Observations on the Reaction of Some Electron Rich Dienes with Hypervalent Iodoarene Difluorides: a Novel Mechanism for Fluorination

Jeremy J. Edmunds and William B. Motherwell*

Department of Chemistry, Imperial College of Science, Technology and Medicine, South Kensington, London SW7 2AY, U.K.

Regiospecific fluorination at the 6-position of dienamine (**1**) using *p*-t-butyl iodobenzene difluoride is improved by addition of *N*-methylviologen as an electron transfer reagent.

Electrophilic fluorination is currently achieved through use of reagents $X^{\delta-}$–$F^{\delta+}$ [X = F_3CO,[1] ClO_3,[2] $(ArSO_2)RN$,[3] $MeCO_2$,[4] $Cs^+OSO_3^-$,[5] pyridinium trifluoromethanesulphonate[6] (triflate)], in which either the charge or the combined electronegativities of the atoms in the attached X grouping serve to outweigh that of fluorine itself, and hence to induce bond polarisation in the indicated sense. A further necessary criterion for success is the selection of a relatively weak bond to the fluorine atom.

We were intrigued, however, by the possible existence of an alternative strategy as outlined in Scheme 1, whereby a similar result would be obtained *via* a double displacement reaction using a hypervalent iodoarene fluoride. Although the chemistry of such reagents has been little explored,[7] we were encouraged by the elegant work of Tsushima describing the formation of an α-fluoro ketone from a silyl enol ether.[8] The tosyloxylation of enolisable carbonyl compounds[9] using Koser's reagent, [(hydroxy)tosyloxyiodobenzene], and the formal introduction of electrophilic triflate in the formation of vicinal ditriflates from alkenes[10] using the Zefirov reagent, {μ-oxobis[(trifluoromethanesulphonyloxy)phenyliodine]}, are also illustrative of this concept. We now report our initial studies towards such a 'pretence' electrophilic fluorination.

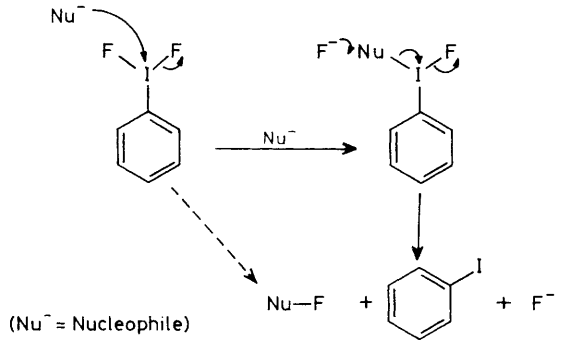
A variety of methods are available for the preparation of the required iodoarene difluorides.[11] Of these, we consider that the exchange reaction of the corresponding dichloride with aqueous hydrofluoric acid in the presence of yellow mercury(II) oxide is the most practical proposition.[12] Although our first experiments were carried out using titrated dichloromethane solutions of the parent iodobenzene difluoride, further work established that the *p*-t-butyl derivative, which could be isolated as a crystalline solid and stored at −20 °C, was preferred.

Initially, we studied the reaction of the steroidal diene derivatives (**1**)—(**3**) with a variety of hypervalent iodine difluorides (**4**)—(**7**). Examination of the results in Table 1 reveals several features of interest. Thus, in contrast to perchloryl fluoride[13] which undergoes exclusive attack at the

Table 1. Reaction of steroidal diene derivatives with a variety of iodine difluorides.

Substrate	Reagent	Products (Yield/%)
(1)	(4)	(8) (18)
(1)	(5)	(8) (17), (9) (6)
(2)	(4)	(8) (14)[a]
(1)	(6)	(8) (14), (11) (4), (9) (3)
(3)	(7)	(8) (11)

[a] Cholest-4-en-3-one was recovered in 47% yield.

