Aromatic trifluoromethyldenitration and trifluoromethyldecyanation using trifluoromethyltrimethylsilane

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Activation of trifluoromethyltrimethylsilane by potassium fluoride in *N*,*N*-dimethylacetamide provides a powerful source of trifluoromethide which is capable of substituting aromatic nitro and cyano groups under nucleophilic conditions, albeit in low yield. The trifluoromethide generated in this system is also a potent base which leads to a number of interesting side reactions *via* deprotonation of the substrate.

Introduction

Trifluoromethyltrimethylsilane (Ruppert's reagent, Me_3SiCF_3) has recently aroused much interest as a source of trifluoromethide ($[CF_3]^-$), and has been used widely for the conversion of an aldehyde or ketone to an α-trifluoromethyl alcohol.[1] This could potentially be used for nucleophilic substitution at an aromatic carbon, but has only been superficially investigated in such reactions.[2] Recent work in our laboratory[3] has shown the use of fluorodenitration reactions for introducing fluorine into an aromatic ring, and it was therefore of interest to see if this approach could be extended to other fluorinated groups. To date, there has been only one report of trifluoromethyldenitration reactions: Prakash reports that pentafluoronitrobenzene reacts with Me_3SiCF_3 in THF to give a mixture of octafluorotoluene and decafluoroxylene.[2] He also reports that reaction with 2,4-dinitrofluorobenzene gives a mixture of trifluoromethylated products, but that no reaction was observed with 4-fluoronitrobenzene. However, no yields were given for either of these reactions. These systems use tetra-*n*-butylammonium fluoride (TBAF) as the activating fluoride source, which gives rise to the unwanted formation of trifluoromethane (HCF_3) as a by-product, presumably due to the presence of water associated with the fluoride source. While TBAF cannot be successfully dried,[4] the drying of other fluoride sources is known to be possible.[5,6] The relatively high cost of Me_3SiCF_3 makes its efficient use desirable. Hence, we decided to investigate trifluoromethyldenitration under more rigorously anhydrous conditions.

Results and discussion

Initial reactions were attempted in THF solvent at room temperature, as used by Prakash,[2] but with dry KF in place of TBAF as the fluoride source. However, no trifluoromethylated products were observed for substrates less activated to nucleophilic attack than those previously reported, even when the reaction temperature was increased to 50 °C. 4-Nitrobenzonitrile, 2-chloro-6-nitrobenzonitrile and 1,3-dinitrobenzene failed to react under these conditions, even though these are all substrates which readily undergo fluorodenitration.[3] ^{19}F-NMR spectroscopy showed that only a small amount of HCF_3 was formed, the majority of the silane being stable under these conditions. However, THF is not a particularly good solvent for nucleophilic aromatic substitution reactions, and dipolar aprotic solvents are generally preferred.[7] Fluorodenitration reactions show a marked solvent dependency, and are most efficient in DMSO or *N*,*N*-dimethylacetamide (DMAc).[8] The $[CF_3]^-$ liberated in the reaction is expected to be strongly basic (pK_a[9] of $HCF_3 = 31$), which will severely limit the range of solvents which may be used for a trifluoromethyldenitration reaction. Unfortunately, although DMSO is a good solvent for nucleophilic aromatic substitution reactions, it is deprotonated by strong bases to form the methylsulfinyl ion.[10] Simple amides, however, appear to be unreactive, despite the fact that Me_3SiCF_3 is frequently used for reaction with carbonyl groups. Indeed, Stahly and Bell have successfully used triethyl(trifluoromethyl)silane in DMF for the trifluoromethylation of quinones.[11] In a control reaction, we found that mixing Me_3SiCF_3 and DMAc in the presence of KF gave no CF_3-containing products (except for a trace of HCF_3). DMAc was therefore chosen as the solvent for our studies, although similar product distributions were obtained in DMF.

Table 1 Reactions of 4-nitrobenzonitrile with Me_3SiCF_3 in DMAc.

