*Journal of Fluorine Chemistry, 43* (1989) 393–403

Received: October 27, 1988; accepted: February 2, 1989

# PARTIALLY FLUORINATED HETEROCYCLIC COMPOUNDS. PART 26[1]. AN INVESTIGATION INTO THE MODE OF CYCLISATION IN THE REACTION OF LITHIUM 1,3,4,5,6,7,8-HEPTAFLUORO-2-NAPHTHALENETHIOLATE WITH DIMETHYL ACETYLENEDICARBOXYLATE

GERALD M. BROOKE

Department of Chemistry, Science Laboratories, South Road, Durham DH1 3LE (U.K.)

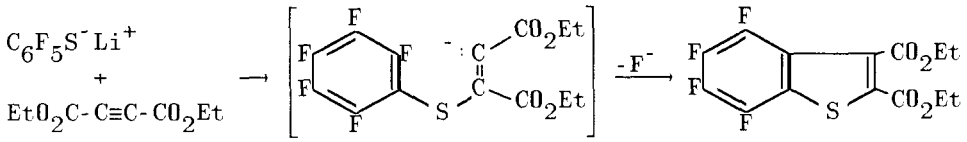
## SUMMARY

Octafluoronaphthalene reacted with sodium hydrosulphide to give 1,3,4,5,6,7,8-heptafluoro-2-naphthalenethiol (4). The lithium salt of (4) and dimethyl acetylenedicarboxylate gave dimethyl 4,5,6,7,8,9-hexafluoronaphtho[2,1-b]thiophen-1,2-dicarboxylate (6) and dimethyl 4,5,6,7,8,9-hexafluoronaphtho-[2,3-b]thiophen-2,3-dicarboxylate (7) in the ratio of 92:8 respectively via intramolecular cyclisation reactions. Compound (6) was converted to 4,5,6,7,8,9-hexafluoronaphtho[2,1-b]thiophen (8) via hydrolysis and decarboxylation. Sodium methoxide in methanol replaced the fluorine at 6-F in 1,3,4,5,6,7,8-heptafluoro-2-naphthyl methyl sulphide (12). The preferred formation of (6) via the replacement of the fluorine at 1-F in the intermediate (5) indicates that localisation energy considerations enhance the selectivity of this orientation reaction.

0022-1139/89/$3.50 

## INTRODUCTION

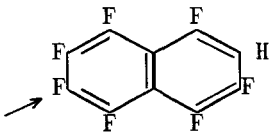
In 1967, the formation of diethyl 4,5,6,7-tetrafluorobenzo-[b]thiophen-2,3-dicarboxylate (1) in 49% yield, by the reaction of lithium pentafluorobenzenethiolate with diethyl acetylene-dicarboxylate in tetrahydrofuran at reflux temperature, was reported from our laboratory [2] (Scheme 1). Later the cyclisation reaction was shown to occur under very mild



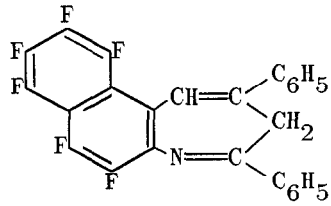

Scheme 1

conditions (-70° to -58°C) in 74% yield and we investigated the scope of the reaction with a variety of acetylenic compounds [3]. In this paper the course of the reaction of lithium 1,3,4,5,6,7,8-heptafluoro-2-naphthalenethiolate with dimethyl acetylene-dicarboxylate is reported. This experiment is of particular interest since being an intramolecular reaction it enabled for the first time a comparison to be made between the relative reactivity of fluorine displacement at two sites in the same ring, namely the 1-F and 3-F. Previously other workers in our department have studied the relative reactivities of highly fluorinated naphthalene derivatives and have found for example that in 1,3,4,5,6,7,8-heptafluoronaphthalene (2) nucleophilic attack takes place only in the fully fluorinated ring (at the site shown) [4]. In a previous paper in this series it was reported that only one

product of a cyclisation reaction between 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine and $\beta$-benzoyl-$\alpha$-methylstyrene had been obtained - the 3H azepine derivative (3) (17%) by displacement of the fluorine at 1-F [1].



