Notes

Substituent Effects in the Fluorination–Rearrangement of 1,1-Diarylethenes with Aryliodine(III) Difluorides

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Aryliodine(III) difluorides represent an interesting and relatively little studied class of fluorinating agents. Early studies were conducted on the generation of phenyliodine(III) difluoride and its reactions with a few selected alkenes.[2-4] Carpenter developed an improved method for the preparation of phenyliodine(III) difluoride from the dichloride and studied its reaction with arylethenes.[5] Zupan and co-workers more recently prepared aryliodine(III) difluorides directly from the iodoaromatic and xenon difluoride and applied their method to the preparation of a polymer-bound phenyliodine(III) difluoride.[6-8]

Carpenter and Zupan et al. also studied the synthetic and mechanistic aspects of the reaction between aryliodine(III) difluorides and 1,1-diarylethylene or norbornene. Their studies provided a fairly mild and selective preparation of 1,1-difluoro-1,2-diphenylethanes (reaction 1) and led to the suggested mechanistic pathway shown

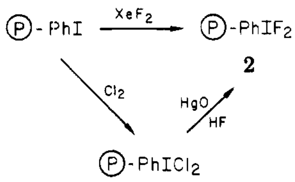
$$ArIF_2 + Ph_2C{=}CH_2 \rightarrow PhCF_2CH_2Ph + ArI \quad (1)$$

in Scheme I.[5,6]

In a continuation of our research into new fluorination methods,[9] we have studied the preparation of several aryliodine(III) difluorides and have explored the scope and mechanism of their reaction with selected 1,1-diarylethenes. This paper reports the results of our investigations.

Results and Discussion

A major problem in the reaction of 1,1-diarylethenes with phenyliodine(III) difluoride (**1**, Ar = Ph) is removal of iodobenzene from the desired products.[2-5] Zupan and co-workers circumvented this problem through the use of polymer-bound phenyliodine(III) difluoride (**2**).[8] The preparation of their polymer, however, involves the use of expensive xenon difluoride. We thus sought to prepare the polymer by application of Carpenter's procedure to polymer-bound phenyliodine(III) dichloride. Unfortunately many attempts to prepare the polymer-bound difluoride by reaction of the dichloride with mercuric oxide and hydrofluoric acid failed to produce the desired product. We then directed our attention to the preparation of (p-iodophenyl)acetic acid difluoride (**3**). Compound **3** would permit easy extraction of the (p-iodophenyl)acetic acid formed in the reaction. The acid function was not placed directly on the aromatic ring because ring deactivators are known to decrease the yield of fluorination products from aryliodine(III) difluorides.[2-7] The desired (p-iodophenyl)acetic acid difluoride was prepared easily from (p-aminophenyl)acetic acid (see the Experimental Section). Although several synthetic steps are required, the reagent is an effective homogeneous fluorinating agent, the products are easily purified, and the recovered (p-iodophenyl)acetic acid is recyclable.



Scheme I

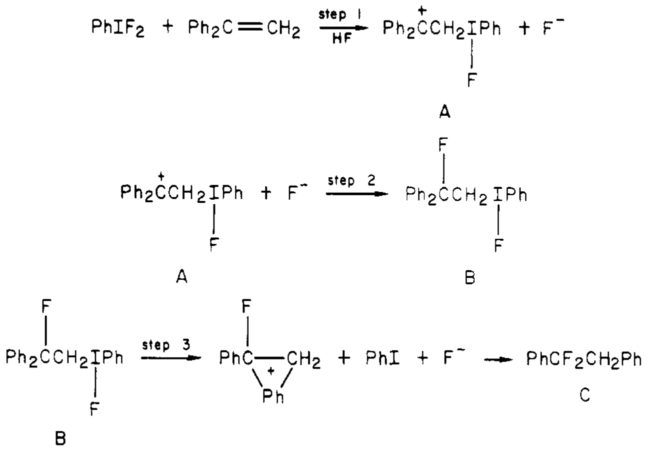


Table I. Relative Reactivity of Diarylethenes with 3

$(RPh)_2C{=}CH_2$	R	relative reactivity[a]
4a	p-OCH_3	200–500
b	p-CH_3	11.0
c	H	1
d	p-Br	0.04

[a] Average of 6–8 determinations.

