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REACTIONS INVOLVING FLUORIDE ION. PART 33 [1]. PERFLUOROAZA-ALKYLATION OF FLUORINATED HETEROAROMATICS WITH PERFLUORO-1-METHYL-1,3-DIAZACYCLOPENT-2- AND -3-ENE

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SUMMARY

The nitrogen anion (1), generated by reaction of fluoride ion with (2), can be trapped by fluorinated heteroaromatics. Reaction of (1) with pentafluoropyridine gives a mono-substituted product. Mono- and di-substituted products are obtained with tetrafluoro-pyridazine and -pyrimidine, and fluoride ion catalysed isomerisation is observed. The mechanistic consequences of this are discussed. Reaction of (1) with trifluoro-1,3,5-triazine gives a tri-substituted product.

INTRODUCTION

We are, at present, developing the chemistry of fluorinated nitrogen anions and are carrying out comparative studies with the known chemistry of fluorinated carbanions [2], as part of this work. Polyfluorocarbanions, generated by reaction of fluoride ion with fluoro-alkenes, can co-oligomerise with perfluoro-alkenes and -cycloalkenes and react with activated heteroaromatics to yield polyfluoroalkylated products [3]. In a previous paper [4] we have reported the co-oligomerisation reactions of nitrogen anion (1), generated from perfluoro-1-methyl-1,3-diazacyclopent-2- and -3-ene (2), and we are now able to report the use of (1) in reactions with fluorinated heteroaromatics. There are few reports in the literature of this type of

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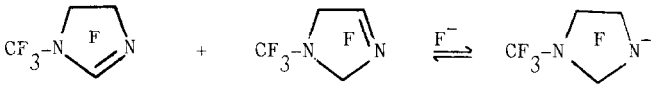
process involving nitrogen anions, with examples being limited to the fluoride ion catalysed reactions of perfluoro-2-azapropene with fluorinated heteroaromatics [5,6]. The synthesis of heteroaromatics substituted with (1) allows a comparison of the influence of a polyfluoroalkyl group with that of a polyfluoroalkylamino group on a site of unsaturation.

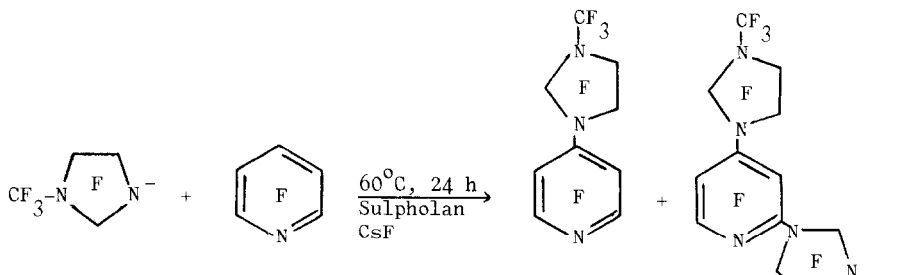


(2a) (2b) (1)

The orientation of substitution in, and reactivity of, fluorinated heteroaromatics is principally determined by the heteroatom. Consideration of the effect of ring nitrogen on the stability of intermediates has allowed the most favourable site of substitution, and subsequent attack, to be determined for a range of fluorinated heteroaromatics [7]. We are now able to use (1) to investigate further these ideas and make comparisons with the similar reactions of polyfluoroalkyl anions.

RESULTS AND DISCUSSION

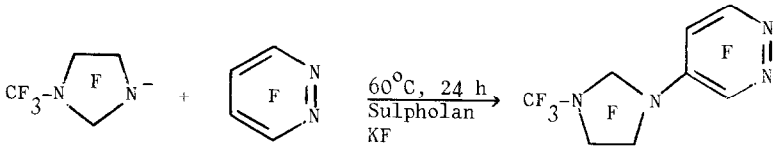
Reaction of (1) with pentafluoropyridine gave principally the 4-substituted product (3), together with a small amount of the 2,4-product (4). The orientation of substitution was determined by ^{19}F nmr spectroscopy and followed a pattern previously observed for carbanions [2].



