

**SYNTHESIS OF 2,3,4,5-TETRAHYDRO-1H-2-BENZAZEPINES VIA  
PUMMERER-TYPE CYCLIZATION OF N-ARYLMETHYL-N-(3-  
PHENYLSULFINYLPROPYL)FORMAMIDES**

Yoshie Horiguchi, Toshiaki Saitoh, Sachiko Terakado, Konomi Honda,

Tomoko Kimura, Jun Toda, and Takehiro Sano\*

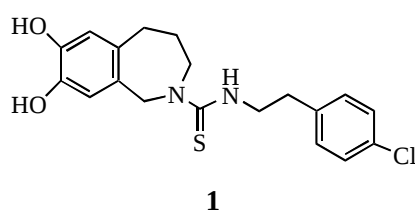
*Showa Pharmaceutical University, 3-3165, Higashi-tamagawagakuen, Machida,  
Tokyo 194-8543, Japan*

**Abstract** A construction of 1H-benzazepine ring system was achieved *via* a modified Pummerer reaction of N-arylmethyl-N-(3-phenylsulfinylpropyl)-formamides (**5**) using trifluoroacetic acid and borontrifluoride etherate. This method provides an effective synthesis of 7,8-dimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (**10a**), the synthetic intermediate of capsazepine (**1**), an antagonist of capsaicin and resiniferatoxin.

It is well known that the *in situ* formed thionium ion generated under the acidic conditions from a sulfinyl precursor (Pummerer reaction) is a powerful electrophilic group reacting efficiently with nucleophilic carbon species such as alkenes, aromatics and enol ethers.<sup>1</sup> This reaction was successfully applied for the synthesis of various carbocycles and heterocycles.<sup>2</sup> Recently, we explored the reaction and used it as the key strategy for the syntheses of 1,2,3,4-tetrahydroisoquinolines,<sup>3</sup> 1,2,3,4-tetrahydroquinolines,<sup>4</sup> erythrinan,<sup>5</sup> isopavine and pavine alkaloids,<sup>6</sup> 2-quinolones,<sup>7</sup> and 2,3,4,5-tetrahydro-1H-3-benzazepines.<sup>8</sup>

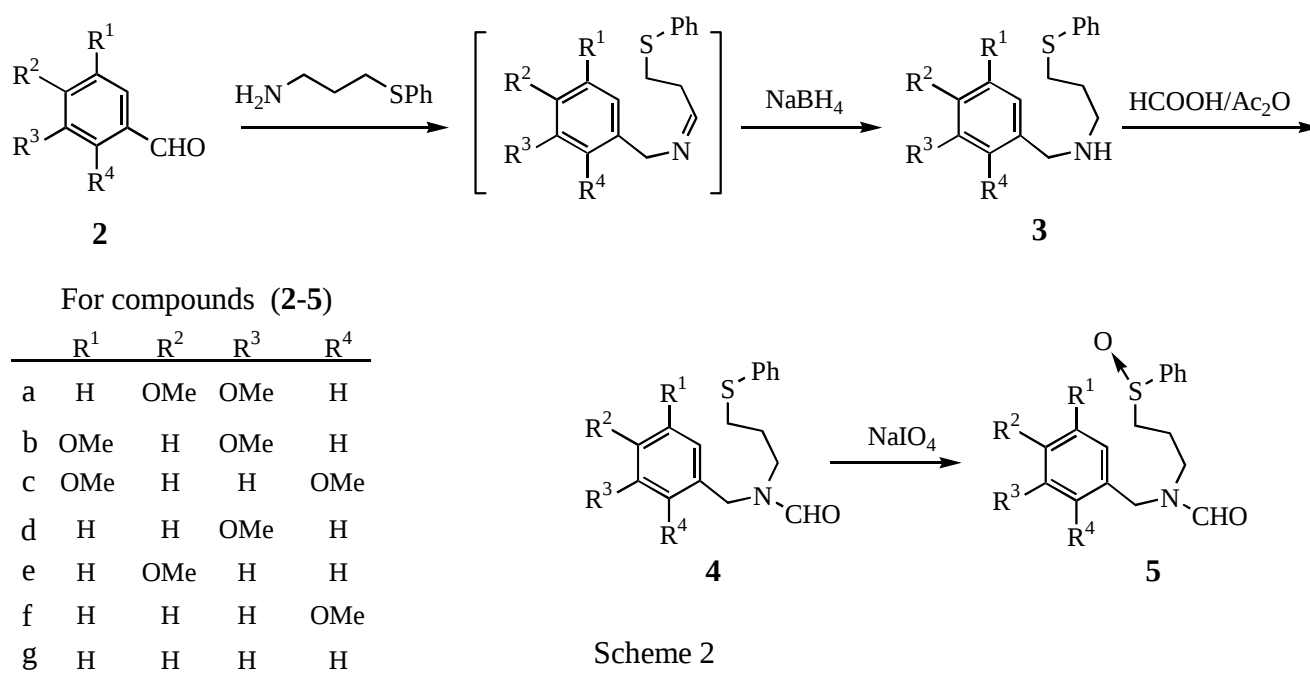
In these studies we have found that the cyclization under a usual Pummerer condition using trifluoroacetic anhydride (TFAA) as a sole reagent highly effectively proceeds at room temperature when the aromatic ring is sufficiently electron-rich (method A).<sup>3,4</sup> On the other hand in the substrates lacking an electron donating substituent on the aromatic ring the method A does not induce the cyclization unless boron trifluoride diethyl etherate ( $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ) is used as an additive reagent.<sup>3a-c,4</sup> This method using TFAA and  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (method B) seems to be effective for the cyclization of a weak nucleophilic aromatic  $\pi$ -bond.

