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Formation of a 2-amino-4*H*-3,1-benzoxathiin from a tetracoordinated 1,2-thiazetidine via the aza-Pummerer type rearrangement

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This paper is dedicated to Professor Juzo Nakayama on the occasion of his 65th birthday and retirement.

A tetracoordinated 1,2-thiazetidine gave a 2-amino-4*H*-3,1-benzoxathiin under thermal conditions. The product was characterized by X-ray crystallographic analysis. The heterocyclic product was considered to be formed via the aza-Pummerer type rearrangement.

Keywords: aza-Pummerer type rearrangement; 4*H*-3,1-benzoxathiin; Pummerer rearrangement; sulfurane; 1,2-thiazetidine

1. Introduction

The Pummerer rearrangement is a good method to convert a sulfoxide to a 1-acyloxyalkyl sulfide, and it is an important reaction in sulfur chemistry (*1–3*). In this reaction, the oxygen atom migrates from sulfur to the α-carbon and sulfur is reduced while adjacent carbon is oxidized. The nitrogen version of the Pummerer rearrangement is also reported for 2-azathiabenzene derivatives to give the corresponding cyclic α-aminomethyl sulfides, but there has been only a few examples to date (*4–8*). In the continuation of our study on four-membered ring compounds containing a highly coordinated chalcogen atom, we have reported several examples of sulfuranes with oxygen, nitrogen or sulfur attaching to the sulfur atom (*9–18*). Some of them gave the corresponding three-membered ring compounds in high yields, the oxiranes, aziridines or thiiranes, under thermal conditions, but a tetracoordinated 1,2-thiazetidine is resistant to the degradation and its prolonged heating in *o*-xylene gave a complex mixture. After further study on the reactivity of the 1,2-thiazetidine, we have found that it undergoes the aza-Pummerer type rearrangement. We report here the aza-Pummerer type rearrangement of a tetracoordinated 1,2-thiazetidine, giving the corresponding 2-amino-4*H*-3,1-benzoxathiin as a final product.

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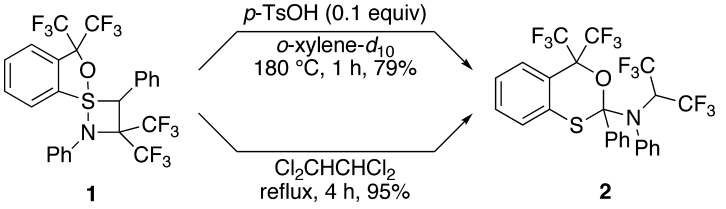
2. Results

The thermal reaction of (**1**) in *o*-xylene-d_{10} at 210 °C for 81 h afforded a complex mixture (*16*). The result suggests that heating for a long time at high temperature might have caused the decomposition of primary products. Therefore, we investigated whether an additive or solvent can accelerate the reaction or not. At first, we found that the use of an acid as an additive is very effective. That is, adding a small amount of *p*-toluenesulfonic acid to an *o*-xylene-d_{10} solution of (**1**) gave 4*H*-3,1-benzoxathiin (**2**) in 79% yield (Scheme 1). The reaction temperature and time were much lower and shorter than those in its reaction without the acid, respectively, and hence the reaction mixture became quite simple compared with that without the acid. Thus, protonation was suggested to help the rearrangement of (**1**). Next, we examined the solvent effects. When 1,1,2,2-tetrachloroethane was used as a solvent, the complete transformation of (**1**) was achieved in 4 h under reflux and (**2**) was formed in 95% yield. The results indicate that the polar solvent also accelerates the reaction and that the reaction proceeds via a polar transition state. The structure of (**2**) was determined by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy and X-ray crystallographic analysis. The ORTEP drawing of (**2**) is shown in Figure 1. Selected bond lengths and angles are summarized in Table 1. Interestingly, both the oxygen and the nitrogen atoms attached to the sulfur atom in (**1**) migrated to the same carbon atom at the benzyl position, and the C–C bond in the thiazetidine ring was cleaved. That is, the nitrogen atom was inserted between the two carbon atoms of the thiazetidine ring of (**1**).

In the crystal structure, the bond lengths in the six-membered heterocyclic ring moiety are quite normal. Both the C1 and the O1 atoms are located below the plane defined by the S1, C2, C7 and C8 atoms in contrast to the solely reported X-ray crystal structure of 4*H*-3,1-benzoxathiin,



Scheme 1.