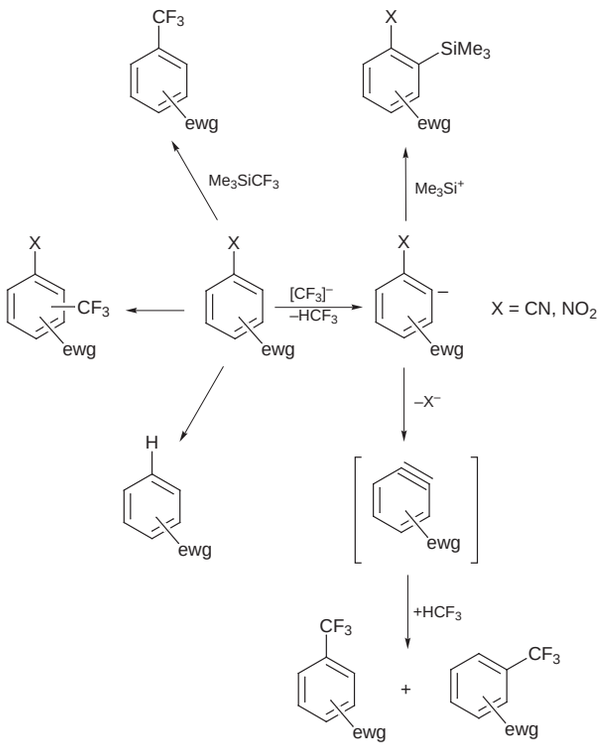
T/°C	KF (equivalents)	Yield (%)
23	2	2
23	10	10
50	10	13

The reaction of 4-nitrobenzonitrile with Me_3SiCF_3 in DMAc in the presence of 2 equivalents of KF at room temperature was found to give traces of 4-trifluoromethylbenzonitrile. Increasing both the amount of fluoride and the temperature of the reaction was found to be beneficial (Table 1). The quantities of fluoride used here contrast with those generally used for reactions of Me_3SiCF_3 with aldehydes and ketones, which often require only catalytic amounts of fluoride; these reactions form oxygen-centred nucleophiles which are capable of attacking further silanes.[1] KF is insoluble in DMAc, and the reaction is therefore heterogeneous. Increasing the quantity of KF will increase the availability of fluoride *via* an increased exposed surface area, and it is presumably this which gives the higher activity. The reaction is very quick, and is complete within a few minutes.

Similarly, other nitroaromatics were found to undergo trifluoromethyldenitration (Table 2). With the exception of the 51% trifluoromethyldenitration seen for 2-chloro-6-nitrobenzonitrile, yields of the desired products were generally low, with many side products being formed. Unsurprisingly, 4-nitrobenzophenone reacted to give exclusively the α-trifluoromethylated alcohol, indicating the relative ease of the more conventional reaction compared to trifluoromethyldenitration.

Remarkably, the reaction between 1,3-dinitrobenzene and

Me_3SiCF_3 gives two isomers of nitrobenzotrifluoride as reaction products. Two isomers are also observed for the trifluoromethyldenitration of both 3,5-dinitrobenzonitrile and 3,5-dinitro-4-chlorobenzotrifluoride. The formation of two isomers in an attempted aromatic nucleophilic substitution reaction is characteristic of a benzyne mechanism, which would require the presence of a base sufficiently strong to deprotonate the aromatic ring of the substrate (Scheme 1). Further evidence



Scheme 1

of deprotonation is supplied by the detection of silylation by-products which would be produced by nucleophilic attack of the aryl anion at a silane silicon centre. That ring deprotonation is possible under these reaction conditions was confirmed by reacting Me_3SiCF_3 with 1,3-dinitro[$^2H_4$]benzene. ^{19}F-NMR confirmed that DCF_3 is formed in this reaction. Since the substrate was the only source of deuterium in the system, this reaction confirmed that the displaced $[CF_3]^-$ is capable of deprotonating this substrate. However, attempts at trapping the postulated benzyne intermediate *via* a Diels–Alder reaction with anthracene or furan failed.

The cyano group is not normally a leaving group in nucleophilic aromatic substitution reactions. The few examples of cyano as a leaving group involve either the use of a Grignard reagent,[12] or arene polycarbonitriles as the substrate.[13,14] These reports do not investigate the possibility of radical processes occurring in the system, even though arene polycarbonitriles typically undergo decyanation reactions under radical (irradiation) conditions.[15,16] In our systems we observed that, in addition to the expected trifluoromethyldenitration products, decyanation was also occurring for some substrates. Indeed, for 2-chloro-6-nitrobenzonitrile (which is an active substrate for fluorodenitration reactions[3,8]), 20% of the substrate reacted *via* decyanation, compared with 51% denitration. For this substrate, no replacement of the chlorine was observed. The –CN group should be highly activated to nucleophilic attack because it is *ortho* to two electron withdrawing groups, but, under normal nucleophilic substitution conditions, no substitution occurs. It is likely that, in this case, the reaction is favourable because of the affinity of the silicon centre for small, hard nucleophiles such as cyanide.[17] It is possible that the silicon centre is somehow assisting the substitution reaction by coordinating the leaving group in the transition state: this would also explain the preference for denitration over dechlorination.

