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THE TRIFLUOROMETHYLATION OF CHLOROAROMATICS USING THE COPPER–CF_2Br_2 – DIALKYLAMIDE REACTION SYSTEM

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SUMMARY

The *in situ* generation of $CuCF_3$ from the reaction of copper, dibromodifluoromethane ai either N,N–dimethylformamide or N,N–dimethylacetamide (Burton's reagent) has been used for the direct substitution of chlorine by CF_3 in a number of aromatic substrates. Particular attention has been paid to the effects of ring substituents on the efficiency of reaction.

INTRODUCTION

The introduction of the CF_3 group into aromatic compounds can greatly affect their physiological activity and this has resulted in considerable interest in the development of inexpensive and convenient routes to trifluoromethylated aromatic molecules. The traditional method of synthesis of these compounds using Swarts chemistry suffers from the use of harsh conditions and the need to prepare the trichloromethylated intermediate[1]. More recently, copper–catalysed substitution of aromatic halogen by CF_3 has been the subject of considerable research and of the various reactions in this class that have been reported[2], the method due to Burton which has difluorodihalomethanes as the fluorine source[3] appears to have the greatest promise. In a recent preliminary communication[4] we reported for the first time that Burton's Cu–CF_2Br_2 –amide solvent reaction system can be used, for the direct substitution of certain aromatic chlorines by the CF_3 group and we now describe our results from a more detailed analysis of this reaction.

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RESULTS AND DISCUSSION

The Reaction Conditions

The mechanism for the formation of '$CuCF_3$' from Cu/CF_2Br_2 is thought to involve the formation of the $:CF_2$ carbene followed by its reaction with the amide solvent to give a difluoroalkylamine, which can act as a source of F^-[5], and the resulting reaction of $:CF_2$ and F^-, in the presence of copper, to give[6] $CuCF_3$. In order to determine the best conditions for trifluoromethyldechlorination we have considered a number of system variables of which the identity of the solvent, the reaction temperature and added fluoride have the most significant effects.

Our results from changing the reaction solvent confirm the need for an amide although this need not be present as the bulk solvent. For a series of bulk dipolar aprotic solvents including amides, dimethylsulphoxide and sulpholane only the amides show any reaction with the model substrate, chloro-2, 4-dinitrobenzene (Fig. 1)[4].

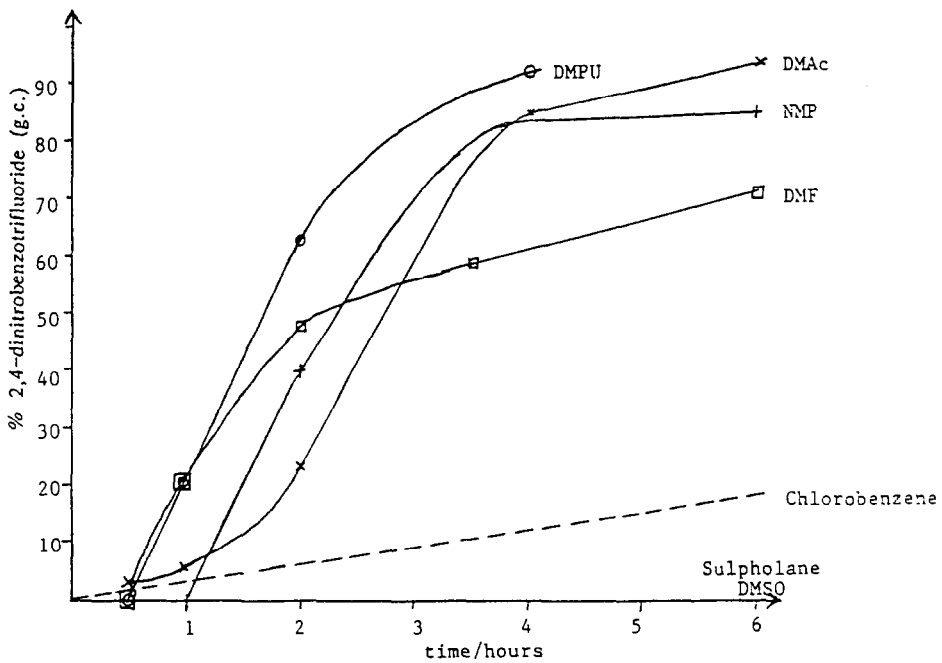


Fig. 1. The reaction of chloro-2, 4-dinitrobenzene (5 mmol) with copper (30 mmol) and CF_2Br_2 (1 cm^3) in at bulk dipolar aprotic solvents (7.5 cm^3) or bulk aromatic solvents (10 cm^3) containing DMF (1.5 cm^3).

Dimethylpropylurea (DMPU) gives the fastest reaction but the desired product, 2,4-dinitrobenzotrifluoride is accompanied by a small quantity (ca. 3%) of longer chain homologue (e.g., $ArCF_2CF_3$) products. All of these reactions gave some (ca. 5% at 100°C) of the dehalogenation product, 1,3-dinitrobenzene. Use of an amide in stoichiometric quantities in bulk chlorobenzene at 100°C also allowed trifluoromethylation to occur although the reaction was slower and less efficient giving a conversion of only 77% to the desired product after 24h along with 18% of 1,3-dinitrobenzene (other aromatic solvents such as nitrotoluene and toluene were considerably less effective). The easier work-up associated with the use of relatively non-polar bulk solvents may well make this method attractive for the reactions of some highly reactive substrates but we chose to focus our attention on bulk N,N-dimethylacetamide (DMAc) as the solvent giving the best combination of reaction rate and efficiency.

Increasing the reaction temperature in the model reaction using DMAc as solvent did significantly increase the rate of reaction but the quantity of 1,3-dinitrobenzene formed also increased from 5% at 100°C to 10% at 150°C. Most of our subsequent studies were based on reaction carried out at 100°C.

