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Iodofluorination of alkenes and alkynes promoted by iodine and 4-iodotoluene difluoride

Pellegrino Conte, Barbara Panunzi and Marco Tingoli*

Facoltà di Agraria, Università di Napoli 'Federico II', I-80055-Portici (NA), Italy

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Abstract—It was found that a mixture of molecular iodine and 4-iodotoluene difluoride are useful to generate in situ the couple 'IF' that was able to add in a Markovnikov fashion and with prevalent *anti*-stereoselectivity to various alkenes and alkynes.

Quite recently, we found that both diphenyldiselenide and molecular iodine acted as powerful electrophiles when allowed to react with unsaturated organic compounds in the presence of different iodine(III) species.[1a,b] One example of this chemistry is a new convenient regio- and stereoselective reaction of phenylselenofluorination of alkenes and alkynes promoted by 4-iodotoluene difluoride (4-tolIF_2) and diphenyldiselenide.[2] This chalcogenated reagent also in the presence of 4-tolIF_2 undergoes a very fast and efficient oxidation and, any competitive reaction between the iodine(III) species and the unsaturated organic compound was avoided.[3]

Now it should be of interest to focus our attention also on the less toxic and more environmentally friendly iodine and taste its reactivity with 4-iodotoluene difluoride in the presence of double or triple C–C bonds. Iodofluorination of unsaturated hydrocarbons under various reaction conditions was studied by several research groups. Some methods described in the literature utilized very difficult to handle reagents like elemental fluorine,[4a,b] potassium fluoride–poly(hydrogen fluoride) salts,[4c] or xenon difluoride in the presence of iodine or NIS.[4d] Other related methods used bis(pyridine)iodonium tetrafluoroborate in the presence of tetrafluoroboric acid at low temperature,[5] or more recently the ionic liquid EMIMF mixed with HF.[6] Also an electrochemical generated iodonium cation is useful to produce both several fluoroiodoalkanes and one fluoroiodoalkene.[7] The common feature of all these synthetic methods is their preferential applicability to the formation of fluoroiodoalkanes while fluoroiodoalkenes are obtained essentially from terminal alkynes and using a two step methodology.[8a]

In a preliminary experiment, cheaper sodium iodide was selected as a potential source of electrophilic iodine. Thus the two electrons oxidation of the iodine anion with 4-iodotoluene difluoride (now commercially available) should be in principle an easy way to get both the electrophilic iodonium and fluorine anion species in solution, ready to add to unsaturated compounds. This reaction indeed proceeded, but the formation of the iodohydrine compound, together with expected iodo–fluoro adduct, was never suppressed, even when starting from anhydrous NaI salt. We have therefore moved successfully our attention to molecular iodine.

The procedure for a typical experiment is as follows: I_2 (0.25 mmol) was dilute in 4 mL of anhydrous CH_2Cl_2 by stirring, in a 10 mL polypropylene tube under Argon atmosphere. 4-Iodotoluene difluoride, **1** (0.35 mmol, reagent to be maintained dry under reduced pressure), was added to this reddish-brown solution at 0–5 °C. After 15 min 4-*tert*-butylstyrene (0.5 mmol) diluted in 1 mL of CH_2Cl_2 was added slowly.[9] The dark brown homogeneous solution thus formed was covered with a plastic screw cap and left in the refrigerator at 4–5 °C overnight. After this time the solution appeared pale pink and transparent. The elimination of traces of unreacted I_2 with a 0.01 M solution of sodium thiosulfate in water, followed by neutralization with dilute NH_4OH and a

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* Corresponding author. Tel.: +39 812539468; fax: +39 812539186; e-mail: tingoli@unina.it

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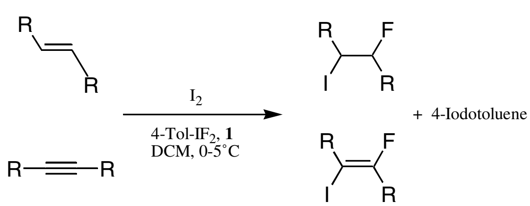
normal work-up, yielded the residue after evaporation of the dried solvent. The GC–MS analysis of this crude material showed only traces (less than 3–5%) of the iodohydrine derivative, together with the desired iodo-fluorination product and obviously, 4-iodotoluene.

