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REACTION OF TERTIARY FORMAMIDES WITH SULPHUR TETRAFLUORIDE. DIRECT SYNTHESIS OF (TRIFLUOROMETHYL)AMINES

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SUMMARY

Treatment of dimethylformamide 1a, diethylformamide 1b, 1-formylpiperidine 3a, 4-formylmorpholine 3b, and ethyl-phenylformamide 5 with sulphur tetrafluoride in the presence of potassium fluoride resulted in a direct conversion of the formyl group to the trifluoromethyl group to give excellent yields of dimethyl(trifluoromethyl)amine 2a, diethyl(trifluoromethyl)amine 2b, 1-(trifluoromethyl)piperidine 4a, 4-(trifluoromethyl)morpholine 4b, and N-ethyl-N-(trifluoromethyl)aniline 6, respectively. The reaction pathway was investigated and the (trifluoromethyl)amines were characterised by spectral methods, elemental analyses, and hydrolysis to corresponding N-(fluoroformyl)amines 11.

INTRODUCTION

Amides, in general, are known to react with sulphur tetrafluoride with cleavage of the carbon-nitrogen bond. N,N-dimethylbenzamide, which gave a small yield of α,α-difluorobenzyldimethylamine was the only reported exception [1] . It has been suggested, that the C-N bond cleavage is caused by trace amounts of hydrogen fluoride, which is usually present in the reaction medium. Our earlier investigations [2] have shown that cleavage

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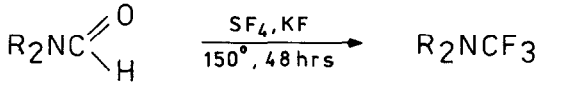
of the C-N bond may be avoided by carrying out the reactions in the presence of potassium fluoride as a hydrogen fluoride bonding agent. Thus, a number of N,N-dialkylbenzamides, when treated with SF_4 and KF, were converted to corresponding dialkyl-α,α-difluorobenzylamines with good yields.

While extending our studies on aliphatic amides we carried out reactions of SF_4 with N,N-dialkylacetamides and N,N-dimethylhaloacetamides but no isolable products were obtained. Also our attempts to obtain the corresponding cyclic fluoroamine in the reaction of N-methylphthalimide with SF_4 failed. This paper describes the unusual results of the reactions of SF_4 with tertiary formamides.

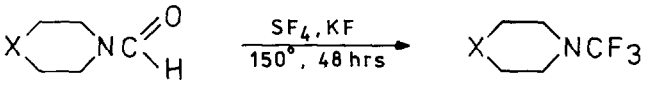
RESULTS AND DISCUSSION

Dimethylformamide 1a reacted with a standard quality SF_4 contaminated with HF at 150° for 48 hours to give a very complex mixture from which no individual compound could be isolated. However, when this reaction was carried out in the presence of dry potassium fluoride, the reactant formamide 1a was fully converted to a single product, viz. dimethyl(trifluoromethyl)amine 2a. Similar results were obtained with other investigated tertiary formamides; thus, the reaction with diethylformamide 1b, 1-formylpiperidine 3a, 4-formylmorpholine 3b, and ethylphenylformamide 5 gave practically quantitative yields of diethyl(trifluoromethyl)-amine 2b, 1-(trifluoromethyl)piperidine 4a, 4-(trifluoromethyl)-morpholine 4b and N-ethyl-N-(trifluoromethyl)aniline 6, respectively.



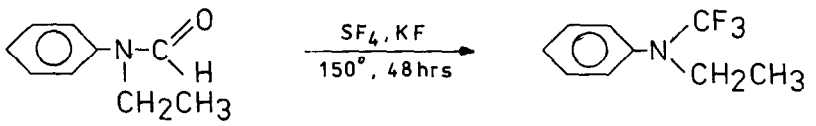
1 2 (90%)

1a, 2a : R = CH_3- , 1b, 2b : R = CH_3CH_2-



3 4 (92-94%)

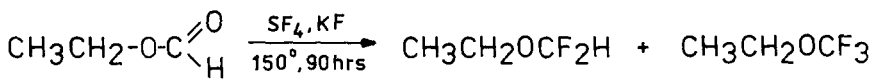
3a, 4a : X = $-CH_2-$, 3b, 4b : X = O



5 6 (94%)

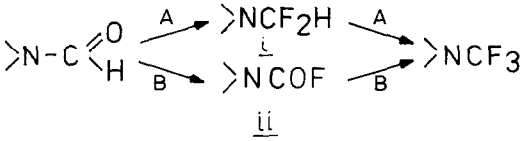
The above results are rather unusual and according to the best of our knowledge these reactions are the first examples of a direct conversion of the formyl group to the trifluoromethyl group.

