Journal of Fluorine Chemistry, 67 (1994) 143–147

Partially fluorinated heterocyclic compounds. Part 30 [1]. Cyclisation reactions of lithium 1,3,4,5,7,8-hexafluoro-6-isoquinolinethiolate and lithium 2,3,5,6,7,8-hexafluoro-4-quinolinethiolate with dimethyl acetylenedicarboxylate

Gerald M. Brooke* and Christopher J. Drury

Chemistry Department, Science Laboratories, South Road, Durham DH1 3LE (UK)

(Received February 19, 1993; accepted June 7, 1993)

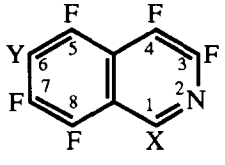
Abstract

The lithium salt of 1,3,4,5,7,8-hexafluoro-6-isoquinolinethiol reacts with dimethyl acetylenedicarboxylate (DMAD) to give dimethyl 4,5,6,8,9-pentafluorothieno[3,2-*f*]isoquinoline-1,2-dicarboxylate and dimethyl 4,5,6,8,9-pentafluoro[2,3-*g*]isoquinoline-1,2-dicarboxylate in the ratio 95:5, respectively. The lithium salt of 2,3,5,6,7,8-hexafluoro-4-quinolinethiol and DMAD give dimethyl 4,6,7,8,9-pentafluorothieno[3,2-*c*]quinoline (74%) and dimethyl 1-(2,3,5,6,7,8-hexafluoro-4-quinolylthio)ethene-1,2-dicarboxylate (13%). No cyclisation to form a six-membered ring was detected in the reaction of the lithium salt of 3,4,5,7,8-pentafluoro-6-phenylthio-1-isoquinolinethiol and DMAD; overall addition of the thiol to the triple bond occurred to give dimethyl 1-(3,4,5,7,8-pentafluoro-6-phenylthio-1-isoquinolylthio)ethene-1,2-dicarboxylate in low yield.

Introduction

In 1967, we described a new cyclisation reaction for the formation of the five-membered heterocyclic ring in a 4,5,6,7-tetrafluorobenzo[*b*]thiophene derivative via the addition of the lithium salt of pentafluorothiophenol to the triple bond in diethyl acetylenedicarboxylate [2]. More recently, the related reaction of lithium 1,3,4,5,6,7,8-heptafluoro-2-naphthalenethiolate with dimethyl acetylenedicarboxylate (DMAD) was reported [3], a reaction of particular interest since cyclisation was shown to give the thiophene derivative **2** (92 parts) in preference to the isomer **3** (8 parts) via the presumed intermediate **1** (Scheme 1). We wished to investigate cyclisation reactions which could take place unambiguously in *one* direction only, for which the best substrates were the 1-isoquinolinethiol **4** which could form a fused *six*-membered sulphur-containing ring by replacement of the peri fluorine at position 8 (and which would constitute a new type of cyclisation reaction), and the 2-quinolinethiol **5** which could form a linearly ring-fused thiophene derivative.

*Author to whom correspondence should be addressed.



