

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

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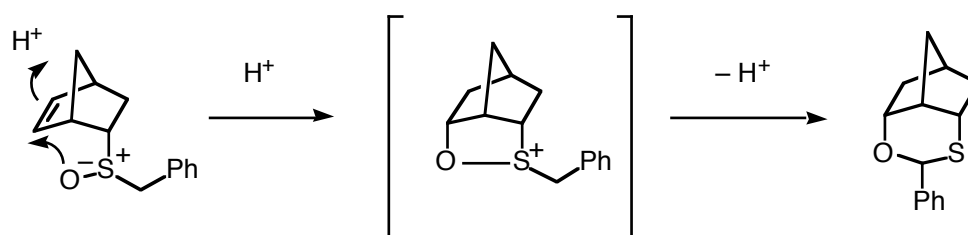
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**Abstract** – Iodooxathianes (**2a** and **2b**) were prepared from the  $\gamma,\delta$ -unsaturated sulfinyl compound (**1**) via the iodonium-promoted intramolecular Pummerer reaction. A two-step conversion of **1** into **2a** and **2b** involving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

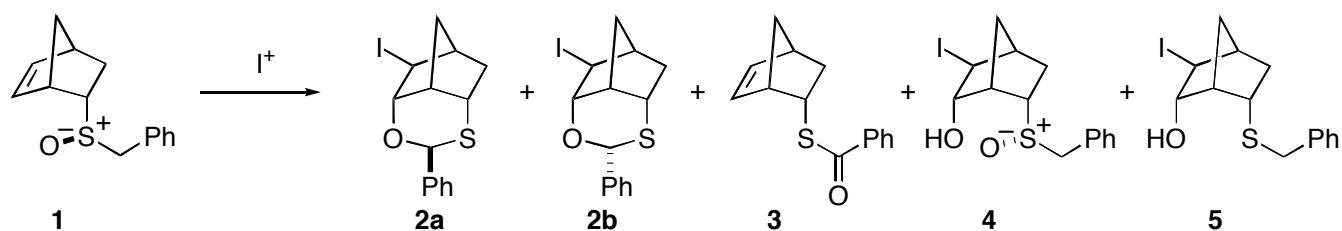
The intramolecular Pummerer rearrangement<sup>1</sup> is a useful method for the preparation of heterocyclic compounds. For example, isoquinolines,<sup>2</sup>  $\beta$ - and other lactams,<sup>3</sup> benzothiazepine,<sup>4</sup> isothiochroman,<sup>5</sup> etc. have been prepared through the intramolecular Pummerer-type reaction of various sulfinyl compounds. 1,3-Oxathianes, which are important functional groups as masked carbonyl compounds and acyl anion equivalents,<sup>6</sup> can be formed not only by the *O,S*-acetalization of the carbonyl group<sup>7</sup> but also by the Pummerer rearrangement of sulfoxides.<sup>8</sup> Recently, we reported that  $\gamma,\delta$ -unsaturated sulfinyl compounds could be transformed into 1,3-oxathianes via the Pummerer reaction using *p*-toluenesulfonic acid (*p*-TSA) as a promotor.<sup>9</sup> 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**



Entry	Reaction conditions	Yield (%) <sup>a</sup>			
		<b>2a + 2b</b> <sup>b</sup>	<b>3</b>	<b>4</b>	<b>5</b>
1	NIS (1 eq.) xylene, reflux, 1 h	23 (36:1)	19	– <sup>d</sup>	17
2	NIS (1 eq.) xylene, reflux, 10 min	15 (35:1)	21	– <sup>d</sup>	– <sup>d</sup>
3	NIS (1.1 eq.) CH <sub>2</sub> Cl <sub>2</sub> , 0 °C, 2 h	9 <sup>c</sup>	– <sup>d</sup>	61	8
4	NIS (1.1 eq.) CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 4 h	– <sup>d</sup>	– <sup>d</sup>	80	– <sup>d</sup>
5	I <sub>2</sub> (1.1 eq.) CH <sub>2</sub> Cl <sub>2</sub> , reflux, 15 min	20 <sup>c</sup>	– <sup>d</sup>	25	37
6	I <sub>2</sub> (1.1 eq.) CH <sub>2</sub> Cl <sub>2</sub> , –20 °C	No reaction			
7	i) I <sub>2</sub> (1.1 eq.) CH <sub>2</sub> Cl <sub>2</sub> , 0 °C ii) DABCO (1.1 eq) rt, 24 h	24 (1:1)	– <sup>d</sup>	69	– <sup>d</sup>