The reaction seems to be specific for the formyl group bound to the nitrogen atom. Comparative reactions of SF_4 with benzaldehyde and propionaldehyde in the presence of KF gave only expected gem—difluoro compounds. The reaction with ethyl formate 7 gave a mixture of ethyl(difluoromethyl) ether 8 and ethyl(trifluoromethyl) ether 9; ether 9 was formed as the minor product.

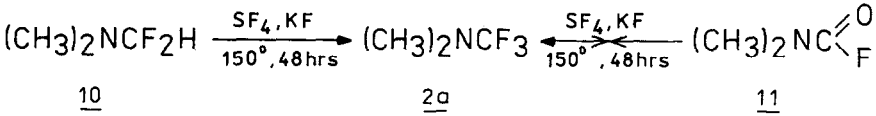


7 8 (35%) 9 (20%)

Conversion of the formyl group to the CF_3 group must involve at least two stages. Alternative routes may be considered as follows: fluorination of the carbonyl group followed by a substitution of fluorine for hydrogen in the CF_2H group of the intermediate gem-difluoroamine i (route A), or a substitution of fluorine for formyl hydrogen prior to fluorination of the carbonyl group of the intermediate N-(fluoroformyl)-amine ii (route B).



In order to verify which route, A or B, takes place, we prepared by other means (see Experimental) both supposed intermediates i and ii and reacted them separately with SF_4 under conditions which were used for the reactions with the formamides. Thus, (difluoromethyl)dimethylamine 10 was fully converted to (trifluoromethyl)amine 2a, while dimethyl-N-(fluoroformyl)amine 11 remained unaffected.



These results rule out route B and support route A, which involves gem-difluoroamines as the intermediates. However, in the reactions of formamides 1,3,and 5 with SF_4, no intermediate compound was observed; decreasing the reaction temperature to 100° resulted only in a lower conversion and mixtures of the (trifluoromethyl)amines (ca.60%) and the unreacted formamides were obtained. This suggests that in the reactions of tertiary formamides with SF_4 in the presence of KF, substitution of fluorine for hydrogen in the CF_2H group of the intermediate gem-difluoroamines proceeds faster than fluorination of the carbonyl group of the reactant formamides, therefore the formation of gem-difluoroamines is the rate determining step.

Fluorination of the carbon-hydrogen bond with SF_4 is not common and, so far, only a few reactions of this type have been noted in the literature; formation of 10,10-difluoroanthrone from anthrone [3] and formation of 2-methyl-1,1,2--trifluorocyclohexane from 2-methylcyclohexanone [4] being the best known examples. A free-radical mechanism was suggested for the reaction of anthrone [4] .

We have found that in the reaction of SF_4 with tertiary formamides, elemental sulphur and hydrogen fluoride are formed, according to the following stoichiometry:

$$2RR'NC(=O)H + 3SF_4 = 2RR'NCF_3 + 2SOF_2 + S + 2HF$$

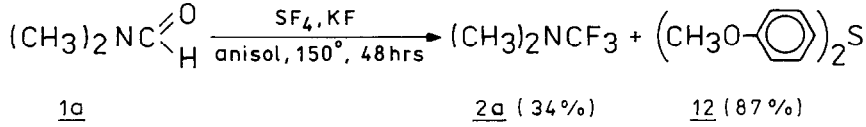
The first step of the reaction is fluorination of the carbonyl group to form gem-difluoroamines $RR'NCF_2H$ and SOF_2 (route A) but the above reaction stoichiometry suggests that the second step i.e. a substitution of fluorine for hydrogen in the CF_2H group of $RR'NCF_2H$ to form $RR'NCF_3$ must be an oxidation-reduction process. The following reaction mechanism may be considered for the reaction of SF_4 with gem-difluoroamines:

