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Reaction of cyclopropane carboxylic acid derivatives with sulphur tetrafluoride — an example of a diastereoselective ring opening

Z. Hell[a,*], Z. Finta[a], W. Dmowski[b], F. Faigl[a], Yu.M. Pustovit[b,1], L. Tőke[a], V. Harmat[c]

[a]*Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest, Hungary*
[b]*Institute of Organic Chemistry, Polish Academy of Sciences, PL 01-224 Warsaw, Poland*
[c]*Department of Theoretical Chemistry, L. Eötvös University, H-1518 Budapest, Hungary*

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Abstract

Cyclopropane carboxylic acid derivatives can be converted into trifluoromethyl group-containing compounds using SF_4. In the case of a bicyclic cyclopropane carboxylic acid lactone, similar treatment with sulphur tetrafluoride resulted in the cyclopropane ring opening in a diastereoselective manner.

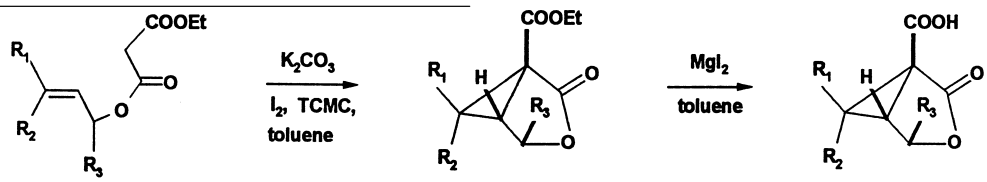
Keywords: Cyclopropane; Sulphur tetrafluoride; Ring opening

1. Introduction

Organic compounds containing trifluoromethyl group possess a great importance in pharmaceutical and agricultural chemistry since the trifluoromethyl group, due to its high electronegativity and lipophilicity, often induces significant changes in the physiological properties of biologically active molecules [1,2]. Cyclopropane derivatives are members of an important class of biologically active substances [3], and several methods for the synthesis of their fluoro [4] and trifluoromethyl [5] group containing analogues have been published.

Introduction of the trifluoromethyl group into an organic compounds may cause difficult problems because of the expensive starting materials and tedious procedures. The carboxylic acid derivatives are important synthons in organic syntheses, since the carboxylic group can be easily introduced into organic molecules and it can be transformed into other functional groups. An efficient method for the transformation of the carboxylic group into a trifluoromethyl group is treatment with SF_4. The method has been applied for the transformation of numerous aliphatic, aromatic and heterocyclic carboxylic acids into the appropriate trifluoromethyl compounds with satisfactory to good yield [6].

For the preparation of multisubstituted cyclopropane carboxylic acid derivatives from CH-acids, e.g. malonic acid esters and olefines, a new convenient phase transfer catalytic method was developed [7]. If the CH-acid moiety and the olefinic bond are in the same molecule in a proper position (e.g. as in the malonic acid substituted allylic esters of type **1**), an intramolecular reaction occurs yielding the bicyclic cyclopropane carboxylic acid lactones **2**. These lactones and their carboxylic acid derivatives **3** [8] can serve as good intermediates for the synthesis of biologically valuable cyclopropane derivatives.



1 **2** **3**

* Corresponding author. Tel.: +361-463-1414; fax: +361-463-3648.
E-mail address: hell@oct.bme.hu (Z. Hell)
[1] Present address: The Ukrainian Academy of Sciences, Institute of Organic Chemistry, Kyiv 252094, Ukraine.

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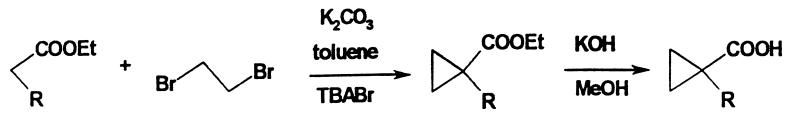
As the transformation of lactones **3** into trifluoromethyl group-containing derivatives can result in the formation of new valuable cyclopropane derivatives we examined the reaction of compounds **3** with SF_4.

