Stereochemistry of Iodofluorination of Phenyl-substituted Olefins with (Difluoroiodo)methane

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(Difluoroiodo)methane reacts with substituted olefins, *e.g. cis*- and *trans*-stilbene, *cis*- and *trans*-β-alkylstyrenes, and indene, to form the corresponding iodo-fluorides. Iodofluorination proceeds with Markovnikov-type regioselectivity and is stereospecifically *anti*, forming the corresponding (±)-*erythro*- or (±)-*threo*-1-fluoro-2-iodo-1-phenylethanes.

THE addition of fluorine to olefins by use of (difluoroiodo)arenes as fluorinating agents has received limited attention,[1-6] possibly because these reagents are difficult to prepare and unstable. We have made recent efforts to develop the polymeric fluorinating agent poly-[*p*-(difluoroiodo)styrene],[7] and have also investigated the fluorination of 1-phenylethylenes with (difluoroiodo)methane. (Difluoroiodo)methane[8] reacts with 1,1-diphenylethylenes in the presence of hydrogen fluoride as catalyst to form the corresponding 1-fluoro-2-iodo-1,1-diphenylethanes[9] and not the rearranged 1,1-difluoro-1,2-diphenylethanes obtained in a similar reaction with (difluoroiodo)arenes.[6] Being interested in learning whether all *cis*- and *trans*-olefin pairs would exhibit the same stereochemistry in the iodofluorination by (difluoroiodo)methane, we chose *cis*- (1a) and *trans*- (2a) 1-phenylpropene, *cis*- (1b) and *trans*- (2b) stilbene, and *cis*- (1c) and *trans*- (2c) 1-phenyl-2-t-butylethylene for study. We have also investigated the iodofluorination of indene.

The preparation of fluoroalkenes presents a different problem from that of other halogenoalkanes, and necessitates a specific method of fluorination.[10] Difficulties involve the handling of anhydrous hydrogen fluoride on the laboratory scale, the need for pressure equipment and low temperatures, and the ease of polymerization of alkenes.[11] Iodofluorination with hydrogen fluoride–pyridine–*N*-iodosuccinimide avoids some experimental difficulties.[12] Following the procedure reported by Gibson,[8] we prepared a solution of (difluoroiodo)methane by the reaction of xenon difluoride with an excess of methyl iodide. The reaction with *cis*- and *trans*-1-phenylpropene in each case resulted in one product. *cis*-1-Phenylpropene (1a) gave (±)-*threo*-1-fluoro-2-iodo-1-phenylpropane (4a), and *trans*-phenylpropene (2a) the *erythro*-isomer (3a). The products were identified on the basis of ^{1}H and ^{19}F n.m.r. data, mass spectra, and the elimination of hydrogen iodide under basic conditions to afford the known[13] *trans*- (8a) and *cis*- (9a) 1-fluoro-1-phenylpropene (Scheme 1). The n.m.r. spectra showed that the elimination of hydrogen iodide proceeded with a high degree of *anti*-stereoselectivity. Prolongation of the reaction (from 1 to 2 h) resulted in a mixture of diastereoisomeric iodo-fluorides (3a) (major product in the reaction with *trans*-phenylpropene) and (4a) (major product in the reaction with *cis*-phenylpropene), traces of difluoride (5a) and (6a), and *ca.* 15% of geminal difluorides (7) (Scheme 2) produced by rearrangement, identical with the products obtained in the fluorination of *trans*-

