Acid catalyzed cyclodimerization of 2,2-bis(trifluoro-methyl)-4-alkoxy-oxetanes and -thietanes. Synthesis of 2,2,6,6-tetrakis(trifluoromethyl)-4,8-dialkoxy-1,5-dioxocanes and 3,3,7,7-tetrakis(trifluoromethyl)-9-oxa-2,6-dithia-bicyclo[3.3.1]nonane

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Full Research Paper

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Abstract

Treatment of 2,2-bis(trifluoromethyl)-4-R-oxetanes (R = C_2H_5O, *n*-C_3H_7O, *n*-C_4H_9O) with $BF_3 \cdot OEt_2$ in CH_2Cl_2 solvent results in spontaneous electrophilic [4 + 4] cyclodimerization with the formation of the corresponding 2,2,6,6-tetrakis(trifluoromethyl)-4,8-dialkoxy-1,5-dioxocanes, isolated in 31–42% yield. The structures of two products (R = C_2H_5O and *n*-C_3H_7O) were established by single crystal X-ray diffraction. The corresponding oxetane carrying the bulky *t*-C_4H_9O group has different reactivity towards $BF_3 \cdot OEt_2$, slowly producing a mixture of two acyclic, unsaturated products.

Clean and spontaneous reaction with alcohols is another interesting transformation of oxetanes described in this paper. The reaction leads to high yield formation of the corresponding acetals $(CF_3)_2C(OH)CH_2CH(OR)OR'$.

Structurally related 2,2-bis(trifluoromethyl)-4-R-thietanes (R = *i*-C_3H_7O, *t*-C_4H_9O and C_2H_5O) have different reactivity towards electrophiles. They are totally inert to the action of $BF_3 \cdot OEt_2$ and rapidly react with a protic acid (H_2SO_4) forming the same product, 3,3,7,7-tetrakis(trifluoromethyl)-9-oxa-2,6-dithia-bicyclo[3.3.1]nonane in 35–50% yield. The structure of this product was established by single crystal X-ray diffraction.

Introduction

Polyfluorinated 2,2-bis(trifluoromethyl)-4-alkoxy-oxetanes and -thietanes are readily available materials, prepared by [2 + 2] cycloaddition of vinyl ethers with hexafluoroacetone [1-3] or hexafluorothioacetone [4,5], respectively. Although both groups of compounds have been known for over 40 years, reports on their chemical transformations are limited. Among the reported reactions of oxetanes are hydrolysis of 2,2-bis(trifluoromethyl)-4-alkoxyoxetanes **1** leading to the formation of 4,4,4-trifluoro-3-(trifluoromethyl)-3-hydroxybutanal [1,6] and thermal or acid catalyzed isomerization of 2,2-bis(trifluoromethyl)-4-*n*-butoxy-oxetane into (*E*)-4-*n*-butoxy-1,1,1-trifluoro-2-(trifluoro-methyl)but-3-en-2-ol [2].

Some compounds containing two 2,2-bis(trifluoro-methyl)oxetane units, such as bis-4,4-(trifluoromethyl)oxetan-2-yl ether, were reported to undergo Lewis acid catalyzed poly-merization [3].