Surprisingly, added fluoride (as KF) causes a decrease in reaction rate in the model reac (despite its assumed role in the trifluoromethylation mechanism) and the halogen exchange product, fluoro-2,4-dinitrobenzene becomes significant. This may be due to the precipitation of copper salts from the reaction system due to the increased anion concentration. The effect of added KI is very similar and here the formation of the fluoroaromatic may be due to the competitive formation of KF by reaction with the F^- generated in the $Cu/CF_2Br_2/DMAc$ reaction. Addition of 10 mole % of KF to reaction involving less reactive substrates such as 2-chlorobenzaldehyde (see later) can completely inhibit any further reaction.

The Effects of Substitutents on Trifluoromethyldechlorination.

The results of the reaction of a wide variety of carbocyclic and heterocyclic aromatic chlorides with the $Cu/CF_2Br_2/DMAc$ reaction system are summarised in the Table. The effects of the identity and relative positions of substituents on the rings on the reaction efficiencies are striking and enable us to establish a list of predictive rules for trifluoromethylation using this reagent system.

The relative reactivities of the three isomers of chloronitrobenzene reveal that the electrc activation of a para-nitro substituent is insufficient to enable significant reaction whereas one ortho-nitro substituent enables quantitative conversion to 2-nitrobenzotrifluoride. This 'ortho effect' can be rationalised in terms of coordination of the copper to the nitro group which acts to hold the copper in the correct geometry for reaction to occur (Fig. 2a).

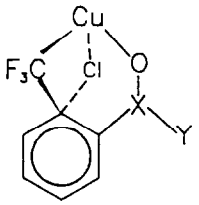


Fig. 2a. The structure of the postulated intermediate.

Electron withdrawing but non-chelating substituents such as CF_3 are ineffective (2-chlorobenzotrifluoride for example is totally unreactive under our reaction conditions). More surprisingly, since the CN group is electron withdrawing and the nitrogen atom has a lone pair which is capable of interacting with the vacant copper 4p orbital, 2-chlorobenzonitrile is equally unreactive but this can be explained by incorrect geometry in the transition state as shown in Fig. 2b. Groups which can interact analogously, albeit

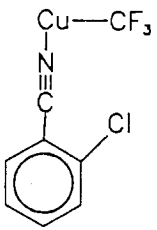


Fig. 2b. The postulated structure of the copper-benzonitrile intermediate.

with the correct geometry, but which are relatively weakly electron withdrawing, such as carbonyl-containing substituents, show moderate reactivity. Such slower reactions generally involve parallel chain extension which may be a result of the increased lifetime of '$CuCF_3$' side group in the reaction system enabling side reactions such as (1) to occur.

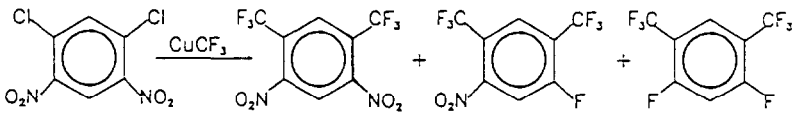
$$CuCF_3 + CF_2 \longrightarrow CuCF_2CF_3 \qquad (1)$$

Increased electronic activation of ortho keto-substrates can get round these problems. Thus 2-chloro-5-nitrobenzophenone can be cleanly converted to 2-trifluoromethyl-5-nitrobenzophenone.

Attempts to extend this chemistry to nitrogen-containing substrates met with mixed succe 2-chloropyridine gave some trifluoromethylation but with accompanying perfluoroalkylation. More active 2-chloropyridines also gave mixtures of products except in the case of 2-chloro-3-nitropyridine which, as expected, quickly gave 2-trifluoromethyl-3-nitropyridine as the only product. Increased amounts of perfluoroalkylation with many of these substrates can be explained by increased stabilisation of $CuCF_3$ by the heteroatom encouraging formation of $Cu(CF_2)_nCF_3$.

Thus it can be seen that the combination of electronic activation towards nucleophilic substitution and an ortho group capable of chelating the copper to give the correct transition state geometry is required for efficient substitution of chlorine by CF_3. Interestingly, 2-bromonitrobenzene and 2-iodonitrobenzene reacted with the Cu/CF_2Br_2/DMAc reaction system to give mostly biphenyl products. It is known that unactivated iodoaromatics react with this system to give the trifluoromethyl products so that the use of these substrates and correctly activated chloroaromatics can be seen as largely complementary and provide routes to many trifluoromethylaromatics.

The observed ortho-effect with chloroaromatics can be used to achieve a high degree of regioselective trifluoromethylation. Thus in the case of 2,3-dichloronitrobenzene, only one isomer, 2-chloro-6-nitrobenzotrifluoride is obtained[4]. More heavily substituted chloronitrobenzenes can lead to complex product mixtures due to fluorodenitration[7], and dehalogenation as well as perfluoroalkylation. Thus 1,3-dichloro-4, 6-dinitrobenzene gives a mixture of the expected bis(trifluoromethyl) product as well as fluorodenitration products presumably arising from reaction with $CH_3CF_2N(CH_3)_2$ which is known to be a source of F^-[5] (these only occur from the more reactive CF_3-containing molecule - see reaction 2).



(2)

2,3,5,6-Tetrachloronitrobenzene gives a complex mixture of products (reaction 3) presumably because the nitro group is twisted out of the plane of the ring by the two ortho chlorines which reduces its mesomeric effect.