As summarized in Scheme 1, the reaction conditions described above were applied to a series of alkenes and simple alkynes.

An analysis of the data depicted in Table 1 shows that the reaction takes place regioselectively and the addition on terminal alkenes, entries 1–4, produced exclusively the isomer predicted by Markovnikov's rule for the addition of electrophilic iodine. Moreover, only one stereoisomer is formed in the cases of 1,2-disubstituted alkenes (Table 1, entries 5 and 6) corresponding to an *anti*-addition of the I–F elements.[10]

A partial loss of stereoselectivity was observed when glycal esters were selected as starting alkenes. Reaction of tri-*O*-acetyl-D-glucal **7** (Table 2), gave a 3:1 mixture of diastereoisomers after flash chromatography. By selected NMR experiments we found that the major stereoisomer **7a** was the 1,2-*trans*-diaxial isomer. Minor stereoisomer **7b**, was the *cis*-isomer with α-configuration at the anomeric carbon but a *gluco*-type configuration at the iodine atom linked to C-2.



Scheme 1.

A second reaction of the couple 4-iodotoluene difluoride/I_2 with 3,4-di-*O*-acetyl-6-deoxy-L-rhamnal **8** (Table 2), also proceeded with partial stereoselectivity, giving the *trans*-diaxial adduct **8a** together with the *cis*-adduct **8b** in a 4:1 ratio. In this experiment trace of *trans*-diequatorial adduct **8c** was also isolated.

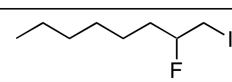
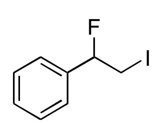
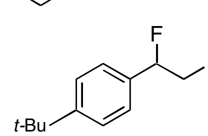
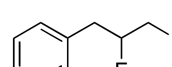
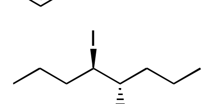
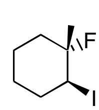
These last two results are in agreement with those reported in the literature for the iodofluorination of the same glucals using bis(*sym*-collidine)iodine(I) tetrafluoborate,[11a] and indicate that an *anti* addition of the 'IF' elements to the enol ethers is prevalent in both cases.

It is also important to observe that these results are slightly different from those encountered in the corresponding phenylselenofluorination of identical glucals. In those cases, the reaction was completely stereoselective producing only trans-diaxial adducts.[3]

The reaction conditions described for alkenes were applied to simple alkynyl derivatives. As depicted in Table 3, three internal alkynes and one terminal alkyne were transformed into the corresponding fluoroiodoalkenes.

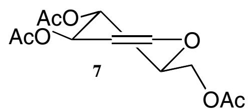
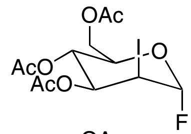
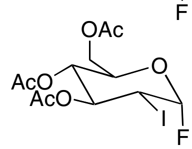
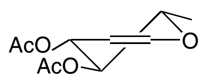
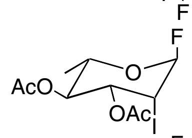
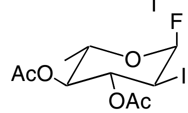
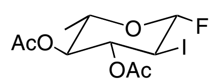
As reported in Table 3, product **12**, derived from an *anti* addition of the I–F elements to phenylacetylene ($J_{F–H}$ = 19.5 Hz in the ^{19}F NMR spectrum of **12** is consistent with the value reported in the literature)[8b] and in a Markovnikov fashion was obtained in a very low yield together with a more abundant, low polar compound. This unexpected product had a M^+ in the GC–MS spec-

Table 1. Iodofluorination of alkenes promoted by iodine and difluoroiodotoluene in CH_2Cl_2 at 0–5 °C