Known reactions of 2,2-bis(trifluoromethyl)-4-alkoxythietanes (R = CH_3O and C_2H_5O) include the formation of 4-(4,4-bis(trifluoromethyl)thietan-2-yloxy)-2,2-bis(trifluoro-methyl)thietane on treatment with H_2SO_4 [4], thiophilic ring opening by the action of alkyl magnesium or lithium reagents [4], the recently reported oxidation with selective formation of the corresponding S-oxides [7], and an unusual reductive ring expansion leading to the corresponding dihydrothiophenes [7].
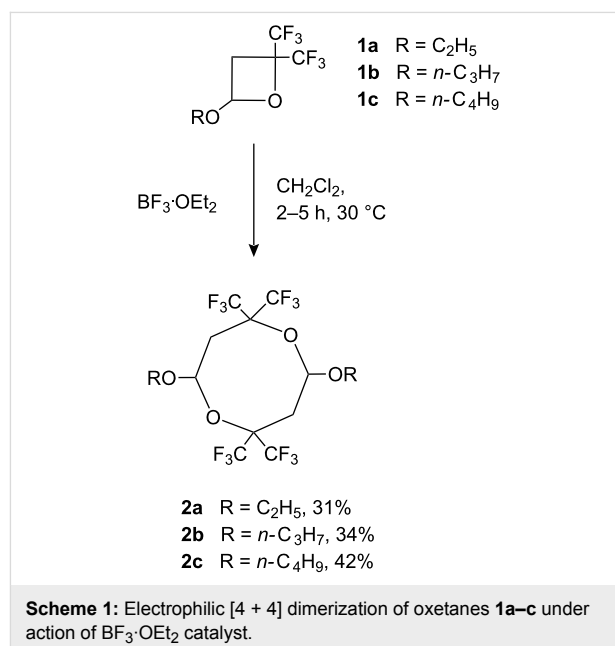
As part of a program to identify new, readily available fluorin-ated monomers, we have carried out a comparative study of the reactivity of 2,2-bis(trifluoromethyl)-4-alkoxy- oxetanes and -thietanes towards acids. The results of this study are reported in this paper.

Results and Discussion

In sharp contrast to the reported isomerization of 2,2-bis(trifluoromethyl)-4-alkoxyoxetanes catalyzed by protic acids [2], the reaction of oxetanes **1a–c** with a catalytic amount of *Lewis acid* leads to a completely different reaction course. The addition of boron trifluoride etherate catalyst to a solution of the oxetane in dichloromethane resulted in a spontaneous and mildly exothermic reaction. A very interesting feature of this process is the appearance of highly intensive blue or blue-green colour upon the addition of the first drop of the catalyst. The colour of the reaction mixture rapidly changes to dark red and finally to brown and, at this stage, usually the formation of a precipitate is observed. The solid products **2a–c** were isolated in moderate yields after filtration of the cold reaction mixture and
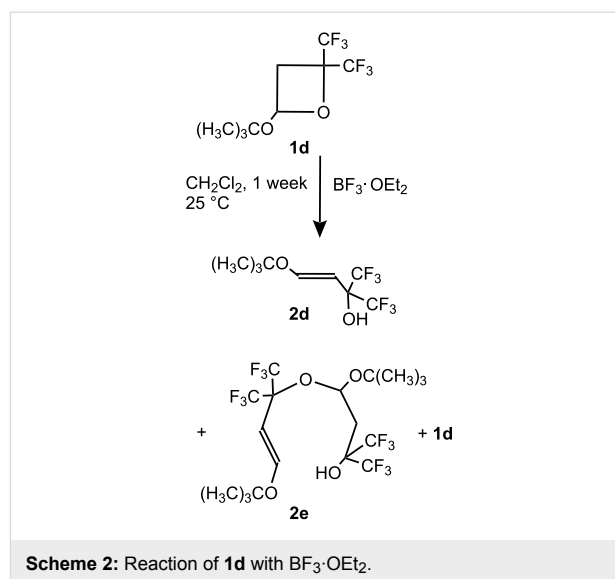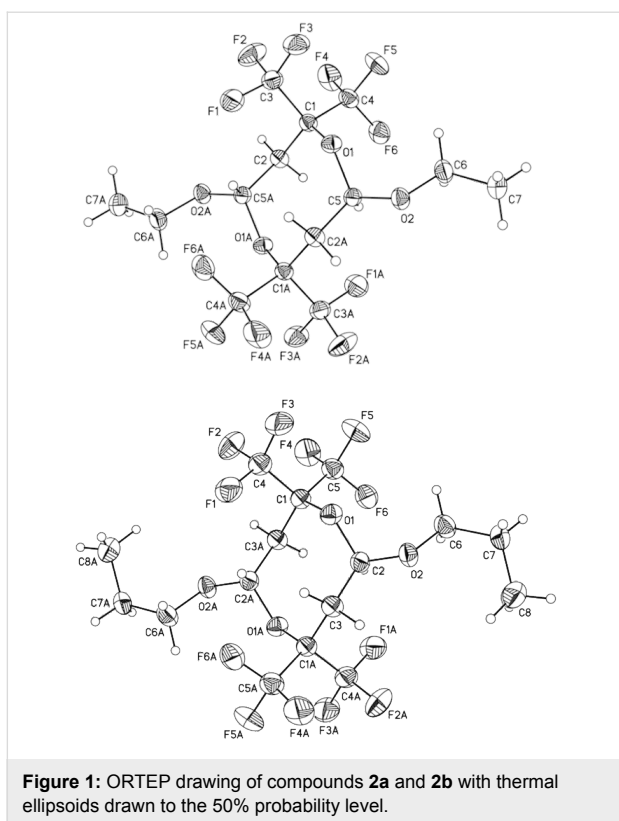
washing of the filter cake with water. Analytically pure samples were prepared by crystallization from hexane. ^{1}H, and ^{13}C NMR and IR spectroscopic data show the absence of a C=C bond in all of the isolated products. Due to the fact, that ^{1}H and ^{19}F NMR spectra of **2a**, **b** (see Supporting Information File 1, Table 1, Entries 1, 2) and starting oxetanes **1a**, **b** have a similar appearance, spectroscopic data were not sufficient for an unam-biguous assignment of the structure. Consequently, structure assignments for **2a** and **2b** were made based on single crystal X-ray diffraction data (see Supporting Information File 2).

