ChemComm

Electrophilic fluorination at saturated sites

Richard D. Chambers,*[a] Mandy Parsons,[a] Graham Sandford*[a] and Roy Bowden[b]

[a] *Department of Chemistry, University of Durham, South Road, Durham, UK DH1 3LE. E-mail: graham.sandford@durham.ac.uk*

[b] *F2 Chemicals Ltd., Lea Lane, Lea Town, Preston, UK PR4 0RZ*

Received (in Liverpool, UK) 23rd February 2000, Accepted 20th April 2000

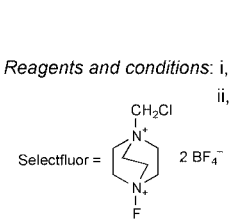
Transformation of carbon–hydrogen bonds to carbon–fluorine bonds at saturated secondary and tertiary carbon sites by electrophilic aliphatic substitution processes is possible using either elemental fluorine or fluorinating reagents of the N–F class.

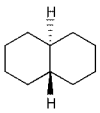
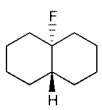
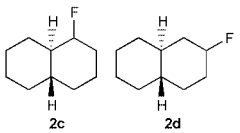
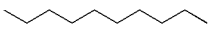
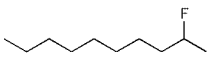
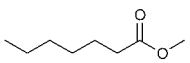
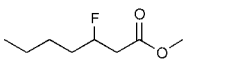
The development of effective methodology for the selective introduction of fluorine atoms into organic molecules has received much attention recently because of the significant effects on the physical, chemical and biological properties that incorporation of one or several fluorine atoms into a substrate can impart.[1] These sometimes unique effects are especially important in the life-science industries and there are now many pharmaceuticals and plant-protection agents that are commercially available which owe their biological activity to the presence of fluorine in their structures.

Synthetic procedures for the selective transformation of carbon–hydrogen bonds to carbon–fluorine bonds offer, in principle, efficient, direct processes for introducing fluorine atoms into organic molecules. In this context, during the last few years we, and others,[2] have been able to demonstrate that elemental fluorine is a viable reagent for selective introduction of fluorine into organic compounds, including aromatic systems[3] and a wide range of carbon sites that are nucleophilic, *e.g.* dicarbonyl compounds,[4] diesters,[5] *etc.* Fluorination of unactivated sp^3 hybridised carbon–hydrogen sites offers significant opportunities for the incorporation of fluorine into an even wider range of hydrocarbon derivatives. However, selective direct fluorination at saturated carbon sites is largely limited to the work of Rozen and co-workers[6] who demonstrated that tertiary C–H sites could be fluorinated using elemental fluorine in a reaction medium of $CHCl_3/CFCl_3$ at −78 °C. These reaction conditions are clearly limiting, especially for scale-up, and therefore we have explored other systems.

We have now established that acetonitrile as a solvent is highly beneficial over a variety of other media that we have investigated. Reactions are conveniently carried out by passing fluorine gas, diluted to a 10% solution (*v/v*) in nitrogen, through a mixture consisting of the substrate and acetonitrile, cooled to 0 °C, and efficient, selective fluorination of a variety of systems has now been achieved this way (see Table 1). Both secondary C–H (**1a** to **2a**) and tertiary C–H sites (*e.g.* **1b** to **2b**) were transformed to C–F bonds using these convenient reaction conditions. Fluorination of cyclohexane **1a**, *trans*-decalin **1b** and norbornane **1c** gave a single mono-fluorinated isomer in each case whereas fluorination of decane **1d** led to a mixture of four mono-fluorinated positional isomers **2f** in similar amounts, indicating that fluorine substitution had occurred at all possible secondary sites of the alkyl chain. In contrast, fluorination of ester **1e** gave a mixture consisting of four mono-fluorinated isomers in a ratio of 5.8:3.9:3.2:1 which were identified by NMR studies to be the 6-, 5-, 4- and 3-fluoroheptanoate derivatives respectively. Therefore, fluorination occurs preferentially at secondary sites that are furthest removed from the electron withdrawing ester group. In all cases the yields quoted are based upon analysis of the crude product obtained after separation from the acetonitrile reaction medium (*i.e.* after washing with water and extraction into dichloromethane). All reactions were clean, in that no tar formation was observed. Additional products contained in the crude product were present in very low concentration and too minor to be identified. Inevitably handling losses on the scale used (*ca.* 5 g of starting material) are relatively high, especially in the cases of very volatile substrates, but would obviously be reduced by an increase in scale.