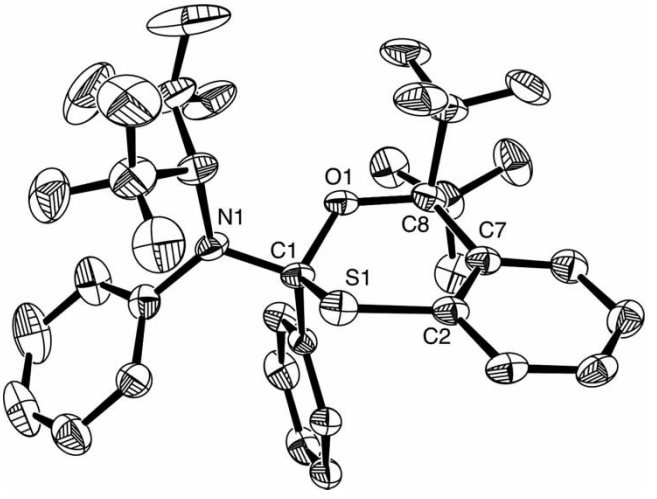


Figure 1. ORTEP drawing of (**2**) with thermal ellipsoid plot (50% probability). Hydrogen atoms are omitted for clarity.

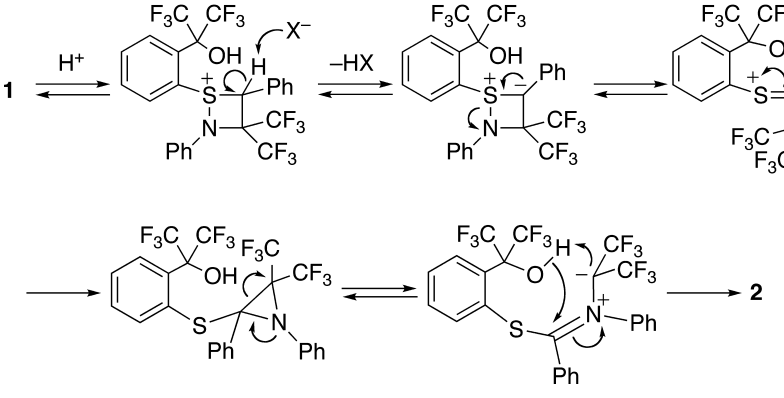
Table 1. Selected bond lengths (Å) and angles (°) of (**2**).

C(1)–O(1)	1.444 (3)
C(1)–N(1)	1.452 (3)
C(1)–C(11)	1.525 (3)
C(1)–S(1)	1.836 (2)
S(1)–C(2)	1.756 (3)
C(2)–C(7)	1.398 (3)
C(7)–C(8)	1.530 (3)
C(8)–O(1)	1.420 (3)
O(1)–C(1)–N(1)	103.40 (17)
O(1)–C(1)–C(11)	110.28 (17)
N(1)–C(1)–C(11)	110.42 (18)
O(1)–C(1)–S(1)	108.92 (14)
N(1)–C(1)–S(1)	108.01 (15)
C(11)–C(1)–S(1)	115.14 (15)
C(2)–S(1)–C(1)	99.30 (10)
C(2)–C(7)–C(8)	121.3 (2)
C(7)–C(2)–S(1)	122.70 (17)
O(1)–C(8)–C(7)	118.16 (18)
C(8)–O(1)–C(1)	123.27 (16)

in which the corresponding carbon and oxygen atoms are located above and below the plane, respectively (*19*). This is the first example of 2-amino-4*H*-3,1-benzoxathiin.

3. Discussion

Considering the formation of (**2**) in the presence of an acid, the suggested mechanism is as follows. Protonation of the oxygen atom occurs and the S–O bond readily cleaves. The resulting sulfonium salt is deprotonated to generate a sulfonium ylide in the four-membered ring, which undergoes an S–N bond cleavage. The resulting amide anion attacks at the benzyl carbon to give an aziridine. In the azomethine ylide which is in equilibration with the aziridine, deprotonation from the hydroxy group by the carbanion followed by nucleophilic attack of the resulting oxide ion at the iminium carbon affords (**2**) (Scheme 2). The first protonation would occur at the oxygen rather than the nitrogen because the oxygen is more polarized than the nitrogen considering the long S–O bond length (*16*). As the sulfonium ylide intermediate has distorted due to the ring strain, the S–N bond cleavage would easily take place to form the betaine, which readily cyclizes to afford the



Scheme 2.

aziridine. Because an aziridine is well known to be in an equilibrium with an azomethine ylide under thermal conditions (*20*), the final product can be formed from the azomethine ylide.

In its reaction without the acid, the reaction can be considered to proceed via a similar reaction mechanism involving heterolysis of the S–O bond followed by the formation of the sulfur ylide intermediate by intramolecular deprotonation by the oxide ion instead of an acid-catalyzed formation of the intermediate. The migration process of the nitrogen atom from the sulfur to the carbon atom resembles the Pummerer rearrangement. So, this reaction can be called the aza-Pummerer type reaction. To trap the nucleophilic intermediate, the reaction was carried out in methyl iodide in the presence of one equivalent of *p*-TsOH and refluxed overnight. However, (**2**) was obtained in 72% yield and there was no methylated adduct at all.

Considering the formation of (**2**), the rearrangement reactivity observed under the thermal conditions is interesting and it is a rare example of the aza-Pummerer type rearrangement.