2. Results and discussion

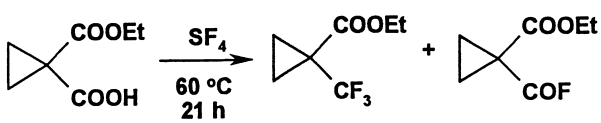
At first we examined reactivities of simple cyclopropane carboxylic acids (**5a**, **5b**) towards SF_4. The model compounds **5** were prepared from malonic acid derivatives and 1,2-dibromoethane using the known phase transfer catalytic method [9] followed by hydrolysis of esters **4** in methanolic KOH.



4a,b **5a,b**

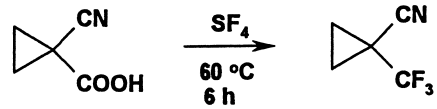
a R = COOEt
b R = CN

The reaction of **5a** with SF_4 in an autoclave at 60°C for 21 h resulted in the formation of two main products **6a** and **6b**. The structures of the products were determined by GC–MS and NMR analysis; the desired trifluoro derivative **6a** and the intermediate acid fluoride **6b** was formed in ca. 1.2:1 ratio.



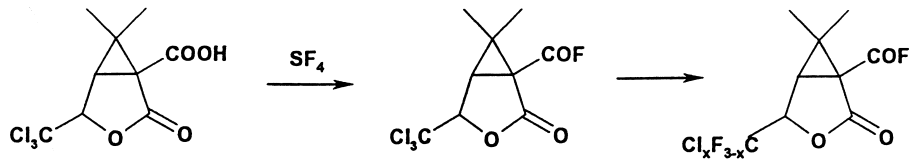
5a **6a** **6b**

The nitrile **5b** proved to be more reactive; after 6 h at 60°C the sole product detected was **7** (the intermediate acid fluoride was not observed). We isolated **7** with less than 40% yield because of its high volatility and decomposition.



5b **7**

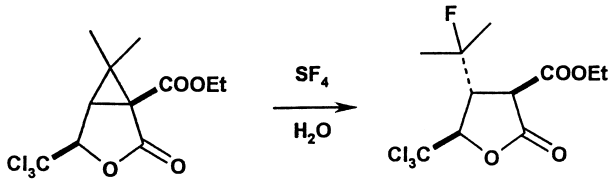
Relaying upon these results we attempted conversion of bicyclic acid **3a** into an appropriate trifluoromethyl derivative. Treatment of **3a** with SF_4 in dichloromethane at 60°C for 4 h provided acid fluoride **8a** as the sole product. Further treatment of this acid fluoride with SF_4 in dichloromethane at 80°C resulted in a preparatively unseparable mixture of products of (partial) halogen exchange **8b**, as found by GC–MS analysis. Similar results were obtained when **3a** was reacted with SF_4 in dichloromethane at 80°C for 6 h or without the solvent at 70°C for 21 h.



3a **8a** **8b**

In the light of the above mentioned results, it was a challenge to investigate the reactivity of **2a** towards sulphur tetrafluoride. The model compound does not contain a free carboxylic acid function but two types of ester groups. Since **2a** does not contain a free carboxylic group, one drop of water was added into the reaction mixture to generate HF from SF_4. Incubation of this mixture at 80°C for 6 h in an autoclave following by the usual workup resulted in consumption of the starting material and appearance of a new crystalline substance as the major product accompanied by resinous materials. The IR spectrum of the crude product showed the presence of unchanged ester and lactone carbonyl groups, and a new set of the signals appeared at 3.33, 3.70 and 5.00 ppm in the ^1H NMR spectra. ^{19}F NMR spectra showed a signal of a fluorine atom coupled to six hydrogens

(doublet of septets). Recrystallization of the product yielded the pure crystalline lactone **9a**. The ^{1}H and ^{19}F NMR spectra of this pure substance showed the same characteristic signals between H-4 and H-5 unambiguously confirming the *trans* relationship between the two bulky substituents at C-4 and C-5, consequently the ring opening occurred stereospecifically. On the basis of the above spectroscopic data, HRMS and LSIMS investigations, we proposed the structure **9a**.



2a **9a**

The relative stereochemistry of compound **9a** was also confirmed by X-ray crystallographical data (Fig. 1). In the crystal, the carbethoxy group and the 2-fluoroisopropyl group are in the *trans* position.

