Formation of 1,1,3,3-tetrafluoro-1,3-dihydroisobenzofurans in reactions of phthalic acids with sulphur tetrafluoride. Evaluation of the steric and electronic effects of the substituents*

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(Received October 20, 1992; accepted December 2, 1992)

Abstract

4,5-Dinitrophthalic acid and 3,6-dimethylphthalic anhydride have been reacted with sulphur tetrafluoride to give mixtures of the corresponding bis(trifluoromethyl)benzenes and 1,1,3,3-tetrafluoro-1,3-dihydroisobenzofurans in a 5:1 and 1:3.6 ratio, respectively. These and earlier results on the reactions of sulphur tetrafluoride with substituted and unsubstituted phthalic and pyromellitic acids are compared and structural factors in the acids influencing the competitive formation of cyclic and non-cyclic products discussed. The stability of 1,1,3,3-tetrafluoro-1,3-dihydroisobenzofurans against cleavage by anhydrous hydrogen fluoride has also been investigated.

Introduction

In the early 1970s, Yagupolskii and co-workers found that sterically crowded benzenepolycarboxylic acids, e.g. 1,2,3,4-benzenetetracarboxylic [1], benzenepentacarboxylic [2] and mellitic [2, 3], react with sulphur tetrafluoride to give, instead of the respective poly(trifluoromethyl)benzenes, cyclic tetrafluoroethers with the same structure as 1,3-dihydroisobenzofurans (phthalans). Also, the phthalans were exclusive or main products of the fluorination of 3,6-bis(trifluoromethyl)phthalic acid [1, 3] and tetrachlorophthalic acid or its anhydride [4]. Treatment of dinitro-, dibromo- and dichloro-pyromellitic acids with sulphur tetrafluoride resulted in high yields of octafluorobenzodifurans [3, 5, 6]. This was in contrast to the fluorination of unsubstituted phthalic and pyromellitic acids which gave exclusively the corresponding bis- and tetrakis-(trifluoromethyl)benzenes [7] and suggested that the formation of cyclic tetrafluoroethers from benzenepolycarboxylic acids during the course of their reactions with sulphur tetrafluoride is forced by steric crowding due to bulky *ortho* substituents or the accumulation of carboxylic groups.

However, it has been found recently in this laboratory that, in contrast to an early report [7], the reaction of unsubstituted pyromellitic acid or its dianhydride with sulphur tetrafluoride gives, in addition to the expected tetrakis(trifluoromethyl)benzene, an 8–12% yield of the cyclic product, 5,6-bis(trifluoromethyl)-1,1,3,3-tetrafluoro-1,3-dihydroisobenzofuran [8]. Furthermore, it has also been found that considerable amounts of cyclic tetrafluoroethers are formed from 4,5-bis(trifluoromethyl)phthalic [8], tetrafluorophthalic and difluoropyromellitic acids [9], despite the absence of bulky *ortho* substituents in these acids. Hence, we came to the conclusion that in reactions of benzenepolycarboxylic acids with sulphur tetrafluoride, in addition to steric factors, an electron-withdrawing effect of the benzene ring substituents contributes significantly to the formation of cyclic tetrafluoroethers.

To evaluate the importance of both steric and electronic effects in phthalic acids on the formation of cyclic products, the reactions of sulphur tetrafluoride with 4,5-dinitrophthalic acid (**1**) and 3,6-dimethylphthalic anhydride (**4**) have been undertaken. The present and the earlier results have been summarised and discussed.

Results and discussion

Neither 4,5-dinitro or 3,6-dimethylphthalic acids are commercially available and are difficult to prepare; hence, the reactions were conducted on a small scale. 3,6-Dimethylphthalic anhydride was used instead of the acid because purification of the latter by sublimation resulted in dehydration.

*This paper formed part of the work presented at the *10th Eur. Symp. Fluorine Chem.*, Padova (Italy), Sept. 1992 [see *J. Fluorine Chem.*, *58* (1992) 145].

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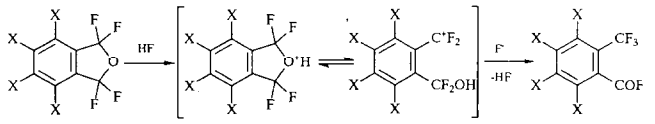


X	Reaction conditions		Yield (%)
	Temp. (°C)	Time (h)	
H	95	3	100
F	300	10	50
Cl	300	10	<5

Scheme 4.

under these same conditions remained virtually unaffected.