Decyanation, albeit at low levels, was also observed for 2-nitrobenzonitrile and 4-nitrobenzonitrile. A benzyne mechanism could, conceivably, be involved for these two substrates. 2-Chloro-6-nitrobenzonitrile, however, lacks a hydrogen *ortho* to the nitrile function, and so a benzyne route cannot account for the decyanation of this substrate. The decyanation product was isolated and compared to a sample of 2-chloro-6-nitrobenzotrifluoride prepared *via* a literature method.[18] The GC, mass, ^{1}H- and ^{19}F-NMR spectra confirmed that the expected isomer was formed and no migration of groups had occurred in the decyanation reaction. No radical containing species could be detected by EPR for this reaction, and irradiating the system for a minute before, and for the duration of the reaction made no difference to the product distribution. Both observations strongly suggest that a radical mechanism is not involved, and that the substitution of the cyano group is entirely nucleophilic. Other reports of radical reactions between benzonitriles (usually di-, tri- or tetra-carbonitriles) and silanes have shown that it is the most *electrophilic* group attached to the silicon which is transferred to the aromatic ring.[15] In our system this would be the methyl group: no methylated products are formed, which again indicates the nucleophilic nature of the process. After reaction, no Me_3SiCN could be detected by IR of the solution, although analysis of the inorganic solids filtered from the reaction vessel indicated a strong CN absorption (2267 cm^{-1}).

Dinitro compounds with a 1,3-substitution pattern were also found to give rise to trifluoromethyl addition products. Again, two isomers were sometimes detected. Although the low ionic stability of the hydride ion generally makes its elimination difficult, such substitution can occur in nitroaromatics.[19] This is effected by the oxidation of the σ-complex formed, with the nitroaromatic itself acting as the oxidising agent.[20] The ease of radical anion formation is thought to give rise to the traces of nitrobenzene found in the denitration of 1,3-dinitrobenzene: Markezich *et al.* have found that the fluorodenitration of 4-nitro-*N*-methylphthalimide gave traces of *N*-methylphthalimide, a process which they attribute to the formation of the radical anion, followed by loss of nitrite and subsequent abstraction of a hydrogen radical from the solvent.[21]

This system showed none of the longer perfluoroalkylated products which are often produced when other sources of $[CF_3]^-$ are used for aromatic trifluoromethylation: for example, $CuCF_3$ reactions are prone to chain extension *via* elimination of fluoride from $[CF_3]^-$ to generate difluorocarbene, which in turn adds to a further $[CF_3]^-$ forming longer perfluoroalkyl groups.[18]

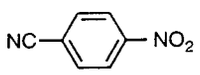
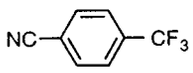
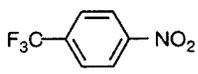
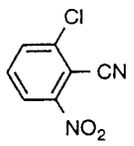
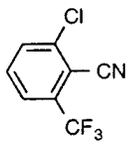
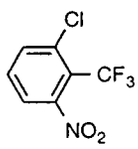
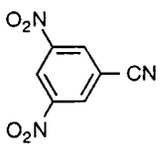
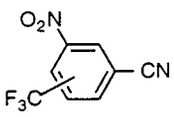
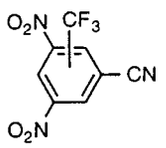
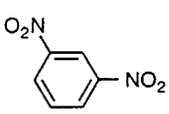
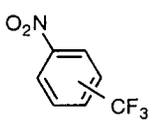
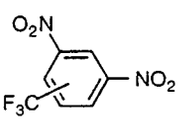
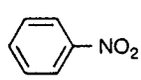
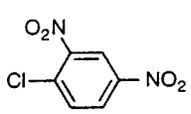
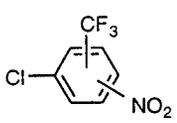
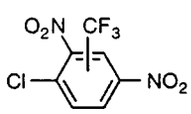
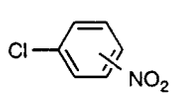
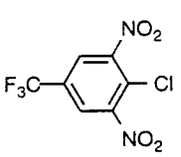
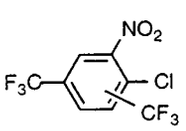
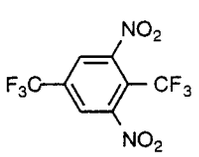
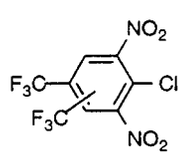
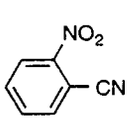
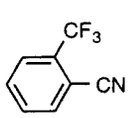
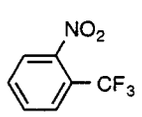
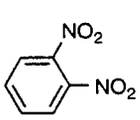
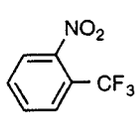
Conclusions