The main crystal building forces are the dipole–dipole interactions (Fig. 2). The lactone carbonyl group is aligned quasi antiparallel to the C7–O9 vector of its symmetry equivalent molecule while the $CF(CH_3)_2$ group forms a looser contact (transformation by the inversion centre (1, 0.5, 0), C2(1)...O9(2) 3.500 Å, O3(1)...C7(2) 3.221 Å, F13(1)...C10(2) 3.357 Å, C14(1)...O9(2) 4.131 Å). There are dipole–dipole interactions between the $CF(CH_3)_2$ groups related by inversion (inversion centre at (1, 0, 0), C15(1)...F13(2) 3.662 Å). The CCl_3 group is polarised by the O and F atoms of the neighbouring molecules in the crystal.

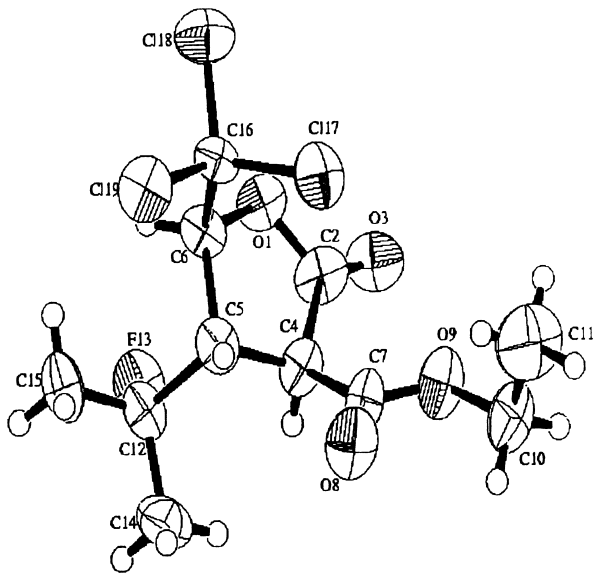


Fig. 1. ORTEP drawing of compound **9a**.

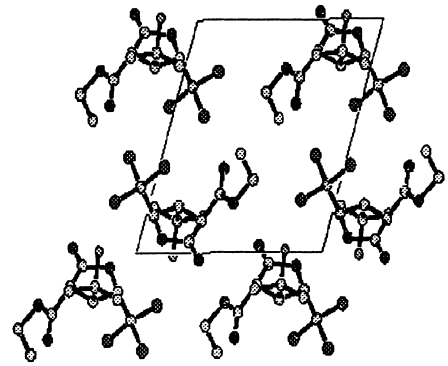


Fig. 2. Packing view of the crystal of **9a**.

3. Conclusions

Cyclopropane ring openings under acidic conditions are well known reactions, e.g. [10]. However, the reaction of the simple cyclopropane derivatives **5a,b** with SF_4 resulted in the formation of the desired trifluoromethylated derivatives without any detectable amount of ring-opened products. At the same time, the conversion of **3a** into the appropriate trifluoromethyl derivative was unsuccessful, the acid fluoride formation and the chlorine to fluorine exchange were the dominant reactions. It seems that in compound **2a**, the effect of the two electron withdrawing carbonyl groups on C(1) atom of the cyclopropane ring and the two electron donating methyl groups at position C(2) makes this compound susceptible to the cyclopropane ring opening. It should be emphasized that this reaction does not occur upon treatment with anhydrous HF in the absence of SF_4.

4. Experimental

Melting points were determined in capillaries and are uncorrected. IR spectra were recorded on Perkin–Elmer Spectrum 1600 and 2000 instruments. ^{1}H NMR spectra were recorded on Bruker AW-250 (250 MHz) or Varian Gemini 200 (200 MHz) spectrometers, chemical shifts are given on the δ scale using TMS as internal standard. ^{19}F NMR spectra were recorded on Varian Gemini 200 (188 MHz) spectrometer, chemical shifts are given on the δ scale using $CFCl_3$ as internal standard. GC–MS analyses were performed with a Hewlett-Packard 5890 instrument using a HP5 column and the following temperature program: 60°C for 4 min then warming with the rate of 20°C/min to 200°C.

