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Fluorocyclisation of 2,5-tetrahydrofurandicarboxylic and 2,3,4,5-tetrahydrofurantetracarboxylic acids with sulphur tetrafluoride leading to bicyclic and tricyclic fluoroethers

Yurii M. Pustovit [1], Wojciech Dmowski *, Valery Nazaretian [2]

Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, Poland

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Abstract

cis-2,5-Tetrahydrofurandicarboxylic acid (**1**) reacts with sulphur tetrafluoride to give comparable amounts of 2,5-bis(trifluoromethyl)tetrahydrofuran (**2**) and the bicyclic tetrafluoroether, 2,2,4,4-tetrafluoro-3,8-dioxa-bicyclo[3.2.1]octane (**3**). Cyclisation of *cis*-2,5-carboxylic groups leading to the tricyclic fluoroethers, *exo*-3,3,5,5,8,8,9,9-octafluoro-4,10-dioxatricyclo[5.2.1.$0^{1,7}$]decane (**6**) and *exo*-3,3,5,5,8,8,10,10-octafluoro-4,9,11-trioxatricyclo[5.3.1.$0^{1,7}$]undecane (**9**) was also found to be the main or equivalent course of the reactions of 3,4-tetrafluoroethano-*cis*-2,5-tetrahydrofurandicarboxylic acid (**4**) and *trans,cis,trans*-2,3,4,5-tetrahydrofurantetracarboxylic acid (**7**); the bis(trifluoromethyl) derivatives, *exo-cis*-2,4-bis(trifluoromethyl)-6,6,7,7-tetrafluoro-3-oxabicyclo[3.2.0]heptane (**5**) and *exo-cis*-2,4-bis(trifluoromethyl)-6,6,8,8-tetrafluoro-3,7-dioxabicyclo[3.3.0]heptane (**8**) are formed in lower or comparable amounts. © 1997 Elsevier Science S.A.

Keywords: 2,5-Tetrahydrofurandicarboxylic acids; 2,3,4,5-Tetrahydrofurantetracarboxylic acid; Fluorination; Sulphur tetrafluoride; Polyfluorobicyclic ethers; Polyfluorotricyclic ethers

1. Introduction

It has been well established that 1,2-dicarboxylic acids, aliphatic, cycloaliphatic and aromatic, react with sulphur tetrafluoride to form, besides trifluoromethylated products, considerable or predominant amounts of cyclic, five-membered tetrafluoroethers, derivatives of tetra- or di-hydrofuran [1–8]. In the aliphatic series, cyclisation of the neighbouring carboxylic groups is governed mainly by steric factors like mutual distance and spatial configuration; particularly high yields of cyclic ethers were obtained from cycloaliphatic 1,2-dicarboxylic acids in which the carboxylic groups were fixed in the *cis*-configuration [7,9]. Cyclisations of 1,3-dicarboxylic acids during their reactions with SF_4 leading to six-membered fluoroethers are somewhat rare; only five such cases having been reported so far. Amongst linear aliphatic dicarboxylic acids, glutaric and diglycolic acids yield 10–16% of 2,2,6,6-tetrafluorotetrahydropyran and 2,2,6,6-tetrafluoro-1,4-dioxane, respectively [9], and tricaballylic acid gives a mixture of five- and six-membered fluoroethers in a 4:1 ratio and total yield of 63% [9]. Cyclisation of 1,3-carboxylic groups in cycloaliphatic acids has been reported for cyclopentanetetracarboxylic acid [7] and for camphoric acid [10], but yields of the corresponding bicyclic tetrafluoroethers were low.

In the present paper we report the rather unusual behaviour of tetrahydrofurancarboxylic acids, whereby treatment with sulphur tetrafluoride causes cyclisation to occur via two carboxylic groups in *cis*-2,5-positions, giving fluorinated, six-membered, 1,4-dioxane rings. This 1,3-cyclisation was found to compete effectively with the conversion of carboxylic groups into trifluoromethyl groups.

2. Results and discussion

Unsubstituted *cis*-tetrahydrofurandicarboxylic acid (**1**), like 2-tetrahydrofurancarboxylic acid [11], was found to be rather unstable under the conditions required for its reaction

* Corresponding author. E-mail: dmowski@ichf.edu.pl. Fax: +48 22 632 6681.

[1] Permanent address: The Ukrainian Academy of Sciences, Institute of Organic Chemistry, Kyiv 252094, Ukraine.