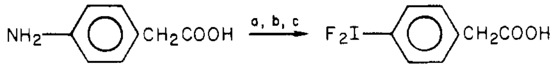
Table II. Relative Migratory Aptitudes

$$R^1Ph(C{=}CH_2)PhR \xrightarrow{3} RPhCF_2CH_2PhR^1$$

	R^1	R	R^1/R ratio
	p-OCH_3	H	large[a]
8a	p-OCH_3	p-Cl	200
8b	p-Ch_3	H	15.4
8c	H	H	1
8d	p-Cl	H	0.48
	m-Cl	H	0[a]

[a] Reference 6.

Reaction of para-substituted 1,1-diphenylethenes (**4a–d**)



a, HNO_2, 0 °C, KI; b, Cl_2; c, HF, HgO

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[1] Taken from the M.S. Theses of (a) J.J.S. (1980), (b) W.E.H. (1976), (c) Y.H.L. (1976), submitted to Southern Illinois University.

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Table III. Yields and Properties of 1,1-Difluoro-1,2-diphenylethanes

$RPhCF_2$-CH_2PhR'	R	R′	% yield	mp, °C	^1H NMR[a]	^{19}F NMR[b]	^{13}C NMR[c]
9a	H	H	60	65-66	3.3	95.2	121.9, 45.9
b*	CH_3	CH_3	65	liquid	3.23 2.25, 2.30 (CH_3)		121.9, 45.2 21.0, 21.1 (CH_3)
c*	Br	Br	50	61-62	3.3	93.3	121.2, 45.1
d*	OCH_3	OCH_3	40	dec	3.25	93.0	*d*
e*	H	OCH_3	40	87-90	3.24 3.7 (CH_3)	95.0	122.0, 44.9 55.0 (CH_3)
f*	H	CH_3	50	liquid	3.3 2.24 (CH_3)		122.0, 45.0 21.0 (CH_3)
g*	Cl	H	40[e]	55[e]	3.24	94.0	*f*
h*	H	Cl	40[e]	55[e]	3.21	95.0	*f*
f*	Cl	OCH_3	30	85-87	3.30 3.7 (CH_3)	 94.0	124.2, 44.9 55.1 (CH_3)
7			53	81-82	4.0 (m)	90.8 (dd)[g] 96.0 (dd)	125.5

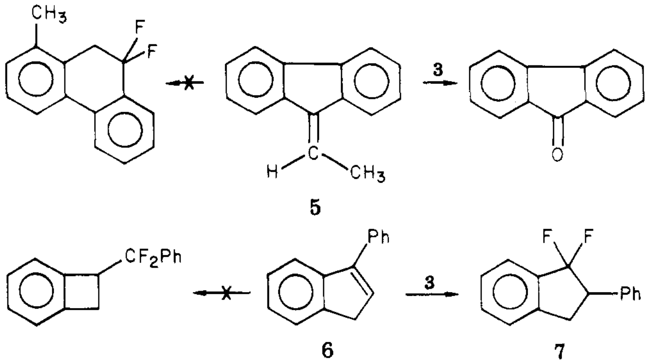
[a] Chemical shift of the CH_2 group observed as a triplet with $J = 18$ Hz. Aromatic protons could be found at δ 7.1-7.3 as muliplets. [b] Chemical shift of the CF_2 group observed as a triplet with $J = 18$ Hz. [c] The first value reported is for the CF_2 carbon observed as a triplet with $J = 240$-244 Hz. The second value is for the CH_2 carbon observed as a singlet. Aromatic carbon signals could be observed at 124-138 ppm. [d] Decomposed. [e] Mixture of 2 parts **9g** and 1 part **9h**. [f] Not recorded. [g] $J_{FF} = 126$, $J_{FH} = 13$ Hz.

with **3** in methylene chloride solution in the presence of HF permitted determination of substituent electronic effects on the relative rates of the fluorination reaction. The observed relative rates given in Table I are typical of a carbocation process in which **3** behaves as an electrophile toward the ethenes.[10] Although step 3 also shows a substituent effect (vida infra), our reaction conditions permitted step 3 to go to completion. Thus the relative rates given in Table I reflect the substituent effect on step 1.