TABLE

Reactions of Aryl Halides with Cu–CF_2Br_2 – DMAc

Substrate	$\%CF_3$	$\%C_2F_5$
2–Chloronitrobenzene	59[a]	0
3–Chloronitrobenzene	0	0
4–Chloronitrobenzene	5	1
Chlorobenzene	0	0[b]
2–Chloro–methoxybenzene	0	0[b]
2–Chloro–methyl–thiobenzene	0	0[b]
2–Chloro–benzotrifluoride	0	0[b]
2–Chloro–benzonitrile	0	0[b]
2–Chloro–benzaldehyde	16	22[c]
2–Chloroacetophenone	38	10
Methyl 2–chlorobenzoate	17	17
2–Chlorobenzophenone	7.0	1.3[c]
4–Chlorobenzophenone	0[d]	3.0
2–Chloro–5–nitrobenzophenone	100	0
Chloro–2,4–dinitrobenzene	100[e]	0
Chloro–3,4–dinitrobenzene	8	8
4–Chloro–3–nitro–benzotrifluoride	97	3
4–Chloro–3–nitro–benzaldehyde	100	0
4–Chloro–3–nitroacetophenone	95[f]	0
4–Chloro–3,5–dinitro–benzotrifluoride	53[g]	
2,3–Dichloro–nitrobenzene	86	0[h]
(2,4–Dichlorophenyl)(4–fluorophenyl)sulphone	6.4	10.1[c]
2,4',4–Trichloro–3'–nitrobenzophenone	68	0[i]
2–Chloroaniline	0	0
2–Chloropyridine	13	23
2–Chloro–3–nitro–pyridine	93[j]	0
2–Chloro–5–nitro–pyridine	48	18
2–Chloro–pyrimidine	46	50
2–Chloro–3–trifluoromethylpyridine	19	13
2–Chloro–6–trifluoromethylpyridine	9	9
1,3–dichloro–4,6–dinitrobenzene	63[k]	—[l]
2,3,5,6–Tetrachloronitrobenzene	—[m]	—
2–Bromonitrobenzene	30	0[n]
2–Iodonitrobenzene	6	0[o]

Notes:

Reactions performed with substrate (5 mmol), copper (30 mmol), dibromodifluoromethane (1 ml), and dimethylacetamide (7.5 ml) for eight hours (unless otherwise stated) at 100°C under a nitrogen atmosphere. All quoted yields are areas from g.c. traces.

a after 16 hours reactions, 100% conversion to (CF_3) derivative

b no reaction by g.l.c. or ^{19}F NMR spectroscopy

c ratio from ^{19}F NMR spectrum; conversion from g.l.c.

d No (CF_3) by ^{19}F NMR

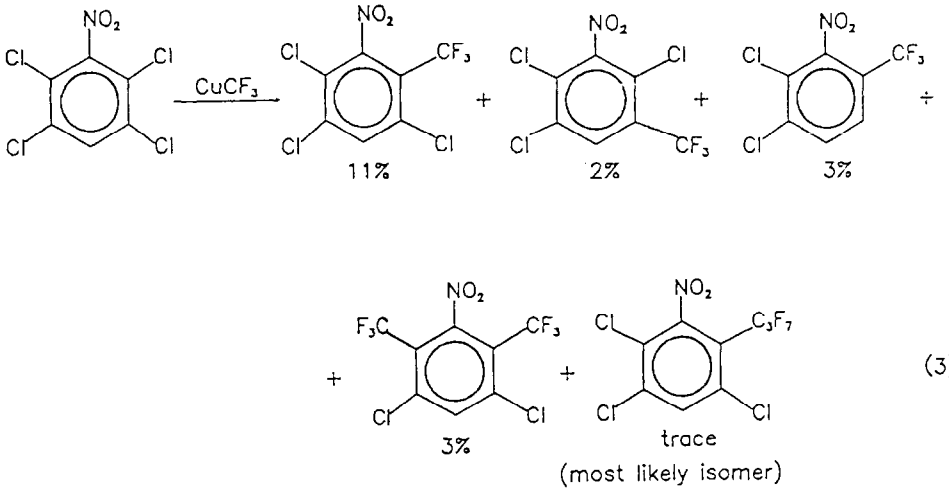
e 93% after 4 hours

f Along with 5% (3–nitroacetophenone)

g After 5 hours along with 15% 3,5–dinitrobenzotrifluoride

h After 5 hours (2–chloro–6–nitrobenzotrifluoride as the only isomer) along with 5% of the bis(trifluoromethyl)nitrobenzene

i Along with 21.5% 4–chloro–2,4'–bis(trifluoromethyl)–3'–nitrobenzophenone



(3)

It is interesting to note that no trifluoromethyldenitration is observed with any of the nitroaromatics studied. This can be compared to the reaction of 2,3,5,6-tetrachloronitrobenzene with F^- which rapidly and selectively gives 2,3,5,6 - tetrachlorofluorobenzene[7]. This serves to highlight the very different chemistries of F^- and 'CF_3^-' reagents.

In conclusion, the $Cu/CF_2Br_2/DMAc$ reaction system at 100°C can be used to accomplish the trifluoromethylation of electronically activated chloroaromatics which contain an ortho substituent capable of chelating the copper in the correct transition state geometry. Less active substrates may fail to react or can give significant quantities of perfluoroalkylated products. Fluorodenitration can also occur in the systems that produce highly activated nitroaromatic products.

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j After 4 hours
k 1,3-bis(trifluoromethyl)-4,6-dinitrobenzene
l Along with the fluorodenitration products (see reaction 2)
m Complex reaction mixture of trifluoromethylated products (see reaction 3)
n After 4 hours along with 70% 2,2'-dinitrobiphenyl
o Along with 94% 2,2'-dinitrobiphenyl

EXPERIMENTAL

Equipment Used

Gas-liquid chromatograms were obtained on a Phillips PU4500 equipped with a Hewlett-Packard 3396A integrator. Unless otherwise specified, the column used was OV101 silicon on chromasorb. Dinitrogen carrier gas and dihydrogen/air flame ionisation detection were employed throughout.

Mass spectra were obtained on a Kratos MS-3074 with Hewlett-Packard 26296 data station, or by chemical ionisation using a Finnigan MAT 4500 g.c.-m.s.

NMR spectra were obtained on a Bruker WP80SY NMR spectrometer at ambient temperatures. Standards used were tetramethylsilane (^{1}H, internal), trichlorofluoromethane (^{19}F internal) or hexafluorobenzene (^{19}F, external, -162.9ppm), positive shifts to high frequency.

