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PREPARATION OF IODO-INDUCED 1,3-OXATHIANE COMPOUNDS *VIA* INTRAMOLECULAR PUMMERER REARRANGEMENT OF 2-BENZYLSULFINYL-BICYCLO[2.2.1]HEPT-5-ENE

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Abstract – Iodooxathianes (**2a** and **2b**) were prepared from the γ,δ-unsaturated sulfinyl compound (**1**) *via* the iodonium-promoted intramolecular Pummerer reaction. A two-step conversion of **1** into **2a** and **2b** involving iodohydrination and the Pummerer rearrangement was also achieved.

The intramolecular Pummerer rearrangement[1] is a useful method for the preparation of heterocyclic compounds. For example, isoquinolines,[2] β- and other lactams,[3] benzothiazepine,[4] isothiochroman,[5] etc. have been prepared through the intramolecular Pummerer-type reaction of various sulfinyl compounds. 1,3-Oxathianes, which are important functional groups as masked carbonyl compounds and acyl anion equivalents,[6] can be formed not only by the *O,S*-acetalization of the carbonyl group[7] but also by the Pummerer rearrangement of sulfoxides.[8] Recently, we reported that γ,δ-unsaturated sulfinyl compounds could be transformed into 1,3-oxathianes *via* the Pummerer reaction using *p*-toluenesulfonic acid (*p*-TSA) as a promotor.[9] Although the detailed reaction mechanism of this transformation is not clear, we propose that a five-membered ring sulfonium ion is plausible as a reactive intermediate (Scheme 1).

In the course of our work directed towards the development of a new type of Pummerer reaction, we investigated the effect of the iodonium ion as a promoting electrophile during the initial step in Scheme 1 instead of protonic acid.

Scheme 1

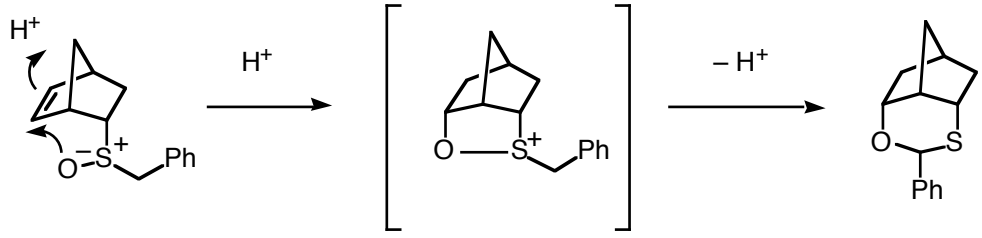
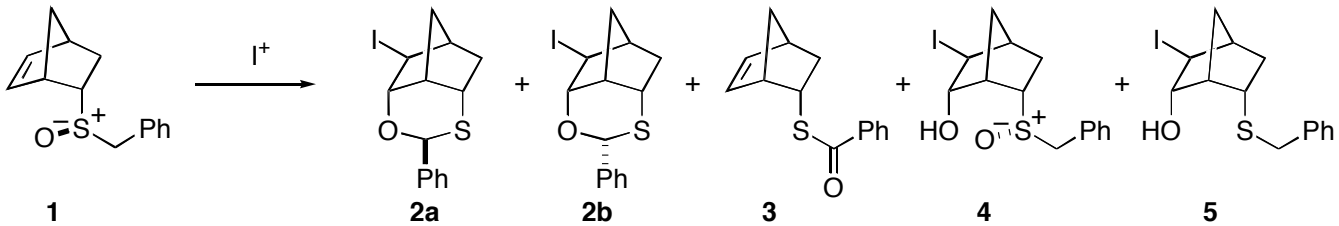


Table 1



1 **2a** **2b** **3** **4** **5**

Entry	Reaction conditions	Yield (%)[a]			
		2a + **2b**[b]	**3**	**4**	**5**
1	NIS (1 eq.) xylene, reflux, 1 h	23 (36:1)	19	– [d]	17
2	NIS (1 eq.) xylene, reflux, 10 min	15 (35:1)	21	– [d]	– [d]
3	NIS (1.1 eq.) CH_2Cl_2, 0 ˚C, 2 h	9[c]	– [d]	61	8
4	NIS (1.1 eq.) CH_2Cl_2, –78 ˚C, 4 h	– [d]	– [d]	80	– [d]
5	I_2 (1.1 eq.) CH_2Cl_2, ruflux, 15 min	20 [c]	– [d]	25	37
6	I_2 (1.1 eq.) CH_2Cl_2, –20 ˚C	No reaction			
7	i) I_2 (1.1 eq.) CH_2Cl_2, 0 ˚C ii) DABCO (1.1 eq) rt, 24 h	24 (1:1)	– [d]	69	– [d]