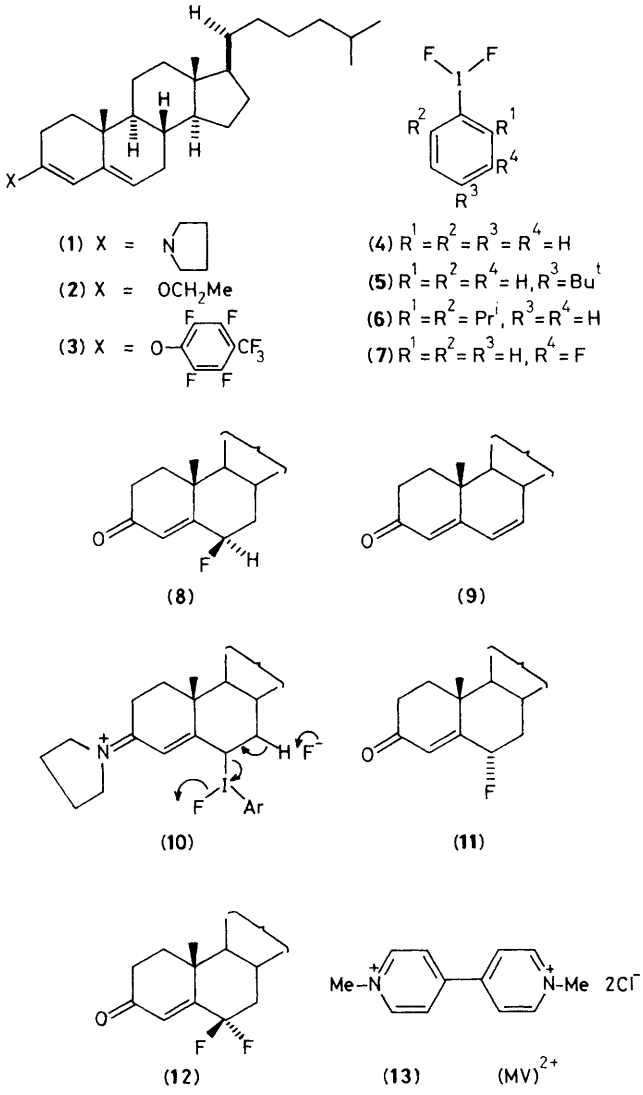


Scheme 1

4-position of dienamine (**1**), hypervalent iodoarene difluorides display a regiospecific preference for the terminus of the diene. Moreover, in all but one of the cases studied, the reaction was stereospecific, with formation of the thermodynamically less stable axial 6β-isomer (**8**). It was also noteworthy that the comparatively poor electron releasing ability of the perfluorotolyl enol ether (**3**) did not significantly inhibit fluorination. The isolation of cholesta-4,6-dien-3-one (**9**) was, however, indicative of a competitive elimination process, possibly as shown, from an iodonium salt of type (**10**). The formation of such a salt, which had failed to evolve to give products, was also held to be responsible for the relatively poor mass balance of chromatographically mobile steroidal material in these reactions. Some support for this hypothesis was obtained from an experiment in which an initial reaction of (**1**) with (**5**) was followed by attempted displacement using caesium fluoride in acetonitrile to give the 6β-fluoro derivative (**8**) (16%) and an improved yield of dienone (**9**) (41%). Use of 2,6-di-isopropyliodobenzene difluoride (**6**), selected in an effort to encourage direct attack of the nucleophile at the fluorine atom by screening the electrophilic iodine centre, also failed to improve the yield, thereby implying that a direct electrophilic fluorination mechanism is not operative.

We have also studied the possibility of effecting induced homolytic cleavage of the putative iodonium salt followed by *in situ* oxidation of the resultant radical. Thus, addition of copper(II) acetylacetonate to a dichloromethane solution of the reaction mixture from (**1**) and (**5**), followed by irradiation provided, after work-up, 6α-fluorocholest-4-en-3-one (**11**) (10%) and the geminal difluoro derivative (**12**) (15%), with complete suppression of the previously observed 6β-adduct.