Infra-red spectra were recorded on a Perkin-Elmer PE-683 ratio-recording machine interfaced to a PE-64K data station.

General procedures

All reactions were carried out under a dinitrogen atmosphere, unless otherwise stated. The dibromodifluoromethane, dimethylformamide, and dimethylacetamide were all distilled and stored over molecular sieves prior to use. It has been found on several occasions that moisture in the system causes failure of the procedure. The copper powder used was 200 mesh (Aldrich).

Work-up of all reactions in Sections A - C was carried out in the same manner. The sample removed was added to water, then this solution was extracted with ether. The ether was then extracted with several aliquots of water (to remove the amide solvent), then a portion of this ethereal solution was injected into the g.l.c. This solution was also used to obtain the g.c.-m.s.

Reactions performed

A Reaction of Aryl Chlorides with '$CuCF_3$'

(1) 2-chloronitrobenzene - Copper powder (1.9g, 30 mmol) and 2-chloronitro-benzene (0.79 g, 5 mmol) were placed in a 25 ml, two-neck, round-bottom flask and a condenser was attached. After flushing out with dinitrogen gas, dimethylacetamide (7.5 ml) and dibromodifluoromethane (1 ml) were added, and the flask was lowered into a previously heated oil-bath at 100°C.

After eight hours, a sample was removed and analysed as described above. The g.l.c. showed two peaks, identified by g.c.-m.s. as: (i) 2-nitro-benzotrifluoride: M^+ 191; 145(100), 95(50), 75(47), 50(29), 125(27), 191(22), 69(17), 161,(13); (ii) 2-chloro-nitrobenzene: M^+ 157; 75(100), 111(57), 99(48), 50(43), 157(32), 127(29), 159(11), 85,(10) $\delta^{19}F$/ppm (in $CDCl_3$) -57.9 ($C\underline{F}_3$), [literature[8] - 59.83] and -81.4 ($CF_2C\underline{F}_3$) and -107.6 ($C\underline{F}_2CF_3$).

The following reactions ((2)-(35)) were carried out in the same manner. The g.l.c. analysis and g.c.-m.s. were used to identify the products. Relative quantities of products are listed in the Table. Certain reactions were repeated using different conditions in order to increase the yields prior to isolating and fully characterising the products. These are listed in Section C.

(2) 3-Chloronitrobenzene - G.l.c. analysis and ^{19}F NMR spectroscopy showed that no reaction had occurred.

(3) 4-Chloronitrobenzene - (i) 4-Chloronitrobenzene: M^+ 157; 157(100), 111(97), 75(71), 127(37), 159(33), 112(29); (ii) 4-nitro-benzotrifluoride: M^+ 191, 145(100), 191(50), 95(36), 133(22), 75(18), 161(15), 50(7), 175(4): (iii) 4-pentafluoroethyl-nitrobenzene: M^+ 241: 145(100), 172(63), 241(41), 195(22), 95(12), 114(12), 126(11), 50(8).

(4) Chlorobenzene - no reaction was observed by either g.l.c. analysis or ^{19}F NMR spectroscopy.

(5) 2-Chloro-methoxybenzene - no reaction was observed by either g.l.c. analysis or ^{19}F NMR spectroscopy.

(6) 2-Chloro-methylthiobenzene - no reaction was observed by either g.l.c. analysis or ^{19}F NMR spectroscopy.

(7) 2-Chloro-benzotrifluoride - no reaction was observed by either g.l.c. analysis or ^{19}F NMR spectroscopy.

(8) 2-Chloro-benzonitrile - no reaction was observed by either g.l.c. analysis or ^{19}F NMR spectroscopy.

(9) 2-Chloro-benzaldehyde - (i) 2-chloro-benzaldehyde: M^+ 140; 139(100), 140(77), 141(36), 111(35), 142(24), 75(18), 50(17), 113(12); (ii) a mixture of (a) 2-pentafluoroethyl-benzaldehyde: M^+ 224; 223(100), 224(62), 145(58), 127(41), 77(7), 50(6), 176(6), 195(6), and (b) 2-trifluoromethyl-benzaldehyde and 2-hepta-

fluoropropyl-benzaldehyde: M^+ 174 and 274 respectively; 273(100), 173(95), 174(77), 274(68), 145(55), 127(40), 96(14), 75(13). $\delta^{19}F$ NMR/ppm = -54.0 ($-C\underline{F}_3$), -77.9, -82.0, -100.6, -103.5, and -122.9 (CF_2CF_3 and $CF_2CF_2CF_3$).

(10) 2-Chloroacetophenone - (i) A mixture of (a) 2-trifluoromethyl-acetophenone: M^+ 188; 173(100), 145(47), 43(24), 95(9) 125(5), 188(5), 50(4), and (b) 2-pentafluoroethyl-acetophenone: M^+ 238; 223(100), 145(80), 43(70), 172(40), 75(8), 224(8), 126(7), 50(4), $\delta^{19}F$ NMR/ppm = -58.9 ($C\underline{F}_3$), -84.3 ($CF_2C\underline{F}_3$) -108.7 ($C\underline{F}_2CF_3$).

(11) Methyl 2-chlorobenzoate - (i) a mixture of methyl 2-trifluoromethyl-benzoate and methyl 2-pentafluoroethyl-benzoate: M^+ 204 and 254 respectively: 223(100), 145(61), 173(34), 254(16), 126(11), 224(10), 204(5), 95(5); (ii) methyl 2-chlorobenzoate: M^+ 170; 139(100), 141(33), 111(33), 170(28), 75(26), 50(13), 113(11), 172(9) $\delta^{19}F$ NMR/ppm = -59.7 ($-C\underline{F}_3$), -83.1 ($-CF_2C\underline{F}_3$), -108.4 ($-C\underline{F}_2CF_3$).