(1) (3) (80%) (4) (2%)

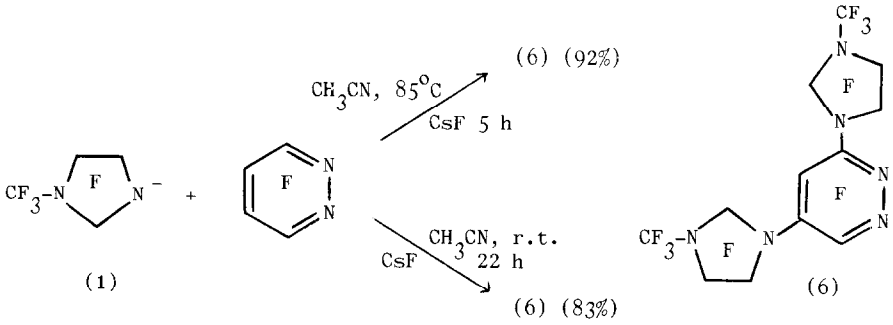
In contrast, the reactions of nitrogen anion (1) with tetrafluoro-pyridazine and -pyrimidine were more complex and clearly indicate the importance of kinetic and thermodynamic control. Reaction of (1) with an

equimolar quantity of tetrafluoropyridazine gave the expected 4-substituted product (5). When caesium fluoride was used as the fluoride ion source,



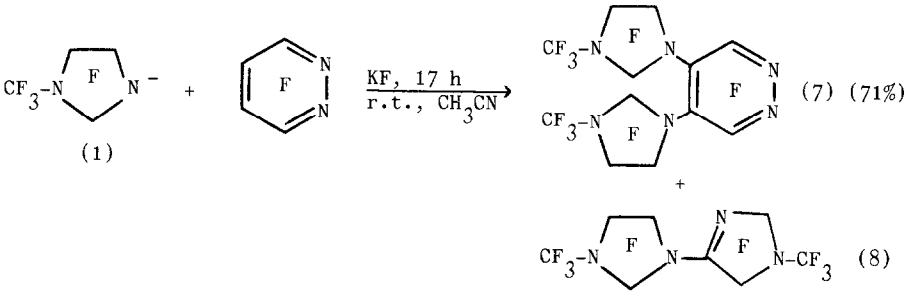
(1) (5) (57%)

with two mole equivalents of (1), disubstitution occurred to give a high yield of the 3,5-substituted pyridazine (6) and none of the expected 4,5-isomer was observed, in marked contrast to polyfluoroalkylation processes [3]. In order to obtain the 4,5-isomer (7) it was necessary



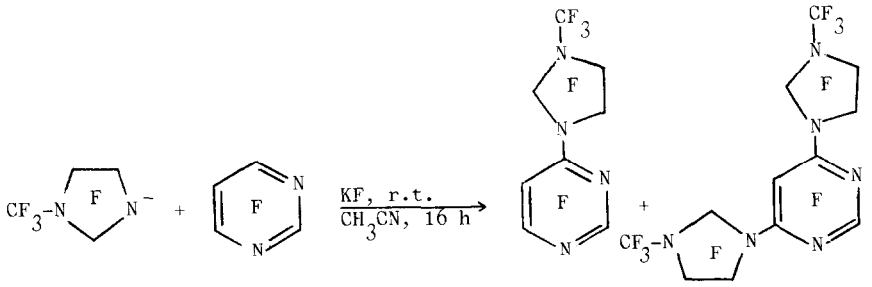
(1) (6)

to use potassium fluoride, which is a less active source of fluoride ion than caesium fluoride. A significant amount of dimer (8) was formed and in a previous paper we have commented on the equilibria between (1), (2) and (8) [4].



