A ONE STEP CONVERSION OF SULFOXIDES TO ALDEHYDES BY THE NEIGHBORING GROUP PARTICIPATION IN THE PUMMERER REARRANGEMENT OF ORTHO-HYDROXYMETHYL ARYL BENZYL SULFOXIDES

Hiroyuki Naka, Soichi Sato, Ernst Horn, and Naomichi Furukawa*

Tsukuba Advanced Research Alliance Center and Department of Chemistry,
University of Tsukuba, Tsukuba, Ibaraki 305, Japan

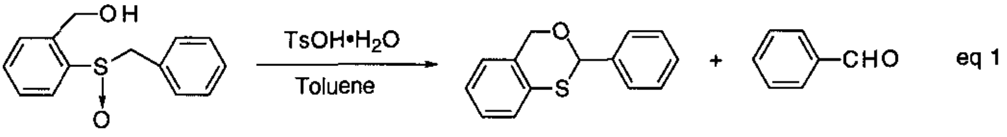
Abstract– Benzyl 2-(hydroxymethyl)phenyl sulfoxides (**1**) treated with *p*-toluenesulfonic acid monohydrate ($TsOH{\bullet}H_2O$) undergo the Pummerer-type rearrangement to give benzaldehydes in one step. The reaction was found to proceed *via* the oxosulfonium salt (**6**) as an intermediate.

The Pummerer rearrangement of sulfoxides has been widely studied, and has received considerable attention as a synthetically useful process.[1] It has been reported that the Pummerer rearrangement of sulfoxides followed by hydrolysis of the α-acetoxysulfides gives aldehydes.[2] However, in practice this method has some limitations for the preparation of aldehydes, since the α-acetoxysulfides are easily converted into vinyl sulfides by β-elimination. In order to avoid β-elimination of the α-acetoxysulfide, trifluoroacetic anhydride is used instead of acetic anhydride for the Pummerer rearrangement at low temperature.[3] A very mild method for the conversion of the sulfoxides to the acetals using iodine in methanol followed by hydrolysis to give the aldehydes has also been reported.[4]

Asymmetric intramolecular Pummerer-type cyclization of the sulfoxides using *O*-methyl-*O*-*tert*-butyldimethylsilyl ketene acetal has been reported and applied in the preparation of β-lactam derivatives.[5]

This paper is dedicated to the memory of the late Prof. Shunichi Yamada.

We tried the preparation of the 1, 3-oxathiane (**2**) from benzyl 2-(hydroxymethyl)phenyl sulfoxide (**1a**) with a catalytic amount of *p*-toluenesulfonic acid monohydrate to investigate the possibility of 1,3-S–O interaction. This reaction gave the desired 1,3-oxathiane (**2**) in 89% yield together with benzaldehyde (**3a**) in 10% yield (eq 1).



eq 1

1a **2** **3a**

We were interested in this one step formation of benzaldehyde from the sulfoxide (**1a**) bearing *o*-hydroxymethyl group in the Pummerer rearrangement. In this article we wish to describe the detailed perspective views for the reactions.

RESULTS AND DISCUSSION

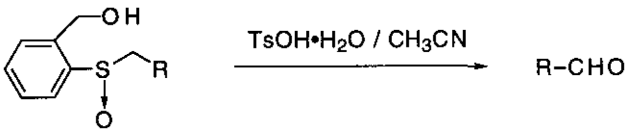
Initially, we examined the optimum oxidation reaction conditions of this one step conversion from benzyl 2-(hydroxymethyl)phenyl sulfoxide (**1a**)^6 with TsOH•H_2O to benzaldehyde (**3a**) as shown in Scheme 1. The best yield of **3a** from the sulfoxide (**1a**) was 65% obtained by treating the latter with 2.0 eq of TsOH•H_2O in acetonitrile at 90 °C for 20 min as shown in Table 1. Although the starting sulfoxide was consumed completely under the reaction conditions, the reason for these rather low yield of benzaldehyde (**3a**) is attributed to the formation of benzyl 2-(hydroxymethyl)phenyl sulfide produced as a by-product in 20% yield *via* the redox reaction between the starting sulfoxide (**1a**) and 2-mercaptobenzyl alcohol.