In this paper we described the synthesis of 2,3,4,5-tetrahydro-1*H*-2-benzazepine *via* cyclization using Pummerer reaction and an application to the synthesis of capsazepine (**1**), an antagonist of the sensory neuron excitants capsaicin and resiniferatoxin.<sup>9</sup>



## Preparation of Sulfoxides

The sulfoxides (**5**), substrates of Pummerer reaction, were prepared from aromatic aldehydes (**2**) and 3-phenylsulfanylpropylamine<sup>4</sup> as follows. Condensation of **2** with the amine in EtOH in the presence of

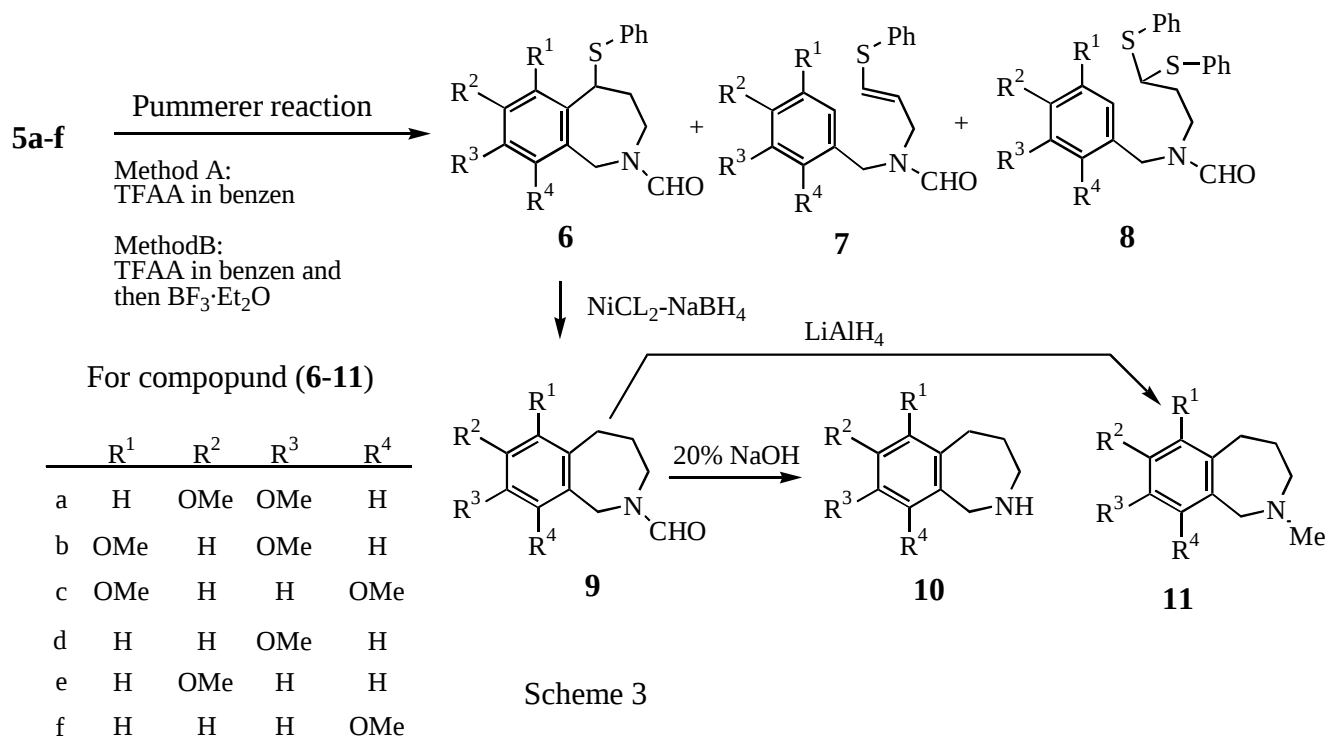


Scheme 2

acetic acid followed by  $\text{NaBH}_4$  reduction of the resulting imine afforded *N*-arylmethyl-3-phenylsulfanylpropylamines (**4**) in good yields. The amines (**3**) were protected by formylation and the resulting formamides (**4**) were oxidized with sodium metaperiodate ( $\text{NaIO}_4$ ) in aqueous methanol to produce **5** in excellent overall yields. The products (**3**), (**4**), and (**5**) were well characterized by MS, IR, and  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectral data (See Experimental).

