Vol. 5 No. 3
Summer 1994

PREPARATION AND ISOMERIZATION OF DICHLOROAMINO-3,5-DIFLUORORO-4-HEPTAFLUOROISOPROPYL-6-METHOXY PYRIDINE

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Abstract

Treatment of 4-heptafluoroisopropyl-2-methoxy-3,5,6-trifluropyridine (4) with aqueous ammonia in THF gave 2-amino-3,5-difluoro-4-heptafluoro-isopropyl-6-methoxy pyridine (5) in 71% yield. Chlorination of this amine with ^{t}ButOCl at -16°C gave an unstable product, namely 2-dichloroamino-3,5-difluoro-4-heptafluoroisopropyl-6-methoxy pyridine (6). Iodine-catalysed rearrangement of this dichloroamino-compound provided a *ca.* 70:30 mixture of 3-chloro-6-chloroimino-3,5-difluoro-4-heptafluoroisopropyl-2-methoxy-1-azacyclohexa-1,4-diene (7) and 5-chloro-6-chloroimino-3,5-difluoro-4-hepta-fluoroisopropyl-2-methoxy-1-azacyclohexa-1,3-diene(8). The ^{13}C NMR spectra of these imines have also been studied.

Introduction

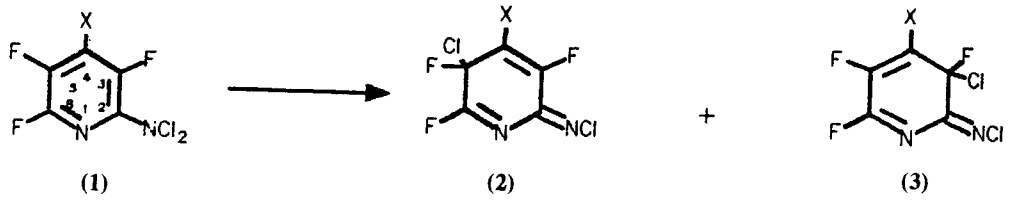
In our previous studies [1,2] on the preparation and isomerization of a series of N-chlorinated perfluoroaminopyridines, we reported that iodine-catalysed isomerization of N,N-dichloroamino-pyridines normally produces a mixture of two imino-compounds (2) and (3) (Scheme I) due to ortho and para-migration of N-chlorine. In the present work, our main objective has been to affect the ratio of imino-isomers, by introducing a relatively bulky group in the position 6 of N,N-dichloroaminopyridine (1) (Scheme I), and to try to make ortho-migration of N-chlorine more facile than para-migration. The target molecule was 2-dichloroamino-3,5-difluoro-4-hepta-fluoro-isopropyl-6-methoxy pyridine (6).

Keywords: Chlorination; Iodine-catalysis; Dichloroamino-compounds

Results and Discussion

Amination of 4-heptafluoroisopropyl-2-methoxy-3,5,6-trifluoropyridine [3] produced only 2-amino-3,5-difluro-4-heptafluroisopropyl-6-methoxy-pyridine (5) in 71% yield which shows the replacement of F-6. This is quite expectable because the order of ease of neucleophilic displacement of ring fluorines in fluoropyridines decreases in the order 4->2-(or 6-) >3- (or 5-) [4,5].

The sublimed product had a good elemental analysis (C, M, F and N) and the IR spectrum showed a doublet at 2.83 and 2.31 μm (N-H stretch) and a triplet centred at 3.36 μm (C-H stretch). The ^{19}F NMR



(1) (2) (3)

X=CH_3: 0% X=CH_3: 100%
X=H : 6% X=H : 94%
X=Cl : 10% X=Cl : 90%

Scheme 1

(4) (5)

Scheme II

spectrum showed three sets of bands at -3.33, 71.0 and 101.5 ppm with relative intensities of 6:2:1 which were assigned to $(CF_3)_2CF$, F-3 and F-5, and $(CF_3)_2CF$, respectively. Nuclei F-3 and F-5 appear to be chemical shift equivalent and give rise to a broad complex band in the ^{19}F NMR spectrum. The ^{13}C NMR (Table 3) spectrum of this compound was analysed on the basis of the information obtained from the perfluoro-(4-isopropylpyridine) (Table 1) and 4-heptafluoroisopropyl-2-methoxy-3,5,6-trifluoropyridine (Table 2). The ^1H NMR (external reference *p*-$C_6H_4Cl_2$, chemical shift positive to the high field of the reference) clearly showed the presence of CH_3O (+3.05, singlet) and -NH_2 (+2.58 ppm broad singlet).