Similarly, the reactions of sulfoxides (**1a-1h**) were examined under the same reaction conditions. The results are summarized in Table 1.

The results in Table 1 reveal that the arylic aldehydes involving phenyl and naphthyl derivatives were prepared in moderate to good yields, whereas the alkyl derivatives gave the corresponding aldehydes in rather low yields together with intractable compounds. 4-Methoxyphenyl compound did not give the aldehyde but gave *N*-(4-methoxyphenylmethyl)acetoamide in 72% yield. This result indicates that the S–C bond of sulfoxide (**1b**) readily cleaved under this reaction condition and produced the 4-methoxybenzyl cation which was then captured by acetonitrile used as a solvent.

In these reactions the *o*-hydroxymethyl group should play an important role for preparation of aldehydes.

Scheme 1



1

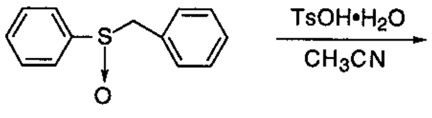
3

Table 1. Conversion of sulfoxides into aldehydes.

sulfoxide	R	TsOH•H_2O (eq.)	solvent (temp.) (°C)	time (min)	aldehyde	yield of **3** (%)
1a	Ph	0.1	toluene(100)	30	**3a**	10
1a	Ph	1.0	toluene(100)	20	**3a**	55
1a	Ph	2.0	toluene(100)	20	**3a**	61
1a	Ph	2.0	toluene(80)	30	**3a**	45
1a	Ph	2.0	CH_3CN(90)	20	**3a**	65
1a	Ph	2.0	CH_3CN(60)	120	**3a**	51
1b	4-$CH_3OC_6H_4$	2.0	CH_3CN(90)	20	**3b**	0
1c	4-$CH_3C_6H_4$	2.0	CH_3CN(90)	20	**3c**	67
1d	4-ClC_6H_4	2.0	CH_3CN(90)	20	**3d**	70
1e	4-$O_2NC_6H_4$	2.0	CH_3CN(90)	20	**3e**	64
1f	1-naphthyl	2.0	CH_3CN(90)	20	**3f**	52
1g	2-naphthyl	2.0	CH_3CN(90)	20	**3g**	64
1h	$CH_3(CH_2)_8$	2.0	CH_3CN(90)	20	**3h**	37

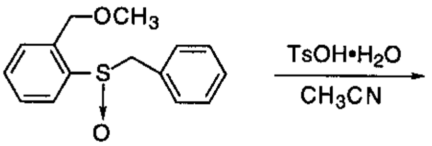
Therefore, in order to understand the role of the *o*-hydroxymethyl group, we prepared benzyl phenyl sulfoxide (**4**) and *o*-methoxymethyl derivative (**5**) and treated them under the same reaction conditions. However, both substrates did not react under the present reaction conditions (eqs 2 and 3). Thus, it appears that the hydroxyl group in the ortho position serves as a fundamental role in the reaction sequence. Under the present reaction conditions, the 1,3-oxathiane (**2**) prepared elsewhere yielded benzaldehyde (**3a**) in only 8% yield, suggesting that the path *via* the 1,3-oxathiane (**2**) is a minor process.

From the experimental observation, we propose that the mechanism for this reaction involves the initial