Both compounds were found to have a symmetrical 2,2,6,6-tetrakis(trifluoromethyl)-1,5-dioxocane core with a trans-orien-tation of two alkoxy groups located at positions 4 and 8 (Scheme 1 and Figure 1 for structure of **2a** and **2b**, Supporting Information File 2 for single crystal X-ray data).

1a R = C_2H_5
1b R = *n*-C_3H_7
1c R = *n*-C_4H_9

$BF_3 \cdot OEt_2$

CH_2Cl_2, 2–5 h, 30 °C

2a R = C_2H_5, 31%
2b R = *n*-C_3H_7, 34%
2c R = *n*-C_4H_9, 42%

Scheme 1: Electrophilic [4 + 4] dimerization of oxetanes **1a–c** under action of $BF_3 \cdot OEt_2$ catalyst.

Since ^{1}H, ^{13}C and ^{19}F NMR spectra of compound **2c** were similar to the NMR spectra of **2a**, **b**, it is assumed that com-pound **2c** also has a 2,2,6,6-tetrakis(trifluoromethyl)-1,5-diox-ocane structure.

Despite the fact that yields of 1,5-dioxocanes **2a–c** in the reac-tion of oxetanes with $BF_3 \cdot OEt_2$ are modest, the process itself is simple, reproducible and provides easy access to this new group of stable polyfluorinated 1,5-dioxocanes. It should also be pointed out, that examples of electrophilic [4 + 4] cycloaddi-
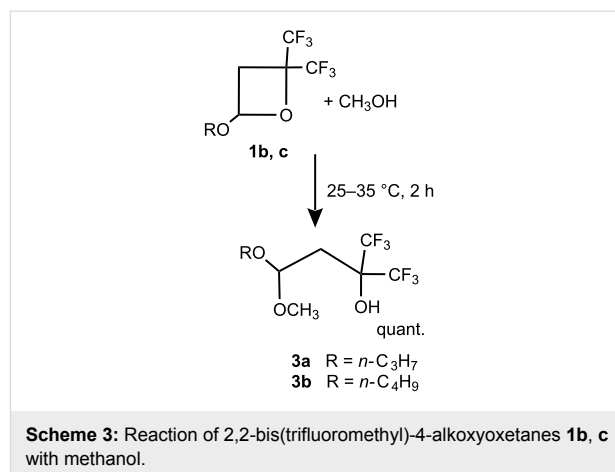
Figure 1: ORTEP drawing of compounds **2a** and **2b** with thermal ellipsoids drawn to the 50% probability level.