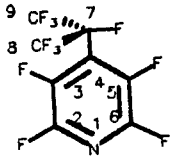


Table 1

Chemical Shift (ppm)*	Assignment	Multiplicity
145.6	C-2 and C-6	d of d of d of d
141.1	C-3 and C-5	d of d of t
120.1	C-4	d of t
92.8	C-7	d of multiplets
120.5	C-8 and C-9	q of d

* Downfield from TMS

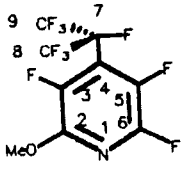


Table 2

Chemical Shifts (ppm)	Assignment	Multiplicity
145.6	C-6	d of d of d
136.1	C-5	d of d of d
116.8	C-4	d of d of d
141.6	C-3	d (of t of d)*
147.8	C-2	d of d of d
92.3	C-7	d of septets of d
120.2	C-8 and C-9	q of d
54.8	CH_3O	q

* These two doublet splittings show only with resolution enhancement (*ca.* 7 and 4 Hz, respectively).

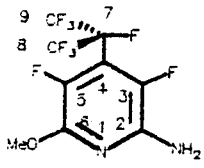
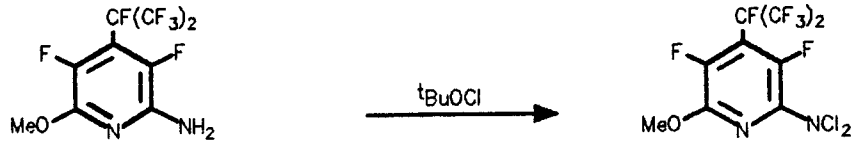


Table 3

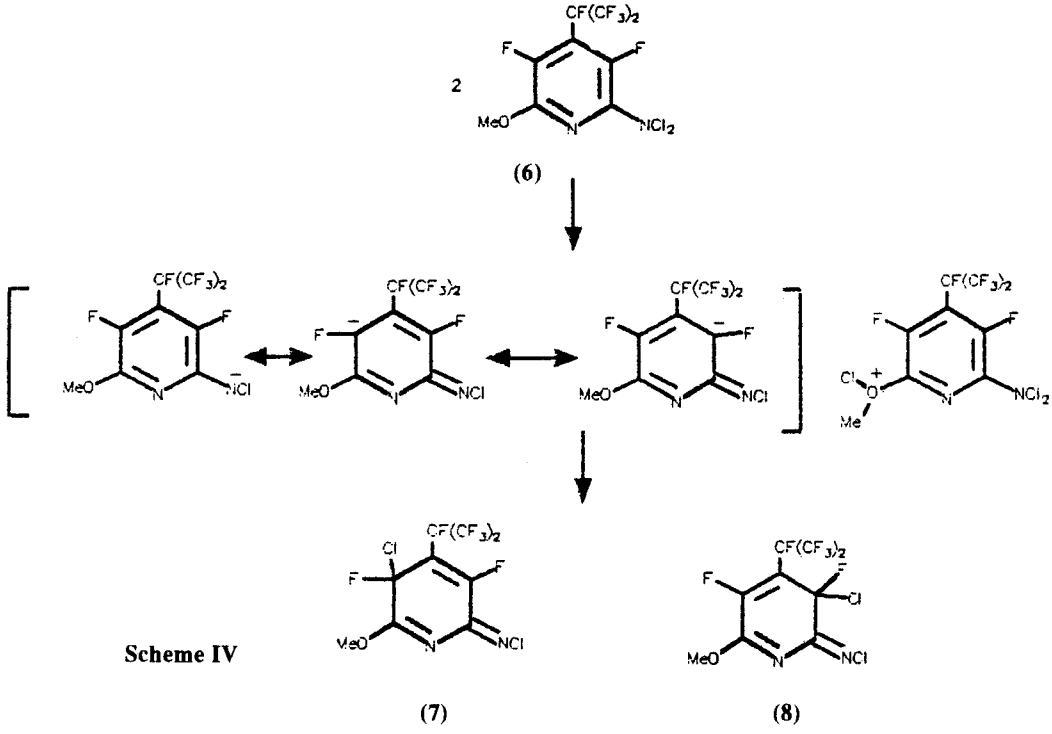
Chemical Shifts (ppm ref. TMS)	Assignment	Multiplicity
141.9	C-2	singlet
113.4	C-4	complex
135.4	C-3 and C-5	d of d
148.5	C-6	complex
92.1	C-7	d of septets
120.2	C-8 and C-9	q of d
53.8	C-10	q