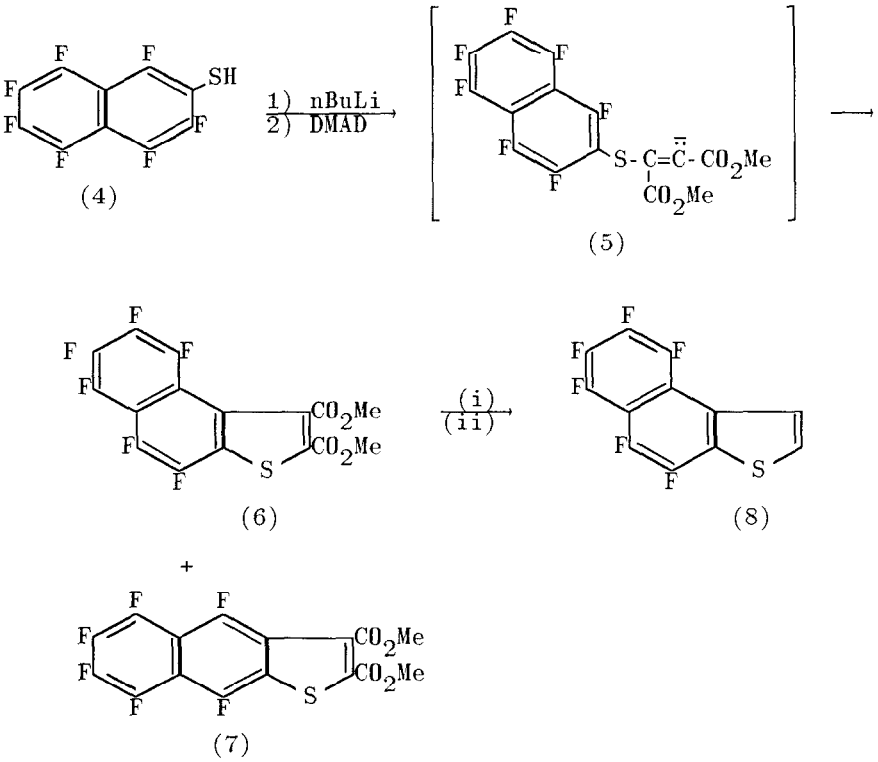
(2)



(3)

RESULTS AND DISCUSSION

1,3,4,5,6,7,8-Heptafluoro-2-naphthalenethiol (4) [5] was isolated in essentially quantitative yield by the addition of sodium hydrosulphide, in a mixture of ethylene glycol and N,N-dimethylformamide, to octafluoronaphthalene. Previously the intermediate thiolate had been reacted *in situ* with prop-2-ynyl bromide [6] and with prop-2-enyl bromide [7] to give sulphides for other investigations. The reaction between the lithium salt of the thiol (4) and dimethyl acetylenedicarboxylate (DMAD) gave a mixture of two cyclised products (6) and (7) via the presumed intermediate (5) (see Scheme 2) in the ratio of 92:8 (by $^{19}F$ n.m.r.) in essentially quantitative yield. The two isomers were separated by crystallisation and by chromatography on silica and their structures were determined by $^{19}F$ n.m.r. spectroscopy. The major isomer had only *one* large peri $J_{F-F}$ coupling constant (74 Hz) and was therefore (6) while the minor component had *two* large peri $J_{F-F}$ coupling constants (58 and 64 Hz) and was therefore (7).



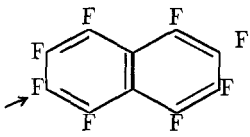

Reagents: (i) 50:50 v/v $H_2O$-$H_2SO_4$; (ii) Cu-quinoline

Scheme 2

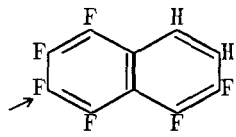
Acid hydrolysis of the diester (6) followed by decarboxylation of the crude product with copper in quinoline gave 4,5,6,7,8,9-hexafluoronaphtho[2,1-b]thiophen (8) (54%).

The greatly preferred formation of (6) by elimination of the fluorine at 1-F in the sulphide (5) is of interest in connection with the study of factors affecting nucleophilic substitution reactions in polyfluorinated aromatic systems. It has been established that fluorine atoms that are substituents at positions ortho- and meta- to the site of attack in highly fluorinated aromatic systems are significantly activating, whereas para-

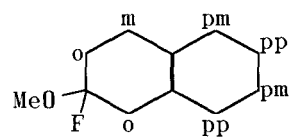
fluorine is slightly deactivating with respect to hydrogen atoms at the same position [8]. In the highly fluorinated naphthalene systems (2), (9) and (10) where nucleophilic attack occurs only in



(9)



(10)



(11)

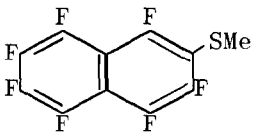
o, m = ortho-, meta-
pm, pp = 'pseudo-meta', 'pseudo-para'

the fully fluorinated rings (as indicated), it has been shown recently that fluorine atoms at sites remote from the reaction site [see structure (11)] follow a similar reactivity pattern, namely 'pseudo-meta' is activating whereas 'pseudo-para' is slightly deactivating with respect to hydrogen at the same sites [4]. An indirect approach was necessary to establish the activating effects of ortho-fluorine but the meta-fluorine effect could not be evaluated. The observed orientation of nucleophilic substitution in octafluoronaphthalene (9) followed from the requirement that the activating influences of fluorine substituents at the site of attack be maximised.