Table 1 Selective fluorination of saturated systems



Substrate	Conditions	Product(s)	Yield (Conv.%)
 **1a**	i	 **2a**	63 (53)
1a	ii	**2a**	22 (100)
 **1b**	i	 **2b**	54 (68)
1b	ii	 **2c** **2d**	23 (81)
 **1c**	i	 *exo* : *endo* = 5 : 1 **2e**	41 (60)
 **1d**	i	 and 3-, 4- and 5-fluorodecane **2f** (2.6 : 1.2 : 1.1 : 1.0)	63 (61)
1d	ii	**2f** (2.4 : 1.3 : 1.1 : 1.0)	58 (84)
 **1e**	i	 and methyl 4-, 5- and 6-fluoroheptanoate **2g** (5.9 : 3.9 : 3.2 : 1.0)	49 (42)
1e	ii	**2g** (3.7 : 1.3 : 1.3 : 1.0)	48 (57)

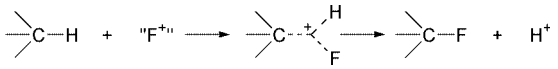
The question of the mechanism of direct fluorination processes arises and the obvious difficulty of distinguishing between electrophilic and radical substitution presents a

DOI: 10.1039/b001624l

problem. Consequently, we have explored corresponding reactions between these hydrocarbon systems and Selectfluor™ (available from Air Products), an easily handled, commercially available fluorinating reagent of the N–F class.[7,8] Selectfluor™ and structurally related N–F reagents have themselves been characterised as electrophilic reagents in mechanistic studies by Wong[9] and Differding[10,11] because no evidence of radical intermediates or products arising from one-electron transfer processes were obtained in radical-clock experiments.

Fluorinations of **1** were achieved by heating a mixture consisting of the substrate, Selectfluor™ and acetonitrile at reflux temperature and, for most of the systems that we have investigated, nearly parallel results to those observed using fluorine were obtained. For example, fluorination of decane **1d** using Selectfluor™ led to a similar product distribution to that obtained when fluorine was used. In the case of decalin, however, fluorine gave products arising from substitution at the tertiary site whereas, in contrast, Selectfluor™ gave fluorine substitution exclusively at the CH_2 sites. We attribute this difference simply to the greater steric requirements of the Selectfluor™ reagent. Therefore, the general similarity in product distribution obtained upon fluorination of saturated systems with both fluorine or Selectfluor™, suggests that these transformations of C–H bonds to C–F bonds may be considered to proceed *via* relatively uncommon aliphatic electrophilic substitution reactions at saturated sites (S_E2) involving 3 centre–2 electron bond transition states[12] (see Scheme 1). Addition of nitrobenzene, a free-radical scavenger, to the direct fluorination reaction medium does not affect product distribution or yield, further supporting an electrophilic process.

In the light of the intense interest in electrophilic N–F reagents[8,13] it is surprising that substitution at saturated sites has been so little developed because the examples shown in Table 1 demonstrate that it is a quite general process. However, Zupan[14] and co-workers have reported unusual fluorinations of methyl groups in tertiary alcohol systems but a mechanism is not advanced for the process.



Scheme 1

In summary, we are confident in describing the reactions of elemental fluorine, shown here, as electrophilic rather than fluorine atom processes. Indeed, the electrophilic fluorination of saturated sites shown here, using either fluorine or N–F fluorinating reagents, are surprisingly efficient, convenient processes.

We thank F2 Chemicals (Studentship to M. P.) for funding and the Royal Society (University Research Fellowship to G. S.).

Notes and references

1 *Organofluorine Chemistry. Principles and Commercial Applications*, ed. R. E. Banks, B. E. Smart and J. C. Tatlow, Plenum, New York, 1994.
2 J. Hutchinson and G. Sandford, *Top. Curr. Chem.*, 1997, **193**, 1.
3 R. D. Chambers, C. J. Skinner, J. Huchinson and J. Thomson, *J. Chem. Soc., Perkin Trans. 1*, 1996, 605.
4 R. D. Chambers, M. P. Greenhall and J. Hutchinson, *Tetrahedron*, 1996, **52**, 1.
5 R. D. Chambers, J. Hutchinson and J. Thomson, *J. Fluorine Chem.*, 1996, **78**, 165.
6 S. Rozen, *Acc. Chem. Res.*, 1988, **21**, 307.
7 R. E. Banks, S. N. Mohialdin-Khaffaf, G. S. Lal, I. Sharif and R. G. Syvret, *J. Chem. Soc., Chem. Commun.*, 1992, 595.
8 G. S. Lal, G. P. Pez and R. G. Syvret, *Chem. Rev.*, 1996, **96**, 1737.
9 S. P. Vincent, M. D. Burkhart, C. Y. Tsai, Z. Zhang and C. H. Wong, *J. Org. Chem.*, 1999, **64**, 5264.
10 E. Differding and G. M. Ruegg, *Tetrahedron Lett.*, 1991, **32**, 3815.
11 E. Differding and M. Wehrli, *Tetrahedron Lett.*, 1991, **32**, 3819.
12 G. A. Olah, G. K. S. Prakash, R. E. Williams, L. D. Field and K. Wade, *Hypercarbon Chemistry*, Wiley-Interscience, New York, 1987.
13 S. D. Taylor, C. C. Kotaris and G. Hum, *Tetrahedron*, 1999, **55**, 12431.
14 S. Stavber and M. Zupan, *J. Chem. Soc., Chem. Commun.*, 1994, 149.