(12) 2-Chloro-benzophenone - (i) a mixture of 2-trifluoromethyl-benzophenone and 2-pentafluoroethyl-benzophenone: M^+ 250 and 300 respectively: 105(100), 250(25), 77(28) 173(17), 145(16), 51(8), 300(3); (ii) 2-chlorobenzophenone: M^+ 216; 105(100), 216(91), 139(53), 77(37), 218(27), 141(18), 51(14); $\delta^{19}F$ NMR/ppm = -58.9($-C\underline{F}_3$), -84.6($CF_2C\underline{F}_3$), -108.8 ($C\underline{F}_2CF_3$).

(13) 4-Chloro-benzophenone - (i) this peak could not be detected by g.c.-m.s. (ii) 4-chloro-benzophenone: M^+ 216: 105(100), 139(89), 216(72), 77(43), 141(29), 111(28), 218(27), 181(18); $\delta^{19}F$ NMR/ppm = -81.66 ($CF_2C\underline{F}_3$) and -122.70 ($C\underline{F}_2CF_3$).

(14) 2-chloro-5-nitro-benzophenone - (i) 2-trifluoromethyl-5-nitro-benzophenone: M^+ 295; 105(100), 77(47), 295(13), 51(13), 144(7), 44(5), 69(3), 276(2); (ii) 2-chloro-5-nitro-benzophenone: M^+ 261; 105(100), 77(38), 261(20), 263(8), 184(6), 138(4), 207(3) $\delta^{19}F$ NMR/ppm = -56.1. For synthesis, see Section C.

(15) Chloro-2,4-dinitrobenzene - (i) 2,4-dinitro-benzotrifluoride: M^+ 236: 144(100), 236(8), 75(55), 125(41), 94(29) 63(16), 44(14), 217(12); (ii) 1,3-dinitrobenzene: M^+ 168; 168(100), 75(73), 50(46), 92(38),122(35), 64(22), 152(7), 39(5); (iii) chloro-2,4-dinitrobenzene; M^+ 202; 202(100), 75(80), 110(48), 44(36), 204(31), 63(30), 126(18), 156(13). $\delta^{19}F$ NMR/ppm = -59.1

(16) Chloro-3,4-dinitrobenzene - (i) chloro-benzotrifluoride; M^+ 180: 180(100), 145(47) 182(33), 75(19), 161(18), 50(13), 130(13), 28(12); (ii) a mixture of 3,4-dinitro-benzotrifluoride and pentafluoroethyl-3,4-dinitro-benzene: M^+ 202; 63(100), 202(69), 75(68), 50(27), 204(24), 98(21), 110(17), 38(11); $\delta^{19}F$ NMR/ppm = -61.4 ($-C\underline{F}_3$), -82.3 ($-CF_2C\underline{F}_3$), -112.0 ($-C\underline{F}_2CF_3$); (iv) chloro-3,4-dinitrobenzene: M^+ 202: 63(100), 202(69), 75(68), 50(27), 204(24) 98(21), 110(19), 38(11).

(17) 4-chloro-3-nitro-benzotrifluoride - (i) 4-pentafluoroethyl-3-nitro-benzotrifluoride: M^+ 309: 213(100), 240(21), 309(20), 290(19), 163(15), 75(13), 125(11), 144(10); (ii) 1,4-bis(trifluoromethyl)-2-nitro-benzene: M^+ 259; 163(100), 213(73), 259(36), 240(29), 75(27), 50(13), 144(21), 194(11), 125(10)

(18) 4-chloro-3-nitro-benzaldehyde - (i) 4-trifluoromethyl-3-nitro-benzaldehyde: M^+ 219: 145(100), 219(87), 218(24), 144(23); 173(20), 95(19), 125(17), (ii) 4-chloro-3-nitro-benzaldehyde; M^+ 185; 75(100), 185(81), 184(68), 187(31), 74(28), 186(28), 111(23), 139(17). $\delta^{19}F$ NMR/ppm = -60.8. See Section C for synthesis.

(19) 4-chloro-3-nitro-acetophenone - (i) 4-trifluoromethyl-3-nitro-acetophenone: M^+ 233: 218(100); 43(96), 172(44), 144(24), 233(15), 219(7), 75(5), 125(4) (ii) 4-chloro-3-nitro-acetophenone: M^+ 199; 184(100), 43(63), 138(39), 186(30), 199(28), 75(20), 110(17), 140(15); $\delta^{19}F$ NMR/ppm = -60.8. See Section C for the synthesis.

(20) 4-chloro-3,5-dinitro-benzotrifluoride - (i) 1,4-bis(trifluoromethyl)-2,6-dinitrobenzene: M^+ 304: 162(100); 304(94), 46(88), 69(46), 285(40), 212(32), 93(21), 123(18) (ii) 3,5-dinitrobenzotrifluoride: M^+ 236; 236(100), 143(93), 75(56), 160(42), 125(27), 190(23), 63(20), 217(17) $\delta^{19}F$ NMR/ppm = -57.5 (i) -63.0 (minor.ii). -63.4(i

(21) 2,3-dichloro-nitrobenzene - (i) 2-chloro-6-nitro-benzotrifluoride: M^+ 225: 179(100); 225(43), 181(33), 75(31), 144(28), 167(19), 69(13), 111(13): (ii) 1,2-bis(trifluoro-methyl)-3-nitrobenzene: M^+ 259: 213(100), 163(70), 259(28), 240(25), 75(18), 144(16), 194(6): (iii) pentafluoroethyl-nitro-benzotrifluoride: M^+ 309: 213(100). 144(16), 240(16), 194(15), 309(14), 75(12), 290(11), 163(10). $\delta^{19}F$ NMR/ppm = -58.9 ($C\underline{F}_3$). Major product identified as this isomer by $^{13}C-\{^1H\}$ NMR spectroscopy. Calculated[9] for 2-chloro-6-nitro-benzotrifluoride: 120.3, ($\underline{C}CF_3$), 121.1 ($\underline{C}H$), 132.4 ($\underline{C}Cl$), 132.9, 134.0 (both $\underline{C}H$), 146.6 ($\underline{C}NO_2$); calculated for 2-chloro-3-nitro-benzotrifluoride: 119.8 ($\underline{C}CF_3$), 126.7 ($\underline{C}Cl$), 126.8, 127.2, 132.4 all ($\underline{C}H$), 148.2 ($\underline{C}NO_2$); found: 120.8 ($\underline{C}CF_3$), 122.1, 133.5, 134.3 (all $\underline{C}H$), 134.9 ($\underline{C}Cl$), 150.5 ($\underline{C}NO_2$). See Section C for the synthesis.