### Pummerer Reaction (method A)

A solution of **5** in benzene was treated with TFAA at room temperature for appropriate times under an argon atmosphere (method A condition). Sulfoxide (**5a**) yielded 5-phenylsulfanylbenzazepine (**6a**) in moderate yield (56%) accompanied with vinyl sulfide (**7a**) as an uncyclized product (31%). The sulfoxide (**5b**) produced the corresponding benzazepine (**6b**) in yield of only 13%, although the aromatic ring is electronically activated by two OMe groups positioned at *para* and *ortho*. In this case no other products were characterized. The reaction of **5c** having two OMe groups at *ortho*- and *meta*-positions yielded no cyclized product. Furthermore, the sulfoxide (**5d**) having a *para* OMe group afforded the corresponding benzazepine (**6d**) in 13% yield. Other monomethoxy sulfoxides (**5e-5f**) having a *meta* OMe group and



sulfoxide (**5g**) with no OMe group, when treated with TFAA, merely yielded complex mixtures. No benzazepines could be obtained in any extent.

### Pummerer Reaction (method B)

The cyclization of sulfoxides (**5**) was examined under the method B conditions. A solution of **5a** in benzene was treated with TFAA for 45 min at room temperature, then  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  was added and the mixture was allowed to react for further 45 min, giving the benzazepine (**6a**) in 66% yield and **4a** in 5% yield. Thus, the yield of **6a** was comparable to that achieved by method A. In the cases of **5b**, **5c**, and **5d** use of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  as an additive improved the ring closure reaction to give **6b**, **6c**, and **6d** in moderate yields as shown in the Table. However, the reactions of **5e-g** on the similar treatment under method B conditions did not caused the desired cyclization in any extent. The sulfoxides (**5e**) and (**5f**) only gave the bis-phenylsulfanyl derivative (**8e**) and (**8f**) respectively.

Table Pummere Reaction of Sulfoxides (**5**)

| sulfoxide ( <b>5</b> ) | Conditions <sup>a)</sup> |                                         |      | Yield (%)        |        |             |    |
|------------------------|--------------------------|-----------------------------------------|------|------------------|--------|-------------|----|
|                        | Reagent                  | Additive                                | Time | PheS-bebzazepine | Others |             |    |
| <b>5a</b>              | TFAA                     | non                                     | 4    | <b>(6a)</b>      | 56     | <b>(7a)</b> | 31 |
| <b>5a</b>              | TFAA                     | $\text{BF}_3 \cdot \text{Et}_2\text{O}$ | 1.5  | <b>(6a)</b>      | 66     | <b>(4a)</b> | 5  |
| <b>5b</b>              | TFAA                     | non                                     | 2    | <b>(6b)</b>      | 13     |             |    |
| <b>5b</b>              | TFAA                     | $\text{BF}_3 \cdot \text{Et}_2\text{O}$ | 1    | <b>(6b)</b>      | 61     |             |    |
| <b>5c</b>              | TFAA                     | non                                     | 12   | <b>(6c)</b>      | b)     |             |    |
| <b>5c</b>              | TFAA                     | $\text{BF}_3 \cdot \text{Et}_2\text{O}$ | 4    | <b>(6c)</b>      | 45     |             |    |
| <b>5d</b>              | TFAA                     | non                                     | 18   | <b>(6d)</b>      | 13     |             |    |
| <b>5d</b>              | TFAA                     | $\text{BF}_3 \cdot \text{Et}_2\text{O}$ | 3    | <b>(6d)</b>      | 78     |             |    |
| <b>5e</b>              | TFAA                     | $\text{BF}_3 \cdot \text{Et}_2\text{O}$ | 4    |                  |        | <b>(8e)</b> | 21 |
| <b>5f</b>              | TFAA                     | $\text{BF}_3 \cdot \text{Et}_2\text{O}$ | 3    |                  |        | <b>(8f)</b> | 33 |
| <b>5g</b>              | TFAA                     | $\text{BF}_3 \cdot \text{Et}_2\text{O}$ | 24   |                  | b)     |             |    |

a) In benzene at room temperature, b) No characterizable products

The results summarized in the Table indicated that the formation of benzazepine ring by Pummerer

reaction of **5** occurred under method B conditions if the nucleophilic center of the aromatic ring is activated by electron donating group such as OMe group, although this cyclization leading to benzazepine ring, particularly under method A conditions, was much less effective when compared with that of *N*-aryl-*N*-arylmethyl-*N*-(3-phenylsulfinylethyl)formamide leading to 1,2,3,4-tetrahydroisoquinoline ring.<sup>4</sup>