4

no reaction eq 2

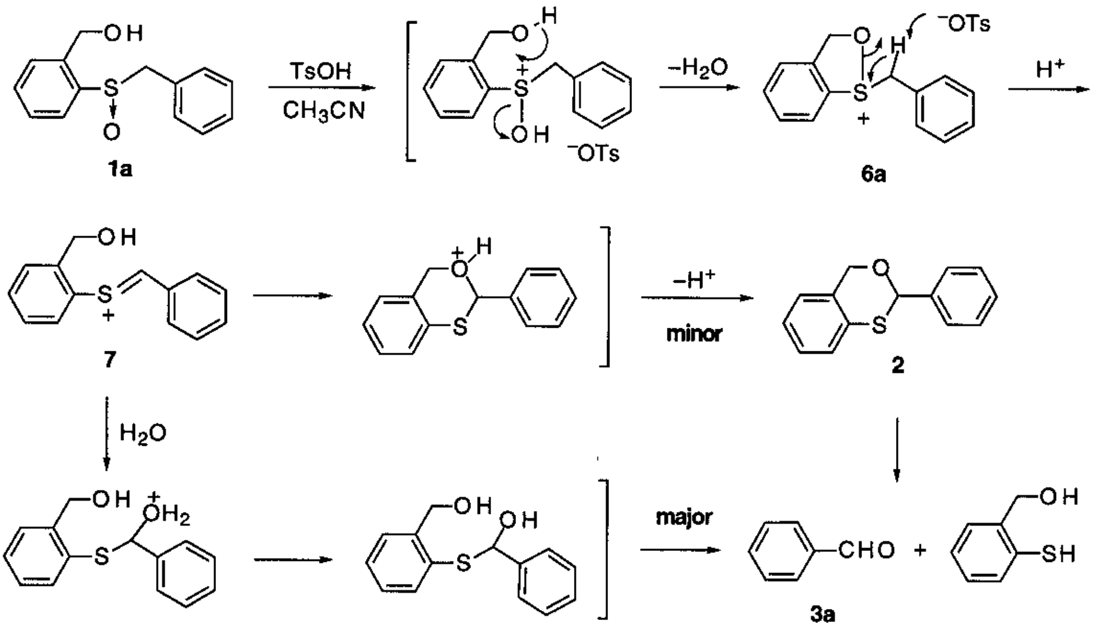


5

no reaction eq 3

formation of the cyclic oxosulfonium salt (**6a**) *via* the neighboring group participation by the *o*-hydroxymethyl group as an intermediate which then undergoes α-deprotection by tosylate anion and hydrolysis as shown in Scheme 2.

Scheme 2



Protonation on the sulfinyl oxygen of the sulfoxide (**1a**) followed by dehydration yields the cyclic oxosulfonium salt (**6a**) which undergoes α-deprotonation to yield the sulfenium cation (**7**). Subsequently, the sulfenium cation (**7**) reacts with either the benzylic hydroxyl group to yield the 1,3-oxathiane (**2**) or reacts intermolecularly with water to yield benzaldehyde (**3a**). A similar mechanism has been proposed to explain the Pummerer–type transformation of 5-methyl-2-(methylsulfinyl)-α-phenethyl alcohol (**8**) into 5-methyl-2-(chloromethylsulfanyl)phenethyl alcohol (**10**) *via* the oxosulfonium salt (**9**).[7]