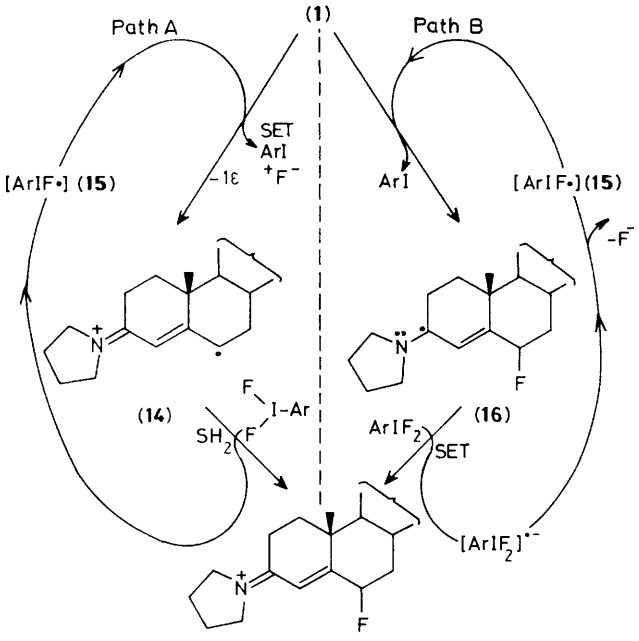
Throughout our study we were aware that electron transfer induced radical reactions[14] of dienamine (**1**) proceed cleanly at the 6-position, and decided accordingly to study a variety of potential catalysts. Of these, mercury(II) chloride, which mass spectroscopic analysis had indicated to be a trace contaminant in the preparation of the iodoarene difluorides, showed a



significant effect. Reaction of (**1**) and (**5**) in the presence of 10 mol% of this salt afforded the 6α,6β, and *gem*-difluoro products [(**11**) (4%), (**8**) (12%), (**12**) (14%)]. In the event, 1,1′-dimethyl-4,4′-bipyridinium dichloride (**13**), (methylviologen) was most effective. In a typical experiment, the iodoarene difluoride (**5**) (1.14 mmol) in dichloromethane (8 ml) was added to an orange suspension of enamine (**1**) (1.14 mmol) and the salt (**13**) (0.38 mmol) in dichloromethane (16 ml) under argon. Work-up and column chromatography after 3 h at room temperature gave (**8**) (21%), (**11**) (8%), and (**12**) (13%), indicating that 55% of the iodoarene difluoride had been successfully involved in formation of fluorinated products. Use of a four-fold excess of reagent (**5**) allowed isolation of (**8**) in 33% yield and only 6% of the dienone (**9**). In a separate experiment, the *gem*-difluoro derivative (**12**) was also obtained (33%), using 6-fluoro-3-pyrrolidino-cholesta-3,5-diene as substrate, thus indicating the sequential nature of fluorine introduction at this site.

From a mechanistic standpoint (Schemes 2 and 3), the primary role of the methylviologen is to mediate electron transfer from the dienamine with concomitant production of the radical cation (**14**), and possibly, *via* the reduced form of the viologen to encourage production of the monofluoroiodoarene radical (**15**) from the iodoarene difluoride.

Two distinct electron transfer chain pathways are then possible. In the first of these (path A), radical cation (**14**)



$$(1) + MV^{2+} \longrightarrow (14) + MV^{\bullet+}$$

$$MV^{\bullet+} + ArIF_2 \longrightarrow [ArIF_2]^{\bullet-} + MV^{2+}$$

$$[ArIF_2]^{\bullet-} \longrightarrow [ArIF\bullet]\ (15) + F^-$$

Scheme 2

undergoes a bimolecular homolytic substitution reaction (S_H2) with the iodoarene difluoride to liberate the chain carrying radical (**15**), which can then function as a one electron oxidant for the dienamine. An alternative role for this key intermediate (**15**) (path B) is that of an electrophilic radical which adds to the terminus of the diene. Subsequent reaction of the resultant readily oxidised α-aminoalkyl radical (**16**) with the iodoarene difluoride then proceeds *via* collapse of the radical anion of the reagent to propagate the chain. In both of these reaction possibilities, the viologen may of course be considered either as an initiator, or as an electron transfer relay catalyst and an integral component of the chain sequence.