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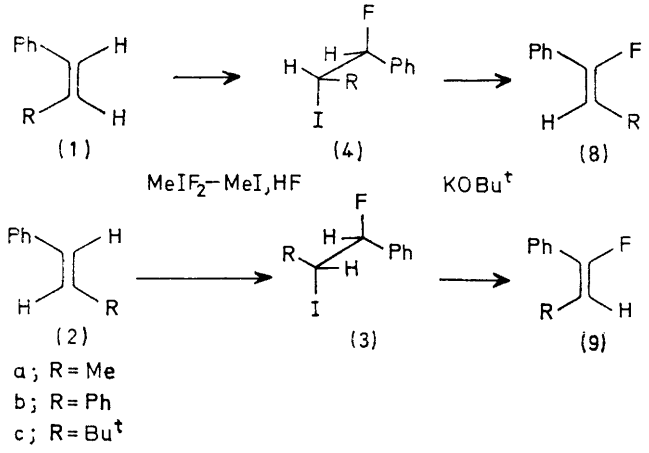
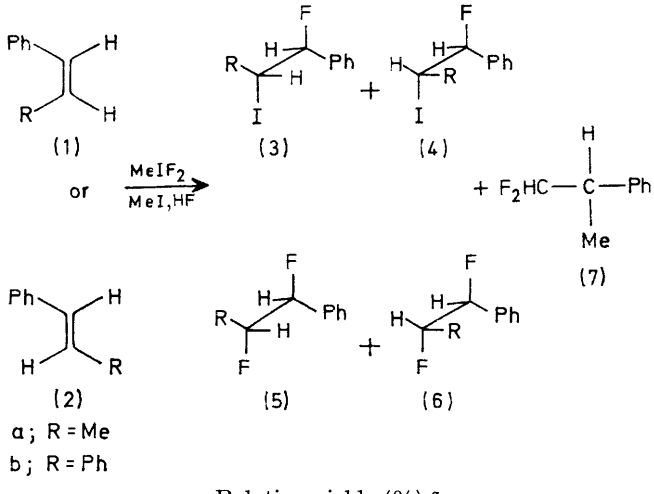
1-phenylpropene with 1-chloro-3-(difluoroiodo)arenes.[9] The structures of the difluorides (5a) and (6a) were assigned on the basis of ^{1}H and ^{19}F n.m.r. data and comparison with independently prepared difluorides.[13] The



SCHEME 1

product distributions (Scheme 2) indicate that iodofluorination of both *cis*- and *trans*-1-phenylpropene is an *anti*-stereoselective process, following Markovnikov-type regioselectivity. The formation of difluorides (5a) and (6a) exhibits lower *anti*-stereoselectivity, which could be explained in terms of S_N1 reaction of iodo-fluorides with hydrogen fluoride.



Relative yields (%) [a]

R	(3)	(4)	(5)	(6)	(7)
(1) Me	4	80		1	15
Ph	10	52	20	18	
(2) Me	78	4	4		14
Ph	56	4	36	3	

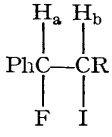
[a] Determined by ^{19}F n.m.r. spectroscopy.

SCHEME 2

The reactions of (difluoroiodo)methane with *cis*- (1b) and *trans*- (2b) stilbene resulted in each case in one product. *cis*-Stilbene (1b) gave (±)-*threo*-1-fluoro-2-iodo-1,2-diphenylethane (4b), and the *trans*-isomer (2b) gave the *erythro*-derivative (3b). The products were identified on the basis of n.m.r. and mass spectral data and their chemical transformation (Scheme 1). Prolongation of the reaction (from 1 to 2 h) resulted in a mixture of diastereoisomeric vicinal iodo-fluorides (3b) (major product in the reaction with *trans*-stilbene) and (4b) (major product in the reaction with *cis*-stilbene) and difluorides (5b) and (6b). The structures of the difluorides were assigned from ^{1}H and ^{19}F n.m.r. data [13,14] and on the basis of comparison with samples prepared independently. As in the iodofluorination of 1-phenylpropenes, *anti*-stereoselectivity was observed.

The reaction with *cis*-1-phenyl-2-t-butylethylene (1c) (1 h) resulted in (±)-*threo*-1-fluoro-2-iodo-1-phenyl-2-t-butylethane (4c), and that of the *trans*-olefin (2c) afforded the *erythro*-isomer (3c). The structures of the isomeric iodofluorides were assigned on the basis of significant differences in their ^{1}H and ^{19}F n.m.r. spectra (Table):

N.m.r. data (δ values; *J* in Hz) for 1-fluoro-2-iodo-1-phenylalkanes



	(±)-*erythro* (3)			(±)-*threo* (4)		
R:	Me	Ph	Bu^t	Me	Ph	Bu^t
δ(F)	−189.5	−180.3	−163	−182	−180	−199
δ(H$_a$)	5.5	5.8	5.6	5.2	5.4	5.2
δ(H$_b$)	4.3	5.2	4.45	4.3	5.1	3.95
δ(R)	1.8	7.2	1.3	1.8	7.2	1.2
δ(Ph)	7.2		7.3	7.2		7.3
J(FH$_a$)	45	46.5	48	45	46.5	48
J(FH$_b$)	19	16.5	6	18	18	36.5
J(H$_a$H$_b$)	6	7.5	9	6	6	<1

