increasingly important role in organic synthesis. Many methods have been reported for the synthesis of trifluoromethyl compounds by various reagents, such as $RBr/CBrF_3$/Cu-anode,[6a] $RCOOH/SF_4$,[6b] ROH/CBr_2F_2,[6c] ROH/KF/CuI/$ClCF_2COOR$,[6d] XCF_2COOR/CuI,[6e] $RCCl_3$/ SbF_3-$SbCl_5$,[6f] $RBr/(CF_3)_2Hg$/Cu.[6g] Recently, addition of HF to 2′,2′–difluorostyrenes contained a strong electron-withdrawing groups (*i.e.*, NO_2) using KF in either DMF or DMSO solution was reported.[6h] We now report a modified process for the preparation of 2′,2′,2′-trifluoroethylarenes containing a wide variety of substituents.



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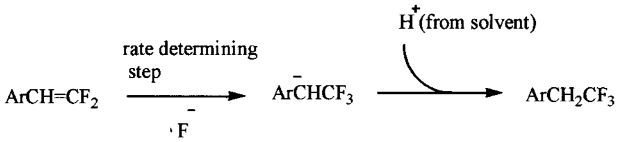
R= a. H; b. 3-CH_3; c. 4-CH_3; d. 3-OCH_3; e. 4-OCH_3; f. 3-Cl; g. 4-Cl; h. 3-Br; i. 4-Br; j. 4-CN; k. 4-F; l. 4-NO_2.

Results and discussion

The 2′,2′-difluorostyrenes were prepared from the reaction of the corresponding benzaldehyde and sodium chlorodifluoroacetate with triphenylphosphine in a diglyme solution in good yield.[7] Reactions of 2′,2′-difluorostyrenes and KF in DMF solution yielded 2,2,2-trifluoroethylarenes containing an electron-withdrawing group, such as nitro.[6h] The conversion ratio (and isolated yields) from the reaction of 2′,2′-difluorostyrene and KF under various conditions are summarized in Table 1. No addition product was observed by gas chromatographic analysis (entries 11, 16, 20, 28) after reaction of KF and 2′,2′-difluorostyrenes containing electron-donating group in DMF solution at 70 °C for one day. Apparently, the electron-withdrawing group activates the olefin of the styrene for addition. During the reaction, an electron-withdrawing group will stabilize a negative charge at the benzylic carbon (*i.e.*, α-position) through resonance of the benzene ring. The partial positive centre accepts a fluoride ion followed by attracting a proton from either solvent or moisture in the mixture (Scheme 1). On the other hand, a less effective electron-withdrawing group or electron-donating group is unable to create a positive centre on the β position leading to poor (or no) conversion.



Scheme 1

Since the addition of HF to difluorostyrenes was so sensitive to the substituents on the phenyl ring, we studied the relation between the reaction rates and the substituents on the phenyl ring. The relative reaction rates were obtained from the mixture of equal equivalent (0.5 mmole) of substituted styrene and unsubstituted styrene (**3a**) and a limiting amount of KF (0.4 mmole) in DMF solution containing water (2.2 mmol). After 1 h reaction, the mixtures were diluted with CH_2Cl_2 for GC-MS analyses. Under these conditions, the reactions of compounds **3j** and **3l** reached maximum conversion within 15 min. The area ratios of the trifluoroethylarenes were used to calculate the relative reaction rate after various reaction periods depending on the nature of substituent (Table 2). A linear regression line was obtained from the correlation between log(relative rate) and Hammett substituent constants with ρ = +4.28 and R^2 = 0.9904 (Fig. 1). Compound **3m** was excluded from this plot because it far below the correlation line. This might be rationalized by limiting diffusion-control under these conditions. The positive slope suggests that the reaction centre bears a positive charge. This is apparently different from the other types of addition to styrenes.[8]

Crown-ethers are well known ligands which chelate with a metal ion allowing the anion to become a naked anion enhanc-

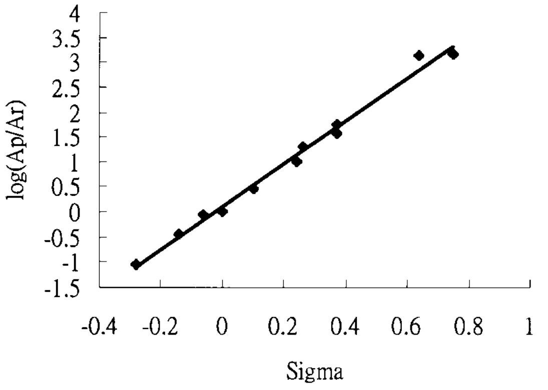


Fig. 1 Correlation between log (relative area ratio, ap/Ar) and Hammett constants for HF addition to 2′,2′-difluorostyrenes. $y = 4.28x + 0.102$; $R^2 = 0.9904$.