(4) X = SH; Y = F

(6) X = Y = F

(8) X = F; Y = SH

(14) X = t-BuS; Y = F

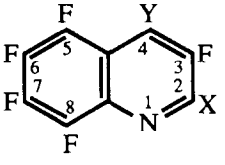
(15) X = F; Y = t-BuS

(16) X = Y = t-BuS

(17) X = F; Y = C_6H_5S

(18) X = SH; Y = C_6H_5S

(19) X = $SC(CO_2Me)=C(H)CO_2Me$; Y = C_6H_5S

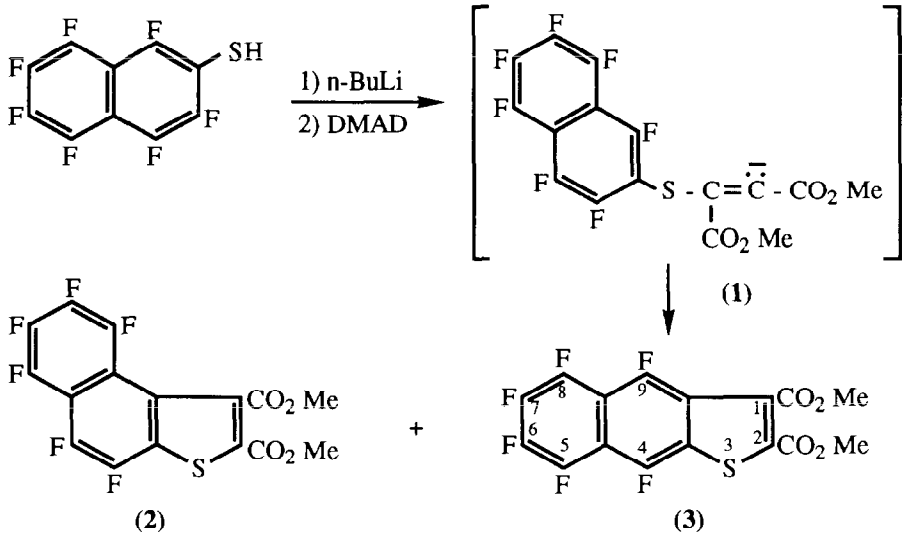


(5) X = SH; Y = F

(7) X = Y = F

(9) X = F; Y = SH

SSDI 0022-1139(93)02942-8

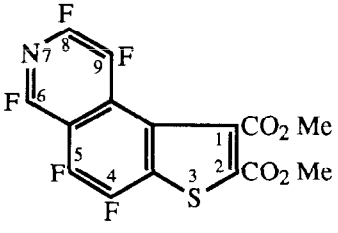


Scheme 1.

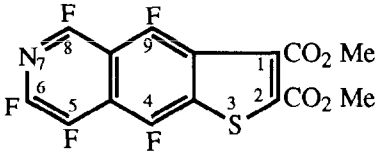
We did not envisage any problems in synthesising the required thiols since it was known from pioneering work on the nucleophilic substitution of fluorine in 1,3,4,5,6,7,8-heptafluoroisoquinoline (**6**) and 2,3,4,5,6,7,8-heptafluoroquinoline (**7**) with various nucleophiles such as sodium methoxide, ammonia and lithium aluminium hydride, that monosubstitution in the isoquinoline occurs at the 1-position, while in the quinoline both the 2- and 4-fluorines are replaced (e.g. in the ratio of 77:23, respectively, with sodium methoxide) [4]. However, when sodium hydrosulphide in ethylene glycol and *N*,*N*-dimethylformamide at *c.* 0 °C was reacted in turn with the isoquinoline **6** and the quinoline **7**, exclusive formation of 1,3,4,5,7,8-hexafluoro-6-isoquinolinethiol (**8**) and 2,3,5,6,7,8-hexafluoro-4-quinolinethiol (**9**), respectively, occurred [5]. We now report on the mode of cyclisation of the lithium salts of these new thiols **8** and **9** with DMAD, for both of which two alternative processes are possible, and also the reaction of the lithium salt of 3,4,5,7,8-pentafluoro-6-phenylthio-1-isoquinolinethiol (**18**) with DMAD for which only one direction of cyclisation is possible.

Results and discussion

The 6-isoquinolinethiol **8** was treated in tetrahydrofuran at < -63 °C with 1 equiv. of n-butyl-lithium in hexane followed by dimethyl acetylenedicarboxylate and the mixture allowed to warm to room temperature. The crude product, examined by ^{19}F NMR spectroscopy consisted of one major component **10** (68%), a minor component **11** (4%) and at least five other unidentified components (28%).



(10)

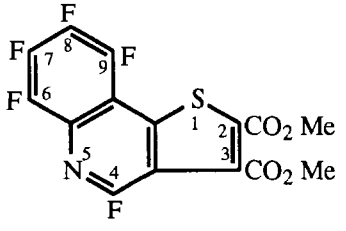


(11)

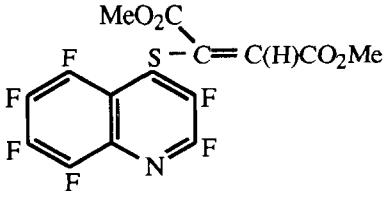
Compound **10**, separated from the product by chromatography, was identified by ^{19}F NMR spectroscopy: the presence of only *one* large peri coupling constant ($J_{5\text{-F},6\text{-F}} = 73.8$ Hz) showed that the 5-F group in thiol **8** had been substituted in the cyclisation reaction. Compound **11**, isomeric with **10**, could only be obtained enriched in a complex mixture by chromatography. It was identified by its five fluorine absorptions, *two* peri coupling constants ($J = 48$, 71 Hz), and by the chemical shifts expected for this mode of ring cyclisation. In the thiophene compound **3** obtained from 1,3,4,5,6,7,8-heptafluoro-2-naphthalenethiol, the fluorines at positions 5, 6, 7 and 8 are shifted to only a small extent (≤ 1.4 ppm), whereas both the 4-F and 9-F groups are deshielded by *c.* 24 ppm relative to the corresponding signals in 1,2,3,4,5,6,7,8-octafluoronaphthalene [3]. The calculated values of the shifts expected for the 4-F ($-145.8 + 24 = -121.8$ ppm) and the 9-F