Cyclopropanecarboxylic acid derivatives **4a**,**b** were prepared following the literature procedure [9]; **4b** was used without further purification.

4.1. Hydrolysis of esters *4a,b*

A solution of potassium hydroxide (0.56 g, 0.01 mol) in ethyl alcohol (5 ml) was added dropwise to a stirred solution

of **4** (0.01 mol) in ethyl alcohol (5 ml) at 25°C. The reaction mixture was stirred at 25°C for the reaction time indicated below, the solvent was evaporated, the residue was dissolved in water (10 ml), extracted with chloroform (10 ml) then the aqueous phase was acidified with conc. HCl, and extracted with chloroform (3×10 ml). The combined organic phases were dried over $MgSO_4$ and the solvent was removed in vacuo.

4a: reaction time: 6 h then standing overnight. Yellowish oil, yield: 1.13 g (71.6%). IR (neat) ν (cm^{-1}): 1758, 1639, ^1H NMR (250 MHz, $CDCl_3$): 1.21–1.34 (m, 3H), 1.77 (s, 4H), 4.24 (q, 2H), 10.8 (s, 1H).

4b: reaction time: 1 h, white solid. Yield: 0.9 g (64.7%), mp 125–127°C. IR (neat) ν (cm^{-1}): 2269, 1747; ^1H NMR (250 MHz, $CDCl_3$): 1.60 (s, 4H).

4.2. Reaction of cyclopropanecarboxylic acids (*4*) with SF_4

The acid **4** (1 mmol) were placed in a 30 ml capacity stainless steel autoclave. The autoclave was immersed in a dry ice-acetone bath (−78°C), evacuated to ca. 2 Torr then SF_4 (7 g, 65 mmol) was condensed into it. The charged autoclave was kept at 60°C for 21 h (**4a**) or 6 h (**4b**). After cooling down to ambient temperature, gaseous products (SOF_2, HF, excess of SF_4) were let off and the liquid reaction mixture was dissolved in dichloromethane (20 ml), washed with water (3×30 ml), dried over $MgSO_4$ and the solvent was removed on a rotary evaporator. The residue was dissolved in ether (10 ml), filtered (removal of elemental sulphur) and evaporated.

6a: colorless liquid. ^1H NMR (250 MHz, $CDCl_3$): 1.24–1.30 (m, 3H), 1.36 (d, 2H, J_{HF}=36 Hz), 1.72 (d, 2H, J_{HH}=14.4 Hz), 4.22 (m, 2H).

GC–MS *m/z* (rel. int, ion): 182 (3, M^+), 137 [100, $(M-C_2H_5O)^+$], 109 [28, $(M-COOC_2H_5)^+$], 69 (15, CF_3^+).

6b: GC–MS *m/z* (rel. int, ion): 115 [100, $(M-C_2H_5O)^+$], 113 [30, $(M-COF)^+$], 87 [7, $(M-COOC_2H_5)^+$], 47 (10, COF^+)

7a: colorless liquid, decomposes.

GC–MS: *m/z* (rel. int., ion): 135 (25, M^+), 116 [27, $(M-F)^+$], 109 [17, $(M-CN)^+$], 69 (60, $CF_3)^+$, 66 [100, $(M-CF_3)^+$].

4.3. Reaction of *3a* with SF_4

A solution of the lactone **3a** (0.57 g, 2 mmol) in dichloromethane (10 ml) was placed in a 30 ml capacity stainless steel autoclave then SF_4 (3.5 g, 32 mmol) was condensed into it. The charged autoclave was kept at 60°C for 4 h and a liquid reaction mixture was washed with water (3×30 ml), dried over $MgSO_4$ and the solvent was removed on a rotary evaporator. The residue was dissolved in ether (10 ml), filtered (removal of elemental sulphur) and evaporated to give compound **8a** as a yellowish semisolid unstable substance, yield: 0.34 g. IR (neat) ν (cm^{-1}): 1791.4 (C=O), 1828.5 (COF).