Scheme 2: Reaction of **1d** with $BF_3 \cdot OEt_2$.

tion reactions are extremely rare and limited to two examples: the reaction of the oxetane (derived from the cycloaddition of 1,1-dimethoxyethylene and 2,2-dimethylcyclopropanone), leading to a stable hydrocarbon 1,5-dioxocane [8] and the formation of the corresponding fluorinated 1,5-dioxocane intermediate [9,10] observed in the isomerization of 2-ethoxy-4-(perfluoropropan-2-ylidene)oxetane [11,12].

The chemical behavior of oxetane **1d** carrying the bulky t-C_4H_9O substituent is different to **1a–c**. The addition of $BF_3 \cdot OEt_2$ as catalyst to a solution of **1d** in CH_2Cl_2 is not exothermic and results only in a faint blue-greenish color in this case. In sharp contrast to the reaction of oxetanes **1a–c** with $BF_3 \cdot OEt_2$, this process is rather slow (85% conversion after 1 week at 25 °C) and it leads to the formation of a mixture of olefinic products **2d** and **2e** (Scheme 2).

A sample of pure **2d** was isolated by fractional distillation of the reaction mixture under reduced pressure. The structure of the olefin **2d** was established by single crystal X-ray diffraction analysis (see Supporting Information File 2).

Hydrocarbon oxetanes were reported to react with alcohols under relatively mild conditions [13]. It is interesting, that electron deficient oxetanes **1** also have similar reactivity and rapidly react with alcohols in the absence of the catalyst. The reaction

leads to a ring opening with the formation of the corresponding acetals of 4,4,4-trifluoro-3-(trifluoromethyl)-3-hydroxybutanal. For example, the addition of **1b** or **1c** to an excess of methanol results in a fast and mildly exothermic reaction, leading to selective formation of acetals **3a** or **3b**, respectively (Scheme 3).

Scheme 3: Reaction of 2,2-bis(trifluoromethyl)-4-alkoxyoxetanes **1b**, **c** with methanol.

Since the vacuum distillation of **3b** lead to decomposition, the isolation of similar products in an analytically pure form was not attempted. However, removal of excess alcohol after the reaction was complete by washing with water afforded products of reasonable purity (96–98%) in >95% yield.

Although kinetic measurements were not carried out in this study, it appears that the reaction time and the exothermicity of the reaction of oxetanes correlates with the acidity of the corresponding alcohol. For example, in contrast to a mildly exothermic reaction of **1b**, **c** with methanol ($pK_a = 15.5$ [14,15])

the interaction of **1c** with more acidic CF_3CH_2OH (pK_a = 12.4, 12.8 [15]) or $(CF_3)_2CHOH$ (pK_a = 9.3 [16]) is significantly more exothermic, leading to products **3c** and **3d**, respectively. All reactions were completed within 1–2 h at ambient temperature. On the other hand, the reaction of **1c** with the less acidic $(CH_3)_2CHOH$ (pK_a = 17.1 [15]) was significantly slower taking >10 h for completion at ambient temperature, as monitored by ^{19}F NMR, and led to acetal **3e** (Scheme 4).

Scheme 4: Reaction of oxetane **1c** with alcohols.
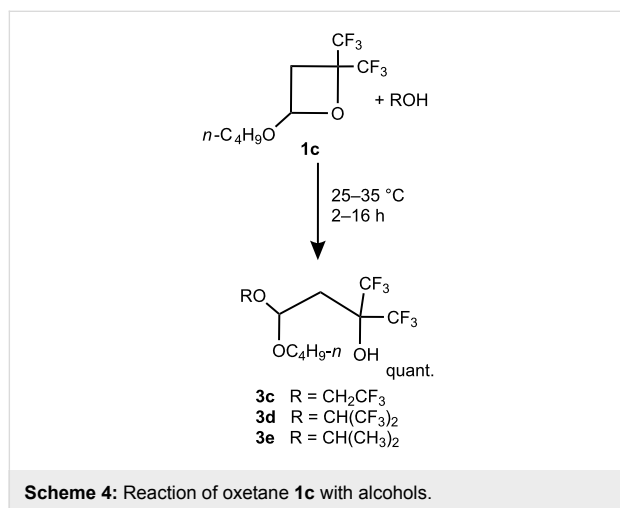
A mechanism for the reaction of these fluorinated oxetanes with Lewis acids and alcohols, is presented by Scheme 5.