(−139.7+24 = −115.7 ppm) groups in structure **11** are in excellent agreement with the observed shifts, i.e. −122.6 and −115.3 ppm, respectively. The proportion of cyclisation to the 5-position relative to the 7-position in the parent thiol **8**, 95:5, is the same order of magnitude as found previously (Scheme 1).

The 4-quinolinethiol **9** was converted into its lithium salt and reacted with DMAD in exactly the same way as in the experiment with the isoquinolinethiol **8**. ^{19}F NMR spectroscopy of the crude product showed the presence of one major product (**12**) (74%), a minor product (**13**) (13%) and at least four unidentified compounds (13%).



(12)



(13)

Compounds **12** and **13** were separated in a separate experiment by chromatography and their structures identified by NMR spectroscopy. The ^{19}F NMR spectrum of **12** showed five absorptions with a low field absorption at −59.8 ppm due to the fluorine at position 4. Its singlet structure, and the fact that it is deshielded by 12.6 ppm [−59.8−(−72.4) ppm] showed clearly that the fluorine at position 3 in the parent thiol **9** had been replaced in the cyclisation reaction. The minor product **13** was identified as the product of the addition of thiol **9** to the triple bond of DMAD: the ^{19}F NMR spectrum had six absorptions, while the ^{1}H NMR spectrum showed a singlet at δ 7.0 ppm due to the alkene hydrogen, and two methyl ester singlets; however, the stereochemistry of the product is not known. The formation of the thiol adduct **13** is the first example of such a reaction involving DMAD; previously [6] the addition of lithium pentafluorophenylthiolate to ethyl phenylpropiolate had been shown to give mainly cyclisation (72%) and *c.* 5% of thiol addition product, while with ethyl propiolate and diphenylacetylene only thiol addition products were formed.

An alternative route to the 1-isoquinolinethiol **4** was investigated via dealkylation of the 1-t-butylthioisoquinoline **14**; compound **14** (16 parts) is formed along with the 6-t-butyl derivative **15** (79 parts) and the 1,6-di(t-butylthio) derivative **16** (5 parts) in the reaction of the isoquinoline **6** with sodium t-butylthiolate [5]. Reaction of **14** with trifluoroacetic acid gave **4** (49%) which rapidly decomposed after isolation, presumably because of intermolecular reactions at the more reactive 6-position with the 1-thiol. In order to eliminate this possibility, 1,3,4,5,7,8-hexafluoro-6-phenylthioisoquinoline (**17**) (i.e. with the 6-position blocked towards nucleophilic attack) [5], was reacted with sodium hydrosulphide in ethylene glycol/*N*,*N*-dimethylformamide to give 3,4,5,7,8-pentafluoro-6-phenylthio-1-isoquinolinethiol (**18**), identified by ^{19}F NMR spectroscopy by the absence of an absorption at *c.* −62 ppm (indicating that the fluorine at C-1 in **17** had been replaced), and by the presence of only one peri coupling constant (60 Hz) due to the fluorines at C-4 and C-5. Compound **18** could not be obtained pure; however, treatment with n-butyl-lithium at −63 °C followed by dimethyl acetylenedicarboxylate and heating the mixture under reflux for 10 d gave a very complex mixture of products from which the only identifiable component after extensive chromatography was compound **19** (10%), the result of the addition of thiol **18** to the triple bond. The structure of this adduct was clearly evident from its elemental analysis and from spectroscopy data: the correct molecular weight by mass spectroscopy; the retention of the five fluorine substituents in its ^{19}F NMR spectrum; and its ^{1}H NMR spectrum showed a singlet at *c.* 7.11 ppm due to the alkene hydrogen, in addition to the two methyl ester singlets and the absorptions due to the phenylthio substituent. Again the stereochemistry of this product is not known.