J(H$_a$H$_b$) 9 (3c) or <1 Hz (4c); *J*(FH$_b$) 9 (3c) or 36.5 Hz (4c). The n.m.r. spectra of the pairs of diastereoisomers (3) and (4) can be shown to be in agreement with the assigned stereochemistry from a consideration of possible conformational isomers. The three main conformations of the (±)-*erythro*-compounds (3) are shown in Newman projections in Scheme 3. Consideration of both electrostatic interactions and steric requirements of I, R, and Ph leaves little doubt that (3A) is of lowest energy and will predominate over the other two. On the basis of the Karplus rule for *J*(FH$_b$),[15,16] the predominant conformer (3A) is the only one in the case of the (±)-*erythro*-compound (3c) having *J*(H$_a$H$_b$) 9 Hz and *J*(FH$_b$) 6 Hz. With regard to the *threo*-iodo-fluorides (4a—c) there is also evidence for the product (4c) existing as the predominant conformer (4C), *J*(H$_a$H$_b$) being 1 Hz and *J*(FH$_b$) 36.5 Hz. N.m.r. data (Table) show very small differences in *J*(H$_a$H$_b$) and *J*(FH$_b$) for the pairs (3a) and (4a), and (3b) and (4b), and for this reason a chemical transformation was needed to determine the structure of

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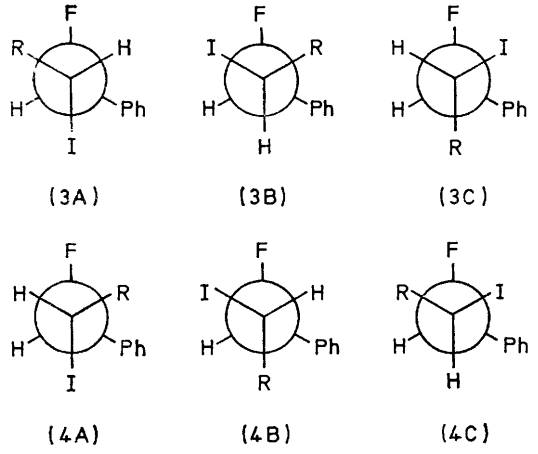
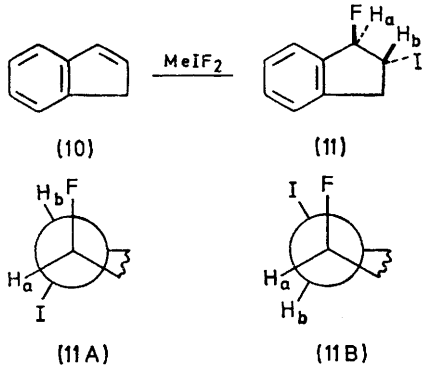
the product. Chemical shifts of the H_a in the *erythro*- and *threo*-iodo-fluorides are characteristic of the stereochemistry, those of the *erythro*-isomers (3) being the greater.



SCHEME 3

In the reaction with indene (10) (Scheme 4) we observed the formation of only one isomer, which showed a double doublet signal at δ −175.5 p.p.m. in its ^{19}F n.m.r. spectrum, with J values of 57 and 18 Hz, characteristic of geminal and vicinal coupling, respectively. The Newman projections of the two possible isomers [the *trans*-adduct (11A) and the *cis*-adduct (11B)] are presented in Scheme 4. On the basis of the Karplus relationship,[15,16] with $J(H_aH_b)$ 3 and $J(FH_b)$ 18 Hz the formation of the *trans*-isomer (11A) was established.

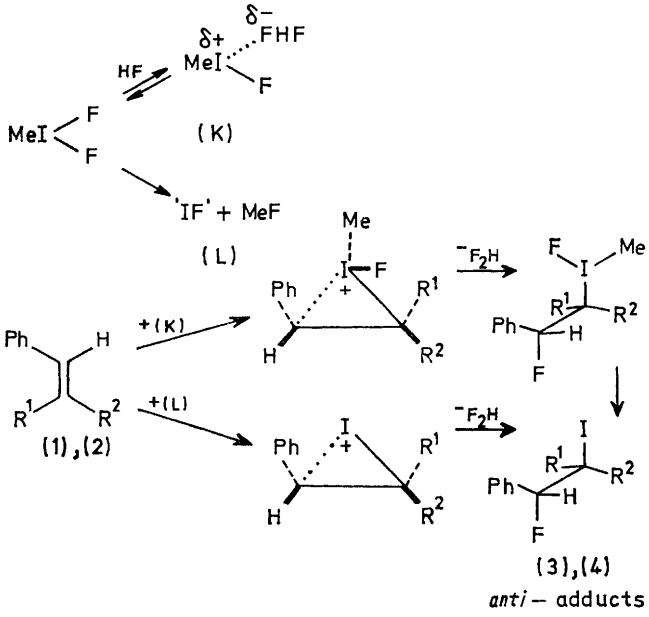
The addition of IF to olefins by (difluoroiodo)methane is in sharp contrast to the reactions of (difluoroiodo)-arenes,[5,6] which react with phenyl-substituted olefins forming 1,1-difluorides, with concomitant phenyl group