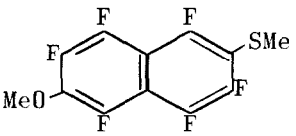
The effect of a sulphide (SMe) substituent in the 4-position of 4-substituted 2-nitrochlorobenzene towards $MeO^-$/MeOH has been shown to be activating compared with a 4-fluorine [8] but there are no data for comparing the relative reactivity of these substituents when ortho- to the site of attack. The intramolecular reaction of the intermediate sulphide (5) necessarily constrains displacement of fluorine to the same ring, so it was of interest to establish which site was really the most

reactive in (5) by using the methyl sulphide (12) as a model compound for an intermolecular reaction.

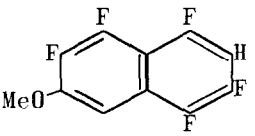
The thiol (4) was converted into the methyl sulphide (12) which in turn was reacted with $MeO^-$/MeOH. Apart from unreacted




(12)




(13)




(14)

(12) (4%) the major product was (13) (88%) accompanied by unidentified material (8%). The structure of (13) was established by Raney nickel desulphurisation to (14) which was identical to the product obtained from (2) and $MeO^-$/MeOH and whose structure had been established previously [4,10]. The 'pseudo-para' 6-F site is therefore the most reactive site in (12) and the same site is presumably the most reactive site in the sulphide (5), so that for the intramolecular cyclisation reaction, a distinction between two less reactive sites at 1-F and 3-F has to be made. It has been shown with increasingly reactive systems that the activating effects of ortho-F: meta-F increase significantly [11] and the converse effect accounts for the relative proportions of the two minor components formed in the reaction involving 1,3,4,5,7,8-hexafluoronaphthalene and methoxide ion where the 1-F site with one meta and one 'pseudo-meta' activating fluorines is more reactive by a factor of two than the 4-F site with one ortho and two 'pseudo-meta' activating fluorines [4]. In (5) the activating effect of ortho-F could be greatly reduced with respect to meta-F, and although 8% of the cyclisation does occur by displacement at

3-F, localisation energy considerations peculiar to the naphthalene ring system clearly enhance the selectivity of the process, the major course of the reaction taking place at 1-F.

## EXPERIMENTAL

N.m.r. spectra were obtained with a Bruker AC 250 [$^{1}H$ (250 MHz) and $^{19}F$ (235 MHz)]. Chemical shifts are downfield from internal $SiMe_4$ ($\delta_H$), or upfield from internal $CFCl_3$ ($\delta_F$). Mass spectroscopy data were obtained with a VG 7070E instrument. Molecular ions $M^+$ are quoted for electron ionisation.

Reaction of octafluoronaphthalene with sodium hydrosulphide. Octafluoronaphthalene (10.62 g) in a mixture of ethylene glycol (25 ml) and anhydrous N,N-dimethylformamide (50 ml) was treated with sodium hydrosulphide (4.47 g) in ethylene glycol (25 ml) and anhydrous N,N-dimethylformamide (50 ml) at $3^{o}$ to $6^{o}C$ over 10 min. The reaction temperature was raised to $20^{o}$, and after 90 min. the mixture was acidified (2 M $H_2SO_4$) extracted with ether, the extracts dried ($MgSO_4$) and the solvent evaporated. Sublimation of the residue at $35\text{-}50^{o}/0.05$ mmHg and crystallisation of sublimate (11.03 g, 99%) from light petroleum (b.p. $30\text{-}40^{o}C$) gave 1,3,4,5,6,7,8-heptafluoro-2-naphthalenethiol (4) m.p. $65.5\text{-}66.5^{o}C$ (Found: C, 42.02; H, 0.29%; $M^+$, 286. $C_{10}HF_7S$ requires C, 41.97; H, 0.35%; M, 286); $\delta_F(CDCl_3)$ 116.4 (dd, peri $J_{1\text{-}F,8\text{-}F}$ 65 Hz, 1-F), 132.9 (d, 3-F), 145.8 (dt, $J_{1\text{-}F,8\text{-}F}$ 65 Hz, 8-F), 146.4, 148.5 (both dt, $J_{4\text{-}F,5\text{-}F}$ 57 Hz, unassigned 4-F, 5-F), 155.1 (complex overlapping multiplets due to 6-F and 7-F); $\delta_H(CDCl_3)$ 3.94 (S-H).