The Me_3SiCF_3/KF/DMAc system is very reactive and is capable of trifluoromethylating many activated nitroaromatics without giving any chain extension. Both nitro and cyano groups may be replaced *via* an aromatic nucleophilic substitution mechanism, which reflects the high affinity of silicon for first row nucleophiles such as nitrite and cyanide.[17] The trifluoromethide anions generated *in situ* are highly basic and can, in some cases, cause deprotonation of the aromatic substrate and lead to a number of side products. Although the yields at present are too low for this to be a useful synthetic method, it demonstrates the potential of this system for the formation of benzotrifluorides *via* nucleophilic aromatic substitution.

Experimental

All chemicals and solvents were purchased from Aldrich Chemical Co., except Me_3SiCF_3 which was purchased from Apollo Scientific Ltd, and 1,3-dinitro[$^2H_4$]benzene, which was

Table 2 Product distributions from reactions of nitroaromatics with Me_3SiCF_3.

Substrate	Products [yield (%)][a]		
	 7%	 Trace	
	 51%	 20%	
	 Two isomers 2%, 3%	 Two isomers 5%, 9%	
	 Two isomers 14%, 1%	 Two isomers 6%, 4%	 Trace
	 5%	 18%	 5%
	 Two isomers 2%, 4%	 3%	 4%
	 10%	 5%	
	 16%		

[a] GC areas, run with an internal standard and corrected for response factors.

synthesised in our laboratory. All were used without further purification, except for KF, which was dried at 300 °C for at least 24 h prior to use, and KNO_3, which was recrystallised from D_2O and vacuum dried at 100 °C.

Gas chromatography was carried out on a packed HP5 column in a Hewlett Packard HP6890 gas chromatograph. GC–MS spectra were obtained on a DB5 capillary column in a Varian 3400 CX gas chromatograph interfaced to a Finnigan Mat Magnum mass spectrometer. Solution state NMR spectra were obtained on a JEOL 270 EX270 spectrometer (operating

at 254 MHz for ^{19}F, referenced to $CFCl_3$). IR spectra were recorded on a Bruker equinox 55 FT-IR spectrometer. EPR spectra were obtained on a JEOL RE1X spectrometer using a glass flat cell.

Trifluoromethyldenitrations (typical reaction conditions)

The aromatic substrate (0.5 mmol) was placed in a 50 ml round bottomed flask along with biphenyl (0.077 g, 0.5 mmol) as a GC internal standard. The flask was then purged with argon and DMAc (10 ml, anhydrous) added. The solution was then heated to 50 °C and KF (0.145 g, 2.5 mmol, dried at 300 °C for at least 24 h) was added. Finally, Me_3SiCF_3 (0.20 g, 1.4 mmol) was added. Samples were periodically removed for analysis, DCM was added and the solution washed once with 1 M HCl and twice with water. The organic solution was then analysed by GC–MS. Analysis by ^{19}F-NMR spectroscopy was carried out by removing a sample from the reaction, adding a few drops of C_6D_6 as a lock and $CFCl_3$ as standard. Substrates and product distributions are given in Table 2.

The reaction of 1,2,4,5-tetracyanobenzene was carried out at room temperature. After 30 min an excess of acetone was added (the substrate and product being poorly soluble in DCM) and the solution filtered, and analysed by GC–MS and ^{19}F-NMR.