Chlorination of 2-amino-3,5-difluoro-4-heptafluoroisopropyl-6-methoxy pyridine (5) with ^{t}butyl hypochlorite in Analar chloroform/carbon tetrachloride mixture at -16°C gave after 2 h a pale yellow solution which was thought, from IR spectroscopic examination (disappearance of N-H stretch bands at 2.83 and 2.31 μm) before removal of the solvent, to contain only 2-(dichloroamino)-3,5-difluoro-4-heptafluoroisopropyl-6-methoxy-pyridine [IR 3.33 (C-H stretch), 6.17, 6.71, 6.99 μm (aromatic C=C stretch)] (6) (Scheme III). After the solvent had been removed under reduced pressure (18°C/0.01 mmHg), the IR spectrum of the residue differed from the previous one and appeared to show that the product was a mixture of the dichloroamino-compound and the rearranged products (appearance of olefinic C=N/C=CF stretching at 6.09 and 6.36 μm, respectively). It is believed that an autocatalytic rearrangement takes place (Scheme IV).



(5) (6)

Scheme III

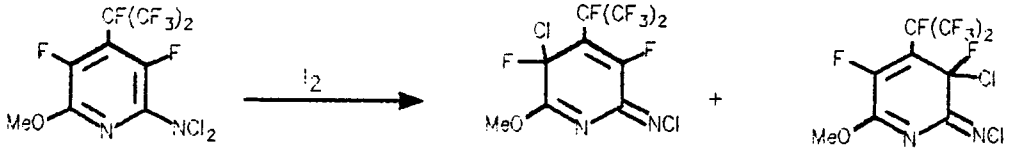


Scheme IV

(7) (8)

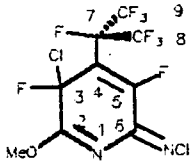
In a repeated reaction before the removal of solvents, isomerization was effected by the addition of a single crystal of iodine. Removal of the solvents under vaccum gave a yellow liquid which was distilled under reduced pressure to provide a *ca.* 70:30 mixture of 3-chloro-6-chloroimino-3,5-difluoro-4-heptafluoro-isopropyl-2-methoxy-1-azacyclohexa-1,4-diene (7) and 5-chloro-6-chloroimino-3,5-difluoro-4-heptafluor-oisopropyl-2-methoxy-1-azacycloexa-1,3-diene (8) (the ratio obtained on the basis of relative integrations of F-5 in the ^{19}F NMR of both isomers) in 89% yield (Scheme V). The elemental analysis of this mixture was entirely consistent with the molecular formula $C_9H_3F_9Cl_2N_2O$ and the IR spectrum showed clearly the existence of olefinic C=N/C=CF stretching at 6.09 and 6.36 μm. The ^{19}F NMR spectrum indicates that it is mainly one component, with a second component largely masked although quite apparent from the integrated spectrum. The major component was identified as the 1,4-diene (7) with absorptions at -5.3 (CF_3 *syn* to Cl), -2.0 (CF_3 *anti* to Cl), +25.8 (=CF), +32.4 (CFCl), and +106.1 (-CF) ppm; also, the spectrum was complex and not well resolved. Consequently, relative coupling constants could not be obtained, but the coupling constant of magnitude 44 Hz was apparent between the fluorines of CFCl group and $-CF(CF_3)_2$ group.

The minor component (*ca.* 30%) showed absorptions at -5.4 (CF_3 *syn* to Cl), the low field absorptions are assigned to the group disposed *syn* to neighbouring chlorine [6,7], -2.0 (CF_3 *anti* to Cl), *ca.* +32.4 (=CF and CFCl) and +106.1 (-CF) ppm and were tentatively identified as 1,3-diene (8). No coupling constants could be obtained. The ^1H NMR spectrum showed an absorption at 4.34 ppm relative to external TMS due to the methoxy groups. The ^{13}C NMR of two isomers was also analysed to provide the data presented in Tables 4 and 5.

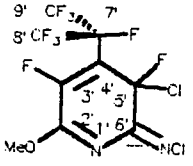


(6) (7) (8)

Scheme V



(7)



(8)

Table 4

Chemical Shifts (ppm ref. TMS)	Assignment	Multiplicity
153.2	C-6	d
152.9	C-5	d of t
*109.5	C-4	-
95.8	C-3	d of d of d
163.8	C-2	d
91.6	C-7	d of septets
119.8	C-8	q of d
56.9	C-9	q

* This band is not distinguishable from the noise in the coupled spectrum, so the assignment is tentative, alternatively the band at 118.3 ppm (see Table 5).