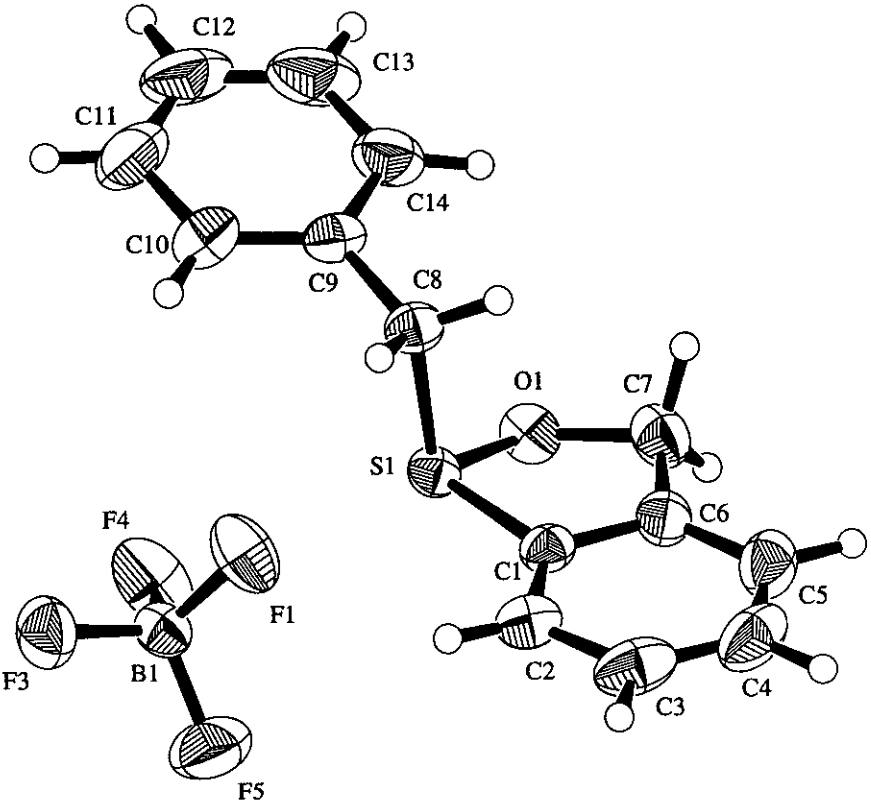


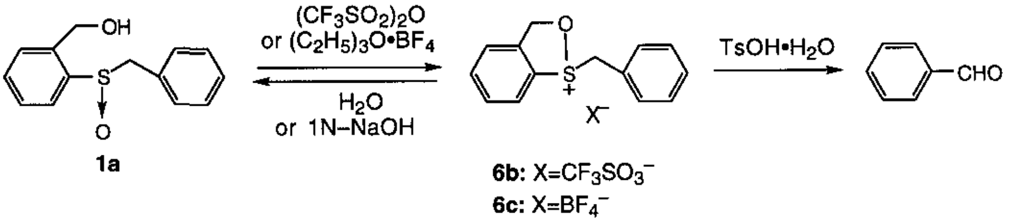
Figure 1. An ORTEP (50% probability ellipsoids) drawing of 1–benzyl–3*H*–2,1–benzoxathiol–1–ium tetrafluoroborate (**6c**). Selected bond lengths (Å) and angles (deg) : S(1)–O(1) = 1.595(2), S(1)–C(1) = 1.775(2), S(1)–C(8) = 1.815(2), O(1)–S(1)–C(1) = 94.5(1), O(1)–S(1)–C(8) = 103.9(1), C(1)–S(1)–C(8) = 100.2(1), S(1)–O(1)–C(7) = 113.2(2).

We tried to isolate the intermediate (**6a**) by the treatment of the sulfoxide (**1a**) with trifluoromethanesulfonic anhydride or triethyloxonium tetrafluoroborate in anhydrous CH_2Cl_2 at –78 to 0 °C. Indeed, the cyclic oxosulfonium salt (**6b** or **6c**) was obtained as colorless solids (eq 4). The oxosulfonium salt (**6b**) was characterized by ^1H, ^{13}C NMR and FABMS.[8] In the ^1H NMR spectrum of **6b** in CD_3CN, the two benzylic methylene protons were observed at the markedly downfield shifts of δ 4.60, 5.04 and 5.20, 5.67

as two sets of AB quartet peaks. The FABMS spectrum (pos.) of **6b** shows the cyclic oxosulfonium cation peak at *m/z* 229 ($[M-CF_3SO_3^-]^+$) together with *m/z* 607 ($[2M-CF_3SO_3^-]^+$).

Finally, the oxosulfonium salt (**6c**) was identified by X-Ray crystallographic analysis.[9] An ORTEP drawing of the compound (**6c**) is shown in Figure 1. This is the first example for X-Ray crystallographic analysis of the cyclic oxosulfonium salt (**6c**). The short intermolecular S–F distance, (2.769(2) Å), which is shorter than the sum of the van der Waals' radii (3.2 Å) of the two elements, shows a strong interaction between the sulfur cation and counter anion. Detailed tables of atomic coordinates, bond length and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