Entry	Substrate	Reaction products		Yield[a] (%)
1	1-Octene		**1a**	67[b]
2	Styrene		**2a**	72
3	4-*tert*-Butylstyrene		**3a**[15]	81
4	Allylbenzene		**4a**	91
5	(*E*)-4-Octene		**5a**[15]	67
6	1-Methyl-1-cyclohexene		**6a**	58[b]

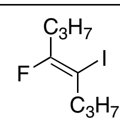
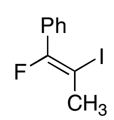
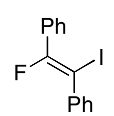
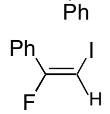
[a] Yields based on isolated products after flash chromatography.
[b] 10% Yields of iodohydrine were also isolated.

Table 2. Iodofluorination of glycal esters

Glycal ester	Products		Yield (%)
 **7**		**7a**[a]	68
		**7b**[b]	
 **8**		**8a**[b]	65
		**8b**[b]	
		**8c**[c]	8

[a] Compounds **7a** and **7b** were isolated as 3:1 mixture.
[b] Compounds **8a** and **8b** were isolated as a 4:1 mixture.
[c] Product **8c** obtained as a pure fraction.

Table 3. Iodofluorination of alkynes promoted by iodine and difluoroiodotoluene in CH_2Cl_2 at 0–5 °C

Entry	Substrate	Reaction products		Yield[a] (%)
1	4-Octene		**9**[15]	73
2	1-Phenyl-1-propyne		**10**	71
3	Diphenylacetylene		**11**[15]	83
4	Phenylacetylene		**12**	16[b]

[a] Yields based on isolated products after flash chromatography.
[b] 1-Iodo-2-phenylethyne (65% yield) was the main product isolated.

trum, of 228, and a ^{1}H NMR spectrum that shows only resonances belonging to the aromatic hydrogen atoms and did not show any signal in the ^{19}F NMR region. These last data are in agreement with those reported in the literature for iodophenylacetylene PhC≡CI.[12]

It is important also to note that the stereochemistry of compounds **9–11** (Table 3), is difficult to assign both by NMR analysis or chemical experiments. Nevertheless, we were able to separate from the pure compound **11**, obtained from flash chromatography, some crystals that we have submitted for X-ray crystallographic analysis. The ORTEP view of **11** is shown in Figure 1 clearly

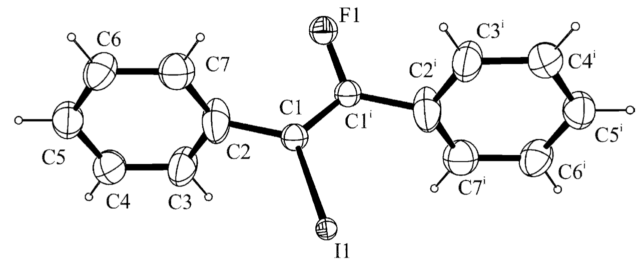


Figure 1. ORTEP view of compound **11** Table 3. Thermal ellipsoids at 30% probability level, ($^i = -x, -y, -z$), the statistical position of C1 not shown for clarity. Relevant structural parameters: I1–C1 2.105(7), F1–C1^i 1.475(9), C1–C1^i 1.38(1) Å, I1–C1–C2–C3 92.4(5), F1–C1^i–C2^i–C3^i 103.3(6)°.

indicates a *trans*-geometry for the IF elements linked to the ethenyl carbon atoms and a consequent (*E*)-absolute configuration for that molecule. Compound **11** shows also a signal in ^{19}F NMR at −77.42 ppm (s) very closed to −78 ppm found by Zupan several years ago.[13] To this last compound was assigned a (*Z*)-configuration that probably needs more experimental data to be confirmed by the author.