Table 5

Chemical Shifts (ppm ref. TMS)	Assignment	Multiplicity
161.7	C-6	d
98.8	C-5	d of d of d
118.3	C-4	-
148.1	C-3	d of t
156.7	C-2	d
91.6	C-7	d of septets
119.8	C-8	q of d
56.5	C-9	q

Experimental Section

The NMR spectra were recorded on a Perkin-Elmer R32 operating at 90 MHz for ^1H and 84.6 MHz for ^{19}F nuclei. NMR data-chemical shifts to high field of reference absorption (external CF_3CO_2H for ^{19}F; external Me_4Si for ^1H) are designated negative.

^{13}C NMR spectra were recorded on a Bruker WP8 operating at 20.1 MHz. Mass spectrometry was carried out using a double focussing A.E.I. MS 902 mass spectrometer. Infra-red absorption spectra were recorded on a Perkin-Elmer Model 197 spectrometer.

2-Amino-3,5-difluro-4-heptafluoroisopropyl-6-methoxy pyridine (5)

A small sample of 4-heptafluoroisopropyl-2-methoxy-3,5,6-trifluoropyridine [3] (1.0 g, 3.02 m.moles) and ammonia (d=0.88, 2 ml) in tetrahydrofuran (THF) (25 ml) were loaded into a Pyrex pressure tube (100 ml) which was sealed under vacuum. The tube was then shaken and heated (60-65°C) for 90 h. The reaction mixture was poured into water (250 ml) and extracted with ether (3×150 ml); the extracts were dried ($MgSO_4$) and evaporated to give a brown solid, sublimation (80°C, 0.03 mmHg) of which produced a pure sample of 2-amino-3,5-difluoro-4-hepta-fluoroisopropyl-6-methoxy pyridine (0.7 g, 2.13 m.moles), 71%, (Found: C, 33.1; H, 1.5; F, 52.3; N, 8.7%, $C_9H_5F_9N_2O$ requires C, 32.9; H, 1.5; F, 52.1; N, 8.5%), a white solid m.p. 93-94°C.

m/e 328 [M^+., 100%]; 309[M^+-F, 8.9%], 69[CF_3^+, 11.4%].

Dichloroamino-3,5-difluro-4-heptafluoroisopropyl-6-methoxypyridine (6)

A pure sample of 2-amino-3,5-difluoro-4-heptafluoroisopropyl-6-methoxypyridine (0.44 g, 1.34 m.moles), dissolved in Analar chloroform (20 ml), was added slowly in 15 mins to a cold (-16°C) stirred solution of ^{t}butylhypochlorite (0.36 g, 3.31 m.moles) in Analar carbon tetrachloride (20 ml). Stirring was continued at this temperature under dry nitrogen for nearly 3 h until no free amine could be detected by IR spectroscopy (disappearance of N-H stretching bands at 2.83 and 2.31 μm). The mixture was connected to a vacuum system via a cold (-196 °C) external trap and the solvent was removed under vacuum without heating. Removal of all the solvent left a pale yellow liquid the IR spectrum of which was a bit different (due to rearrangement which had taken place) from the one taken during the reaction, which was believed to be that of dichloroamino-3,5-difluoro-4-heptafluoroisopropyl-6-methoxypyridine.

3-Chloro-6-chloroimino-3,5,difluoro-4-heptafluoroisopropyl-2-methoxy-1-azacyclohexa-1,4-diene and 5-chloro-6-chloroimino-3,5,difluoro-4-heptafluoroisopropyl-2-methoxy-1-azacyclohexa-1,3-diene (7 and 8)

A crystal of iodine was added to a solution of dichloroamino-3,5-difluoro-4-heptafluoroisopropyl-6-methoxypyridine obtained from the above reaction and the mixture was stirred for nearly 2 h at room temperature. Evaporation of the solvents under reduced pressure gave a yellow liquid which was distilled in a semi-micro distillation unit using a nitrogen bleed to give a (*ca.* 70:30) mixture of 3-chloro-6-chloroimino-3,5-difluoro-4-heptafluoroisopropyl-2-methoxy-1-azacyclohexa-1,4-diene and 5-chloro-6-chloroimino-3,5-difluoro-4-heptafluoroisopropyl-2-methoxy-1-azacyclohexa-1,3-diene (0.47 g 1.18 m.moles), 89%, (Found: C, 27.4; H, 0.6; F, 43.1; N, 6.8% $C_9H_3F_9Cl_2N_2O$ requires: C, 27.2; H, 0.7; F, 43.0; N, 7.0%) b.p. 77°C at 0.2 mmHg; m/e: 396 [M^+, 12.5%], 398 [M^++2, 8.4%]; 400 [M^++4, 1.5%]; 300 [$C_8H_3F_9NO^+$, 100%], 69 [CF_3^+, 68.4%].

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