Analytical data

Due to low yields and the complexity of the reaction mixtures, isolation of the products was not viable. However, with the exception of the reaction of 4-chloro-3,5-dinitrobenzotrifluoride, all of the products have previously been reported, and GC retention times and mass spectra of the reaction products matched those of authentic samples. The remaining compounds have been assigned on the basis of their mass spectra, and by analogy to the other reactions. All trifluoromethylated aromatic compounds gave ^{19}F-NMR chemical shifts between −58 and −73 ppm: the product mixtures generally showed several peaks in this region. *4-Trifluoromethylbenzonitrile* *m/z* M^+ 171: 171 (100%), 121 (45), 152 (36), 75 (18), 170 (18), 50 (10), 102 (9), 51 (9). *Trimethysilyltrifluoromethylbenzonitrile* *m/z* M^+ 243: 56 (100%), 130 (95), 73 (80), 132 (75), 43 (69), 228 (50), 75 (5), 174 (4).† *4-Nitro-1-trifluoromethylbenzene* *m/z* M^+ 191: 145 (100%), 191 (42), 95 (23), 75 (22), 50 (16), 133 (16), 125 (13), 172 (8). *2-Chloro-6-nitro-1-trifluoromethylbenzene* *m/z* M^+ 225: 179 (100%), 225 (49), 209 (41), 144 (37), 167 (36), 181 (32), 143 (19), 75 (18). *Trimethylsilyltrifluoromethylbenzonitrile* *m/z* M^+ 243: 130 (100%), 132 (48), 228 (45), 73 (31), 244 (25), 223 (20), 316 (18), 75 (15).†‡ *Trifluoromethylnitrobenzonitrile* *m/z* M^+ 216: 170 (100%), 216 (40), 75 (18), 120 (17), 100 (15), 69 (14), 143 (12), 99 (10).†‡ *Dinitrotrifluoromethylbenzonitrile* *m/z* M^+ 261: 169 (100%), 261 (91), 100 (54), 99 (44), 119 (40), 168 (39), 150 (30), 75 (21).† *2,4,5-Tricyano-1-trifluoromethylbenzene* *m/z* M^+ 221: 221 (100%), 171 (32), 202 (23), 69 (10), 222 (12), 75 (7), 125 (6), 100 (5). *Dicyanobis(trifluoromethyl)benzene* *m/z* M^+ 264: 264 (100%), 195 (52), 245 (49), 214 (35), 69 (21), 75 (10), 164 (10), 219 (8).† *Trifluoromethane* (HCF_3) δ_F −79 (d, $^2J_{FH}$ = 79 Hz). *d-Trifluoromethane* (DCF_3) δ_F −80 (t, $^2J_{FD}$ = 12 Hz). *Fluorotrimethylsilane* (Me_3SiF) δ_H 0.2 (d, $^3J_{FH}$ = 7 Hz); *m/z* M^+ 92: 77 (100%), 47 (26), 63 (5), 92 (3). Bis(trimethylsilyl) ether ($Me_3SiOSiMe_3$) *m/z* M^+ 162: 147 (100%), 73 (16), 66 (14), 45 (8).

Preparation of 1,3-dinitro[$^2H_4$]benzene[22]

KNO_3 (15 g, 150 mmol) and concentrated D_2SO_4 (17 ml) were placed in a round bottomed flask and cooled in an ice bath. C_6D_6 (2.0 ml, 0.19 g, 23 mmol) was added, and the mixture was then heated to 95 °C for 1 h. The mixture was then poured into D_2O (50 ml), in which the product formed a yellow precipitate. This was filtered, redissolved in dichloromethane, dried over magnesium sulfate, filtered again, and the solvent removed *in vacuo* (crude yield 3.12 g, 80%). The crude product was recrystallised from ethanol before use. *m/z* M^+ 172: 94 (100%), 156 (82), 80 (63), 52 (48), 172 (40), 66 (32), 126 (10), 110 (8).

Isolation of 2-chloro-6-nitrobenzotrifluoride

2-Chloro-6-nitrobenzonitrile (0.182 g, 1.0 mmol) was placed in a 50 ml round bottomed flask fitted with an argon purge. DMAc (anhydrous, 20 ml) was added, and the flask heated to 50 °C. KF (0.29 g, 5.0 mmol), and then Me_3SiCF_3 (0.40 g, 2.8 mmol) were added, and the reaction was stirred for 30 min. The reaction mixture was then cooled in an ice bath, and diethyl ether and 1 M aqueous HCl were added. The layers were separated and the organics washed three times with water, dried over magnesium sulfate, and the solvent removed on a rotary evaporator to leave a mixture of 2-chloro-6-nitrobenzotrifluoride and 2-chloro-6-trifluoromethylbenzonitrile.