Furthermore, treatment of this cyclic oxosulfonium salt (**6b**) with H_2O or 1N-NaOH again resulted in the formation of benzyl 2-(hydroxymethyl)phenyl sulfoxide (**1a**). This result obviously demonstrates the formation of cyclic oxosulfonium salt. We carried out the reaction of the cyclic oxosulfonium salt (**6c**) with 2.0 equiv. of $TsOH{\bullet}H_2O$ in acetonitrile at 90 °C for 20 min to ascertain that **6** is a real intermediate of this reaction. This reaction gave benzaldehyde in 86% yield. From this result, this reaction was found to proceed *via* the oxosulfonium salt (**6**) as an intermediate.



eq 4

ACKNOWLEDGMENT

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6. **1a** : mp 99–101 °C; ^{1}H NMR (400 MHz, CD_3CN) δ 3.61 (dd, *J* = 4.6 and 6.5 Hz, 1H), 3.97, 4.24 (ABq, *J* = 12.8 Hz, 2H), 4.53 (dd, *J* = 6.5, 12.8 Hz, 1H), 4.60 (dd, *J* = 4.6, 12.8 Hz, 1H), 7.08–7.12 (m, 2H), 7.25–7.34 (m, 3H), 7.39–7.50 (m, 3H), 7.59–7.62 (m, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ 143.5, 139.9, 132.0, 131.7, 131.3, 129.3, 129.2, 129.1, 128.8, 125.1, 63.3, 61.6; MS ESI(pos.) m/z 247 ($[MH]^+$); Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.27; H, 5.73. Found: C, 68.24; H, 5.73.

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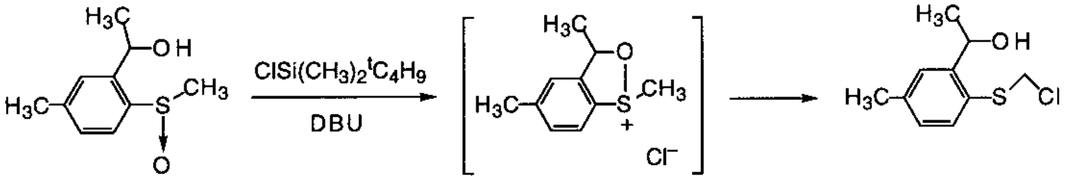

8 **9** **10**

8. **11** : yield 27% , white crystals, mp 102–104 °C (decomp); ^{1}H NMR (400 MHz, CD_3CN) δ 4.60, 5.04 (ABq, *J* = 14.1 Hz, 2H), 5.20, 5.67 (ABq, *J* = 12.8 Hz, 2H), 7.08–7.11 (m, 2H), 7.28–7.34 (m, 2H), 7.42–7.50 (m, 2H), 7.73–7.82 (m, 2H), 7.99–8.03 (m, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ 139.3, 135.4, 132.3, 131.8, 131.3, 130.0, 128.8, 126.4, 125.5, 123.7, 85.2, 59.0; ^{19}F NMR (376 MHz, CD_3CN) δ –75.7 (relative to $PhCF_3$), FABMS (pos.) 229 ($[M-CF_3SO_3^-]^+$), 607 ($[2M-CF_3SO_3^-]^+$) (matrix: 2-nitrophenyl octyl ether).

9. Crystal data for **6c**. $C_{14}H_{13}OSBF_4$, monoclinic, space group $P2_1/c$(#14), $a = 8.408(1)$, $b = 16.154(2)$, $c = 10.823(1)$ Å, $\beta = 100.26(1)$ °, $V = 1446.6(3)$ Å^3, $Z = 4$, ρcalcd = 1.451 g cm^{-3}, $\mu = 2.61$ cm^{-1}, $R(R_w) = 0.039$ (0.035), Temperature = –20 °C. All measurements were made on a Rigaku AFC-7R diffractometer with graphite monochromated Mo-Kα radiation and a rotating anode generator. The data were corrected for Lorentz and polarization effects, and for crystal absorption (min and max transmission factors = 0.79 and 1.00). Three standard refrections measured every 150 reflections showed no crystal decay. The structure was solved by direct methods[10] and expanded using Fourier

techniques.[11] All non-hydrogen atoms were refined anisotropically. The final cyclic of full-matrix least-squares refinement was based on 2224 observed reflections ($I > 3.00\sigma(I)$) and 229 variable parameters.

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