Treatment of the thiol (4) with excess diazomethane in ether gave 1,3,4,5,6,7,8-heptafluoro-2-naphthyl methyl sulphide (12) mp

65.5-66.5°C [from light petroleum (bp 60-80°C)] (Found: C, 43.83; H, 0.99%. $C_{11}H_3F_7S$ requires C, 44.01; H, 1.01%); $\delta_F(CDCl_3)$ 112.0 (dd, peri $J_{1\text{-}F,8\text{-}F}$ 70 Hz, 1-F), 130.9 (d, 3-F), 144.2 (dt, $J_{1\text{-}F,8\text{-}F}$ 70 Hz; 8-F), 146.4, 148.6 (both dt, $J_{4\text{-}F,5\text{-}F}$ 58 Hz, unassigned 4-F, 5-F), 153.7, 155.6 (both t, unassigned 6-F, 7-F); $\delta_H(CDCl_3)$ 2.60 ($SCH_3$).

Reaction of lithium 1,3,4,5,6,7,8-heptafluoronaphthalene-2-thiolate with dimethyl acetylenedicarboxylate. 1,3,4,5,6,7,8-Heptafluoro-2-naphthalenethiol (4) (1.01 g) in dry tetrahydrofuran (10 ml) was treated at ≤ -64°C with n-butyl-lithium in hexane (2.22 ml, 1.585 M) over 15 min, and dimethyl acetylenedicarboxylate (0.526 g) in dry tetrahydrofuran (3 ml) was added over 15 min, the internal reaction temperature being maintained at ≤ -64°C. The reaction mixture was warmed rapidly to 20°C, maintained at this temperature for 30 min, acidified (2 M $H_2SO_4$) and extracted with chloroform. The chloroform extracts were dried ($MgSO_4$) and the solvent evaporated to give a solid (1.494 g) which was examined by $^{19}F$ nmr spectroscopy. The major products were two isomers present in the ratio 92:8. The major isomer, obtained by recrystallisation of the mixture five times from toluene - light petroleum (bp 100-120°C) was dimethyl 4,5,6,7,8,9-hexafluoronaphtho[2,1-b]-thiophen-1,2-dicarboxylate (6) mp 152.5-153.5°C (Found: C, 47.25; H, 1.39%; $M^+$, 408. $C_{16}H_6F_6O_4S$ requires C, 47.07; H, 1.48%; M, 408); $\delta_F(CDCl_3)$ 135.2 (nm), 139.0 (nm), 144.1 (dt, peri AB, $J_{5\text{-}F,6\text{-}F}$ 74 Hz, unassigned 5-F/6-F), 144.7 (dd, peri AB, $J_{5\text{-}F,6\text{-}F}$ 74 Hz, unassigned 5-F/6-F), 154.2 (t) and 154.7(t); $\delta_H(CDCl_3)$ 3.98 (S, $CH_3$) and 4.08 (S, $CH_3$). The minor component was separated from the major component by flash chromatography of a

mixture of isomers (2.17 g) on a silica column (6" x 2") and eluting with toluene. The earlier fractions eluting (0.171 g) were enriched in the minor component and subjected to thick layer chromatography on silica using benzene to give the crude minor product (0.154 g). Recrystallisation of this material six times from toluene - light petroleum (bp 100-120°) gave pure dimethyl 4,5,6,7,8,9-hexafluoronaphtho[2,3-b]thiophen-2,3-dicarboxylate (7) (0.030 g) mp 178.6-180.5°C (Found: C, 47.40; H, 1.45%; $M^+$, 408. $C_{16}H_6F_6O_4S$ requires C, 47.07; H, 1.48%; M, 408); $\delta_F(CDCl_3)$ 121.8 (overlapping cm, $J_{4\text{-}F,5\text{-}F}$ and $J_{8\text{-}F,9\text{-}F}$, unassigned 58 and 64 Hz, for unassigned 4-F and 9-F), 144.9 (dt, $J_{peri}$ 64 Hz, unassigned), 146.4 (dt, $J_{peri}$ 58 Hz, unassigned), 153.3 (t) and 155.5 (t) in the ratio 2:1:1:1:1 respectively; $\delta_H(CDCl_3)$ 3.99 (S, $CH_3$) and 4.09 (S, $CH_3$).