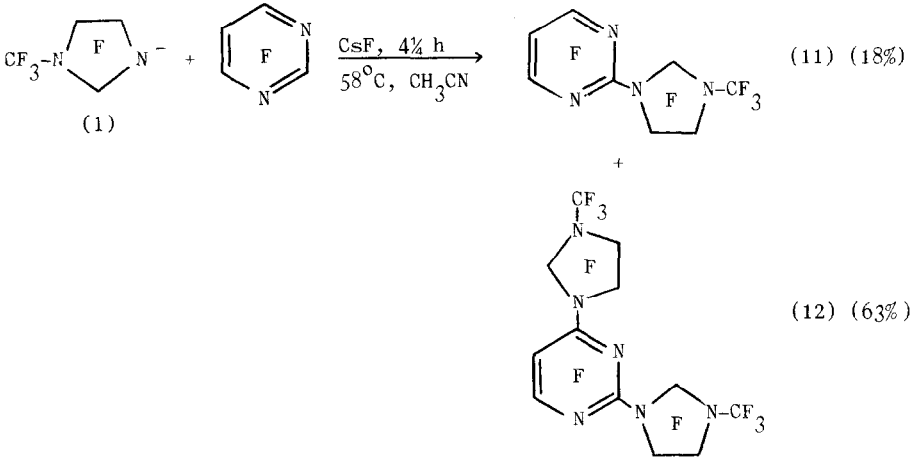
(1) (7) (71%) (8)

Similarly, mono- and di-substitution was observed by reaction of (1) with tetrafluoropyrimidine. Reaction of (1), generated using potassium fluoride, with tetrafluoropyrimidine at room temperature gave the expected 4- and 4,6-substituted products (9) and (10). In contrast, when caesium fluoride was used as the fluoride ion source, and at a higher temperature, 2- and 2,4-



(1) (9) (11%) (10) (51%)

substituted pyrimidines, (11) and (12), were obtained. This unusual substitution pattern is a result of fluoride ion catalysed isomerisations

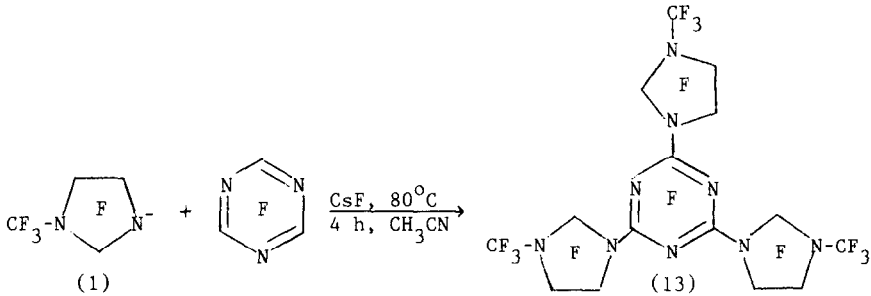


(1) (11) (18%) (12) (63%)

[8] and this was confirmed by the observation that (10) could be transformed to (12) by caesium fluoride.

(10) $\xrightarrow[22\ h,\ CH_3CN]{CsF,\ r.t.}$ (12) (49%)

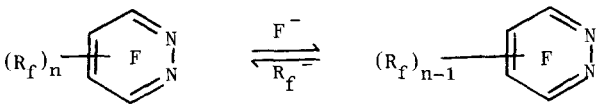
The highly activated nature of the triazine ring system is well illustrated by the formation of the tri-substituted compound as the only product in the reaction of (1) with trifluoro-1,3,5-triazine. Reactions carried out using acetonitrile or sulpholan, with a stoichiometry aimed



(1) (13) (66%)

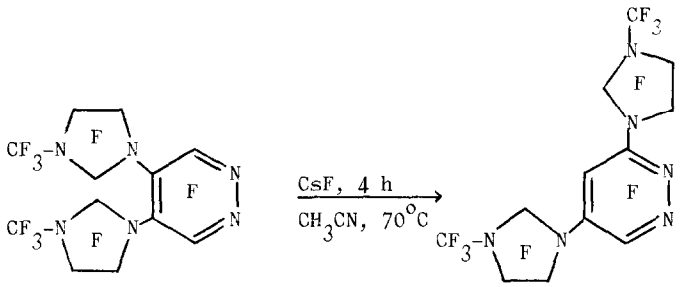
at the mono-substitution product, still led to (13) as the sole isolated product.