In summary, the present reaction of electron rich dienes with hypervalent iodoarene difluorides displays the characteristics of a single electron transfer process, and hence provides a novel method for formation of the carbon–fluorine bond. An attractive feature of the overall system is that substituent modification of the aromatic nucleus may be used to tune the redox potential of these reagents and hence to permit application to other types of substrate.

We acknowledge the S.E.R.C. and I.C.I. Pharmaceuticals for the provision of a CASE studentship (to J. J. E.), and thank Dr. M. Ferreira (University of Lisbon, Summer Academic Visitor, 1985) for some preliminary experiments in this area.

Received, 27th January 1989; Com. 9/00464E

References

1 D. H. R. Barton, J. Lister-James, R. H. Hesse, M. M. Pechet, and S. Rozen, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1105 and references therein.
2 C. E. Inman, R. E. Oesterling, and E. A. Tyczkowski, *J. Am. Chem. Soc.*, 1958, **80**, 5286; R. B. Gabbard and E. V. Jensen, *J. Org. Chem.*, 1958, **23**, 1406.
3 W. E. Barnette, *J. Am. Chem. Soc.*, 1984, **106**, 452.
4 S. Rozen and O. Lerman, *J. Am. Chem. Soc.*, 1979, **101**, 2782.
5 S. Stauber and M. Zupan, *J. Chem. Soc., Chem. Commun.*, 1981, 795.
6 T. Umemoto, K. Kawada, and K. Tomita, *Tetrahedron Lett.*, 1986, **27**, 4465.
7 A. Bowers, A. D. Cross, and P. G. Holton, *Steroids*, 1963, **2**, 71; B. Sket, M. Zupan, and P. Zupet, *Tetrahedron*, 1984, **40**, 1603; A. Gregoricic and M. Zupen, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1446; T. B. Patrick, J. J. Scheibel, W. E. Hall, and Y. H. Lee, *J. Org. Chem.*, 1980, **45**, 4492.
8 T. Tsushima, T. Tsuji, and K. Kawada, *Tetrahedron Lett.*, 1982, **23**, 1165.
9 L. Rebrovic and G. F. Koser, *J. Org. Chem.*, 1984, **49**, 2462.
10 N. S. Zefirov, V. V. Zhdankin, Y. V. Dan'kov, and A. S. Koz'min, *J. Org. Chem. USSR (Engl. Trans.)*, 1984, **20**, 401; R. T. Hembre, C. P. Scott, and J. R. Norton, *J. Org. Chem.*, 1987, **52**, 3650.
11 D. Naumann and G. Reuther, *J. Fluorine Chem.*, 1980, **15**, 213; N. W. Alcock and T. C. Waddington, *J. Chem. Soc.*, 1963, 4103; H. Schmidt and H. Meinert, *Angew. Chem.*, 1960, **72**, 109; O. Dimroth and W. Bockemuller, *Ber.*, 1931, **64B**, 516.
12 W. Carpenter, *J. Org. Chem.*, 1966, **31**, 2688.
13 R. Joly and J. Warnant, *Bull. Soc. Chim. Fr.*, 1961, 569.
14 S. K. Malhotra, J. J. Hostynek, and A. F. Lundin, *J. Am. Chem. Soc.*, 1968, **90**, 6565; C. S. Rondestvedt, *Org. Reactions*, 1976, **24**, 225; M. Allard and J. Levisalles, *Bull. Soc. Chim. Fr.*, 1972, 1926.