$$RR'NCF_2H + SF_3^+ \longrightarrow \underset{\text{iii}}{RR'N{=}{=}\overset{+}{C}F_2} + HF + SF_2$$

$$\underset{\text{iii}}{RR'N{=}{=}\overset{+}{C}F_2} + SF_4 \longrightarrow RR'NCF_3 + SF_3^+$$

$$2SF_2 \longrightarrow SF_4 + S$$

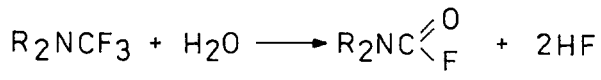
In the above mechanism fluorination of the carbon-hydrogen bond involves an abstraction of hydride anion (H^-) by the SF_3^+ cation to form hydrogen fluoride, sulphur difluoride, and a resonance-stabilised cation iii, which in turn reacts with sulphur tetrafluoride to form a new carbon-fluorine bond and to reform the SF_3^+ cation. Sulphur difluoride, the suspected product of the sulphur tetrafluoride reduction, is very unstable compound and disproportionates readily to SF_4 and elemental sulphur [5]. The presence of SF_3^+ or SF_2 species in the reaction medium has been proved as follows: when the reaction of dimethylformamide 1a with SF_4 was conducted in an excess of anisole, besides (trifluoromethyl)amine 2a, p-p'-dimethoxydiphenyl sulphide 12 was obtained in high yield.



1a 2a (34%) 12 (87%)

The reaction of tertiary formamides with SF_4 in the presence of potassium fluoride, because of excellent yields and the availability of formamides seems to be superior to the other synthetic methods which have been reported so far for preparation of tertiary (trifluoromethyl)amines [6,7,8].

(Trifluoromethyl)amines 2,4, and 6 are very reactive compounds; all of them fume in air and they react vigorously with water. Hydrolysis of dialkyl-(trifluoromethyl)amines 2a and 2b gave the corresponding dialkyl-N-(fluoroformyl)amines 11a and 11b.



2 11

2a, 11a: R=CH_3-

2b, 11b: R=CH_3CH_2-

The chemical properties of tertiary (trifluoromethyl)amines, particularly as fluorinating agents, will be reported in a forthcoming publication (see also following paper).

EXPERIMENTAL

Boiling points (uncorrected) were estimated by distillation. NMR spectra were recorded with a JEOL JNM-4H-100 spectrometer; chemical shifts are in p.p.m. from internal CCl_3F for ^{19}F spectra (positive upfield) and from internal

TMS for ^1H spectra (positive downfield). Mass spectra were obtained with an Analytical GCMS System LKB-2091. Fluorine was determined after the sample had been burnt in oxygen by the Schöniger method, and nitrogen was determined by a conventional semimicro method.

Sulphur tetrafluoride was prepared by a standard technique used in this laboratory [9].

Dialkyl- and alkyl-arylformamides were prepared from formic acid and the corresponding amines using a standard procedure [10].

Reactions of tertiary formamides 1,3, and 5 with SF_4

The reactions were carried out in a 0.03 dm^3 stainless steel autoclave. Amide (3.0g,0.023-0.041 mole) and freshly dried potassium fluoride (3.0g,0.05 mole) were placed in the autoclave, the autoclave was cooled in a dry ice-acetone mixture and evacuated to 1-2 mm Hg. Then, sulphur tetrafluoride (ca.12g,0.1 mole) was liquified in it. The charged autoclave was heated in a rocking muffle furnace at 150° for 48 hours. After completion of the reaction, the autoclave was allowed to cool to ambient temperature.

(Trifluoromethyl)amines 2a and 2b, formed from formamides 1a and 1b, respectively, were directly distilled out of the autoclave, first at 20° then the autoclave was gradually warmed up to 120°, and the crude amines were condensed in a glass trap kept at -15°, while the excess of SF_4 and SOF_2 were let out through a tube filled with anhydrous calcium chloride.