The ready formation of polysubstituted products in the reaction of nitrogen anion (1) with fluorinated diazines and triazines is a consequence of the highly activated nature of these heteroaromatics. From other work [7], it has been shown that ring nitrogen is the dominant influence activating ortho- and para-positions. The orientation on substitution of, for example, the heptafluoroisopropyl anion in reaction with tetrafluoropyrimidine is in the order 4 > 6 > 2. It has been previously noted however that thermodynamic control can have an influence on the final outcome of polyfluoroalkylation reactions [8]. The rearrangement of perfluoroalkylpyridazines can be used to illustrate this. Consider the equilibrium between (14) and (15); the ease with which this is set up will be primarily dependent on the stability of R_f^- and, to a lesser extent, on the activity of F^-. It has been found that for perfluoroalkyl anions of low



(14) (15)

stability, e.g. $C_2F_5^-$, kinetic control predominates, whereas for relatively stable anions, e.g. $(CF_3)_3C^-$, the equilibrium is more readily established and thermodynamic control becomes more important. However we now find that, with nitrogen anions, the nature of the product depends on the activity of the fluoride ion source i.e. it is possible to obtain the kinetically-controlled product, using KF, and convert it to the thermodynamic product with CsF. For example, (10) to (12) and, similarly, (7) to (6). It is



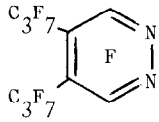
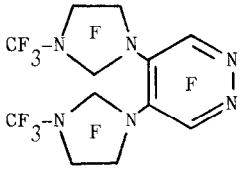
(7) (6) (67%)

clear that nitrogen anion (1) is a member of the group of more stable anions and consequently the orientation of substitution observed in the isolated product is due to a competition between kinetic and thermodynamic control. Indeed, we have commented on the stability of (1), as an observable anion, in an earlier paper [4] and the results obtained here are a consequence of this stability and the associated ease of displacement from an aromatic ring.

Ultra-violet spectroscopy is a probe for comparisons of the electronic influence of substituents on an aromatic ring. A comparison of the λ_{max} of substituted pyridazines allows, therefore, an assessment to be made of the electron-donating ability, or otherwise, of the perfluoro-(3-methylimidazolidin-1-yl) group (Table 1). The results indicate that the bathochromic shift due to the perfluoro(3-methylimidazolidin-1-yl) group is only slightly less than that arising from the perfluoroisopropyl group. It follows, therefore, that the electron-donating ability of nitrogen is almost entirely overcome by the inductive effect of the fluorocarbon substituents. Clearly, the chemistry of the perfluoro(3-methylimidazolidin-1-yl) substituted heteroaromatics will be similar to that of perfluoroalkyl substituted analogues, although in the former instance steric effects will become important.

TABLE 1

U.V. spectra in cyclohexane

	λ_{max} (ϵ)	
	$\pi \rightarrow \pi^*$	$n \rightarrow \pi^*$
	246 (1400)	334 (360)
	248 (4160)	283 (900)
	278 (4100)	340 (370)
	273 (3460)	337 (310)

EXPERIMENTAL

^{19}F nmr spectra were recorded at 20°C using a Varian EM360L spectrometer, with trichlorofluoromethane as external reference and upfield shifts quoted as positive. Gas chromatography was carried out using columns packed with 20% Krytox fluid* on celite (column K) or 20% Fomblin fluid** on celite (column F). Percentage yields quoted were either by weighing or by glc analysis using a gas-density balance detector, and are based on compounds (2) or (8) [which are sources of the anion (1)] consumed. Mass spectra were recorded on a V.G.-Micromass 12B linked with glc.