$\delta(F)$	−175.5 (dd)	$J(FH_a)$	57 Hz
$\delta(H_a)$	5.9 (dd)	$J(FH_b)$	18 Hz
$\delta(H_b)$	4.4 (dm)	$J(H_aH_b)$	3 Hz
$\delta(CH_2)$	3.4 (m)		
$\delta(Ph)$	7.2 (m)		

SCHEME 4

migration. Carpenter [6] suggested that a (difluoroiodo)-arene behaves as an electrophile in the presence of hydrogen fluoride (reactions were completely quenched when no hydrogen fluoride was added), and adds to an olefin forming a carbocation which is then attacked by fluoride ion. In the next step, dissociation of the carbon–iodine bond results in a carbocation, and phenyl group migration occurs. There are two possible explanations for the unusual behaviour of (difluoroiodo)methane (Scheme 5). Either the reagent decomposes in the presence of hydrogen fluoride as catalyst to methyl fluoride and a reactive species (L), which subsequently adds IF to the double bond, or the hydrogen fluoride polarizes the I–F bond of the reagent, thus forming an electrophile (K), which attacks the olefinic carbon atom, methyl fluoride being eliminated in a later stage. The intermediate must be of a highly bridged nature (similar to accepted halogeno-cationic intermediates), since otherwise such high *anti*-stereoselectivity would not be observed. The formation of difluorides (5)—(7) could be explained in terms of the S_N1 substitution reactions, and was observed in the reaction with olefins bearing at least one methyl or phenyl group, which facilitates S_N1 substitution by



SCHEME 5

virtue of mesomeric and inductive effects. Following some reactions by their ^{19}F n.m.r. spectra, we observed first the formation of iodo-fluorides only, but in the later stages of the reaction ^{19}F peaks corresponding to vicinal or geminal difluorides appeared.

(Difluoroiodo)methane appears to be a mild, selective reagent for the iodofluorination of olefins, with stereospecific *trans*-addition.

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 257 spectrometer, and ^1H and ^{19}F n.m.r. spectra with a JEOL JNM-PS-100 instrument (solvent CCl_4; Me_4Si or CCl_3F as internal reference). Mass spectra, including high resolution measurements were taken with a CEC-21-110 spectrometer. G.l.c. was carried out on a Varian Aerograph 1800 instrument and t.l.c. on Merck silica gel F-254.

Pure samples of *cis*-1-phenylpropene,[17] *trans*-1-phenylpropene,[18] *cis*-1-phenyl-2-t-butylethylene,[19] and *trans*-1-phenyl-2-t-butylethylene [19] were prepared by the methods indicated. Other olefins were commercially available and purified before use by g.l.c. Methyl iodide was purified and distilled before use.[20] Hydrogen fluoride (Fluka Purum) was used. Xenon difluoride was prepared by photosynthetic methods [21] and its purity was >99%.

Addition and Isolation Procedures.—In a Kel-F vessel, xenon difluoride (1.3 mmol) was dissolved in methyl iodide (2 ml) at room temperature, and anhydrous hydrogen fluoride (trace) was introduced. After 20 min, to the resulting brown solution of (difluoroiodo)methane the olefin (1 mmol) was added and the mixture was left at room temperature for 1 h. Methylene chloride (10 ml) was then added, and the solution was washed with aqueous sodium hydrogen sulphite (10%; 10 ml), aqueous sodium hydrogen carbonate (10%; 10 ml), and water (10 ml; twice) and dried (Na_2SO_4). A catalytic amount of tributylamine was added in order to prevent decomposition of the product. The solvent was evaporated off *in vacuo* at room temperature and the crude products were analysed by n.m.r. (see Table) and then separated by preparative t.l.c. [SiO_2 activated 2 h at 120 °C with a solution containing cyclohexane (95%), methylene chloride (4%), and tributylamine (1%)].