Scheme 5: Putative mechanism for the reaction oxetanes **2a–d** with BF₃·OEt₂ and alcohols.
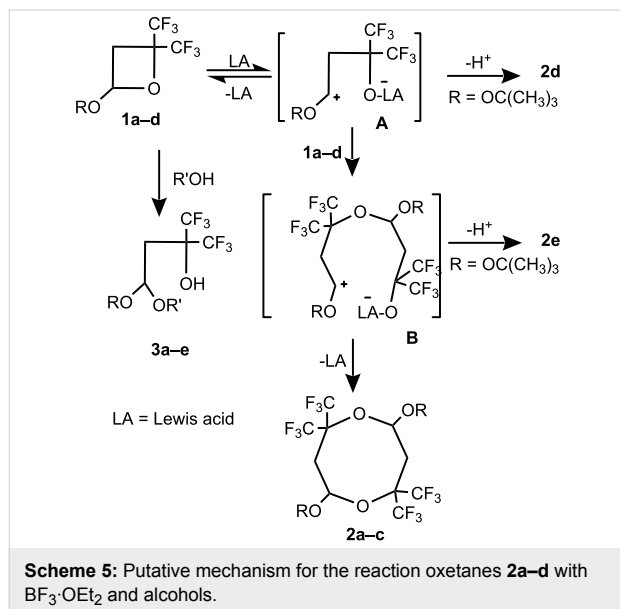
Coordination of the Lewis acid with the oxetane ring oxygen results in the formation of stabilized zwitterion **A**, which probably exists in equilibrium with the starting material. The reaction of **A** with a second mole of oxetane then leads to the

formation of zwitterion **B**, which can undergo intramolecular cyclization with formation of 1,5-dioxocanes **2a–c**. The Lewis acid liberated in this process is free to carry out the next catalytic cycle. It should be pointed out, that recently a zwitterion similar to **B** was observed in the isomerization of the cycloadduct of bis(trifluoromethyl)ketene and ethyl vinyl ether [9,10].

In the case of oxetane **1d**, the main channel of the reaction involves stabilization of intermediates **A** and **B** by H⁺ elimination, leading to the formation of olefins **2d** and **2e**, respectively. Such a distinct difference in the reactivity of **1d** may be a result of steric hindrance of the carbocationic center in intermediates **A** or **B**, created by the bulky $(CH_3)_3CO$-group, which favors elimination and the formation of olefins **2e** and **2d.**
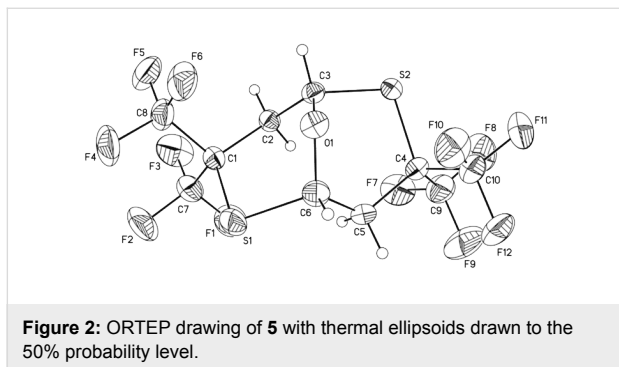
The addition of alcohols to oxetanes **1a–c** probably involves the protonation of the oxetane ring oxygen atom as the first step, followed by ring opening and addition of the alkoxy anion. This mechanism agrees well with the observed order of reactivity of alcohols, with the acidic alcohols being more reactive towards the oxetane. It should be pointed out, however, that an alternative mechanism involving the "concerted" addition of the alcohol to the oxetane cannot be ruled out at this point.

Despite the structural similarity shared with oxetanes, thietanes **4a–c** display a totally different reactivity (Scheme 6, Scheme 7).