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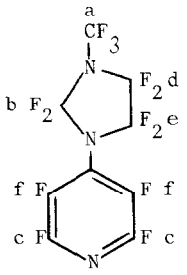
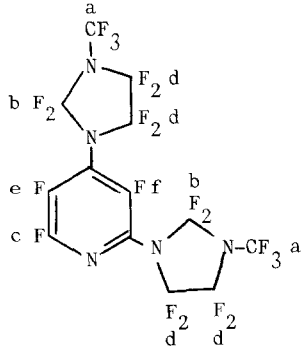
Reaction of nitrogen anion (1) with heteroaromatics

(a) Pentafluoropyridine

A mixture containing pentafluoropyridine (1.48 g, 8.8 mmol), caesium fluoride (0.61 g, 3.9 mmol), sulpholan (10 ml), and perfluoro-1,3-diaza-1-methylcyclopent-2- and -3-ene (2) (2.1 g, 9.2 mmol) was stirred at 60°C for 42 h. Volatiles were transferred under vacuum into a trap cooled in liquid air. A lower layer (3.2 g) was isolated and a further quantity of fluorocarbon was obtained by the addition of water to the upper layer. Separation by preparative scale glc (column K, 150°C) gave perfluoro-4-(3-methylimidazolidin-1-yl)pyridine (3) (nc) (2.8 g, 80%) b.p. 166°C, (Found: C, 27.1; F, 62.5; N, 10.8%; M^+, 397. $C_9F_{13}N_3$ requires C, 27.2; F, 62.2; N, 10.6%; M, 397); λ_{max} (CH_3CN) 278 nm; δ_F 58.2 (3F, F_a), 65.1 (2F, F_b), 88.9 (2F, F_c), 92.6 (2F, F_d or F_e), 94.1 (2F, F_e or F_d), and 144.2 (2F, F_f) and perfluoro-2,4-bis(3-methylimidazolidin-1-yl)pyridine (nc) (4) (0.09 g, 2%), (Found: C, 25.2; N, 11.1%; M^+, 625. $C_{13}F_{12}N_5$ requires C, 24.96; N, 11.2%; M, 625); δ_F (d_6-acetone), 58.3 (6F, m, F_a), 64.8 (4F, m, F_b), 83.4 (1F, dd, J 22 and 27 Hz, F_c), 92.1 (2F, m), 92.9 (2F, brm), 93.6 (2F, brm), 94.5 (2F, brm) (all due to F_d), 127.9 (1F, complex m, F_e), and 130.4 (1F, dm, J 22 Hz, F_f).



(3)

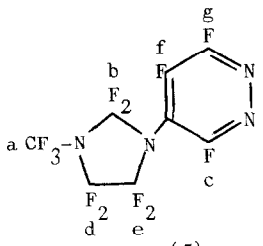


(4)

(b) Tetrafluoropyridazine

(i) Equimolar mixture with potassium fluoride. A mixture containing tetrafluoropyridazine (2.11 g, 13.9 mmol), sulpholan (20 ml), potassium fluoride (1.0 g, 17.2 mmol), and (2) (2.90 g, 12.7 mmol) was stirred at 60°C for 24 h. Reduced pressure distillation gave perfluoro-4-(3-methylimidazolidin-1-yl)pyridazine (nc) (5) (2.77 g, 57%), b.p. 60-65°C

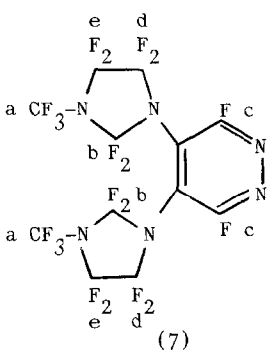
(5 mm Hg), (Found: C, 25.5; N, 14.4%; M^+, 380. $C_8F_{12}N_4$ requires C, 25.25; N, 14.7%; M, 380); δ_F 58.7 (3F, F_a), 65.2 (2F, F_b), 83.5 (F_c), 93.4 (F_d or F_e), 94.8 (F_e or F_d), 95.0 (F_f) (overall integration 5F), and 124.4 (1F, F_g).