The relative rates reported in Table I were determined from competitive reactions in which 1,1-diphenylethene was used as the standard. The ratios reflect the relative amounts of 1,1-difluoro-1,2-diphenylethane products formed as determined from ^{19}F NMR and mass spectral measurements. Relative rates for **4a** were difficult to obtain because the product reacted further to give a complex mixture.

A study of structural effects and migratory aptitudes on the rearrangement step of the reaction sequence gave interesting results. 9-Ethylidenefluorene (**5**) reacted with **3** to produce only 9-fluorenone. Ring expansion to a fluorophenanthrene derivative was not observed, but the observed oxidation is in agreement with the carbocation requirement as addition to **5** would require the formation of an antiaromatic 9-fluorenyl cation.[11] Thus, oxidation is preferred. 1-Phenylindene (**6**) was used as a substrate to probe whether ring contraction to a benzocyclobutane would occur. The major product, however, was **7** from phenyl migration, and no spectral evidence for a benzocyclobutane was observed.

The migratory aptitude of the aryl groups in substituted diphenylethenes was studied with the series of compounds (**8a-d**) shown in Table II. The phenyl ring which migrates preferentially is bonded to the methylene group in the product. Rearrangement product ratios were determined from ^{19}F NMR measurements and from mass spectrometric measurements of the tropylium ion fragments. Zupan and Gregorcic previously reported exclusive migration of *p*-methoxyphenyl over phenyl and exclusive migration of phenyl over *m*-chlorophenyl.[6] Our results combined with those of Zupan, reported in Table II, give evidence consistent with the formation of a phenonium ion (C) in the rearrangement step.[12] The observed migratory aptitudes are *p*-OCH_3 > *p*-CH_3 > H > *p*-Cl > *m*-Cl.



In conclusion, we have shown that **3** is an effective and economical reagent for homogeneous fluorination of 1,1-diphenylethenes. The substituent effects and migratory aptitudes observed are consistent with an electrophilic addition of **3** to the diarylethene followed by a rearrangement step involving a phenonium ion. The results thus confirm the previously suggested Carpenter-Zupan mechanistic pathway shown in Scheme I.[5,6] The reported isolation of a phenyliodine(III) difluoride addition adduct with a steroid dienone lends support for intermediate B.[13] However, we were unable to detect B in low-temperature ^1H NMR experiments.

Experimental Section

General. Temperature readings are uncorrected. ^1H NMR spectra were recorded at 60 MHz on a Perkin-Elmer R24B instrument with internal tetramethylsilane (δ 0.0) as a standard. ^{19}F NMR spectra were recorded at 84.6 MHz on a JEOL FX-90Q spectrometer with internal Freon-11 (ϕ 0.0) as a standard. ^{13}C NMR spectra were recorded on a JEOL FL-60Q spectrometer at 15.0 MHz with internal tetramethylsilane (δ 0.0) as a standard. Deuteriochloroform was used as the solvent in all cases. Mass spectra were recorded at 80 eV on a Varian MAT-111 spectrometer. Samples were introduced through a direct inlet probe. All new compounds, marked with an asterisk, gave elemental analyses within ±0.3% of the theoretical by Industrial Testing Laboratories, St. Louis, MO.