The stabilising effect of electron-withdrawing substituents on the phthalan ring can be attributed to the diminished basicity of the oxygen atom and, therefore, to the reduced susceptibility towards acidolysis. The high stability of *ortho*-substituted phthalans to protolytic ring opening may be interpreted in terms of the proximity of two CF_2 groups in the protonated compound; steric crowding pushes these groups together thus favouring the cyclic form.

Experimental

^1H, ^{19}F and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Varian 200 MHz spectrometer; chemical shifts are quoted in ppm from internal TMS for protons and carbon nuclei (positive downfield) and from internal $CFCl_3$ for fluorine nuclei (positive upfield). The IR spectra were measured with a Beckmann Acculab instrument. GLC analyses were performed with a Shimadzu GC-14A chromatograph using a 3.5 m×2 mm column packed with 5% silicone oil SE-52 on Chromosorb G. For preparative GLC work, a GCHF-18.3 apparatus (Germany) equipped with a 4.0 m×10 mm column was used.

Starting materials

4,5-Dinitrophthalic acid (**1**) was prepared by oxidation of 4,5-dinitro-1,2-dimethylbenzene with nitric acid according to the literature procedure [11].

3,6-Dimethylphthalic anhydride (**4**) was obtained by stirring dimethyl 3,6-dimethylphthalate [12] (18.4 g, 83 mmol) and 20% aqueous potassium hydroxide (70 ml) vigorously at 80 °C for 2 h then overnight at ambient temperature. The alkaline solution was washed with ether (20 ml) and acidified with concentrated hydrochloric acid. A brown precipitate of crude 3,6-dimethylphthalic acid (9 g) was filtered off and dried under vacuum over P_4O_{10}. Sublimation at 100–130 °C/0.5 Torr gave 3,6-dimethylphthalic anhydride (**4**) as white crystals (6.8 g, yield 46%), m.p. 142 °C (uncorrected). Elemental analysis: Found: C, 68.1; H, 4.5%. $C_{10}H_8O_3$ requires: C, 68.2; H, 4.6%. ^1H NMR δ: 2.68 (s); 7.52 (3) ppm.

Reaction of 4,5-dinitrophthalic acid (1) with sulphur tetrafluoride

Acid **1** (0.45 g, 1.76 mmol) and liquid anhydrous hydrogen fluoride (1 ml) were placed in a 30 ml stainless-steel autoclave, the autoclave was immersed in an acetone/Dry Ice bath, evacuated and then sulphur tetrafluoride (*c.* 4 g, 37 mmol) was condensed into it. The charged autoclave was heated in a rocking muffle at 180 °C for 20 h. After completion of the reaction, the autoclave was allowed to cool to ambient temperature, the gases (SOF_2, SF_4, HF) expelled and the contents of the autoclave poured into ice water and neutralised with ammonia. A solid material was extracted with methylene chloride and the extract dried over $MgSO_4$. The crystalline solid obtained after evaporation of the solvent (0.18 g) showed no carbonyl absorption in its IR spectrum. Recrystallisation from n-hexane gave orange crystals (m.p. 100 °C) identified by ^1H, ^{19}F and ^{13}C NMR spectra as a 5:1 mixture of compounds **2** and **3**.

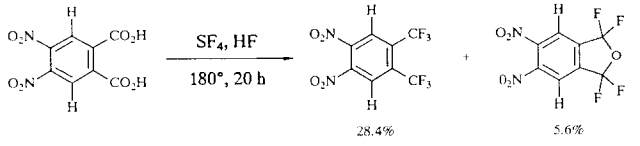
1,2-Bis(trifluoromethyl)-4,5-dinitrobenzene (**2**): ^1H NMR δ: 8.44 (s) ppm. ^{19}F NMR δ: 60.2 (s) ppm. ^{13}C NMR δ: 120.7 (q, CF_3, $^1J_{C-F}=276$ Hz); 125.8 (s, C-3, C-4); 133.8 (q, C-1, C-2, $^2J_{C-F}=38.5$ Hz); 144.0 (m, C-4, C-5) ppm.

5,6-Dinitro-1,1,3,3-tetrafluoro-1,3-dihydroisobenzofuran (**3**): ^1H NMR δ: 8.29 (s) ppm. ^{19}F NMR δ: 69.4 (s) ppm. ^{13}C NMR δ: 120.7 (s, C-4, C-7); 124.3 (t, CF_2, $^1J_{C-F}=261$ Hz); 133.8 (t, C-8, C-9, $^2J_{C-F}=32$ Hz); 144 (m, C-5, C-6) ppm.