4. Experimental

4.1. *Formation of 4H-3,1-benzoxathiine (2)*

A 1,1,2,2-tetrachloroethane solution (10 ml) of thiazetidine (**1**) (120 mg, 0.198 mmol) was refluxed for 4 h. After removal of solvents under reduced pressure, recrystallization from hexane gave 4,4-bis(trifluoromethyl)-2-phenyl-2-[*N*-phenyl-*N*-(2,2,2-trifluoro-1-triflluoromethyl)]amino-4*H*-3,1-benzoxathiine (**2**) (114 mg, 95%). Data of (**2**): colorless crystals, mp. 151.2–151.8 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.41 (sept, $^{3}J_{HF} = 7.0$ Hz, 1H), 6.90–7.06 (m, 6H), 7.13-7.18 (m, 3H), 7.35 (dt, $J = 7.6$, 1.2 Hz), 7.39 (d, $^{3}J = 8.1$ Hz), 7.42 (dd, $J = 7.9$, 1.4 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 61.28 (sept, $^{2}J_{CF} = 31$ Hz), 82.66 (sept, $^{2}J_{CF} = 30$ Hz), 105.58 (s), 121.82 (q, $^{1}J_{CF} = 290$ Hz), 122.01 (s), 122.10 (q, $^{1}J_{CF} = 285$ Hz), 122.40 (q, $^{1}J_{CF} = 290$ Hz), 122.66 (q, $^{1}J_{CF} = 286$ Hz), 126.65 (s), 127.38 (br s), 127.58 (s), 128.12 (s), 128.25 (br s), 129.24 (s), 129.57 (s), 130.69 (s), 131.93 (s), 134.09 (s), 135.92 (s), 138.93 (s); ^{19}F NMR ($CDCl_3$, 471 MHz) δ − 65.34 (dq, $^{4}J_{FF} = 10.1$ Hz, $^{3}J_{HF} = 7.0$ Hz, 3F), −66.07 (dq, $^{4}J_{FF} = 10.1$ Hz, $^{3}J_{HF} = 7.0$ Hz, 3F), −68.18 (q, $^{4}J_{FF} = 9.9$ Hz, 3F), −75.15 (q, $^{4}J_{FF} = 9.9$ Hz, 3F). MS (FAB) m/z 606 ([M + H]$^{+}$). Analytically calculated for $C_{25}H_{25}F_{12}NOS$: C, 49.59; H, 2.50; N, 2.31. Found: C, 49.20; H, 2.65; N, 2.18%.

4.2. *Thermal reaction of 1 in the presence of p-toluenesulfonic acid*

An *o*-xylene-d_{10} solution (0.5 mL) of thiazetidine (**1**) (20 mg, 0.033 mmol) and *p*-toluenesulfonic acid (0.6 mg, 0.003 mmol) was heated at 180 °C for 1 h in a sealed NMR tube. Formation of (**2**) (79%) was confirmed by ^{1}H and ^{19}F NMR spectra. The reaction in methyl iodide was carried out using a solution of (**1**) (40 mg, 0.066 mmol) and TsOH (11.4 mg, 0.066 mmol) in MeI (20 ml) and the formation of (**2**) (72%) was similarly confirmed.

4.3. *X-ray crystallographic analysis of (2)*

A colorless block crystal of $C_{25}H_{15}F_{12}NOS$ having approximate dimensions of 0.45 × 0.45 × 0.25 mm was mounted on a glass fiber, and all data were measured with a Rigaku Mercury CCD with graphite monochromated Mo–Ka radiation ($\lambda = 0.71070$ Å). The data were collected at a temperature of 120 K to a maximum 2θ value of 50.0°. The data were collected and processed using CrystalClear (Rigaku). Of the 15656 reflections that were collected, 4323 were unique ($R_{int} = 0.0292$). An empirical absorption correction was applied. The data were corrected for

Lorentz and polarization effects. The structure was solved by direct methods with SHELX-97 and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed at calculated positions. Crystal data of (**2**): $C_{25}H_{15}F_{12}NOS$, FW = 605.45, monoclinic, space group $P2_1/n$ (#14); $a = 11.075(5)$, $b = 15.208(6)$, $c = 14.781(6)$ Å, $\beta = 96.334(6)^\circ$, $V = 2474.3(18)$ Å (3), $Z = 4$, $D_{calc} = 1.625\,g/cm^3$, $\mu = 0.242\,mm^{-1}$, $R1\,(I > 2\sigma(I)) = 0.0517$, w$R2$ (all data) = 0.0999, GOF = 1.195. Crystallographic data for the structural analysis have been deposited at the Cambridge Crystallographic Data Center, CCDC-700690 for (**2**).[1]

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Note

1. Copies of this information can be obtained from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033; Email: deposit@ccdc.cam.ac.uk).

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