(22) (2,4-dichlorophenyl)(4-fluorophenyl)sulphone - (i) 4-chloro-2-pentafluoroethyl -phenyl)(4-fluorophenyl)sulphone: M^+ 388; 95(100); 159(54), 147(32), 277(28), 75(26), 111(25), 388(12), 179(11): (ii) (4-chloro-2-trifluoromethyl-phenyl)(4-fluoro-phenyl)sulphone: M^+ 338; 95(100). 159(60), 148(50), 111(44), 227(36), 338(22), 75(20), 88(15); (iii) (2,4-dichlorophenyl)(4-fluorophenyl)sulphone: M^+ 304; 143(100), 95(58), 193(32), 75(30), 304(29), 195(18), 306(16), 32(13). $\delta^{19}F$ NMR/ppm = -57.9 ($C\underline{F}_3$). -82.1 ($CF_2\underline{C}F_3$), -104.5 ($C\underline{F}_2CF_3$), -104.2, -104.5, -104.3 (all aryl-$\underline{F}$).

(23) 2,4,4'-trichloro-3'-nitro-benzophenone: (i) (4-chloro-2,4'-bis(trifluoromethyl)-3'-nitro-benzophenone: M^+ 397: 207(100); 218(33), 209(32), 179(30), 144(24), 162(22), 397(17), 75(12); (ii) (2,4-dichloro-4'-trifluoromethyl-3'-nitro-benzophenone: M^+ 363: 173(100), 175(65); 145(19), 363(18), 75(11), 219(10), 177(10), 75(10): (iii) 2,4,4'-tri-chloro-3-nitro-benzophenone: not observed by g.c.ms - confirmed as starting material by retention time on g.c. $\delta^{19}F$ NMR/ppm = -60.4 (i); -61.0 (ii); -61.1 (i).

(24) 2-chloro-aniline. No reaction was observed by either g.l.c. analysis or ^{19}F NMR spectroscopy.

(25) 2-chloro-pyridine - (i) 2-chloro-pyridine: M^+ 113: 78(100); 113(74), 51(29), 115(22); (ii) 2-trifluoromethyl-pyridine: M^+ 147: 78(100), 147(60), 51(19), 69(4); (iii) 2-pentafluoroethyl-pyridine: M^+ 197: 128(100), 78(60), 197(47), 51(22), 129(9), 178(8). (iv) 2-heptafluoropropyl-pyridine: M^+ 247: 128(100), 78(63), 51(36), 247(26), 228(4), 207(4): $\delta^{19}F$ NMR/ppm = -66.8 ($C\underline{F}_3$), -82.2, - 85.1 and -115.4 (higher homologues).

(26) 2-chloro-3-nitro-pyridine; (i) 2-trifluoromethyl-3-nitro-pyridine: M^+ 192: 146(100); 96(64), 51(48), 192(27), 69(26), $\delta^{19}F$ NMR/ppm = -63.8 ($C\underline{F}_3$), -79.7 ($-CF_2C\underline{F}_3$), -110.4 ($-C\underline{F}_2CF_3$).

(27) 2-chloro-5-nitro-pyridine - (i) 2-pentafluoroethyl-5-nitro-pyridine: M^+ 242: 51(100); 146(90), 196(80), 69(50), 242(38), 119(35), 100(18), 173(15). (ii) 2-trifluoromethyl-5-nitro-pyridine: M^+ 192: 146(100), 51(60), 69(56), 192(46), 126(31), 96(30), 75(13), 73(7): (iii) 2-chloro-5-nitro-pyridine: M^+ 158: 112(100), 76(81), 50(63), 158(60), 86(60), 114(33), 100(29), 160(20). $\delta^{19}F$ NMR/ppm = -66.1 ($C\underline{F}_3$). -81.1 ($-CF_2C\underline{F}_3$), -114.5 ($-C\underline{F}_2CF_3$).

(28) 2-chloro-pyrimidine - (i) 2-heptafluoropropyl-pyrimidine: M^+ 248: 129(100); 79(23), 248(22), 69(13), 52(11), 229(8), 102(3), 119(2); (ii) 2-pentafluoroethyl-pyrimidine: M^+ 198: 129(100), 198(86), 79(38), 52(22), 179(15), 69(14), 119(8), 102(6): (iii) 2-trifluoromethyl-pyrimidine: M^+ 148: 148(100), 79(55), 87(54), 52(16), 69(14), 129(9), 121(9), 149(8); (iv) 2-chloro-pyrimidine: M^+ 114: 114(100), 79(82), 116(32), 52(23), 87(22), 60(12), 44(12), 36(11). $\delta^{19}F$ NMR/ppm = -68.3 ($C\underline{F}_3$). -80.4 ($-CF_2C\underline{F}_3$), -115.0 ($-C\underline{F}_2CF_3$).