[2] Permanent address: The Ukrainian Academy of Sciences, Institute of Organic Chemistry, Kyiv 252094, Ukraine.

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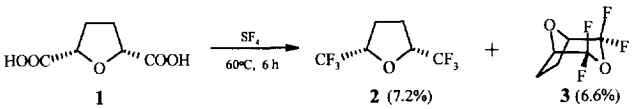
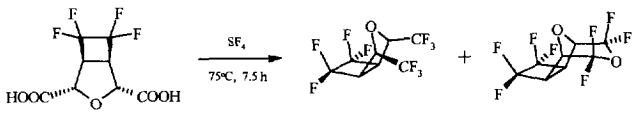
with sulphur tetrafluoride. Intense charring occurred, but nevertheless, a 1.2:1 (GLC estimate) mixture of two products, bis(trifluoromethyl) derivative **2** and bicyclic tetrafluoroether **3**, was isolated in 14% yield.



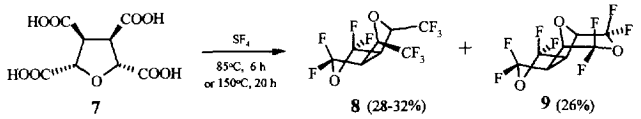
1 **2** (7.2%) **3** (6.6%)

The high proportion of the bicyclic compound **3** was rather unexpected and prompted us to investigate the reactions of SF_4 with two available derivatives of **1**. The tetrafluorinated bicyclic acid **4** was stable enough to react with SF_4 at 70–75 °C without considerable charring and yielded an 88.5% yield of an ca. 1:1.35 mixture of bis(trifluoromethyl) derivative **5** and tricyclic ether **6**.



4 **5** (36%) **6** (52%)

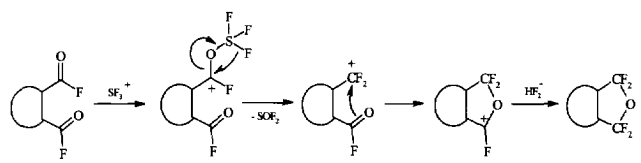
Treatment of *trans,cis,trans*-tetrahydrofurantetracarboxylic acid (**7**) with SF_4 at 85 °C or 150 °C gave 53–57% total yields of an ca. 1.4:1 mixture of bicyclic and tricyclic ethers **8** and **9**. In this particular case, as expected from the close proximity, vicinal 3,4-carboxylic groups showed a higher tendency to cyclise than the 2,5-carboxylic groups; no tetrakis(trifluoromethyl) derivative was detected in the product.



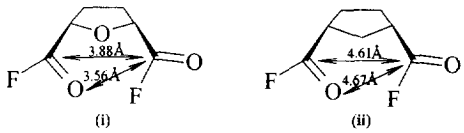
7 **8** (28-32%) **9** (26%)

Attention has been given to the reason why 2,5-carboxylic groups on a tetrahydrofuran ring cyclise more easily then 1,3-carboxylic groups on an carbocyclic ring, e.g. in 1,3-cyclopentanedicarboxylic acid which gives only low yield of the cyclisation product [7]. According to the general mechanism accepted for reactions of carboxylic acids with SF_4 [1,2,12], acyl fluorides (**i**) and (**ii**) should be primary intermediates on route to both trifluoromethyl derivatives and cyclic fluoroethers:

$$SF_4 + HF \rightleftharpoons SF_3^+ + HF_2^-$$



Application of semiempirical structure modeling for both (**i**) and (**ii**) (AM1, MOPAC 6.0 package), suggests that the carbonyl groups in 2,5-tetrahydrofuranoyl difluoride (**i**) are 0.73 Å closer each to other than the carbonyl groups in *cis*-1,3-cyclopentanoyl difluoride (**ii**) (measured between carboxylic carbon atoms), which is not surprising as the ring C–O bond is shorter than the corresponding C–C bond (1.428 Å [13] and 1.539 Å [14], respectively). Moreover, the minimum distance between the oxygen atom of one COF group and the carbon atom of the other COF group, in a conformation enabling the ring closure, is 1.11 Å shorter in (**i**) as compared with (**ii**). These findings give satisfactory explanation to the observed difference between a ring forming ability in reaction of *cis*-2,5-tetrahydrofurandicarboxylic acids and *cis*-1,3-cyclopentanedicarboxylic acids with sulphur tetrafluoride; ratios of cyclic products to bis (trifluoromethyl) derivatives are between 1:1 and 1.4:1 for the former and ca. 1:5 for the latter.