In order to determine the reaction stoichiometry, the reaction of dimethylformamide 1a with SF_4 was carried out on a 0.6 mole scale in a 0.5 dm^3 autoclave. When the reaction had run to completion, dimethyl(trifluoromethyl)amine 2a was

removed as it was described above, and then elemental sulphur was extracted from the autoclave by heating with carbon disulphide (300 ccm) at 135° for 70 hours.
A solution of sulphur in CS_2 was separated from solid material by filtration, and a residue obtained after evaporation of the solvent was analysed for sulphur. Hydrogen fluoride formed in the reaction was determined as KF·HF in a mixture of salts insoluble in CS_2.

Dimethyl(trifluoromethyl)amine 2a: yield 89% (4.13g,0.057 mole). B.p. 19-20°(lit.20° [6]). Calculated for $C_3H_6F_3N$; F,51.0%. Found: F,50.5%. ^1H and ^{19}F NMR : $\delta(CH_3)$ = 2.52 ppm (s), $\phi(CF_3)$ = 69.8 ppm (s). M.S.: in agreement with reference [6].

Diethyl(trifluoromethyl)amine 2b: yield 89.5% (3.75g,0.0266 mole). B.p. 71-2° (lit.34-35°/180 mmHg [6]). Calculated for $C_5H_{10}F_3N$: N,9.9; F,40.4%. Found: N,9.8; F,40.5%. ^1H and ^{19}F N.M.R.: $\delta(CH_3)$ = 1.15 ppm(t), $\delta(CH_2)$ = 2.97 ppm (q), $\phi(CF_3)$ = = 60.8 ppm (s), $^3J(HH)$ = 6.95 Hz.
MS: 141 (14%) $[M]^{+\cdot}$, 126 (63%) $[C_4H_7F_3N]^+$, 98 (100%) $[C_2H_3F_3N]^+$, 78 (15%) $[C_2H_2F_2N]^+$, 69 (10%) $[CF_3]^+$, 29 (53%) $[C_2H_5]^+$, 27 (19%) $[CHN]^+$, $[C_2H_3]^+$.

1-(Trifluoromethyl)piperidine 4a: yield 93% (3.78g,0.025 mole). B.P.107°(lit.44° /68 mmHg [6]). Calculated for $C_6H_{10}F_3N$: N, 9.15; F, 37.3%. Found: N, 8.95; F, 37.3%. ^1H and ^{19}F NMR : $\delta(CH_2)$ = 1.60 ppm (m) and 2.87 ppm (m), relative intensities being as 3:2, $\phi(CF_3)$ = 67.6 ppm (s). MS: 153 (42%) $[M]^{+\cdot}$, 152 (100%) $[C_6H_9F_3N]^+$, 112 (77%) $[C_5H_5F_3N]^+$, 98 (27%)$[C_2H_3F_3N]^+$, 69 (20%) $[CF_3]^+$, 55 (27%) $[C_3H_5N]^{+\cdot}$, 39 (15%)$[C_2HN]^+$, 32 (16%) $[CHF]^{+\cdot}$, 31 (22%)$[CF]^+$, 29 (15%) $[C_2H_5]^+$, 28 (35% $[CH_2N]^{+\cdot}$,$[C_2H_4]^{+\cdot}$.

4-(Trifluoromethyl)morpholine 4b (nc): yield 92% (3.70g,0.0236 mole).B.p.109°. Calculated for $C_5H_8F_3NO$: N,8.9; F,36.7%. Found: N,9.0; F,36.8%. ^1H and ^{19}F NMR: $\delta(CH_2)$ = 3.91 ppm (m) and 3.72 ppm (s), relative intensities being as 1:1, $\phi(CF_3)$ = 68.7 ppm (s). MS: 155 (62%) $[M]^{+\cdot}$, 154 (11%) $[C_5H_7F_3NO]^+$, 125 (31%) $[C_4H_6F_3N]^{+\cdot}$, 124 (12%) $[C_4H_5F_3N]^+$, 98 (44%) $[C_2H_3F_3N]^+$, 96 (12%) $[C_2HF_3N]^+$, 92 (17%) $[C_3H_4F_2N]^+$, 69 (25%) $[CF_3]^+$, 56 (26%) $[C_3H_4O]^{+\cdot}$, 31 (15%) $[CF]^+$, 28 (100%) $[CH_2N]^+$, $[C_2H_4]^{+\cdot}$, 27 (19%) $[CHN]^{+\cdot}$, $[C_2H_3]^+$.