The present work establishes that ring cyclisation with the 4-quinolinethiol **9** with DMAD occurs by replacement of the fluorine at position 3 in the heterocyclic ring. Although the formation of the five-membered ring is clearly more favoured, the possibility of replacement of the fluorine at C-5 in the carbocyclic ring in **9** with the formation of a six-membered sulphur-containing ring cannot be ruled out completely, as it could have been present among the minor components of the reaction. However, failure to detect any cyclised product from the potentially unambiguous reaction of the lithium salt of the 1-isoquinolinethiol derivative **18** with DMAD and isolation of only the thiol adduct to the triple bond of DMAD after work-up, **19**, indicates that this mode of cyclisation is very unfavourable. It is not obvious that steric factors could be responsible for this lack of reaction.

Experimental

NMR spectra were obtained with a Bruker AC 250 [^{1}H (250 MHz) and ^{19}F (235 MHz) instrument. Chemical shifts are positive up-frequency (downfield) from TMS and $CFCl_3$, hence all the ^{19}F resonance values are negative]. For isoquinoline **6**: ^{19}F NMR ($CHCl_3$) δ: −62.1 (1-F); −96.7 (3-F); −155.7 (4-F); −145.8 (5-F); −145.4 (6-F); −153.1 (7-F); −139.7 (8-F) ppm. For quinoline **7**: ^{19}F NMR ($CHCl_3$) δ: −72.4 (2-F); −160.8 (3-F); −124.1 (4-F); −146.1 (5-F); −154.3 (6-F); −150.5 (7-F); −148.3 (8-F) ppm. Mass spectroscopy data were obtained with a VG 7070 E instrument. Molecular ions M^+ are quoted for electron ionisation unless chemical ionisation (CI) is stated.

Reaction of the lithium salt of 1,3,4,5,6,7-hexafluoro-6-isoquinolinethiol (8) with dimethyl acetylene-dicarboxylate (DMAD)

Thiol **8** (2.410 g, 8.96 mmol) in anhydrous THF (25 ml) was treated at < −63 °C with n-butyl-lithium in hexane (1.53 M; 5.9 ml, 9.02 mmol) and DMAD (1.366 g, 9.62 mmol) in anhydrous THF (5 ml) was added over 15 min at < −63 °C. The reaction temperature was rapidly raised to 20 °C and maintained at this temperature for 1 h. The mixture was acidified (2 M H_2SO_4), extracted with chloroform, the extracts dried ($MgSO_4$) and the solvents evaporated to give a solid (3.773 g) which was examined by ^{19}F NMR spectroscopy. The mixture consisted of two isomers present to the extent of 68% and 4%, accompanied by 28% unidentified material (at least four components). The major isomer was separated by a combination of flash chromatography on silica using chloroform as eluant and recrystallisation to give dimethyl 4,5,6,8,9-pentafluoro-thieno[3,2-*f*]-isoquinoline-1,2-dicarboxylate (nc) (**10**), m.p. 174.8–177 °C [from toluene/light petroleum (b.p. 100–120 °C)]. (Analysis: Found: C, 45.81; H, 1.36; N, 3.45%; M^+, 391. $C_{15}H_6F_5NSO_4$ requires: C, 46.05; H, 1.55; N, 3.58%; M, 391).^{19}F NMR ($CDCl_3$) δ: −63.6 (dddd, 6-F); −93.8 (m, 8-F); −137.9 (dm, 4-F); −141.5 (ddm, 5-F); −145.3 (ddm, 9-F) ppm; $J_{4\text{-F},5\text{-F}}$ = 18.4 Hz, $J_{5\text{-F},6\text{-F}}$ = 73.8 Hz, $J_{6\text{-F},9\text{-F}}$ = 30.5 Hz, $J_{8\text{-F},9\text{-F}}$ = 19.3 Hz. ^{1}H NMR ($CDCl_3$) δ: 4.01 (s, CH_3); 4.09 (s, CH_3) ppm. The fraction just prior to that yielding **10** contained three components, one of which was **10**, but another was dimethyl 4,5,6,8,9-pentafluoro-thieno[2,3-*g*]isoquinoline-1,2-dicarboxylate (nc) (**11**). ^{19}F NMR ($CDCl_3$) δ: −57.9 (8-F); −98.0 (6-F); −115.3 (9-F); −122.6 (4-F); −156.9 (5-F) ppm; $J_{8\text{-F},9\text{-F}}$ = 71 Hz, $J_{4\text{-F},5\text{-F}}$ = 48 Hz.