Configurations of compounds **2**, **3**, **5**, **6**, **8** and **9** follow from the configurations of the starting acids **1**, **4** and **7**. The presence of one symmetry plane in these compounds is reflected by their NMR spectra; in all cases the number of signals for H,F and C atoms and CF_3 groups is reduced by half in respect to the number of such atoms and groups existing in the molecules. The presence of CF_3 and CF_2 groups is clearly shown by the multiplicities of the respective ^{13}C-NMR signals. The ^{19}F-NMR signals of the CF_2 groups appear as AB spin systems with large geminal coupling constants, thus showing high magnetic non-equivalence of axial end equatorial fluorine atoms. All new compounds gave mass spectra consistent with the structures assigned, and for compounds **3**, **6** and **9** exact masses of molecular ions were determined by high-resolution mass spectrometry.

3. Experimental details

Melting points were determined in capillaries and are uncorrected. ^1H-, ^{19}F- and ^{13}C-NMR spectra were recorded in $CDCl_3$ with a Varian Gemini 200 spectrometer at 200, 188 and 50 MHz, respectively. Chemical shifts are quoted in ppm from internal tetramethylsilane (TMS) for protons and carbon nuclei (positive downfield) and from internal $CFCl_3$ for fluorine nuclei (positive upfield). Crude mixture of products were analysed with a Shimadzu GC-14A Chromatograph using a 5 m × 2 mm column packed with 5% silicone oil SE-52 on Chromosorb G. GC–MS analyses were performed with a Hewlett–Packard 5890 apparatus (70eV) using a 30 m capillary column coated with HP5 oil. High-resolution mass spectra were obtained with an AMD-604 spectrometer, and IR spectra with a Perkin–Elmer 1640 instrument.

3.1. Starting materials

cis-2,5-Tetrahydrofurandicarboxylic acid (**1**) was prepared from *meso*-2,5-dibromoadipic acid according to the literature procedure [15] and purified from the DL isomer by conversion into its cyclic anhydride followed by hydrolysis [16]. 3,4-Tetrafluoroethano-*cis*-2,5-tetrahydrofurandicar-

boxylic acid (**4**) was prepared by cycloaddition of furan to 3,3,4,4-tetrafluorocyclobutene, followed by oxidation of the adduct [17]. *cis,trans,cis*-2,3,4,5-Tetrahydrofurantetracarboxylic acid (**7**) was a 'pure grade' commercial product (Fluka AG) the single isomer status of which was supported by its melting point (208 °C [18]) and ^{1}H-NMR parameters.

3.2. Reactions of acids *1*, *4*, and *7* with sulphur tetrafluoride: general procedure

The acid was placed in a 30 ml stainless steel autoclave; the autoclave was immersed in a dry ice–acetone bath, evacuated, and then sulphur tetrafluoride was condensed into it. The charged autoclave was heated in a water bath at 65–85 °C for 6 h or, if at higher temperature, in a rocking electric furnace. After the autoclave had cooled to ambient temperature, gaseous products (SOF_2, HF, unreacted SF_4) were released and the involatile product was poured into 10% aqueous solution of KOH (ca. 50 ml) and the mixture was vigorously agitated at ambient temperature for 5 h. The remaining organic material was extracted with CH_2Cl_2, the extract was dried over $MgSO_4$ and the solvent was removed under atmospheric pressure to give an oily mixture of products which was subjected to GLC, GC–MS and NMR investigations.

3.2.1. Reaction of cis-2,5-tetrahydrofurandicarboxylic acid (*1*) with SF_4

Acid **1** (2.4 g, 0.015 mol) and SF_4 (14 g, 0.13 mol) were heated together at 65 °C for 6 h. The resultant tar-like material (3 g) was treated with KOH as described above, then volatile products were steam distilled to give a colourless oil (0.44 g, total yield ca. 14%) which was found by GLC to consist of compounds **2** (51%) and **3** (42%) and unidentified impurities.

cis-2,5-Bis(trifluoromethyl)tetrahydrofuran (**2**): ^{1}H NMR δ: 2.12–2.23 (complex multinuclear system, 2×CH_2); 4.39 (m, 2×CH) ppm. ^{19}F NMR δ: 78.9 (d, $^3J_{FH}$=7.1 Hz, 2×CF_3) ppm. ^{13}C NMR δ: 25.6 (s, C-3, C-4); 78.1 (q, $^2J_{CF}$=34 Hz, C-2, C-5); 124.1 (q, $^1J_{CF}$=280 Hz, 2×CF_3) ppm. GC–MS *m/z* (relative intensity, ion): 207 [<1, (M–H)$^+$]; 189 [5, (M–F)$^+$]; 139 [95 (M–CF_3)$^+$]; 91 (100, $C_4H_5F_2^+$); 69 (80, CF_3^+).

