Organic Reactions of Fluoroxy Compounds—Fluorination of Imines

By DEREK H. R. BARTON, ROBERT H. HESSE, THOMAS R. KLOSE, and MAURICE M. PECHET
(*Research Institute for Medicine and Chemistry, Cambridge, Massachusetts* 02142)

Summary Schiff's bases react smoothly with CF_3OF to afford, in *alcoholic media*, *NN*-difluoroamines; the reaction provides a convenient conversion of amines into *NN*-difluoroamines under mild conditions.

WE have recently reported that imino ethers react smoothly with fluoroxy-reagents to afford *NN*-difluoroamino-compounds, which are not readily available by other methods.[2] We now describe an alternative procedure on more accessible substrates.

$$R^1N{=}C(OEt)R^2 \xrightarrow{R_FOF} R^1NF_2 + R^2CF_2OEt \quad (1)$$

We expected that the non-activated carbon-nitrogen double bond of an imine (**1**) would undergo two successive reactions with a fluoroxy-reagent[1] producing the *NN*-difluoroammonium ion (**2**) (Scheme 1). Now if R^2 were sufficiently electron releasing (*e.g.* R^2=Ph), then cleavage 'a' should predominate leading to the required product, R^1NF_2 (**3**).

The fluorination of imines with elemental fluorine has been shown[3] to occur as in Scheme 1, with added complexity due to competitive dehydrofluorination of the intermediate *N*-fluoroamine (**4**; X = F). The resulting imido-fluoride (**5**; X = F) undergoes further fluorination leading to a variety of products. Recently, the reaction of a number of imines with the fluoroxy-reagent CF_3OF in non-nucleophilic solvents has also been shown[4] to follow a similar complex course.

We found that the reaction of CF_3OF (2 mol. equiv.) with *N*-benzylidene-1-adamantylamine[5] in dichloromethane leads to a very complex mixture of fluorine-containing products. We report now that in the presence of a suitable nucleophile such as methanol the course of the reaction is dramatically altered. Thus, the imine (**1**; R^1 = adamantyl, R^2 = Ph) on treatment with CF_3OF (2 mol. equiv.) in dichloromethane in the presence of methanol (15—100% v/v), at 0°, leads cleanly to *NN*-difluoro-1-adamantylamine[1] (**10b**) in 60—75% yield. A second product of this reaction is benzaldehyde dimethylacetal (**6**; X = OMe, R^2 = Ph). Similarly, while *N*-(*p*-nitrobenzylidene)-1-adamantyl-

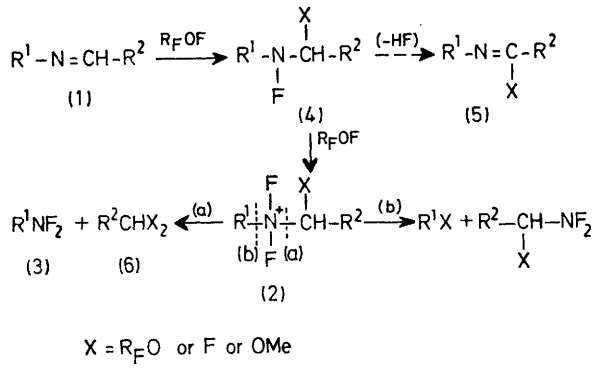
TABLE

Synthesis of difluoroamino-compounds

Substrate RNH_2	Method used[a]	Yield of product RNF_2, %	^{19}F-n.m.r. (p.p.m. from $CFCl_3$)	Product difluoramines
(**10a**)	1	(**10b**)	−19·9	M.p. 113·5—115°
	2	55—75	(br,s)	
		(**10b**) 70		
(**11a**)	2	(**11b**)[b]	−42·4 (m)	Unstable oil
(**12a**)	2	(**12b**) 76	−39·5 (m)	Oil: b.p. 85—86 at 15 mm Hg[1]
(**13a**)[c]	1	(**13b**) 57	−55·3 (m)	Oil: $(M-15)^+$ 280·0993[d]
	2	(**13b**) 71		
(**14a**)	2	(**14b**) 68	−67·5 (br.s)[e]	Oil: M^+ 219·0114
(**15a**)	1[f]	(**15b**) 64	−56·1 (t) J_{HF} 29 Hz	B.p. 52—54° at 15 mm Hg[2e]

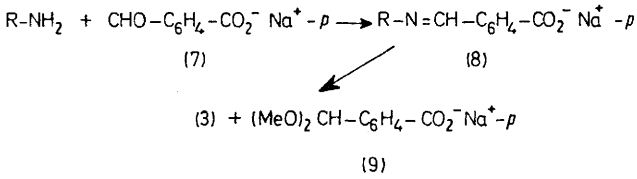
[a] Method 1—Fluorination of the benzylidine imine in MeOH–CH_2Cl_2 (1 : 4 v/v); method 2—Fluorination of sodium salt of the *p*-carboxybenzylidine imide in MeOH–CH_2Cl_2 (see text). [b] The difluoroamine from nor-ephedrine was unstable and the yield could not be accurately determined (see text). [c] Preparation by the method of Whistler and Doner.[6] [d] Acetonides always show an intense $M - CH_3$ (*i.e.* $M - 15$) species (but no M^+)[7] making calculation of the molecular formula possible. [e] Previously prepared by reaction of fluorine with 2,4-dinitroaniline[2g] but not obtained pure. [f] Reaction performed on the sodium salt of the benzylidine imine.

amine gave almost exclusively products derived from the adamantyl cation when fluorinated in the absence of nucleophilic solvent, in the presence of methanol *NN*-difluoro-1-adamantylamine (**10b**) was again obtained in good yield.