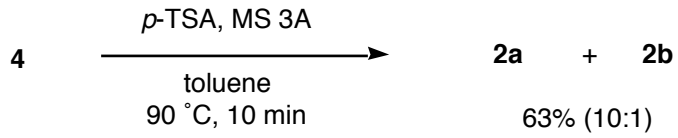
a) Isolated yield. b) Values in parentheses are the ratios of **2a** and **2b** (**2a**:**2b**). The ratio was determined by ^{1}H-NMR integration. c) The ratio was not determined. d) Not detected.

First, the reaction of the *γ*,*δ*-unsaturated sulfinyl compound (**1**)[9b] with *N*-iodosuccinimide (NIS) was carried out under heating conditions. These results are summarized in Table 1. In this reaction, iodooxathianes (**2a** and **2b**), the *S*-benzoyl compound (**3**), and the unexpectedly reduced iodohydrin (**5**) were obtained as isolable products (Entry 1).[10] The short reaction time lowered the yield of the oxathiane (**2**) and suppressed the generation of the iodohydrin (**5**) (Entry 2). When the reaction was carried out in CH_2Cl_2 at 0 ˚C, iodohydrin (**4**)[11] was mainly obtained along with small amounts of **2** and **5** (Entry 3). The reaction with NIS at -78 ˚C gave **4** as the sole product (Entry 4). The use of iodine as an electrophile in refluxing CH_2Cl_2 afforded **2**, **4**, and **5** (Entry 5), whereas the reaction at -20 ˚C resulted in the quantitative recovery of the starting sulfoxide (**1**) (Entry 6). The combination of iodine and DABCO

produced **2** and **4** without the generation of reduced iodohydrin (**5**) (Entry 7). Further efforts to obtain the iodooxathianes (**2a** and **2b**) in higher yield were unsuccessful.

An alternative method for the preparation of iodooxathiane (**2**) was investigated. In the previous report, we described the intramolecular Pummerer rearrangement of *ortho*-hydroxymethylphenyl sulfoxides to afford 1,3-oxathianes using the *p*-TSA – molecular sieves (MS) 3A system.[12] Application of this reagent system to iodohydrin (**4**) was examined. As shown in Scheme 2, the reaction of **4** with the *p*-TSA –MS 3A system in toluene at 90 ℃ afforded the 1,3-oxathiane (**2a** and **2b**) in 63% yield with a 10:1 ratio.[13] This result means that it is possible to transform γ,δ-unsaturated sulfinyl compound (**1**) into iodooxathiane (**2**) in two steps.

Scheme 2



In conclusion, we have now demonstrated the first example of the iodonium-promoted Pummerer reaction of a γ,δ-unsaturated sulfinyl compound and two-step conversion of **1** into **2** involving iodohydrination and the Pummerer rearrangement process.

ACKNOWLEDGMENT

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EXPERIMENTAL

General: Melting points were measured using a Yanagimoto micro melting point hot-plate apparatus and are uncorrected. IR spectra were recorded on a JASCO A-102 or FTIR-350 spectrophotometer. NMR spectra were taken with a Varian VXR-500 or VXR-200 instrument with the chemical shifts being reported as δ ppm and couplings expressed in Hertz. FAB-MS were obtained with a VG-70SE instrument using *m*-nitrobenzyl alcohol as the matrix. Silica gel column chromatography was carried out with Wako-gel C-200. Merck Silica-gel 60 F254 plates (No. 5744) were used for the preparative TLC. All reactions were carried out under argon atmosphere.