(5)

(ii) Reaction in the presence of potassium fluoride and excess (2).

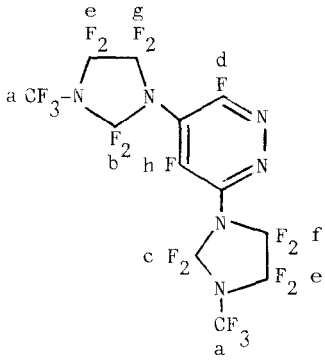
A mixture containing (2) (3.78 g, 16.6 mmol), tetrafluoropyridazine (1.30 g, 8.6 mmol), potassium fluoride (ca. 1 g), and acetonitrile (4 ml) was stirred at room temperature for 17 h. Volatile material was transferred into a trap cooled in liquid air to leave a white solid from which sublimation under vacuum gave perfluoro-4,5-bis-(3-methylimidazolidin-1-yl)-pyridazine (7) (nc) (mp 76-78°C) (2.01 g, 71%) (Found: C, 23.4; F, 62.9; N, 13.9%; M^+, 608. $C_{12}F_{20}N_6$ requires C, 23.68; F, 62.5; N, 13.8%; M, 608); δ_F (acetone) 56.0 (3F, brs, F_a), 61.3 (2F, brs, F_b), 80.2 (1F, brs, F_c), 90.0 (2F, brs, F_d), and 92.7 (2F, brs, F_e). The lower layer of the volatile component was isolated and shown by mass spectrometry-glc (column



(7)

K, 110°C) to be perfluoro-4-(3-methylimidazolidin-1-yl)-1-methyl-2,5-dihydroimidazole (8) (1.65 g) by comparison with an authentic sample [9].

(iii) Reaction in the presence of caesium fluoride at 85°C. A mixture containing (2) (6.30 g, 27.6 mmol), tetrafluoropyridazine (2.0 g, 13.2 mmol), caesium fluoride (ca. 1 g), and acetonitrile (3 ml) was stirred at 85°C for 5 h. Volatile material was transferred under vacuum into a trap cooled in liquid air and the lower layer (8.16 g) was isolated and shown to be predominantly one component by glc. Preparative scale glc (column F, 200°C) gave perfluoro-3,5-bis-(3-methylimidazolidin-1-yl)pyridazine (6) (92%) (nc) (Found: C, 23.9; F, 62.0; N, 13.6%; M^+, 608. $C_{12}F_{20}N_6$ requires C, 23.68; F, 62.5; N, 13.82%; M, 608); δ_F 56.7 (6F, p, J 6.9 Hz, F_a), 62.5 (2F, m, F_b or F_c), 63.2 (2F, m, F_c or F_b), 79.0 (1F, m, F_d), 90.5 (4F, m, F_e), 92.3 (2F, m, F_f or F_g), 93.2 (2F, m, F_g or F_f), and 112.2 (1F, m, F_h).



(6)

(iv) Reaction in the presence of caesium fluoride at room temperature. A mixture containing (2) (3.61 g, 15.8 mmol), tetrafluoropyridazine (1.20 g, 7.9 mmol), caesium fluoride (ca. 1 g), and acetonitrile (3 ml) was stirred at room temperature for 22 h. Volatile material was transferred under vacuum into a trap cooled in liquid air and the lower layer (4.75 g, 99% recovery) was shown by mass spectrometry-glc (column F, 160°C) and ^{19}F nmr spectroscopy to be (6) (83%).