N-Ethyl-N-(trifluoromethyl)aniline 6 (nc): yield 94% (3.58g,0.019 mole). B.p. 78°/47 mmHg. Calculated for $C_9H_{10}F_3N$: C,57.1; H,5.3; N,7.4; F,30.2%. Found: C,56.9; H,5.3; N,7,8; F,30.2%. ^1H and ^{19}F NMR: $\delta(CH_3)$ = 0.99 ppm (t), $\delta(CH_2)$ = 3.35 ppm (q), $\phi(CF_3)$ = = 58.2 ppm (s), $^3J(HH)$ = 7.5 Hz. MS: 189 (43%) $[M]^{+\cdot}$, 174 (100%) $[C_8H_7F_3N]^+$, 105 (19%) $[C_7H_7N]^{+\cdot}$, 77 (65%) $[C_6H_5]^+$, 69 (18%)$[CF_3]^+$, 51 (26%)$[CHF_2]^+$, 39 (13%) $[C_2HN]^{+\cdot}$, 29 (17%) $[C_2H_5]^+$, 27 (18%) $[CHN]^{+\cdot}$,$[C_2H_3]^+$.

Reaction of ethyl formate 7 with SF_4

The reaction was carried out as described above using 27g (0.365 mole) of ethyl formate, 27g (0.47 mole) of KF, and 70g (0.65 mole) of SF_4. The reaction products were distilled off the autoclave and condensed in a trap kept at -25°. The crude product was shown by ^1H NMR spectroscopy to consist of unreacted ethyl formate 7 (45%), ethyl(difluoromethyl) ether 8 (35%),and ethyl(trifluoromethyl) ether 9 (20%).

^1H and ^{19}F NMR of ethyl(difluoromethyl) ether 8: $\delta(CH_3)$ = 1,32 ppm (t), $\delta(CH_2)$ = 3.95 ppm (q), $\delta(CF_2\underline{H})$ = 6.27 ppm (t), $\phi(C\underline{F}_2H)$ = = 84.0 ppm (d), $^2J(HF)$ = 77.5 Hz, $^3J(HH)$ = 7.5 Hz.

^{1}H and ^{19}F NMR of ethyl(trifluoromethyl) ether 9: $\delta(CH_3)$ = 1.32ppm (t), $\delta(CH_2)$ = 4.24 ppm (q), $\phi(CF_3)$ = 61 ppm (s), $^{3}J(HH)$=7.5 Hz.

Preparation of dimethyl(difluoromethyl)amine 10

Compound 10 was prepared following a procedure described by Arnold[11].
B.p.48-50°(in agreement with ref .[11]). Calculated for $C_3H_7F_2N$: N,14.7; F,40.0%. Found: N, 14.5; F,39.9%. ^{1}H and ^{19}F NMR: $\delta(CH_3)$ = 2.48 ppm (s),$\delta(CF_2\underline{H})$ = 5.98 ppm (t), $\phi(C\underline{F}_2H)$ = = 100.0 ppm (d), $^{2}J(HF)$ = 64.5 Hz. MS: 95 (23%) $M^{+\cdot}$, 94 (35%) $[C_3H_6F_2N]^{+}$, 76 (46%) $[C_3H_7FN]^{+}$, 60 (22%) $[C_2H_3FN]^{+}$, 51 (20%) $[CHF_2]^{+}$, 44 (100%) $[C_2H_6N]^{+}$, 42 (73%) $[C_2H_4N]^{+}$, 33 (14%) $[CH_2F]^{+}$, 30 (12%) $[CH_4N]^{+}$, 28 (27% $[CH_2N]^{+}$, $[C_2H_4]^{+\cdot}$.