GC–MS data of derivatives **8b**: **8b**(x=1): *m/z* (rel. int., ion): 273 (35, M^+), **8b**(x=2): *m/z* (rel. int., ion): 289 (29, M^+)

4.4. Reaction of the lactone *2a* with SF_4

A solution of the lactone **2a** (316 mg, 1 mmol) in dichloromethane (10 ml), one drop of water (a source of HF) and SF_4 (7 g, 65 mmol) were reacted at 20°C for 16 h followed by 9 h at 70–75°C. A liquid reaction mixture was washed with water (3×30 ml), dried over $MgSO_4$ and the solvent was removed on a rotary evaporator. The residue was dissolved in ether (10 ml), filtered (removal of elemental sulphur) and evaporated. A semi-solid residue (300 mg) was dissolved in a minimal amount of ether and left overnight in a refrigerator for crystallization. Crystals were filtered off, washed with cold ether (2×1 ml) and dried in air to give a white crystalline product (110 mg, yield 30%). mp 122–124°C.

Analysis: found: Cl, 32.0; F, 5.8%. Calculated for $C_{11}H_{14}Cl_3FO_4$: Cl, 31.7; F, 5.7%.

^1H NMR (200 MHz, DMSO-d_6): 1.32 (t, $^3J_{HH}$=7.1 Hz, $\underline{CH_3}CH_2$); 1.46 (d, $^3J_{HF}$=21.0 Hz, CH_3); 1.59 (d, $^3J_{HF}$=21.0 Hz, CH); 3.33 (ddd, $^3J_{HF}$=23.0 Hz, $^3J_{HH}$=4.8 Hz and 2.7 Hz, 1H); 3.70 (d, $^3J_{HH}$=4.8 Hz, 1H); 4.3 (qd, $^3J_{HH}$=7.1 Hz, J=0.7 Hz, $CH_3\underline{CH_2}$); 5.0 (d, $^3J_{HH}$=2.7 Hz, 1H). ^{19}F NMR (188 MHz, DMSO-d_6): 142.2 (d sept, $^3J_{HF}$=23 and 21 Hz, 1F).

IR (KBr) ν (cm^{-1}): 1735.1 and 1798.4 (vs, C=O).

MS (EI, 70 eV) *m/e* (rel. int., ion): 289 [5, $(M-COOH)^+$], 273 [23 $(M-C(CH_3)_2F)^+$], 201 (20, $C_5H_4Cl_3O_2{}^+$l), 197 (53, $C_{10}H_{13}O_4{}^+$), 151 (100, $C_8H_7O_3{}^+$), 123 (12, $C_7H_7O_2{}^+$), 115 (10, $C_5H_7O_3{}^+$), 61 [25, $C(CH_3)_2F^+$],

HRMS: 306.96969 $(C_9H_{11}Cl_3FO_4)^+$; 286.96399 $(C_9H_{10}Cl_3O_4)^+$; 272.94964 $[M-C(CH_3)_2F]^+$

LSIMS: 341, 339, 337 $(M+H)^+$; 363, 359, 357 $(M+Na)^+$.

X-ray diffraction study: single crystals from **9a** were obtained by slow evaporation of the isopropyl alcoholic solution of the compound. Data were collected on a Rigaku AFC6S diffractometer (λ=1.5418 Å, T=293 K). The crystal data were as follows: $C_{11}H_{14}Cl_3FO_4$, M=335.57, crystal size 0.25mm×0.4mm×0.45 mm, space group: P-1, a=9.914(9) Å, b=10.330(8) Å, c=8.333(4) Å, α=113.64(4)°, β=95.23(8)°, γ=70.6(1)°, V=737(1) $Å^3$, D_{calc}=1.513 gcm^{-3}, Z=2, μ=5.819 mm^{-1}, N_{tot}=1433, N_{obs}=968 ($I>2\sigma(I)$), $2\theta_{max}$=125.00. Structure solution with direct methods was carried out with the teXsan package [11]. The refinement was carried out using the SHELXL-97 program [12] with full matrix least squares method on F^2. Rigid bond restraints were included for the atoms of the lactam group in the refinement. Hydrogen atoms were generated and their positions were refined by the riding model. Final R indices: R_1=0.0712, wR_2=0.1821 for $I>2\sigma(I)$, R_1=0.1205, wR_2=0.2458 for all data. Full data are deposited at the Cambridge Structural Database, Deposition No.: CCDC 139604.

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