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[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Conversion ratio in the addition of HF into difluorostyrene in the various conditions[a]

Entries	R^1	R^2	σ^b	Solvent	Crown	Temp. (°C)	Time (h)	Conversion ratio^c (isolated yield)
1	3-Br	F	0.39	DMF	N	70	4	68^{6a}
2				DMF	Y	70	4	100 (85)
3	3-Cl	F	0.37	DMF	N	70	8	57^{6e}
4				DMF	Y	70	4	100 (88)
5	4-Br	F	0.23	DMF	N	70	8	55^{6e}
6				DMF	Y	70	4	100 (92)
7	4-Cl	F	0.23	DMF	N	70	8	39^{6e}
8				DMF	Y	70	5	100 (90)
9				NMP	N	180	8	100
10				NMP	Y	70	8	100
11	H	F	0.00	DMF	N	70	8	0
12				DMF	Y	70	8	60^{6e}
13				DMF	Y	150	8	100 (75)
14				NMP	Y	70	8	0
15				NMP	N	180	4	76
16	3-Me	F	–0.07	DMF	N	70	16	0
17				DMF	Y	70	8	40^{6e}
18				DMF	Y	150	6	100 (80)
19				NMP	Y	180	8	100
20	4-Me	F	–0.17	DMF	N	70	16	0
21				DMF	Y	70	8	35^{6e,f}
22				DMF	Y	150	8	100 (85)
23				NMP	Y	180	8	85
24	3-OMe	F	–0.12	DMF	N	70	24	4
25				DMF	Y	70	8	24
26				DMF	Y	150	8	100 (78)
27				NMP	Y	180	8	95^d
28	4-OMe	F	–0.27	DMF	N	70	24	0
29				DMF	Y	70	8	32
30				DMF	Y	150	10	100 (80)
31				NMP	Y	70	8	0
32				NMP	Y	180	8	89^d
33	H	H		DMF	Y	150	8	0
34				NMP	Y	180	8	0
35	4-NO_2H			DMF	Y	150	8	0
36				NMP	Y	180	8	0
37	4-Me	H		DMF	Y	150	8	0
38				NMP	Y	180	8	0

[a] DMF: dimethylforamide; NMP: N-methylpyrrolidine; crown: 18-crown-6.
[b] Hammett constant of the substituent on the phenyl ring.
[c] Estimated from the area ratio obtained from GC–MS analyses.
[d] Partial decomposition to give toluene derivatives.

ing its reactivity. In this work, we found that the crown-ether enhanced the reactivity of fluoride toward difluorostyrenes. In the presence of a crown-ether, HF added to 2′,2′-difluorostyrenes at 70°C in despite of nature of the substituents (entries 2, 4, 6, 8, 12, 17, 21, 25 29). For the compounds containing –Me, –OMe (entries 18, 22, 26, 30), the reaction proceeded to complete conversion at 150°C within 8 h (10 h for 4-OMe). However, no HF addition to vinylarene (entries 33~38) was observed under our conditions further suggesting that the participation of fluorine atom at vinyl group creates a negative charge at the benzylic carbon after the addition of fluorine ion.

Table 2 Relative area ratio between 2′,2′,2′-trifluoroethylarenes to 2′,2′,2′-trifluoroethylbenzene in competitive reactions from GC-MS analyses[a]

R	Hammett constant (α)	Ap/Ar	log(Ap/Ar)
4-OMe	–0.28	0.0896	–1.047
4-Me	–0.14	0.347	–0.459
3-Me	–0.06	0.847	–0.0721
3-OMe	0.10	2.82	0.450
4-Cl	0.24	9.67	1.00
4-Br	0.26	20.37	1.309
3-Cl	0.37	35.59	1.551
3-Br	0.37	57.28	1.758
4-CN	0.64	1324	3.122
4-NO2	0.75	1447	3.161

[a] The conditions were described in the experimental section. The results are average from duplicated runs. Ap/Ar = area of 2′,2′,2′-trifluoroethylarene/ area of 2′,2′,2′-trifluoroethylbenzene.

N-Methylpyrrolidine (NMP) is a polar solvent with a high boiling point which is expected to enhance the reaction rate for a reaction through a polar (or ionic) transition state. In this work, we could not find any significant advantage in the conversion ratio in using this solvent. On the other hand, dark solutions were obtained and 3-bromotoluene was observed from the reaction of 3-bromo-2′,2′-difluorovinylbenzene based on the GC–MS analysis. Both factors would be drawbacks in the use of NMP for this system.