(29) 2-chloro-3-trifluoromethyl-pyridine - (i) a mixture of (a) 2,3-bis(trifluoromethyl)-pyridine: M^+ 215: 146(100); 215(73), 196(24), 69(23), 126(15), 75(7), 50(5), 99(3) and (b) 2-pentafluoroethyl-3-trifluoromethyl-pyridine: M^+ 265; 196(100), 145(55), 215(32), 126(22), 69(20), 246(17), 265(16), 50(11): (ii) 2-chloro-3-trifluoromethyl-pyridine: M^+ 181: 146(100), 181(77), 112(46), 126(45), 183(24), 69(18), 76(18), 50(15) $\delta^{19}F$ NMR/ppm = -59.6 (t. 19Hz $-CF_2C\underline{F}_3$), -64.3 (ii) -81.4 and -111.6 (q, 19Hz., $C\underline{F}_2CF_3$).

(30) 2-chloro-6-trifluoromethyl-pyridine - (i) a mixture of 2,6-bis(trifluoromethyl)-pyridine: M^+ 215: 146(100); 215(75), 126(29), 69(24), 196(22), 75(10), 50(5), 96(4). (b) 2-pentafluoroethyl-6-trifluoromethyl-pyridine: M^+ 265: 196(100), 146(41), 265(27), 69(18), 246(18), 126(18), 126(13), 215(5), 50(5) and (c) 2-heptafluoropropyl-6-trifluoromethyl-pyridine: M^+ 315; 196(100), 146(33), 196(19), 315(16), 69(9), 126(5); (ii) 2-chloro-6-trifluoromethyl-pyridine: M^+ 181: 146(100), 181(94), 126(29), 183(28), 69(24), 50(13), 75(12), 162(7).

(31) 1,3-dichloro-4,6-dinitrobenzene - For this reaction, 0.59g (2.5 mmol) substrate was used. (i) 5-fluoro-2,4-bis(trifluoromethyl)nitrobenzene: M^+ 277: 231(100); 69(68), 277(64), 181(62), 162(42), 211(35), 143(25), 258(22); 69(50), 242(38), 119(35), 100(18),

173(15). (ii) 2,4-bis(trifluoromethyl)-1,5-dinitrobenzene: M^+ 304: 162(100), 46(65), 304(64), 242(52), 69(40), 285(22), 93(20), 239(17); (iii) 2,4-dinitro-benzotrifluoride: M^+ 236: 143(100), 75(83), 132(52), 236(46), 94(46), 96(38), 57(33), 43(28), 162(15): $\delta^{19}F$ NMR = several singlets in the region −57 to −63ppm.

(32) 2,3,5,6-tetrachloronitrobenzene - (i) $C_9HCl_2F_8NO_2$, (trifluoromethyl)(pentafluoroethyl) di-chloronitrobenzene: M^+ 377: 69(100); 85(96), 44(68), 377(50), 262(40), 379(31), 281(25), 119(22) (ii) $C_8HCl_2F_6NO_2$ bis(trifluoromethyl)dichloronitrobenzene: M^+ 327; 69(100), 327(42), 246(39), 85(37), 46(34), 329(30), 231(35), 281(21) (iii) $C_8HCl_2F_6NO_2$ bis(trifluoromethyl)dichloronitrobenzene: M^+ 327: 69(100), 44(39), 85(30), 327(26), 119(20), 131(18), 281(15), 169(13). (iv) $C_9HCl_3F_3NO_2$, (heptafluoropropyl)trichloro-nitrobenzene: M^+ 393, 69(100), 274(44), 276(39), 247(32), 85(31), 343(29), 345(25), 248(22) (v) $C_3H_2Cl_2F_3NO_2$ (trifluoromethyl)dichloronitrobenzene: M^+ 259; 213(100), 259(62), 215(58), 261(43), 143(31), 62(18), 93(10): (vi) $C_7HCl_3F_3NO_2$ (trifluoromethyl)trichloronitrobenzene: M^+ 293; 295(100), 293(99), 247(84), 249(83), 200(61), 177(59), 69(40), 108(32): (vii) $C_7HCl_3F_3NO_2$ (trifluoromethyl)trichloro-nitrobenzene: M^+ 293; 179(100), 257(86), 225(84), 143(57), 108(55), 74(47), 293(41) 249(38) (viii) $C_6HCl_4NO_2$ tetrachloronitrobenzene: M^+ 259; 203(100), 108(69), 261(43), 143(41), 178(40), 73(37), 259(35), 263(20).

(33) 2,3,5,6-tetrachloro-dinitrobenzene - For this reaction, 1.25 mmol of substrate was used. (i) 2,3,5,6-tetrakis(trifluoromethyl)nitrobenzene: M^+ 395: 46(100); 299(65), 345(64), 249(58), 69(53), 230(29), 161(19), 295(15); (ii) (pentafluoroethyl)(trifluoromethyl)-dinitrobenzene: M^+ 354: 69(100), 43(75), 212(62), 143(50), 354(38), 258(30), 285(20), 323(20); $\delta^{19}F$ NMR/ppm = −55.3.

(34) 2-bromonitrobenzene - (i) 2-nitro-benzotrifluoride: M^+ 191: 77(100); 123(52), 51(50), 145(38), 191(17), 95(13), 65(11), 133(8) (ii) 2,2'-dinitro-phenyl): M^+ 244 (not observed); 198(100, 139(43), 168(41), 115(35), 63(21), 39(17), 51(15), 75(13). $\delta^{19}F$ ($CDCl_3$) = −60.6ppm

(35) 2-iodonitrobenzene - (i) 2-nitro-benzotrifluoride and (ii) 2,2'-dinitro-biphenyl); g.c.-m.s. data the same as that for (34).