***endo*-2-Benzylsulfinylbicyclo[2.2.1]hept-5-ene** (**1**): This compound was prepared by previously reported method.[9b]

Reaction of 1 with NIS under heating (**Table, Entry 1**)

NIS (56.2 mg, 0.25 mmol) was added to a solution of **1** (58.1 mg, 0.25 mmol) in xylene (3 mL) and the mixture was heated for 1 h under reflux. After being poured into a saturated $NaHCO_3$ aqueous solution, the mixture was extracted with CH_2Cl_2. The organic layer was washed with a saturated $Na_2S_2O_3$ aqueous solution and brine, dried over $MgSO_4$, and evaporated to give a residue. Repeated silica gel column

chromatography and preparative TLC with AcOEt–hexane or Et_2O–CH_2Cl_2 afforded **2** (20.5 mg, 23%, **2a**:**2b** = 36:1), **3** (10.9 mg, 19%), and **5** (15.4 mg, 17%). The ratio of **2a** to **2b** was determined by ^{1}H-NMR integration. The major oxathiane (**2a**) was isolated by recrystallization from Et_2O–CH_2Cl_2 to give colorless needles.

2-Iodo-5-phenyl-4-oxa-6-thiatricyclo[5.2.1.0^{3,8}]decane (**2a**): mp 129 ℃. IR ($CHCl_3$) cm^{-1}: 2980, 1460, 1300, 1270, 1150, 1130, 1085, 1060. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.62 (d, 1H, *J* = 11.0), 1.90 (dt, 1H, *J* = 14.0, 3.5), 2.04 (d, 1H, *J* = 11.0), 2.34 (br s, 1H), 2.44 (ddd, 1H, *J* = 14.0, 12.0, 4.5), 2.70 (d, 1H, *J* = 4.5), 3.19 (dt, 1H, *J* = 12.0, 3.5), 4.38 (t, 1H, *J* = 3.0), 5.11 (br s, 1H), 5.92 (s, 1H), 7.30–7.38 (m, 3H), 7.48–7.51 (m, 2H). FAB-MS (positive ion mode) *m*/*z*: 359 $(M+1)^+$. *Anal*. Calcd for $C_{14}H_{15}OIS$: C, 46.94; H, 4.22. Found: C, 46.96; H, 4.33.

***endo*-*S*-Bicyclo[2.2.1]hept-5-en-2-yl thiobenzoate** (**3**): Oil. IR (neat) cm^{-1}: 3000, 1660, 1590, 1455, 1345, 1080, 915. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.05 (dt, 1H, *J* = 12.4, 3.0), 1.44 (d, 1H, *J* = 8.6), 1.54–1.63 (m, 1H), 2.42 (ddd, 1H, *J* = 12.4, 9.0, 3.6), 2.96 (br s, 1H), 3.19 (br s, 1H), 4.12 (dt, 1H, *J* = 9.0, 3.8), 6.08 (dd, 1H, *J* = 5.6, 2.8), 6.27 (dd, 1H, *J* = 5.6, 3.2), 7.36–7.60 (m, 3H), 7.90–7.97 (m, 2H). FAB-MS (positive ion mode) *m*/*z*: 321 $(M+1)^+$.

Benzyl 6-hydroxy-5-iodobicyclo[2.2.1]heptan-2-yl sulfide (**5**): Oil. IR (neat) cm^{-1}: 3430, 3000, 1460, 1155, 1145, 1055, 945. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.33 (ddd, 1H, *J* = 13.6, 5.6, m2.8), 1.42 (ddt, 1H, *J* = 11.0, 3.6, 1.8), 2.03 (ddt, 1H, *J* = 11.0, 2.8, 1.4), 2.21 (ddd, 1H, *J* = 13.6, 11.6, 5.4), 2.48 (br s, 1H), 2.60 (d, 1H, *J* = 5.4), 3.16 (dddd, 1H, *J* = 13.6, 5.4, 3.6, 2.0), 3.74 (t, 1H, *J* = 3.6), 3.86 (s, 2H), 4.68–4.86 (m, 1H), 4.99 (d, 1H, *J* = 10.8), 7.21–7.37 (m, 5H). FAB-MS (positive ion mode) *m*/*z*: 361 $(M+1)^+$. *Anal*. Calcd for $C_{14}H_{17}OIS$: C, 46.68; H, 4.76. Found: C, 46.72; H, 4.70.

Reaction of 1 with NIS at –78 ˚C (Table, Entry 4)

NIS (37.1 mg, 0.17 mmol) was added to a solution of **1** (34.8 mg, 0.15 mmol) in dry CH_2Cl_2 (3 mL) at -78 ℃. The reaction mixture was stirred for 4 h at -78 ℃, and then the cooling bath was removed. The entire mixture was poured into a saturated $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2. The organic layer was washed with a saturated $Na_2S_2O_3$ aqueous solution and brine, dried over $MgSO_4$, and evaporated. A residual mixture was subjected to preparative TLC with AcOEt to give pure **4** (45.3 mg, 80%). An analytical sample was obtained by recrystallization from benzene.