Reaction of the lithium salt of 2,3,5,6,7,8-hexafluoro-4-quinolinethiol (9) with dimethyl acetylenedicarboxylate

Quinolinethiol **9** (0.097 g, 0.36 mmol) in anhydrous THF (15 ml) was treated at −63 °C with butyl-lithium (0.25 ml, 1.6 M, 0.40 mmol), followed by DMAD (60 μl, 0.069 g, 0.48 mmol) in THF (5 ml) at −63 °C over 1 min. The mixture was allowed to warm up to 10 °C, and worked-up as in the previous experiment. The crude residue (0.164 g) was shown by ^{19}F NMR spectroscopy to contain the cyclised product **12** (74%), the non-cyclised product **13** (13%) and unknown compounds (at least four) (13%). The crude products from several similar experiments were combined and separated by flash chromatography on silica using dichloromethane as eluant. The fastest eluting component was dimethyl 1-(2,3,5,6,7,8-hexafluoro-4-quinolylthio)ethene-1,2-di-carboxylate (nc) (**13**), m.p. 109.0–109.5 °C [from light petroleum (b.p. 60–80 °C)]. (Analysis: Found: C, 43.50; H, 1.62; N, 3.29%; M^+, 411. $C_{15}H_7F_6NO_4S$ requires: C, 43.81; H, 1.72; N, 3.41%; M, 411). ^{19}F NMR ($CDCl_3$) δ: −77.0 (d, 2-F); −128.5 (d, 3-F); −140.6 (t, 5-F); −147.9 (t); −152.2 (td); −154.3 (td) (all unassigned) ppm; $J_{2\text{-F},3\text{-F}}$ = 31 Hz. ^{1}H NMR ($CDCl_3$) δ: 3.87 (s, CH_3); 3.63 (s, CH_3); 7.00 (s, alkenic C–H) ppm. The second eluting component was dimethyl 4,6,7,8,9-pentafluoro-thieno[3,2-*c*]quinoline-1,2-dicarboxylate (nc) (**12**), m.p. 117.0–117.5 °C [from light petroleum (b.p. 60–80 °C)]. (Analysis: Found: C, 45.79; H, 1.47; N, 3.48%; M^+, 391. $C_{15}H_6F_5NO_4S$ requires: C, 46.05; H, 1.55; N, 3.58%; M, 391). ^{19}F NMR ($CDCl_3$) δ: −59.8 (s, 4-F); −140.2 (td, 9-F); −146.5 (td); −151.4 (t); −155.7 (td) (all unassigned) ppm. ^{1}H NMR ($CDCl_3$) δ: 4.10 (s, CH_3); 4.02 (s, CH_3) ppm.

Dealkylation of 3,4,5,6,7,8-hexafluoro-1-(t-butylthio)-isoquinoline (14)

The 1-(t-butylthio)isoquinoline **14** (0.047 g, 0.14 mmol) and trifluoroacetic acid (2.5 ml) were heated together under reflux for 10 h. The mixture was cooled to room temperature, the acid evaporated *in vacuo* at 0.01 mmHg and the crude residue sublimed at room temperature/0.01 mmHg to give a mixture (0.017 g) consisting of the unreacted 1-(t-butylthio)isoquinoline (**14**) (11 parts) and the 3,4,5,6,7,8-hexafluoro-1-isoquinolinethiol (nc) (**4**) (89 parts) (by ^{19}F NMR spectroscopy). The 1-isoquinolinethiol **4** in the mixture: ^{19}F NMR ($CDCl_3$) δ: −95.7 (d, 3-F); −136.9 (broad s, 8-F); −145.1 (dt, 5-F); −147.5 (broad s, 6-F); −154.7 (t, 7-F); −158.2 (dd, 4-F) ppm; $J_{4\text{-F},5\text{-F}}$ = 51.8 Hz MS (EI, 70 eV) *m/z*: M^+, 269. C_9HF_6NS requires: M, 269. This material decomposed rapidly in solution, but column chromatography on silica using CH_2Cl_2/light petroleum (b.p. 60–80 °C) enabled the slower eluting thiol to be obtained free from starting material.