Synthesis of (*p*-Iodophenyl)acetic Acid Difluoride (3). (*p*-Iodophenyl)acetic Acid.* A solution of 1.6 g of sodium nitrate in 20 mL of water was added slowly at 0-10 °C to a mixture of (*p*-aminophenyl)acetic acid (3.0 g, 0.02 mol) in 50 mL of 3 N hydrochloric acid. A solution of potassium iodide (3.0 g) in 10 mL of water was added after several hours. The dark mixture

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was extracted with ether and dioxane, and the organic extracts were washed with sodium bisulfite. Removal of the solvents gave a yellow solid which was recrystallized from ethanol-water to give 5.0 g (95%) of the iodo acid: mp 129-133 °C; ^{1}H NMR δ 3.6 (s, CH_2), 7.2-7.7 (dd, aromatic), 11.2 (OH); ^{13}C NMR δ 40.5 (CH_2), 92.8, 131.2, 132.7, 137.6 (aromatic), 177.1 (COOH); IR (KBr) 3200-2900 (OH), 1690 (C=O) cm^{-1}. Anal. C, H, I.

(*p*-Iodophenyl)acetic Acid Dichloride. A solution of (*p*-iodophenyl)acetic acid (3.0 g) in 50 mL of chloroform in a three-necked flask protected from the light was treated with dry chlorine gas at 0 °C for 10 min. The dichloride precipitated from the solution and was collected by filtration. The yield of pure product was 86%: mp 88-90 °C dec; ^{1}H NMR δ 3.7 (s, CH_2), 7.2-7.5 (aromatic), 10.0 (OH).

(*p*-Iodophenyl)acetic Acid Difluoride (3). A mixture of 1.5 g of mercuric oxide, 100 mL of methylene chloride, and 2.3 g of dichloride was treated with 2 mL of 48% hydrofluoric acid, and the mixture was shaken vigorously for 8-10 min. The methylene chloride layer was decanted and used immediately. The yield of **3** by titration of the iodine liberated after reaction with potassium iodide was 95%.

Reaction of 3 with 1,1-Diarylethenes. General Procedure.[5] The reaction with 1,1-diphenylethylene is typical. A solution of 2.0 g (11 mmol) of 1,1-diphenylethylene in 8 mL of methylene chloride was added at 0 °C during 10 min to a solution (1 equiv) of **3** in methylene chloride. The mixture was stirred at 0 °C for 3 h. The mixture was extracted with sodium bicarbonate solution, and the organic phase was separated, dried, concentrated, and chromatographed on silica gel (hexane) to give pure 1,1-difluoro-1,2-diphenylethane in 60% yield, mp 64-66 °C (lit.[5] mp 65-66 °C). Unreacted starting material accounted for a 95% material balance.

The sodium carbonate solution was acidified and extracted with ether. The dried ether solution was concentrated to give (*p*-iodophenyl)acetic acid with about 95% recovery.

Yields and spectral data of 1,1-difluoro-1,2-diarylethanes are reported in Table III. Anal. C, H, Br, or Cl.

Preparation of 1,1-Diarylethenes. All 1,1-diarylethenes used in this study were prepared by the dehydration of the appropriate alcohol obtained from a Grignard reaction. All of the compounds are known and had spectral and physical properties consistent with reported values.[14]

Relative Reactivity Studies. To a freshly prepared solution of **3** (3.3 mmol, iodometric analysis) in 20 mL of methylene chloride contained in a polyethylene bottle was added a solution containing at least a 10-fold exess of each of the competing ethene and 1,1-diphenylethene. The mixture was stirred at 0 °C for 1 h and washed with dilute sodium bicarbonate. The methylene chloride solution was analyzed immediately by ^{19}F NMR spectroscopy. Relative areas of the CF_2 triplet signal in the products were used to determine relative ratios. Experiments performed for 30 min, and 3 h gave identical results. The results are reported in Table I. An average of six to eight experiments was performed for each determination. Several substrate ratios were used to substantiate the results.