Benzyl 6-hydroxy-5-iodobicyclo[2.2.1]heptan-2-yl sulfoxide (**4**): mp 193 ℃ (decomp). IR (KBr) cm^{-1}: 3190, 2970, 1160, 1060, 990, 765, 700. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.54 (ddt, 1H, *J* = 10.5, 3.0, 1.5), 1.92 (ddd, 1H, *J* = 13.0, 11.5, 5.0), 2.17 (d, 1H, *J* = 10.5), 2.23 (ddd, 1H, *J* = 13.0, 5.5, 3.0), 2.55 (br s, 1H), 2.69 (d, 1H, *J* = 4.0), 2.93 (dt, 1H, *J* = 11.0, 5.0), 3.63 (t, 1H, *J* = 3.5), 3.86 (d, 1H, *J* = 12.5), 4.13 (d, 1H, *J* = 12.5), 4.57 (t, 1H, *J* = 4.0), 7.25–7.27 (m, 2H), 7.36–7.41 (m, 3H). FAB-MS (positive ion mode) *m*/*z*: 377 $(M+1)^+$. *Anal*. Calcd for $C_{14}H_{17}O_2IS$: C, 44.69; H, 4.55. Found: C, 44.44; H, 4.54.

Reaction of 1 with I_2 and DABCO (Table, Entry 7)

Sublimated I_2 (41.9 mg, 0.17 mmol) was added to a solution of **1** (34.8 mg, 0.15 mmol) in dry CH_2Cl_2 (3 mL) at 0 ℃, and then stirred for 3 h. After DABCO (18 mg, 0.16 mmol) was added at 0 ℃, the reaction mixture was stirred for 2 h at 0 ℃ and for 18 h at rt. The entire mixture was poured into 10% HCl aqueous solution and extracted with CH_2Cl_2. The organic layer was washed with a saturated $NaHCO_3$ aqueous solution, $Na_2S_2O_3$ solution, and brine. After drying over $MgSO_4$ and evaporation, the resulting residue was purified by preparative TLC with AcOEt–hexane (1:5) to give a mixture of **2a** and **2b** (14.0 mg, 24%, **2a**:**2b** = 1:1), and **4** (38.9 mg, 69%).

Reaction of 4 with *p*-TSA and MS 3A

A mixture of **4** (90 mg, 0.24 mmol), MS 3A (900 mg), anhydrous *p*-TSA (8.3 mg, 0.048 mmol), and dry toluene (3 mL) was stirred for 10 min at 90 ℃, and then filtered. The filtrate was poured into a saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a brown residue. Purification by silica gel column chromatography with CH_2Cl_2–hexane (1:3) afforded **2** (54.2 mg, 63%, **2a**:**2b** = 10:1). After recrystallization from benzene to remove most of **2a**, the residual mixture of **2a** and **2b** was subjected to repeated preparative TLC with a solvent system of CH_2Cl_2–ether or CH_2Cl_2–hexane. Minor oxathiane (**2b**) (1.0 mg) was isolated in a pure form.

Minor oxathiane (**2b**): Oil. IR ($CHCl_3$) cm^{-1}: 2930, 1465, 1300, 1135, 1060. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.77 (ddt, 1H, *J* = 10.5, 3.0, 1.5), 1.82 (ddd, 1H, *J* = 13.0, 4.5, 2.5), 2.29–2.36 (m, 2H), 2.34 (br s, 1H), 2.71 (d, 1H, *J* = 5.0), 2.93 (br s, 1H), 3.53 (dddd, 1H, *J* = 11.0, 6.5, 4.5, 2.5), 4.24 (dd, 1H, *J* = 3.0, 1.5), 5.19 (d, 1H, *J* = 5.0), 6.05 (s, 1H), 7.31–7.36 (m, 3H), 7.43–7.46 (m, 2H). HRMS (FAB): Calcd for $C_{14}H_{16}OIS$ $(M+H)^+$: 358.9967. Found: 359.0002.

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10. We assume that the thioester (**3**) was generated by the decomposition of 1,3-oxathiane (**2**). However, the mechanism for the generation of the reduced iodohydrin (**5**) is ambiguous at present.
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13 The major **2a** may be thermodynamically controlled product. Studies on the precise mechanism are now under investigation.