Preparation of the 6-phenylthio-1-isoquinolinethiol 18

1,3,4,5,7,8-Hexafluoro-6-phenylthioisoquinoline (**17**) (0.537 g, 1.56 mmol) [5] in ethylene glycol (EG) (2.5 ml) and dry dimethylformamide (DMF) (5 ml) at < −10

°C was treated with sodium hydrosulphide (0.462 g, 8.2 mmol) in EG (2.5 ml) and DMF (5 ml) at < -10 °C. The mixture was stirred for 10 min, poured into iced water, acidified (2 M H_2SO_4) and the product extracted with ether. The extracts were washed with base (2 M NaOH), the aqueous layer acidified (2 M H_2SO_4) and again extracted with ether, and the extracts dried ($MgSO_4$). Evaporation of the solvent gave the crude product (0.418 g) shown by ^{19}F NMR spectroscopy to be slightly impure (*c.* 95%) 3,4,5,7,8-pentafluoro-6-phenylthio-1-isoquinolinethiol (nc) (**18**). ^{19}F NMR ($CDCl_3$) δ: -96.2 (d, 3-F); -110.3 (dd, 5-F); -129.9 (d, 7-F); -140.2 (broad s, 8-F); -156.6 (dd, 4-F) ppm; $J_{4\text{-F, }5\text{-F}} = 60$ Hz, $J_{3\text{-F, }4\text{-F}} = 19$ Hz. ^1H NMR ($CDCl_3$) δ: 7.42 (m, HC_{arom}); 7.31 (m, HC_{arom}); 4.63 (broad s, –SH) ppm. MS (ET, 70 eV) *m/z*: M^+, 359. $C_{15}H_6F_5NS_2$ requires: M, 359.

Reaction of the lithium salt of 3,4,5,7,8-pentafluoro-6-phenylthio-1-isoquinolinethiol (18) with dimethyl acetylenedicarboxylate

The 6-phenylthio-1-isoquinolinethiol **18** (0.418 g, 1.16 mmol) in anhydrous THF (250 ml), cooled to -63 °C, was treated with butyl-lithium (0.65 ml, 1.6 M, 1.0 mmol) and after 15 min DMAD (0.13 ml, 1.1 mmol) in THF (5 ml) was added. The mixture was allowed to warm to room temperature and then heated under reflux for 10 d. The mixture was worked-up as before and the crude residue separated by chromatography on silica using $CHCl_3$/light petroleum (b.p. 40–60 °C) (1:1 v/v) as eluant. Three fractions were collected, only one of which showed promising fluorine absorptions, i.e. fraction 3 (0.255 g) which contained the non-cyclised DMAD adduct material **19** and other impurities. Fraction 3 was re-chromatographed as before and six fractions were collected; fraction 5 contained dimethyl 1-(3,4,5,7,8-pentafluoro-6-phenylthio-1-isoquinolylthio)-ethene-1,2-dicarboxylate (nc) (**19**) (0.056 g), m.p. 116.0–116.5 °C [from light petroleum (b.p. 60–80 °C)]. (Analysis: Found: C, 50.69; H, 2.43; N, 2.73%; M^+ 502 [CI]. $C_{21}H_{12}F_5NO_4S_2$ requires: C, 50.30; H, 2.41; N, 2.79%; M, 501). ^{19}F NMR ($CDCl_3$) δ: -97.3 (d, 3-F); -110.3 (dd, 5-F); -129.1 (d, 7-F); -136.9 (t, 8-F); -155.2 (dd, 4-F) ppm; $J_{4\text{-F, }5\text{-F}} \approx 61$ Hz; $J_{3\text{-F, }4\text{-F}} \approx 18$ Hz. ^1H NMR ($CDCl_3$) δ: 7.43 (m, HC_{arom}); 7.32 (m, HC_{arom}); 7.11 (s, C=CH); 3.82 (s, CH_3); 3.79 (s, CH_3) ppm.

Acknowledgement

One of us (C.J.D.) thanks the Science and Engineering Research Council for a grant.

References

1 Part 29. G.M. Brooke, R.S. Matthews, M.E. Harman and M.B. Hursthouse, *J. Fluorine Chem., 53* (1991) 339.
2 G.M. Brooke and Md. Abul Quasem, *J. Chem. Soc. C,* (1967) 865.
3 G.M. Brooke, *J. Fluorine Chem., 43* (1989) 393.
4 R.D. Chambers, M. Hole, W.K.R. Musgrave, R.A. Storey and (in part) B. Iddon, *J. Chem. Soc. C,* (1966) 2331.
5 G.M. Brooke, (in part) M.J. Bower, R.D. Chambers and C.J. Drury, *J. Chem. Soc., Perkin Trans. 1,* (1993) 2201.
6 G.M. Brooke and Md. Abul Quasem, *J. Chem. Soc., Perkin Trans. 1,* (1973) 429.