B Non-Standard Reactions

(1) 2-chloro-methoxybenzene. Reaction repeated at 150°C. Five products identified: (i) (89%) 2-chloromethoxybenzene: M^+ 142: 142(100, 99(98), 127(51), 144(32), 101(30), 73(22), 63(21), 129(17); (ii) (11%) 2-bromo-methoxybenzene: M^+ 186: 188(100), 186(98), 143(64), 145(60), 63(45), 99(44), 81(38), 77(34): (iii) (trace) (dimethylamino)-methoxy-benzotrifluoride: M^+ 219: 176(100), 44(43), 72(34), 133(33), 146(22), 100(20), 219(19), 113(17): (iv) (trace) chloro-trifluoromethyl-methoxybenzene:

M^+ 210: 210(100), 132(45), 212(37), 167(32), 195(30), 197(12), 147(11), 75(8):
(v) (trace) a mixture of chloro-trifluoromethyl-methoxy-benzene and chloro-pentafluoroethyl-methoxybenzene: M^+ 210 and 260 respectively: 210(100), 132(45), 212(37), 167(32), 197(17), 75(13), 148(12), 260(11).

(2) 2-chloro-benzonitrile. No reaction at 150°C, as evidenced by g.l.c. and ^{19}F NMR spectroscopy.

C Synthesis and Isolation of Products

(1) 2-nitro-benzotrifluoride

Reaction 1, (above) went to completion after sixteen hours.

The product was identified as 2-nitrobenzotrifluoride by: accurate mass spectrum. $C_7H_4F_3NO_2$ requires 191.019407: found 191.01995. NMR parameters/ppm: δ^1H = 7.6 - 8.0 (multiplet); $\delta^{19}F$ = -60.5; $\delta^{13}C$ = 148.3 (s, C-NO_2). 133.4, 132.8 (both s, C-H). 128.0 (q, 5Hz., C-H). 125.0 (s, C-H), 123.7 (q, 34.2 Hz, C-CF_3) and 122.2 (q, 273.4 Hz, C-CF_3).

(2) 2-chloro-5-nitro-phenyl)phenylmethanone

Reaction allowed to go to completion.

The product was identified as 2-trifluoromethyl-5-nitrobenzophenone.

Accurate mass spectrum: found 295.04594: $C_{14}H_8NO_3F_3$ requires 295.045619.

NMR parameters/ppm: $\delta^{19}F$ = -58.9; δ^1H = 7.2 - 8.6 (multiplet); $\delta^{13}C$ = 124.7 (C-H). 128.7 (q) 128.9 (C-H). 130.2 (C-H). 134.7 (C-H), 135.3 (C-CO). 140.0 (C-CO). 149.3 (C-NO_2). 192.7 (C=0). C-CF_3 and CF_3 not observed.

(3) 4-chloro-3-nitro-benzotrifluoride

The product was identified as 1,4-bis(trifluoromethyl)-2-nitrobenzene by:

NMR parameters/ppm: $\delta^{19}F$ = -60.9 and -64.0: δ^1H = 8.2 and 8.3; $\delta^{13}C$ = 149.0 (C-NO_2). 136.5 (q, 35Hz, C-CF_3). 130.3 (q, 3.5 Hz. C-H), 130.0 (q, 5.2 Hz, C-H), 127.6 (q, 35Hz, C-CF_3). 123.1 (q, 3.7 Hz, C - H), 122.9 (q, 273.1 Hz, CF_3). 122.2 (q, 127.8 Hz, CF_3).

(4) 4-chloro-3-nitro-benzaldehyde

The product was identified as 4-trifluoromethyl-3-nitro-benzaldehyde by:

accurate mass spectrum: $C_8H_4F_3NO_3$ requires 219.014321, found 219.01406. NMR parameters/ppm: $\delta^{19}F$ = -60.8: δ^1H = 8.0 - 8.4 (multipet, aromatic C-H and 10.2 (s, CHO); $\delta^{13}C$ = 188.4 (CHO). 149.0 (C-NO_2). 139.7 (C-CO), 132.8 (C-H), 129.2(q, C-H). 125.2 (C-H) - C-CF_3 and CF_3 not observed.

(5) Chloro-2,4-dinitrobenzene

The product was identified as 2,4-dinitro-benzotrifluoride by: NMR parameters/ppm: $\delta^{19}F$ = -60.7: $\delta^{1}H$ = 8.1, 8.2, 8.6 and 8.7; $\delta^{13}C$ = 150.1 (C-NO_2), 148.8 (C-NO_2), 130.0 (q, 6 Hz, C-H), 128.5 (q, 20.8 Hz, C-CF_3), 127.1 (C-H). 121.1 (q, 275 Hz, CF_3), 120.6 (C-H).

(6) 4-chloro-3-nitro-acetophenone

The product was identified as 4-trifluoromethyl-3-nitro-acetophenone by: accurate mass spectrum: $C_9H_6F_3NO_3$ requires 233.029970, found 233.02935. NMR parameters/ppm: $\delta^{1}H$ = 2.7 ($COCH_3$) 8.0 (d, 2Hz) 8.3 (d, 2Hz). 8.5 (d, 2Hz) (all aromatic C-H): $\delta^{13}C-\{^{1}H\}$ = 184.7 (C-O). 148.5 (C-NO_2). 140.9 (C-CO), 131.7 (C-H), 128.9 (q, 5Hz. C-H) 127.9 (q, 34.8 Hz, C-CF_3), 124.5 (C-H). 121.6 (q, 274 Hz, CF_3) 26.8 (CH_3).

(7) 2,3-dichloronitrobenzene

The product was isolated using column chromatography (silica gel: eluent, ethyl acetate: petroleum ether (40 - 60 fraction) = 15:85. Identified as 2-chloro-6-nitro-benzotrifluoride by: accurate mass spectrum: $C_7H_3ClF_3NO_2$ requires 224.980436, found 224.98086. NMR parameters/ppm: $\delta^{19}F$ = -58.9: $\delta^{1}H$ = 7.6 - 8.0 (multiplet); $\delta^{13}C$ = 150.5 (C-NO_2). 134.9 (d, 3Hz, C-Cl), 134.4 (C-H), 133.5 (C-H) 122.1 (C-CF_3), 121.2 (C-H). 121.2 (q, 276 Hz, CF_3), 120.8 (q, 33 Hz, C-CF_3). For calculated ^{13}C NMR spectra, see Section A(23).

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