Fluoride ion induced isomerisation of (7)

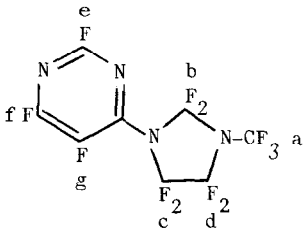
A mixture containing perfluoro-4,5-bis-(3-methylimidazolidin-1-yl)-pyridazine (7) (0.24 g, 0.4 mmol), caesium fluoride (ca. 0.5 g), and acetonitrile (1 ml) was stirred at 70°C for 4 h. Volatile material was transferred under vacuum into a trap cooled in liquid air and added to water

The lower layer (0.16 g, 67%) was isolated and shown by ^{19}F nmr spectroscopy to be perfluoro-3,5-bis-(3-methylimidazolidin-1-yl)pyridazine (6).

Tetrafluoropyrimidine

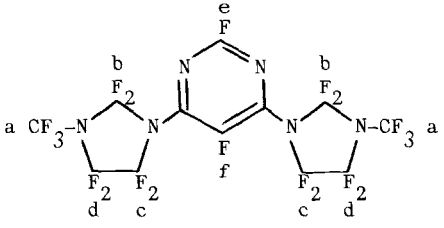
(a) Reaction in the presence of potassium fluoride

A mixture containing (2) (3.30 g, 14.5 mmol), tetrafluoropyrimidine (1.24 g, 8.2 mmol), potassium fluoride (ca. 1 g), and acetonitrile (3 ml) were stirred under nitrogen at room temperature for 16 h. Volatile material was transferred under vacuum into a trap cooled in liquid air and the lower fluorocarbon layer (3.47 g) was isolated. Separation by preparative scale glc (column F, 170°C) gave perfluoro-4-(3-methylimidazolidin-1-yl)pyrimidine (9) (nc) (11%) (Found: F, 59.4; N, 15.2%; M^+, 380. $C_8F_{12}N_4$ requires; F, 60.0; N, 14.7%; M, 380); δ_F 47.5 (1F, d, J 29.3 Hz, F_e), 58.6 (3F, br, F_a), 63.9 (2F, br, F_b), 73.9 (1F, d, J 19.6 Hz, F_f), 93.8 (2F, d, J 29.3 Hz, F_c), 95.5 (2F, br, F_d), and 163.8 (1F, m, F_g) and perfluoro-4,6-bis-



(9)

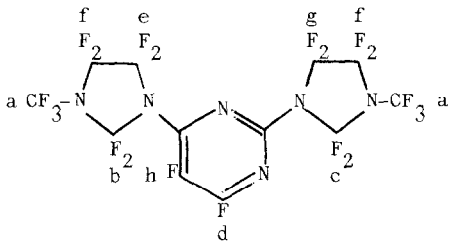
(3-methylimidazolidin-1-yl)pyrimidine (10) (nc) (51%), (Found: C, 23.5; F, 61.7; N, 13.8%; M^+, 608. $C_{12}F_{20}N_6$ requires C, 23.68; F, 62.5; N, 13.8%; M, 608); δ_F (acetone) 46.9, (1F, br, F_e), 55.8 (6F, br, F_a), 61.2 (4F, br, F_b), 90.7 (4F, d, J 29.3 Hz, F_c), 93.2 (4F, br, F_d), and 147.1 (1F, m, F_f).



(10)

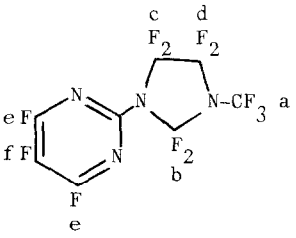
(b) Reaction in the presence of caesium fluoride