Finally, the complete consumption of iodine observed both in the addition to alkenes and alkynes is a clear indication that the couple 4-tolIF_2/I_2 produces in a very mild condition vicinal fuoroiodoalkanes and fluoroiodoalkenes, most likely through the formation of iodonium cation intermediate followed by nucleophilic attack of fluorine anion.

Furthermore, our simple protocol represents a complete new entry to disubstituted fluoroiodoalkenes characterized by (*E*)-configuration, useful intermediates for tri- and tetra-alkylated olefins preparation and for fluorinated enynes synthesis.[8b,14]

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.029.

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9. The sequence of the addition of reagents and the reaction time suggested for the preparation of activated iodine species are very important: if an unreacted part of 4-tol-IF_2 remained in the reaction mixture, it can add to the starting alkene or alkynes to produce other fluorinated materials detected by GC–MS analysis. It is also important to avoid a long time exposure of I_2 to hypervalent iodine: this caused electrophilic iodination of the 4-iodotoluene ($M^+ = 344$ in the GC–MS spectrum was found), and the yield of the iodofluorinated product was lowered.
10. All the compounds are stable enough to be purified by standard flash chromatography, using a mixture of hexane–*tert*-butyl methyl ether as eluant. The yields are calculated towards iodine initially added. The chemical shift δ on ^{19}F NMR spectra are expressed in ppm using fluoro trichloromethane as internal reference. Products **1a**,[4a] **2a** and **6a**,[7] and **4a**,[5] **10**, **11**,[13] and **12**[8b] have spectral data consistent with those previously reported. Assignment of configurations for **7a**,**b**, **8a**,**b**, and **8c** were based on chemical shifts and J_{HF} obtained by ^{19}F NMR spectrometry and are in accordance with values reported previously.[11a,b]
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14. Eddarir, S.; Francesch, C.; Mestdagh, H.; Rolando, C. *Bull. Soc. Chim. Fr.* **1997**, *134*, 741–755.
15. Physical data of selected compounds: **3a**: ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$ (AA′XX′ system, $J_{AX} = 8.5$ Hz, 4H), 5.5 (ddd, $J = 4.7$, 8.0 Hz, $J_{HF} = 46.7$ Hz, 1H), 3.7–3.4 (m, 2H), 1.35 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3/C_6H_5CF_3$): $\delta = 166.25$ (ddd, $J = 14.7$, 26.3, 46.7 Hz, 1F); GC–EIMS: m/z 306 (M^+) (4), 286 (6), 271 (13), 179 (50), 149 (16), 127 (10), 57 (100). Anal. Calcd for $C_{12}H_{16}FI$: C, 47.08; H, 5.27. Found: C, 47.01; H, 5.20.
Compound **5a**: ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.47$–4.30 (m, 1H), 4.22–4.13 (m, 1H), 1.9–1.3 (m, 8H), 1.1–0.95 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3/C_6H_5CF_3$): $\delta = -174.05$ to -174.37 (m, 1F); GC–EIMS: m/z 258 (M^+) (2), 131 (12), 127 (8), 77 (25), 69 (100), 55 (82). Anal. Calcd for $C_8H_{16}FI$: C, 37.23; H, 6.25. Found: C, 37.30; H, 6.31. Compound **9**: ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.65$–2.4 (m, 2H), 2.27–2.2 (m, 2H), 1.8–1.4 (m, 4H), 1.1 (t, $J = 7.3$ Hz, 3H) 0.85 (t, $J = 7.3$ Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3/C_6H_5CF_3$): $\delta = 94.7$ (t, $J = 23.3$ Hz, 1F); GC–EIMS: m/z 256 (M^+) (75), 227 (11), 185 (18), 127 (6), 99 (88), 87 (40), 85 (46), 79 (47), 73 (59), 67 (63), 59 (97), 55 (100). Anal. Calcd for $C_8H_{14}FI$: C, 37.52; H, 5.51. Found: C, 37.60; H, 5.47. Compound **11**: solid, mp 162–65 °C (with decomposition), showed a solid to solid transition between 92 and 96 °C. ORTEP view of compound **11** is shown in Figure 1.