The two products could not be efficiently separated by column chromatography, and so the residual benzonitrile was converted to the corresponding amide by the method of Katritzky *et al.*[23] To the organic products were added DMSO (3.0 ml) and potassium carbonate (0.20 g, 1.98 mmol), and the reaction mixture was cooled in an ice bath. Hydrogen peroxide (30%, 2.0 ml) was added and the reaction was allowed to warm to room temperature. Ether was added, separated, and washed with 1 M aqueous NaOH, and then 1 M aqueous HCl. The organic product was then purified by column chomatography in dichloromethane over 60 Å silica gel. The spectroscopic data obtained for this compound matched those for an authentic sample prepared by reaction of 2,3-dichloronitrobenzene with $CuCF_3$ according to a literature method.[18] *m/z* M^+ 225; 179 (100%), 225 (49), 209 (41), 144 (37), 167 (36), 181 (32), 143 (19), 75 (18). $\delta_H(CDCl_3)$ 7.71–7.44 (m); $\delta_F(CDCl_3)$ −58.4.

Irradiation conditions

The reaction was performed in a pyrex glass round bottomed flask, and photolysed for 1 min before the addition of Me_3SiCF_3, and for the duration of the reaction (30 min), using a 125 W mercury lamp.

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References

1 G. K. S. Prakash and A. K. Yudin, *Chem. Rev.*, 1997, **97**, 757.
2 G. K. S. Prakash, in *Synthetic Fluorine Chemistry*, ed. G. A. Olah, R. D. Chambers and G. K. S. Prakash, Wiley, New York, 1992, ch. 10.
3 D. J. Adams, J. H. Clark and D. J. Nightingale, *Synth. Commun.*, in the press.
4 J. L. Fry and R. K. Sharma, *J. Org. Chem.*, 1983, **12**, 2112.
5 J. H. Clark, *Chem. Rev.*, 1980, **80**, 429.
6 K. O. Christie, W. W. Wilson, R. O. Wilson, R. Bau and J. Feng, *J. Am. Chem. Soc.*, 1990, **112**, 7619.
7 C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, VCH, New York, 2nd edn., 1988.
8 J. H. Clark and D. J. Macquarrie, *J. Fluorine Chem.*, 1987, **35**, 591.
9 S. Andreades, *J. Am. Chem. Soc.*, 1964, **86**, 2003.
10 E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1962, **84**, 866.
11 G. P. Stahly and D. R. Bell, *J. Org. Chem.*, 1989, **54**, 2873.
12 D. J. Milner, *J. Organomet. Chem.*, 1986, **302**, 147.
13 J.-M. Adam and T. Winkler, *Helv. Chim. Acta*, 1983, **66**, 411.
14 W. J. Smith III and J. S. Sawyer, *Tetrahedron Lett.*, 1996, **37**, 299.

† Substitution patterns are undetermined.
‡ Two isomers were observed.

15 M. Mella, N. d'Alessandro, M. Freccero and A. Albini, *J. Chem. Soc.*, *Perkin Trans. 2*, 1993, 515.
16 M. Fagnoni, M. Vanossi, M. Mella and A. Albini, *Tetrahedron*, 1996, **52**, 1785.
17 *The Chemistry of Organic Silicon Compounds*, ed. S. Patai and Z. Rappoport, Wiley, New York, 1989.
18 J. H. Clark, J. E. Denness, M. A. McClinton and A. J. Wynd, *J. Fluorine Chem.*, 1990, **50**, 411.
19 Th. J. de Boer and I. P. Dirkx, in *The Chemistry of the nitro and nitroso groups*, ed. H. Feuer, Wiley, New York, 1970.
20 G. A. Russell, E. G. Janzen and E. T. Strom, *J. Am. Chem. Soc.*, 1964, **86**, 1807.
21 R. L. Markezich and O. S. Zamek, *J. Org. Chem.*, 1977, **42**, 3431.
22 Adapted from B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, Longman, New York, 5th edn., 1989, 855.
23 A. R. Katritzky, B. Pilarski and L. Urogdi, *Synthesis*, 1989, 949.

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