Studies on Fluoroalkylation and Fluoroalkoxylation. Regioselective Synthesis of Fluoroalkylated Imidazoles

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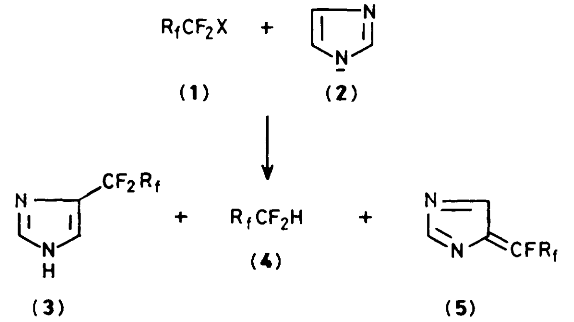
High yields of 4-fluoroalkylimidazoles are obtained regioselectively by the reactions of an imidazole anion and fluoroalkyl iodides or bromides under mild conditions; an $S_{RN}1$ mechanism is proposed.

Organofluorine chemistry has found increasing applications in medicine and biochemistry,[1] heteroaromatic compounds often being involved. However, few methods for the direct fluoroalkylation of heteroaromatic rings have been reported.[2] We have recently synthesized 2-fluoroalkylpyrroles by the reactions of fluoroalkyl iodides with pyrrole in the presence of copper,[3] and we now report a convenient and efficient regioselective synthesis of 4-fluoroalkylimidazoles.[4]

Treatment of sodium imidazolide (**2**) with fluoroalkyl iodides or bromides (**1**) gave the 4-fluoroalkylated products (**3**) in high yields in one step (see Scheme 1).†

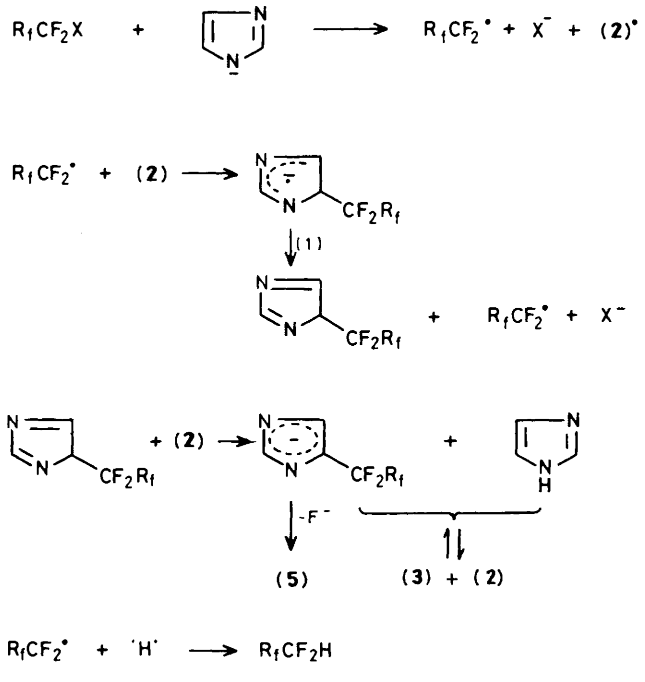


a; $R_f = CF_3[CF_2]_4$, $X = I$
b; $R_f = Cl[CF_2]_3$, $X = I$
c; $R_f = Cl[CF_2]_5$, $X = I$
d; $R_f = Cl[CF_2]_7$, $X = I$
e; $R_f = I[CF_2]_5$, $X = I$
f; $R_f = Cl[CF_2]_3$, $X = Br$
g; $R_f = Cl[CF_2]_5$, $X = Br$

Scheme 1

The conversion was mainly dependent on the ratio of reactants, going to completion when (**1**) and (**2**) were in a 1 : 3 ratio, but only 46.5% of fluoroalkyl iodide being converted for (**1**) : (**2**) = 1 : 1. It was also found that the extent of conversion of fluoroalkyl bromides [(**1f**) and (**1g**)] was lower than that of the iodides [(**1a**)—(**1e**)], possibly owing to the slower radical chain transfer of the bromide.

The reaction could be partially suppressed by *p*-DNB (20 mol%) or hydroquinone (20 mol%). The conversion also



Scheme 2

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† A typical procedure is as follows. To the solution of (**2**) in dimethylformamide (DMF), the fluoroalkyl iodide or bromide was added in one portion, at 10 °C, under laboratory light. The mixture was stirred under N_2 and became red after a few minutes. Stirring for several hours and work-up gave the product (**3**) in high yields (Table 1).

Table 1. The reaction of fluoroalkyl iodides (**1**) with imidazole anion (**2**).[a]

R_fCF_2X [(**1**):(**2**)]	Additive[b]	T/h	Conversion/%[c]	Yield/%[d]		Other
				(**3**) (m.p.)	(**4**)	
(**1a**) (1:3)	—	6	100	68.7 (147 °C)	23.5	
(**1b**) (1:3)	—	5	100	62.8 (137 °C)	20.3	
(**1b**) (1:3)	Hydroquinone	5	57.2	68.5[c]	21.5[c]	
(**1b**) (1:3)	DAE[b]	10	50	43.0	17.2	21.3[e]
(**1b**) (1:2)	—	7	80.4	70.7[c]	29.3[c]	
(**1b**) (1:2)	in the dark	10	50.3	86.2[c]	5.0[c]	
(**1b**) (1:2)	*p*-DNB	7	63.7	79.2[c]	18.5[c]	
(**1b**) (1:1)	—	13	46.5	81.8[c]	18.2[c]	
(**1c**) (1:3)	—	3	100	62.5 (136 °C)	18.3	
(**1d**) (1:4)	—	2.5	100	58.8 (158 °C)	20.3	
(**1e**) (1:3)	—	7	95	52.3 (154 °C)	22.8	8.5[f]
(**1f**) (1:3)	—	7	65.7	54.3	21.0	
(**1g**) (1:3)	—	12	58.2	52.0	22.8	

[a] In DMF at 10 °C, traces of 2-fluoroalkyimidazoles and (**5**) were also observed. [b] 20 mol% of hydroquinone and *p*-dinitrobenzene (DNB) were used; DAE = diethyl ether; (**1**): DAE = 1:2. [c] Determined by ^{19}F n.m.r. spectroscopy, based on fluoroalkyl halides. [d] Isolated yield unless noted otherwise; all the new compounds were identified by elemental analyses, ^{19}F, ^{1}H n.m.r., i.r., and mass spectroscopy; [e] 3-(6-Chloro-2,2,3,3,4,4,5,5,6,6-decafluorohexyl)-4-methylenetetrahydrofuran. [f] 1,6-Di-imidazol-4-ylperfluorohexane.

decreased, to 50%, when the reaction was carried out in the dark rather than in laboratory light (80%, see Table 1). Furthermore, the addition of DAE resulted in the formation of the tetrahydrofuran derivative.[5] All these results in addition to the known resistance to displacement of halides from perfluoroalkyl halides by S_N1 or S_N2 processes[5,6] and the possible ability of imidazole to act as an electron donor in basic media under irradiation,[7] indicate the possibility of an $S_{RN}1$ mechanism (Scheme 2).

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