A mixture containing tetrafluoropyrimidine (2.85 g, 18.8 mmol), caesium fluoride (ca. 1 g), acetonitrile (7 ml), and (2) (7.65 g, 33.5 mmol) was stirred at 58°C for $4^1/4$ h. Volatiles were transferred under vacuum at room temperature into a trap cooled in liquid air to leave a white solid. Sublimation under vacuum gave perfluoro-2,4-bis(3-methylimidazolidin-1-yl)-pyrimidine (12) (nc) (mp 123-5°C) (6.6 g, 63%) (Found: C, 23.8; F, 62.0; N, 13.6%; M^+, 608. $C_{12}F_{20}N_6$ requires C, 23.68; F, 62.5; N, 13.82%; M, 608); δ_F (acetone) 57.3 (6F, p, J 7.5 Hz, F_a), 62.7 (2F, dsx, J 24.5 and 7.5 Hz, F_b), 66.3 (2F, m, J 7.5 Hz, F_c), 75.7 (1F, d, J 21.6 Hz, F_d), 92.7 (2F, dt, J 26.8 and 6.5 Hz, F_e), 94.5 (4F, m, F_f), 96.8 (2F, t, J 16.0 Hz, F_g), and 162.7 (1F, m, F_h). The volatile components of the product



(12)

mixture were poured into water and the lower layer (2.43 g) was isolated and separated by preparative scale glc (column K, 100°C) to give perfluoro-2-(3-methylimidazolidin-1-yl)pyrimidine (11) (nc) (18%) (Found: C, 25.3; F, 60.4; N, 14.6%; M^+, 380. $C_8F_{12}N_4$ requires C, 25.3; F, 60.0; N, 14.7%; M, 380); δ_F 58.3 (3F, p, J 7.5 Hz, F_a), 67.5 (2F, m, J 7 Hz, F_b), 75.3 (2F, d, J 19 Hz, F_e), 94.8 (2F, sx, J 7.0 Hz, F_d), 97.8 (2F, t, J 6.6 Hz, F_c), and 176.6 (1F, t, J 19 Hz, F_f).



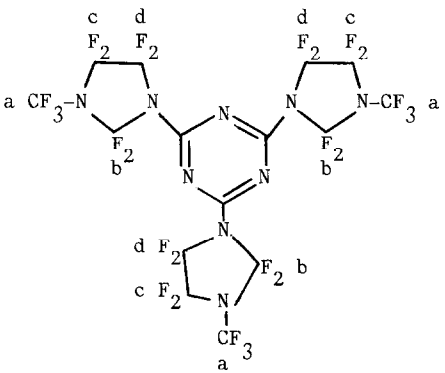
(11)

Fluoride ion induced isomerisation of (10)

A mixture containing perfluoro-4,6-bis-(3-methylimidazolidin-1-yl)-pyrimidine (10) (0.43 g, 0.7 mmol), caesium fluoride (ca. 0.5 g), and acetonitrile (1 ml) was stirred at room temperature for 22 h. Volatile material was transferred under vacuum into a trap cooled in liquid air. The fluorocarbon product (0.21 g, 49%) was isolated and shown to be perfluoro-2,4-bis-(3-methylimidazolidin-1-yl)pyrimidine (12) by ^{19}F nmr.

Trifluoro-1,3,5-triazine

A mixture containing (2) (3.80 g, 16.7 mmol), trifluoro-1,3,5-triazine (1.0 g, 7.4 mmol), caesium fluoride (1.10 g, 7.2 mmol), and acetonitrile (5 ml) was stirred under nitrogen at 80°C for 4 h. Volatile material was transferred under vacuum into a trap cooled in liquid air, and acetonitrile and trifluoro-1,3,5-triazine were removed by molecular distillation to leave a white solid. Vacuum sublimation (120-122°C, 0.004 mm Hg) gave perfluoro-2,4,6-tris(3-methylimidazolidin-1-yl)-1,3,5-triazine (13) (nc) (mp 164-166°C) (3.01 g, 66%) (Found: C, 22.1; F, 63.0; M^+, 819. $C_{15}F_{27}N_9$ requires C, 21.98; F, 62.64; M, 819); δ_F (C_6F_6) 54.8 (3F, p, J 7.5 Hz, F_a), 63.1 (2F, m, F_b), 90.7 (2F, m, F_c), and 93.7 (2F, t, J 6 Hz, F_d).



(13)

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