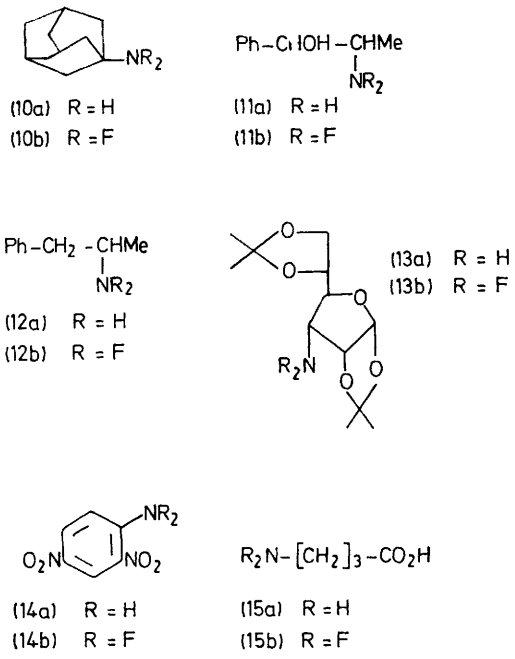


SCHEME 1

The isolation of the dimethylacetal (**6**; X = OMe, R^2 = Ph) establishes the course of the reaction as that depicted in Scheme 1, *via* intermediates (**4**) and (**2**) (X = OMe). The methoxy-group of (**2**) now provides the dominant driving force for cleavage 'a' to occur as desired.



To simplify the separation and purification of the product difluoroamines (**3**), we examined the fluorination of imines derived from sodium 4-formylbenzoate (**7**). Although such imines (**8**) are rapidly and completely hydrolysed on protonation, we find that fluorination of the sodium salts (**8**) with CF_3OF (2 mol.equiv.) proceeds at 0° in methanol–dichloromethane (1 : 4, v/v) with a suitable buffer (KOAc). The by-product acetal (**9**) can then be extracted into aqueous base. In this way, 1-adamantylamine (**10a**) can be converted into its *NN*-difluoro derivative (**10b**) in good yield (70%) and without isolation of any intermediates (Scheme 2).



SCHEME 2

This method provides a general, effective, and convenient synthesis of *NN*-difluoroamino-compounds from the parent amino-compound. The Table summarizes the application of the new imine fluorinations to the synthesis of *NN*-difluoroamino-derivatives. The limitation lies in the intrinsic stability of the product. For example, the imine (**8**) from nor-ephedrine (**11a**) is fluorinated smoothly to give *NN*-difluoro-nor-ephedrine (**11b**). However, (**11b**) on standing or attempted purification, fragments into benzaldehyde and acetonitrile. We find this cleavage to be a general reaction of α-hydroxy-*NN*-difluoroamines. Thus the saccharide (**13b**) undergoes such a cleavage slowly on attempted purification and instantly on attempted hydrolysis.

(*Received*, 4*th October* 1974; *Com.* 1248.)

[1] D. H. R. Barton, R. H. Hesse, M. M. Pechet, and H. T. Toh, *J.C.S. Perkin I*, 1974, 732.
[2] (a) W. H. Graham and J. P. Freeman, *J. Amer. Chem. Soc.*, 1967, **89**, 716; (b) R. C. Petry and J. P. Freeman, *J. Org. Chem.*, 1967, **32**, 4034; (c) V. Grakauskas and K. Baum, *J. Amer. Chem. Soc.*, 1969, **91**, 1679; (d) *J. Org. Chem.*, 1969, **34**, 2840; (e) *ibid.*, p. 1545; (f) C. M. Sharts, *J. Org. Chem.*, 1968, **33**, 1008; (g) C. L. Coon, M. E. Hill, and D. L. Ross, *ibid.*, p. 1387.
[3] R. F. Merrit and F. A. Johnson, *J. Org. Chem.*, 1967, **32**, 416.
[4] J. Leroy, F. Dudragne, J. C. Adenis, and C. Michaud, *Tetrahedron Letters*, 1973, 2771.
[5] M. Paulshock and J. C. Watts, U.S.P. 3,310,469 (1967) (*Chem. Abs.*, 1967, **67**, 11,275c).
[6] R. L. Whistler and L. W. Doner, *J. Org. Chem.*, 1970, **35**, 3562.
[7] H. Budzikiewicz, C. Djerassi, and D. H. Williams, 'Structure Elucidation of Natural Products by Mass Spectrometry,' vol II, p. 227, Holden-Day, San Francisco, 1964.