1-Fluoro-2-iodo-1-phenylpropane (3a) or (4a) was an oily product; yield for (3a) 38%, for (4a) 41% (Found: M^+, 263.9810. Calc. for $C_9H_{10}FI$: M, 263.9833), *m/e* 264 (M^+, 5%), 137 (67), 136 (100), 109 (46), 101 (30), 83 (19), and 68 (21).

1-Fluoro-2-iodo-1,2-diphenylethane (3b) or (4b) was also an oily product; yield for (3b) 28%, for (4b) 25% (Found: M^+, 325.9978. Calc. for $C_{14}H_{12}FI$: M, 325.9987), *m/e* 326 (M^+, 4%), 199 (50), 189 (100), 109 (51), 90 (20), 83 (20), and 77 (25).

1-*Fluoro*-2-*iodo*-1-*phenyl*-2-*t*-*butylethane* (3c) or (4c) was an oily product; yield for (3c) 52%, for (4c) 46% (Found: M^+ 306.0291. Calc. for $C_{12}H_{16}FI$: M, 306.0303), *m/e* 306 (M^+, 7%), 179 (52), 178 (100), 109 (38), 101 (20), and 83 (22).

The yields of the isolated products are low because of their instability at room temperature. Those of the crude products are higher than 70%. The n.m.r. data of the crude reaction mixtures did not show the presence of any other products. The products must be stored at −20 °C and in the presence of catalytic amounts of tributylamine. Microanalytical data were inaccurate, with >0.4% deviations from calculated values. The structures of the products were confirmed by their transformations into known fluoro-olefins.

Iodofluorination of the *cis*- and *trans*-olefins (1) and (2) was repeated five times, and ^{19}F and ^{1}H n.m.r. spectra were recorded on the crude reaction mixtures. To test the stability of the iodo-fluoride products a sample (0.25 g) of (3a or b) or (4a or b) was added to methyl iodide (2 ml), hydrogen fluoride was introduced, and the mixture was stirred for 1 h. After work-up in the usual fashion, n.m.r. showed the presence of vicinal difluorides and rearranged products.

Under the conditions mentioned above (reaction time of 2 h and work-up procedure), mixtures of up to four products were observed by n.m.r. as follows:

for olefin (1a): (3a) (4%), (4a) (80%), (6a) (1%), (7) (15%)

(2a): (3a) (78%), (4a) (4%), (5a) (4%), (7) (14%)

(1b): (3b) (10%), (4b) (52%), (5b) (20%), (6b) (18%)

(2b): (3b) (56%), (4b) (4%), (5b) (36%), (6b) (4%)

The structures of the difluorides (5)—(7) were determined by comparison with independently prepared samples.[13,14]

Dehydroiodination of (±)-threo- (4) *and* (±)-erythro-1-*Phenyl*-1-*fluoro*-2-*iodoalkanes* (3).—The iodo-fluoride (3) or (4) (0.5 mmol) was stirred with potassium t-butoxide (1M; 2.5 ml) at 50 °C for 1 h. The mixture was then cooled, mixed with water (15 ml), and extracted with methylene chloride. The extract was washed with dilute acid and water, dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was analysed by g.l.c. and n.m.r. The *trans*- (9) or *cis*- (8) fluoro-olefin, the only product, was purified by preparative g.l.c. N.m.r., i.r., and mass spectral data were in agreement with reported data [J_{FH} 22 Hz for *cis*- (9) and 37 Hz for *trans*- (8)].[13,14]

Iodofluorination of Indene (10).—Xenon difluoride (1.3 mmol) was dissolved in methyl iodide (2 ml) at room temperature and anhydrous hydrogen fluoride (trace) was introduced. After 20 min to the resulting brown solution indene (10) (1 mmol) was added, and the mixture was left at room temperature for 1 h. Methylene chloride (10 ml) was then added and the solution was washed with aqueous sodium hydrogen sulphite (10%; 10 ml), aqueous sodium hydrogen carbonate (10%; 10 ml), and water (10 ml; twice), and dried (Na_2SO_4). A catalytic amount of tributylamine was added to prevent decomposition of the product. The solvent was evaporated off *in vacuo* at room temperature and the crude product was analysed by n.m.r. and then separated by preparative t.l.c. as before. N.m.r. data are given in Scheme 4. *trans*-1-Fluoro-2-iodoindane was a yellow oil (63%) (Found: M^+, 261.9656. Calc. for C_9H_8FI: M, 261.9675), *m/e* 262 (M^+, 17%), 135 (56), 133 (18), 116 (70), 115 (100), 89 (12), and 63 (20).

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