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

First, the reaction of the  $\gamma,\delta$ -unsaturated sulfinyl compound (**1**)<sup>9b</sup> with *N*-iodosuccinimide (NIS) was carried out under heating conditions. These results are summarized in Table 1. In this reaction, iodoxathianes (**2a** and **2b**), the *S*-benzoyl compound (**3**), and the unexpectedly reduced iodohydrin (**5**) were obtained as isolable products (Entry 1).<sup>10</sup> 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<sub>2</sub>Cl<sub>2</sub> at 0 °C, iodohydrin (**4**)<sup>11</sup> 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<sub>2</sub>Cl<sub>2</sub> 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.<sup>12</sup> 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 °C afforded the 1,3-oxathiane (**2a** and **2b**) in 63% yield with a 10:1 ratio.<sup>13</sup> This result means that it is possible to transform  $\gamma,\delta$ -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  $\gamma,\delta$ -unsaturated sulfinyl compound and two-step conversion of **1** into **2** involving iodohydration and the Pummerer rearrangement process.

## ACKNOWLEDGMENT

We are grateful to the SC-NMR Laboratory of Okayama University for the high-field NMR experiments.

## 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  $\delta$  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.<sup>9b</sup>

### 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<sub>3</sub> aqueous solution, the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with a saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> aqueous solution and brine, dried over MgSO<sub>4</sub>, and evaporated to give a residue. Repeated silica gel column

chromatography and preparative TLC with AcOEt–hexane or Et<sub>2</sub>O–CH<sub>2</sub>Cl<sub>2</sub> 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 <sup>1</sup>H-NMR integration. The major oxathiane (**2a**) was isolated by recrystallization from Et<sub>2</sub>O–CH<sub>2</sub>Cl<sub>2</sub> to give colorless needles.

**2-Iodo-5-phenyl-4-oxa-6-thiatricclo[5.2.1.0<sup>3,8</sup>]decane (2a):** mp 129 °C. IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 2980, 1460, 1300, 1270, 1150, 1130, 1085, 1060. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) 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)<sup>+</sup>. *Anal.* Calcd for C<sub>14</sub>H<sub>15</sub>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<sup>-1</sup>: 3000, 1660, 1590, 1455, 1345, 1080, 915. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) 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)<sup>+</sup>.

**Benzyl 6-hydroxy-5-iodobicyclo[2.2.1]heptan-2-yl sulfide (5):** Oil. IR (neat) cm<sup>-1</sup>: 3430, 3000, 1460, 1155, 1145, 1055, 945. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) 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)<sup>+</sup>. *Anal.* Calcd for C<sub>14</sub>H<sub>17</sub>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<sub>2</sub>Cl<sub>2</sub> (3 mL) at –78 °C. The reaction mixture was stirred for 4 h at –78 °C, and then the cooling bath was removed. The entire mixture was poured into a saturated NaHCO<sub>3</sub> aqueous solution and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with a saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> aqueous solution and brine, dried over MgSO<sub>4</sub>, 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 °C (decomp). IR (KBr) cm<sup>-1</sup>: 3190, 2970, 1160, 1060, 990, 765, 700. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) 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)<sup>+</sup>. *Anal.* Calcd for C<sub>14</sub>H<sub>17</sub>O<sub>2</sub>IS: C, 44.69; H, 4.55. Found: C, 44.44; H, 4.54.

#### Reaction of **1** with I<sub>2</sub> and DABCO (Table, Entry 7)

Sublimated I<sub>2</sub> (41.9 mg, 0.17 mmol) was added to a solution of **1** (34.8 mg, 0.15 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (3 mL) at 0 °C, and then stirred for 3 h. After DABCO (18 mg, 0.16 mmol) was added at 0 °C, the reaction mixture was stirred for 2 h at 0 °C and for 18 h at rt. The entire mixture was poured into 10% HCl aqueous solution and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with a saturated NaHCO<sub>3</sub> aqueous solution, Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution, and brine. After drying over MgSO<sub>4</sub> 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 °C, and then filtered. The filtrate was poured into a saturated NaHCO<sub>3</sub> aqueous solution and extracted with CHCl<sub>3</sub>. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and evaporated to give a brown residue. Purification by silica gel column chromatography with CH<sub>2</sub>Cl<sub>2</sub>–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<sub>2</sub>Cl<sub>2</sub>–ether or CH<sub>2</sub>Cl<sub>2</sub>–hexane. Minor oxathiane (**2b**) (1.0 mg) was isolated in a pure form.

**Minor oxathiane (2b):** Oil. IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 2930, 1465, 1300, 1135, 1060. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) 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<sub>14</sub>H<sub>16</sub>OIS (M+H)<sup>+</sup>: 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.