Reaction of 3,6-dimethylphthalic anhydride with sulphur tetrafluoride

Anhydride **4** (1.76 g, 10 mmol), water (0.56 ml, 30 mmol) and sulphur tetrafluoride (11 g, 100 mmol) were placed in a 30 ml autoclave and heated at 150 °C for 20 h. The resulting mixture was then worked-up as described above for acid **1**. Distillation of the brown oil obtained after evaporation of the solvent gave a colourless liquid (0.71 g, b.p. 110 °C/35 Torr). GLC analysis revealed two components and the IR spectrum showed a strong carbonyl absorption at 1830 cm^{-1}. Both components were isolated by preparative GLC and identified from their ^1H and ^{19}F NMR spectra as 3,6-dimethyl-2-trifluoromethylbenzoyl fluoride (**5**) (the minor component) and 3,6-dimethyl-1,1,3,3-tetrafluoro-1,3-dihydroisobenzofuran (**6**) (the major component). Integrated NMR spectra of the mixture of products showed the ratio of **5** to **6** to be 1:3.6.

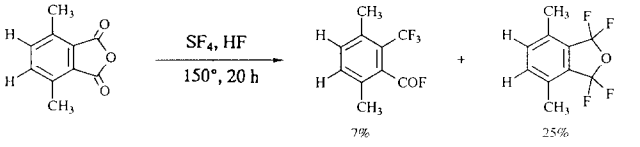
The reactivity of 4,5-dinitrophthalic acid (**1**) towards sulphur tetrafluoride is relatively low (and comparable to that of tetrafluorophthalic acid [9]), such that high temperature and an excess of anhydrous hydrogen fluoride were necessary for the fluorination to proceed. Reaction at 180 °C gave an orange crystalline product which was purified by recrystallisation from n-hexane. This product was found via ^{19}F and ^{13}C NMR spectroscopy to be a mixture of 1,2-bis(trifluoromethyl)-4,5-dinitrobenzene (**2**) and 5,6-dinitro-1,1,3,3-tetrafluoro-1,3-dihydroisobenzofuran (**3**). The integrated signals of the CF_3 and CF_2 groups in the ^{19}F NMR spectrum allowed determination of the ratio of the compounds **2** and **3** as 5:1 (overall yield, 34%). This ratio, as expected by considering the strong electron-withdrawing power of the nitro groups, is more favourable towards the cyclic product than in the reactions with 4,5-bis(trifluoromethyl)phthalic [8] and tetrafluorophthalic acids [9].



1 **2** **3**

Scheme 1.

3,6-Dimethylphthalic anhydride (**4**) was chosen as a model compound to examine the purely steric effect of *ortho* substituents in phthalic acids on the formation of tetrafluorophthalans in reactions with sulphur tetrafluoride. The bulk of the methyl group is similar to that of a bromine atom but it does not exert any electron-withdrawing properties. The reaction of 3,6-dimethylphthalic anhydride (**4**) with sulphur tetrafluoride and hydrogen fluoride (generated *in situ* by addition of water) at 100 °C resulted in only 10% conversion, but at 150 °C a 32% yield of fluorinated product was obtained together with a brown tar. The product, isolated as a colourless liquid, was shown via the integrated ^1H and ^{19}F NMR spectra to be a 1:3.6 mixture of 3,6-dimethyl-2-trifluoromethylbenzoyl fluoride (**5**) and 3,6-dimethyl-1,1,3,3-tetrafluoro-1,3-dihydroisobenzofuran (**6**). The predominant formation of the cyclic ether **6** unequivocally demonstrates the effect of steric crowding in phthalic acids on the formation of cyclic tetrafluoroethers in reactions with sulphur tetrafluoride.



4 **5** **6**

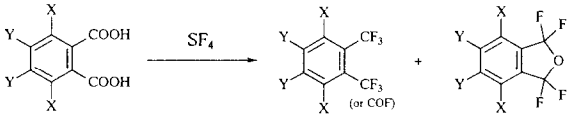
Scheme 2.

The effect of substituents in the phthalic acids on the ratio of cyclic and non-cyclic products formed in reactions with sulphur tetrafluoride are summarised below (Scheme 3).