4,5,6,7,8,9-Hexafluoronaphtho[2,1-b]thiophen (8). A mixture of the diesters (6) and (7) (7.05 g) was boiled with sulphuric acid (100 ml, 50% v/v) for 18 h, and the product extracted first with ethyl acetate then with ether. The extracts were dried ($MgSO_4$), the solvents evaporated and the crude product (4.38 g), copper powder (3.6 g) and quinoline (20 ml) were heated under reflux for 1 h. The solution was acidified (2 M $H_2SO_4$), extracted with ether, and the extracts dried ($MgSO_4$) and evaporated to give the crude product (3.58 g). Flash chromatography of this material on silica (6" x 2") using chloroform as eluant followed by re-chromatography on silica using light petroleum (b.p. 60-80°C) gave pure 4,5,6,7,8,9-hexafluoronaphtho[2,1-b]thiophen (8) (2.72 g, 54%) mp 114.5-115°C [from light petroleum (bp 60-80°C)] (Found: C, 49.16; H, 0.56%; $M^+$, 292. $C_{12}H_2F_6S$ requires C, 49.32, H, 0.69%; M, 292); $\delta_F(CDCl_3)$ 139.9 (nd), 142.4 (t), 146.0 (dm,

$J_{5\text{-}F,6\text{-}F}$ 63 Hz, 6-F), 151.8 (dd, $J_{5\text{-}F,6\text{-}F}$ 63 Hz, 5-F), 157.2/157.5 (overlapping m); $\delta_H(CDCl_3)$ 7.70 and 8.07 (unassigned 2-H, 3-H).

Reaction of 1,3,4,5,6,7,8-heptafluoro-2-naphthyl methyl sulphide (12) with sodium methoxide in methanol. The sulphide (12) (0.4046 g; 1.349 mmol) was heated under reflux with sodium methoxide (1.348 mmol) in methanol (15 ml) for 2 h. The mixture was acidified (2 M $H_2SO_4$), extracted with ether and the extracts dried ($MgSO_4$). The solvent was evaporated and the residue (0.4083 g) examined in $CDCl_3$ by $^{19}F$ nmr showed the presence of unreacted starting materials (12) (4%), the major product (13) (88%) and an unidentified material 8%. Recrystallisation of the product from a larger scale reaction from light petroleum (bp 100-120°C) gave the major reaction product 2-methoxy-6-thiomethoxy-1,3,4,5,7,8-hexafluoronaphthalene (13) mp 103.5-105°C (Found: C, 46.28; H, 1.90%; $M^+$, 312. $C_{12}H_6F_6OS$ requires C, 46.16; H, 1.94%; M, 312).

Desulphurisation of (13) (0.826 g) with Raney nickel (25 g) in ethanol (30 ml) under reflux for 6 h gave 2-methoxy-1,3,4,5,7,8-hexafluoronaphthalene (14) mp 52.0-52.5°C which was identical with the material obtained from 1,3,4,5,6,7,8-heptafluoronaphthalene and sodium methoxide in methanol [10].

ACKNOWLEDGEMENTS

The author wishes to thank Professor R.D. Chambers and Dr. D.L.H. Williams for their helpful comments during the course of this work.

REFERENCES

1 Part 25. Gerald M. Brooke and Raymond S. Matthews, J. Fluorine Chem., 40 (1988) 109.

2 G.M. Brooke and Md. Abul Quasem, J. Chem. Soc., (C), (1967) 865.

3 G.M. Brooke and Md. Abul Quasem, J. Chem. Soc. Perkin Trans. I, (1973) 429.

4 R.D. Chambers, M.J. Seabury, D.L.H. Williams and N. Hughes, J. Chem. Soc., Perkin Trans. I, (1988) 251.

5 This compound has been prepared before, but no data has been published, P. Sartori, private communication.

6 G.M. Brooke and J.R. Cooperwaite, J. Chem. Soc., Perkin Trans. 1, (1985) 2643.

7 G.M. Brooke and G. Plews, J. Fluorine Chem., 34 (1986) 117.

8 R.D. Chambers, D. Close and D.L.H. Williams, J. Chem. Soc., Perkin Trans. II, (1980), 778.

9 J. Miller, 'Aromatic Nucleophilic Substitution', Monograph No. 8, Eds. C. Eaborn and N.B. Chapman, Elsevier, Amsterdam/London/New York, (1968) 88.

10 R. Bolton and J.P.B. Sandall, J. Chem. Soc., Perkin Trans. 2, (1978) 746, and references therein.

11 R.D. Chambers, M.J. Seabury, D.L.H. Williams and N. Hughes, J. Chem. Soc., Perkin Trans. I, (1988) 255.