2,2,4,4-Tetrafluoro-3,8-dioxabicyclo[3.2.1]octane (**3**): ^{1}H NMR δ: 2.12–2.23 (complex multinuclear system, 2×CH_2); 4.51 (m, 2×CH) ppm. ^{19}F NMR δ: 74.6 and 84.6 (AB system, J_{AB}=155 Hz, 2×CF_2) ppm. ^{13}C NMR δ: 23.2 (d, $^3J_{CF}$=5.4 Hz, C-6, C-7); 74.7 (dd, $^2J_{CF}$=33.6 and 28.8 Hz, C-1, C-5); 120.4 (ddd, $^1J_{CF}$=277 and 258 Hz, $^3J_{CF}$=5.3 Hz, 2×CF_2) ppm. GC–MS *m/z* (ion, relative intensity): 186 (30, M$^+$); 139 [10, (M–COF)$^+$]; 99 [20, (M–COF–2HF)$^+$]; 91 (38, $C_4H_5F_2^+$); 77 (70, $C_3H_3F_2^+$); 55 (100, $C_3H_3O^+$); 51 (50, CHF_2^+). HRMS: found 186.03063. $C_6H_6F_4O_2$ requires: 186.03039.

3.2.2. Reaction of 3,4-tetrafluoroethano-cis-2,5-tetrahydrofurandicarboxylic acid (*4*) with SF_4

Acid **4** (2.58 g, 0.01 mol) and SF_4 (14 g, 0.13 mol) were heated together at 60–75 °C for 7.5 h. The resultant material was treated as described above (general procedure) to give an oil (2.8 g, total yield ca. 88%) which, according to GLC analysis, consisted of compounds **5** (39.4%) and **6** (53.3%). The oil was dissolved in diethyl ether, small amount of elemental sulphur (0.2 g) was decanted and the solution was left overnight in an refrigerator at 0–5 °C after which time compound **6** crystallised out. The crystals were separated by filtration, washed with small amount of cold ether and the residual solvent was removed under vacuum, affording chromatographically pure compound **6**.

exo-cis-2,4-Bis(trifluoromethyl)-6,6,7,7-tetrafluoro-3-oxabicyclo[3.2.0]heptane (**5**): ^{1}H NMR δ: 3.66 (m, 2×CH); 4.77 (m, 2×CH) ppm. ^{19}F NMR δ: 78.3 (sharp m, 2×CF_3); 114.3 and 119.6 (AB system, J_{AB}=215 Hz, 2×CF_2) ppm. ^{13}C NMR δ: 47.9 (m, C-1, C-5); 78.3 (q, $^2J_{CF}$=36 Hz, C-2, C-4); 115.9 (tt, $^1J_{CF}$=294 Hz, $^2J_{CF}$=28 Hz, C-6, C-7); 122.8 (q, $^1J_{CF}$=280.5 Hz, 2×CF_3). GC–MS *m/z* (ion, relative intensity): 287 [5, (M–F)$^+$]; 237 [80, (M–CF_3)$^+$]; 187 [30, (M–CF_3–CF_2)$^+$]; 145 (100, $C_4H_2F_5^+$); 137 [90, (M–CF_3–C_2F_4)$^-$]; 95 (60, $C_3H_2F_3^+$); 69 (85, CF_3^+).

exo-3,3,5,5,8,8,9,9-Octafluoro-4,10-dioxatricyclo-[5.2.1.0^{1,7}]decane (**6**): m.p. 86 °C. ^{1}H NMR δ: 3.62 (m, 2×CH); 4.87 (m, 2×CH) ppm. ^{19}F NMR δ: 75.0 and 83.6 (AB system, J_{AB}=157.5 Hz, 2×CF_2O); 113.8 and 123.5 (AB system, J_{AB}=220 Hz, 2×CF_2) ppm. ^{13}C NMR δ: 45.4 (m, C-1, C-7); 74.0 (t, $^2J_{CF}$=33.3 Hz, C-2, C-6); 116.4 (ddd, $^1J_{CF}$=293.2 and 299.6 Hz, $^2J_{CF}$=27 Hz, C-8, C-9); 118.5 (ddd, $^1J_{CF}$=280 and 260 Hz, C-3, C-5) ppm. GC–MS *m/z* (ion, relative intensity): 284 (1, M$^+$); 237 [3, (M–COF)$^+$]; 126 (100, $C_4H_2F_4^+$); 101 (10, $C_2HF_4^+$); 75 (12, $C_3HF_2^+$). HRMS: found 284.00835. $C_8H_4F_8O_2$ requires: 284.00833.