The ratio of cyclic to non-cyclic products evidently increases with an increase in the electron-withdrawing power of the substituents, even if they are at positions 4 and 5 from which steric influence has to be excluded. Nevertheless, the steric effect of the *ortho* substituents, as evidenced by the reaction of 3,6-dimethylphthalic anhydride, is much more effective than the mesomeric or inductive effects of the electronegative substituents. A particularly high ratio of the cyclic tetrafluorophthalan to the trifluoromethyl derivative (95:5) in the reaction with tetrachlorophthalic acid or its anhydride is due both to the electronic effect of the four chlorine atoms and to steric crowding created by two chlorine atoms in positions *ortho* to the carbonyl groups.

The final conclusion is that in reactions of phthalic acids, and generally of benzenepolycarboxylic acids, with sulphur tetrafluoride, the ratio of cyclic to non-cyclic products is affected both by steric and electronic factors but steric crowding is the dominating factor. In practice, benzenepolycarboxylic acids which preferentially exist as anhydrides react with sulphur tetrafluoride to give predominantly cyclic tetrafluoroethers, rather than trifluoromethyl derivatives.

The ratio of cyclic tetrafluoroethers to trifluoromethyl derivatives follows the stability order of the former against protolytic cleavage under highly acidic conditions in the reactions of benzenecarboxylic acids with sulphur tetrafluoride. It has been demonstrated that unsubstituted 1,1,3,3-tetrafluorophthalan readily cleaves when treated with anhydrous hydrogen fluoride at temperature below 100 °C, and hence it has no chance to survive the conditions which are required for the reaction of phthalic acid with sulphur tetrafluoride [10]. In contrast, heating octafluorophthalan with hydrogen fluoride at 300 °C for 10 h resulted in only 50% cleavage, but 4,5,6,7-tetrachloro-1,1,3,3-tetrafluorophthalan



Y	X	Product ratio	
H	H	100	0
CF_3	H	89	11
F	F	85	15
NO_2	H	82	18
H	CH_3	22	78
Cl	Cl	5	95

Scheme 3.

3,6-Dimethyl-2-trifluoromethylbenzoyl fluoride (**5**): Elemental analysis: Found: C, 54.5; H, 3.5; F, 34.2%. $C_{10}H_8F_4O$ requires: C, 54.6; H, 3.7; F, 34.5%. ^{1}H NMR δ: 2.39 (d, CH_3, $^5J_{H-F}=1.3$ Hz); 2.49 (q, CH_3, $^5J_{H-F}=2.3$ Hz); 7.34 (s, H_{arom}) ppm. ^{19}F NMR δ: −57.0 (m, COF); 57.9 (dq, CF_3, $^5J_{F-F}=5.7$ Hz, $^5J_{H-F}=2.3$ Hz) ppm.

3,6-Dimethyl-1,1,3,3-tetrafluoro-1,3-dihydroisobenzofuran (**6**): Elemental analysis as for compound **5**. ^{1}H NMR δ: 2.43 (s, CH_3); 7.33 (s, H_{arom}) ppm. ^{19}F NMR δ: 70.9 (s) ppm. ^{13}C NMR δ: 16.2 (s, CH_3); 126.8 (tt, CF_2, $^1H_{C-F}=258$ Hz, $^3J_{C-F}=3.3$ Hz); 130.6 (t, C-8, C-9, $^2J_{C-F}=30$ Hz); 131.7 (s, C-4, C-7); 134.6 (s, C-5, C-6) ppm.

Cleavage of octafluoro-1,3-dihydroisobenzofuran and 4,5,6,7-tetrachloro-1,1,3,3-tetrafluoro-1,3-dihydroisobenzofuran with anhydrous hydrogen fluoride

The isobenzofuran (2 g) and liquid anhydrous hydrogen fluoride (5 ml) were placed in a 30 ml autoclave and heated at 300 °C for 10 h. After completion of the reaction, the autoclave was allowed to cool to ambient temperature and the excess of hydrogen fluoride slowly distilled off by warming to 30–40 °C. The residue was diluted with methylene chloride, dry sodium fluoride (HF scavanger) was added and the solution left overnight. The products obtained after evaporation of the solvent were subjected to ^{19}F NMR investigation. A comparison of the spectra of the products with those previously reported for 3,4,5,6-tetrafluoro-2-trifluoromethylbenzoyl fluoride [9] and 3,4,5,6-tetrachloro-2-trifluoromethylbenzoyl fluoride [4] unequivocally identified these compounds in the reaction mixture. Ratios of unreacted isobenzofurans to the corresponding 2-trifluoromethylbenzoyl fluorides were determined by integration of the CF_2 and CF_3 group signals (1:1 and 95:5, respectively).

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