Reaction of(difluoromethyl)dimethylamine 10 with SF_4

The reaction was carried out as described for formamides 1 using 3g (0.0316 mole) of compound 10, 3.0g (0.05 mole) of KF, and 11g (0.1 mole) of SF_4. Distillation gave 3.25g (0.0287 mole) of product, which was identified by NMR and mass spectrometry as dimethyl(trifluoromethyl)amine 2a. Yield 91%.

Reaction of dimethyl-N-(fluoroformyl)amine 11 with SF_4

The reaction of compound 11 (3.0g,0.033 mole) prepared as described below, KF (3.0g,0.05 mole), and SF_4 (11g,0.1 mole) gave no volatile products. The residue in the autoclave was found by NMR and MS spectroscopy to be unreacted 11.

Hydrolysis of dialkyl(trifluoromethyl)amines 2a and 2b

Dialkyl(trifluoromethyl)amine 2a or 2b (0.115 mole) was added dropwise to 100g of crushed ice. A vigorous exothermic reaction took place. The reaction mixture was extracted with ether, the extract was dried with $MgSO_4$ and after removal of the solvent, the residue was distilled under reduced pressure to give dialkyl-N-(fluoroformyl)amines 11a and 11b, respectively.

Dimethyl-N-(fluoroformyl)amine 11a (nc): yield 71% (0.082 mole). B.p. 85-89°/200 mmHg. Calculated for C_3H_6FNO: F,20.9%. Found: F,20.8%. ^1H and ^{19}F NMR: $\delta(CH_3)$ = 3.00 ppm (s), ϕ(COF) = 23.9 ppm (s). IR: $\nu(C=O)$= 1800 cm^{-1}. MS: 91 (82%) $[M]^{+\cdot}$, 90 (100%) $[C_3H_5NF_3O]^+$, 76 (23%)$[C_2H_3NFO]^+$, 72 (30%) $[C_3H_6NO]^+$, 60 (13%) $[C_2H_3NF]^+$, 56 (59%) $[C_3H_6N]^+$, 47 (26%) $[COF]^+$, 44 (41%)$[C_2H_6N]^+$, 43 (88%) $[C_2H_4N]^+$, 41 (56%) $[C_2H_3N]^{+\cdot}$, 40 (13%) $[C_2H_2N]^+$, 33 (57%) $[CH_2F]^+$, 31 (56%) $[CH_3O]^+$, 29 (31%) $[C_2H_5]^+$, 28 (35%) $[C_2H_4]^{+\cdot}$,$[CO]^{+\cdot}$,$[CH_2N]^+$, 27 (24%) $[CHN]^{+\cdot}$, $[C_2H_3]^+$.

Diethyl-N-(fluoroformyl)amine 11b (nc): yield 75.6% (0.1 mole). B.p. 155°. Calculated for $C_5H_{10}FNO$: C,50.4; H,8.4; N,11.8; F, 16.0%. Found: C,50.5; F,8.8; N,11.9; F,16.0%. ^1H and ^{19}F NMR: $\delta(CH_3)$ = 1.09 ppm (t),$\delta(CH_2)$ = 3.21 ppm and 3.23 ppm (two rotamers), ϕ (COF) = 23.3 ppm (s), $^3J(HH)$ = 8.14 Hz. IR: $\nu(C=O)$= = 1790 cm^{-1}. MS: 119 (17%) $[M]^{+\cdot}$, 104 (60%) $[C_4H_7NFO]^+$, 91 (11%) $[C_3H_4NFO]^{+\cdot}$, 76 (100%) $[C_2H_3NFO]^+$, 71 (12%) $[C_4H_9N]^{+\cdot}$, 56 (41%) $[C_3H_6N]^+$, 47 (29%) $[COF]^+$, 42 (34%) $[C_2H_4N]^+$, 41 (11%)$[C_2H_3N]^{+\cdot}$, 29 (71%) $[C_2H_5]^+$, 28 (35%) $[C_2H_4]^{+\cdot}$, $[CO]^{+\cdot}$, $[CH_2N]^+$, 27 (82%) $[CHN]^{+\cdot}$, $[C_2H_3]^+$.

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