3.2.3. Reaction of cis,trans,cis-2,3,4,5-tetrahydrofurantetracarboxylic acid (*7*) with SF_4

Acid **7** (5.0 g, 0.02 mol) and SF_4 (22 g, 0.2 mol) were reacted at 85 °C for 6 h. The resultant material was treated as described above (general procedure) to give an oil (4.2 g, total yield 57%) which according to GLC analysis consisted of compounds **8** (49%) and **9** (36%) and a number of unidentified impurities. The oil was left in a refrigerator (ca. 4 °C) overnight after which time compound **9** crystallised out. The crystals were separated by filtration, washed with small amount of cold n-hexane and dried under vacuum. A similar fluorination at 150 °C for 20 h gave a mixture (4.5 g, total yield 61%) containg 48% of **8** and 34% of **9**.

exo-cis-2,4-Bis(trifluoromethyl)-6,6,8,8-tetrafluoro-3,7-dioxabicyclo[3.3.0]octane (**8**): ^{1}H NMR δ: 3.77 (m, 2×CH); 4.78 (m, 2×CH) ppm. ^{19}F NMR δ: 64.2 and 75.8

(AB system, $J_{AB}=145$ Hz, $2\times CF_2$); 78.7 (sharp m, $2\times CF_3$) ppm. ^{13}C NMR δ: 50.9 (dd, $^2J_{CF}=33$ and 24 Hz, C-1, C-5); 78.6 (qt, $^2J_{CF}=35$ Hz, $^3J_{CF}=4$ Hz, C-2, C-4); 122.4 (q, $^1J_{CF}=281$ Hz, $2\times CF_3$); 126.4 (tdd, $^1J_{CF}=266$ Hz, $^3J_{CF}=5.6$ and 2.5 Hz, C-6, C-8) ppm. GC–MS m/z (ion, relative intensity):322 (10, M^+); 275 [50, $(M-COF)^+$]; 253 [15, $(M-CF_3)^+$]; 236 [20, $(M-COF_2-HF)^+$]; 227 [30, $(M-CF_3CHCH)^+$]; 188 (50, $C_6H_2F_6^+$); 167 (99, $C_6H_3F_4O^+$); 139 (100, $C_5H_3F_4^+$); 95 (50, $C_3H_2F_3^+$); 69 (60, CF_3^+).

exo-3,3,5,5,8,8,10,10-Octafluoro-4,9,11-trioxatricyclo-[5.3.1.$0^{1,7}$]undecane (**9**): m.p. 58 °C. ^1H NMR δ: 3.77 (m, $2\times CH$); 4.95 (m, $2\times CH$) ppm. ^{19}F NMR δ: 59.0 and 76.9 (AB system, $J_{AB}=144$ Hz, $2\times CF_2$); 75.9 and 84.4 (AB system, $J_{AB}=158$ Hz, $2\times CF_2$) ppm. ^{13}C NMR δ: 49.5 (ddd, $^2J_{CF}=35$ and 24 Hz, $^3J_{CF}=6$ Hz, C-1, C-7); 75.7 (tdd, $^2J_{CF}=33.3$ Hz $^3J_{CF}=7.5$ and 4.8 Hz, C-2, C-6); 117.9 (ddd, $^1J_{CF}=280$ and 260 Hz, $^3J_{CF}=6$ Hz, C-3, C-5); 126.8 (td, $^1J_{CF}=265$ Hz, $^3J_{CF}=6$ Hz, C-8, C-10) ppm. GC–MS m/z (ion, relative intensity): 300 (2, M^+); 281 [18, $(M-F)^+$]; 253 [18, $(M-COF)^+$]; 234 [20, $(M-COF_2)^+$]; 178 [30, $(M-2COF-CO)^+$]; 159 [75, $(M-3COF)^+$]; 139 [70, $(M-3COF-HF)^+$]; 95 (30, $C_3H_2F_3^+$); 64 (100, $C_2H_2F_2^+$). HRMS: found 300.00327. $C_8H_4F_8O_3$ requires: 300.00307.

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