Migratory Aptitudes. A solution of **3** (10 mmol) and unsymmetrical 1,1-diarylethene **8** (10 mmol) were stirred at 0 °C for 2 h in a polyethylene bottle. The mixture was extracted with sodium bicarbonate solution. The methylene chloride solution was analyzed by ^{19}F NMR for the relative amounts of product, which were confirmed by mass spectrometric analysis of the concentrated methylene chloride solution. The tropylium ion and substituted tropylium ion could be easily detected, and relative peak heights could be used to determine relative product ratios. ^{19}F NMR and mass spectral measurements agreed to within 3% of each other. The results given in Table II represent an average of five runs.

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Influences of Alkyl Groups on the Rates of Decomposition of *N*-Nitrosoureas in Basic Aqueous Solution

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Alkyl groups exert an important influence on the rate of hydrolysis of the *N*-nitrosoureas in basic solution. Garrett and his associates reported that *N*-cyclohexyl-*N*-nitrosourea decomposes about 40-fold more rapidly than *N*-methyl-*N*-nitrosourea.[1] On the other hand, Lijinsky and Taylor noted that compounds such as *N*,*N'*,*N'*-trimethyl-*N*-nitrosourea react very slowly.[2] Indeed, the relative rate of hydrolysis of *N*-methyl-*N*-nitrosourea compared to *N*,*N'*,*N'*-trimethyl-*N*-nitrosourea is 2.17×10^4.[3] Our interest in the factors governing the course of the decomposition reactions of these compounds led us to examine the reactivity of other alkylnitrosoureas.

Results and Discussion

The nitrosoureas were prepared as described previously.[4] The procedures used for the study of the decomposition of these molecules in basic solution were also described previously.[3] All the nitrosoureas examined in this study decomposed in first-order processes at pH 9.75. The kinetic data for the decomposition of the *N*-alkyl-*N*-nitrosoureas in basic solution are summarized in Table I.

Garrett and his associates established that the *N*-alkyl-*N*-nitrosoureas decompose in specific base-catalyzed reactions near pH 7.[1] The rate data provided by these workers indicate that all of the *N*-alkyl compounds with primary alkyl groups decompose at similar rates. Neither the allyl nor the benzyl derivative is significantly more reactive than the methyl derivative. In contrast, *N*-cyclohexyl-*N*-nitrosourea decomposes much more rapidly than *N*-methyl-*N*-nitrosourea.[1] It was our intention to study the rates of hydrolysis of *N*-isopropyl- and *N*-*tert*-butyl-*N*-nitrosourea. Regrettably, these compounds were quite unstable and could not be purified without concomitant decomposition. However, several samples of *N*-isopropyl-*N*-nitrosourea hydrolyzed immeasurably rapidly at pH 9.75 ($k_{obsd} > 1$ s^{-1}). The compound also decomposed upon being allowed to stand in anhydrous chloroform. Isopropylurea was not present in the products of the decomposition reaction.

The fact that secondary alkyl groups accelerate the decomposition reaction while allyl and benzyl groups have only a modest influence on the reaction suggests that steric interactions are significant. To study this aspect of the reaction, we investigated the *N*-methyl-*N'*-alkyl- and *N*-methyl-*N'*,*N'*-dialkyl-*N*-nitrosoureas. The kinetic results are summarized in Tables II and III.

N,*N'*-Dimethyl-*N*-nitrosourea is much less reactive than *N*-methyl-*N*-nitrosourea, $k_{obsd}(\mathrm{DMNU})/k_{obsd}(\mathrm{MNU}) = 3.0 \times 10^{-3}$. Somewhat surprisingly, the other compounds with *N'*-alkyl groups exhibit the same degree of reactivity whether the *N'*-alkyl group is primary, secondary, or tertiary. The introduction of the third methyl group also retards the reaction, $k_{obsd}(\mathrm{TMNU})/k_{obsd}(\mathrm{MNU}) = 5.0 \times 10^{-5}$. The *N*,*N'*-diethyl compound and the other *N'*,*N'*-dialkyl derivative are about tenfold less reactive than the

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