Experimental

General: ^{1}H NMR spectra were recorded at 250 MHz and ^{13}C NMR at 62.86 MHz at ambient temperature. Chemical shifts for the samples in

Table 3 Concentration of 2′,2-difluorostyrene **3a** in the various time during HF addition course[a]

Time (min)	concentration (nM)
0	6.00 x 10-3
5	5.39 x 10-3
10	4.78 x 10-3
15	4.28 x 10-3
20	3.81 x 10-3

[a] The details conditions has been described, the results are average from duplicated runs.

deuteriochloroform solution are reported δ units relative to tetramethylsilane. EI mass spectra were obtained on a GC (Fisons 8000 series) /MS (Finnigan MD-800) at an ionization potential of 70 eV. Infrared spectra were determined with a Perkin-Elmer model 883 grating infrared spectrophotometer using a potassium bromide pellet.

Typical addition procedure: A mixture of 3-(2′.2′-difluorovinyl)anisole (**3d**, 1.0 g, 5.8 mmol), potassium fluoride (1.0 g, 17.3 mmol), and 18-crown-6 ether (0.08 g, 0.3 mmol) in DMF (10 mL) containing H_2O (0.1 mL, 5.5 mmol) was heated at 150°C with stirring for 8 h. The reaction mixture was poured into water (100 mL), extracted with ether (100 mL × 3), organic layer was washed with water (100 mL × 3), dried (Na_2SO_4), and solvent was removed under reduced pressure. 3-(2′,2′,2′-trifluoroethyl)anisole (**1d)** was distilled off at 72°C/210 torr (0.87 g, 78%) as a clear liquid. IR 1841, 1256, 1138 cm^{-1}; ^{1}H NMR δ 3.37 (q, 2H, *J* 10.8 Hz), 3.84 (s, 3H), 6.90~6.94 (m, 2H), 6.95 (s, 1H), 7.32(t, 1H, *J* 7.6 Hz); ^{13}C δ NMR 40.08 (q, *J* 29.6 Hz), 55.05, 125.79 (q, *J* 276.6 Hz), 113.35, 115.92, 121.44, 129.63, 131.48, 159.70; ^{19}F NMR δ –67.05; MS (*m/z*, %) 190(M$^+$, 100), 121(63), 91(41); *Anal. Calcd for* $C_9H_9OF_3$: C, 56.84; H, 4.77. Found: C, 56.69; H, 4.70.

4-(2′,2′,2′-trifluoroethyl)anisole (**1e**): liquid, bp 86°C/200 torr; 80% yield; IR 1841, 1262, 1136 cm^{-1}; ^{1}H NMR δ 3.32 (q, 2H, J 10.86 Hz), 3.82 (s, 3H), 6.91 (d, 2H, *J* 8.5 Hz), 7.24 (d, 2H, *J* 8.5 Hz); ^{13}C NMR δ 39.31 (q, *J* 29.7 Hz), 55.16, 125.90 (q, *J* 276.5 Hz), 114.04, 122.11, 131.24, 159.42; ^{19}F NMR δ–67.69; MS (*m/z*, %) 190(M$^+$, 23.7), 121 (100); *Anal. calcd for* $C_9H_9OF_3$: C, 56.84; H, 4.77. Found: C, 56.65; H, 4.74.

Competition reaction: A mixture of substituted difluorostyrene (0.50 mmole), difluorostyrene (0.50 mmole), KF (0.4 mmole), in DMF (1.0 mL) containing H_2O (40 µL, 2.2 mmole) were heated at 150 ± 2°C for 1.0 h. The mixture (0.5 mL) were diluted with CH_2Cl_2 (1.0 mL) for GC–MS analyses. The relative rates were estimated according to the ratio of the product areas from chromatographic analyses (Table 2).

Kinetic runs: KF (23 mg, 0.50 mmole) was added. To a mixture of 2′,2′-difluorostyrene (70 mg, 0.40 mmole), and biphenyl (40 mg, 0.26 mmole, as internal standard) in DMF (1.0 mL) containing H_2O (40 µL, 2.2 mmol) at 150 ± 2°C. Aliquots (0.2 mL) were sampled at 10, 20, 40, 60, and 80 min, respectively and then were diluted with CH_2Cl_2 (1.0 mL) for GC–MS analyses. The relative areas of 2′,2′-difluorostyrene to biphenyl from the chromatogram were used to calculate the initial rate for the HF addition (Table 3). Under this reaction condition, the reaction rate was approximate 7.0 × 10^{-3} mol/L min.

We thank the National Science Council (NSC 88-2113-M-126-006) for the financial support.

Received 14 October 1999; accepted 3 January 2000
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