For example, no reaction was detected between thietane **4a** and an excess of either methanol or hexafluoroisopropanol (25 °C, 16 h, NMR) and both **4a** and **4b** were found to be inert towards BF₃·OEt₂ (25 °C, 10 h, CH₂Cl₂, NMR). However, the addition of compounds **4a** or **4b** to concentrated H_2SO_4 resulted in an

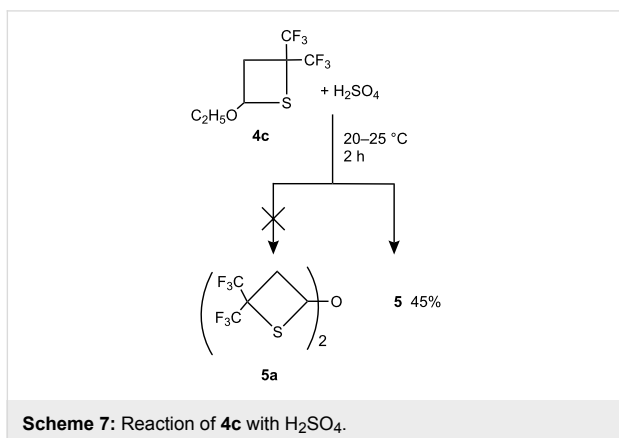**Scheme 6:** Reaction of thietanes **4a, b** with H_2SO_4 to generate **5**.
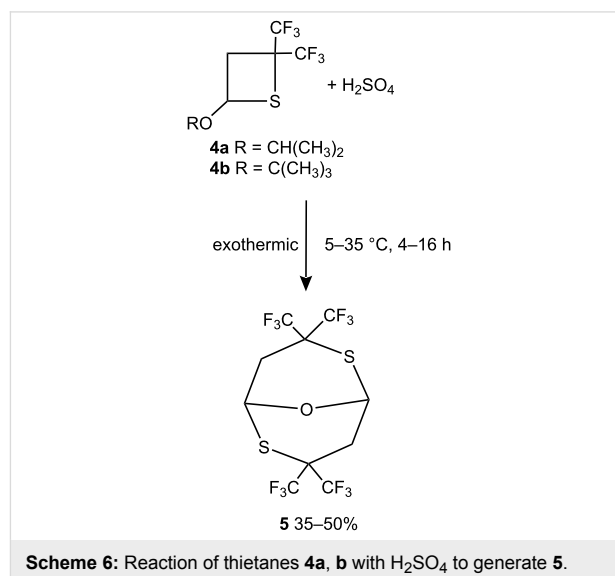
exothermic reaction and formation of a product, which, after single crystal X-ray diffraction analysis, was shown to be 3,3,7,7-tetrakis(trifluoromethyl)-9-oxa-2,6-dithia-bicyclo[3.3.1]nonane (**5**) (Scheme 6, Figure 2, Supporting Information File 2).

Figure 2: ORTEP drawing of **5** with thermal ellipsoids drawn to the 50% probability level.

A solid product with similar melting point (91–92 °C) was observed earlier [4] in the reaction of thietanes **4** (R = CH_3 and C_2H_5) with concentrated H_2SO_4. Based on a combination of ^{1}H, ^{19}F NMR, mass spectrometry and elemental analysis data, the structure of 4-[4,4-bis(trifluoromethyl)thietan-2-yloxy]-2,2-bis(trifluoromethyl)thietane **5a** was proposed for that product [4].

In order to clarify this result, thietane **4c** (R = C_2H_5) was treated with H_2SO_4 (Scheme 7) under conditions similar to those reported previously [4]. A solid product was isolated in 45% yield, which had a similar melting point and identical ^{1}H, ^{19}F NMR spectra to that reported for **5a** (see Supporting Information File 1, Table 1, Entry 11 and footnotes f,h), but also identical to the analytical data for compound **5** prepared from oxetanes **4a** and **4b**.

Scheme 7: Reaction of **4c** with H_2SO_4.

Since all experimental data obtained for the reaction of thietanes **4a–c** with H_2SO_4 in this work are consistent, it is concluded

that the main product of this reaction is dithiocin **5**, rather than the isomeric ether **5a**, proposed in reference [4].

A possible mechanism describing the formation of compound **5** is depicted by Scheme 8.

Scheme 8: Putative mechanism for the formation bicyclic ether **5**.
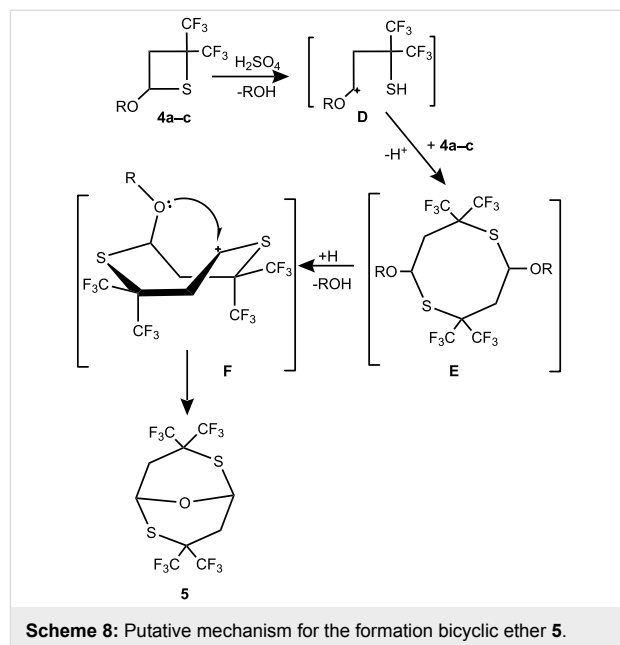
Protonation of the thietane sulfur of **4**, followed by ring opening, results in the formation of an oxygen stabilized carbocation **D**. Electrophilic attack of **D** at the sulfur of the second thietane molecule and loss of H^+ would lead to the formation of intermediate **E**, structurally similar to cyloadducts **2a–c**. However, the process does not stop at this stage. Protonation of the alkoxy group of **E**, followed by the elimination of alcohol leads to the cyclic cation **F**, which further undergoes cyclization through intramolecular electrophilic attack on oxygen of the alkoxy group, resulting in the formation of 3,3,7,7-tetrakis(trifluoromethyl)-9-oxa-2,6-dithia-bicyclo[3.3.1]nonane (**5**).

Conclusion

Despite the structural similarity, 2,2-bis(trifluoromethyl)-4-alkoxy-oxetanes and thietanes have very different reactivity towards Lewis and protic acids. While the reaction of 2,2-bis(trifluoromethyl)-4-R-oxetanes (R = C_2H_5, *n*-C_3H_7, *n*-C_4H_9) with $BF_3 \cdot OEt_2$ results in the fast formation of the corresponding 2,2,6,6-tetrakis(trifluoromethyl)-1,5-dioxocanes **2a–c**, the corresponding thietanes **4b**, **c** (R = *i*-C_3H_7, *t*-C_4H_9) are inert towards this Lewis acid, but rapidly react with concentrated H_2SO_4 with the formation of bicyclic 3,3,7,7-tetrakis(trifluoromethyl)-9-oxa-2,6-dithia-bicyclo[3.3.1]nonane **5**. Reinvestigation of a previously reported reaction of **4c**, (R = C_2H_5) with

H_2SO_4, led us to the conclusion, that the product formed in this process has the structure 3,3,7,7-tetrakis(trifluoromethyl)-9-oxa-2,6-dithia-bicyclo[3.3.1]nonane (**5**), rather than 4-[4,4-bis(trifluoromethyl)thietan-2-yloxy]-2,2-bis(trifluoromethyl)-thietane (**5a**) as proposed earlier [4].

Supporting Information

Supporting Information File 1
Experimental details and analytical data for compounds **2a–2e**, **3a–3e** and **5**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-46-S1.pdf]

Supporting Information File 2
X-ray data for compounds **2a**, **2b**, **2d** and **5**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-46-S2.cif]

Acknowledgements

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