### Preparation of Benzazepines

Reductive removal of the phenylsulfanyl group readily proceeded on treatment with NiCl<sub>2</sub>-NaBH<sub>4</sub> in MeOH-THF to give *N*-formyl-benzazepines (**9**) in good yields. Deprotection of the *N*-formyl group was achieved by conventional methods. Alkaline hydrolysis gave the benzazepines (**10**). Reduction of **9** with LiAlH<sub>4</sub> gave *N*-methylbenzazepines (**11**).

The synthesis using this route provides 7,8-dimethoxy- (**10a**), 6,8-dimethoxy- (**10b**), 6,9-dimethoxy- (**10c**), 8-methoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**10d**), and their *N*-methyl derivatives (**11**) in moderate overall yields. 7,8-Dimethoxy derivative (**10a**) is the synthetic precursor of capsazepine (**1**).<sup>9,10</sup>

## EXPERIMENTAL

**General Notes** Unless otherwise noted, the following procedures were adopted. Melting points were taken on a Yanagimoto SP-M1 hot-stage melting point apparatus and are uncorrected. IR spectra were obtained as films for oils and gums, and KBr disks for solids with a JASCO FT/IR-5000 spectrometer, and are given in cm<sup>-1</sup>. NMR spectra were measured on a JEOL JNM-AL 300 (<sup>1</sup>H-NMR, 300 MHz; <sup>13</sup>C-NMR, 75 MHz) NMR spectrometer in CDCl<sub>3</sub> with tetramethylsilane as an internal standard at room temperature and the chemical shifts are given in δ values. LR-MS were taken on JMS-AM20, and high resolution MS (HR-MS) on a JEOL JMS-D300 spectrometer at 70 eV [electron ionization MS (EI-MS)] or at 270 eV [chemical ionization (CI-MS)], reactant gas: *iso*-butane) using direct or GC/MS inlet systems. Elemental analyses were recorded on a Yanaco-CHN-corder MT-3. Thin layer chromatography (TLC) was performed on Merck precoated Silica gel 60 F<sub>254</sub> plates (Merck).

Column chromatography was carried out with silica gel (Wakogel C-200). The organic extract from each reaction mixture was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to dryness.

**Preparation of *N*-(3,4-Dimethoxyphenyl)methyl-(3-phenylsulfanyl)propylamine (3a). Typical**

**Procedure.** A solution of 3,4-dimethoxybenzaldehyde (**2a**) (1.19 g, 7.2 mmol), 3-phenylsulfanylpropylamine (1.2 g, 7.2 mmol)<sup>4</sup> and acetic acid (5.184 g, 8.64 mmol) in EtOH (250 mL) was refluxed for 23 h. NaBH<sub>4</sub> (272 mg, 7.2 mmol) was added slowly to a reaction mixture at 0°C and stirred for 30 min at rt. Water was added to the reaction mixture. After removal of the solvent *in vacuo*, the residue was extracted with CHCl<sub>3</sub>. The residual oil was purified by column chromatography with ethyl acetate to give **3a** (1.40g, 74%) as a yellow oil. IR (film): 3316, 1590. <sup>1</sup>H-NMR: 1.9-2.2 (2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 2.7-3.1 (4H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh and -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.83 (3H, s, OMe), 3.90 (2H, s, -NHCH<sub>2</sub>Ar), 3.92 (3H, s, OMe), 6.7-7.0 (3H, m, ArH), 7.1-7.4 (5H, m, SPh). <sup>13</sup>C-NMR: 25.6 (t), 31.0 (t), 44.7 (t), 50.8 (t), 55.8 (q), 56.2 (q), 110.9 (d), 112.8 (d), 122.6 (d), 123.4 (s), 126.3 (d), 129.0 (dx2), 129.6 (dx2), 135.3 (s), 149.3 (s), 149.5 (s). LRMS *m/z*: 317 (M<sup>+</sup>).

***N*-(3,5-Dimethoxyphenyl)methyl-(3-phenylsulfanyl)propylamine (3b):** From 3,5-dimethoxybenzaldehyde (**2b**) (1.19 g, 7.2 mmol) and 3-phenylsulfanylamine (1.2g, 7.2 mmol); column chromatography with ethyl acetate gave **3b** (1.50 g, 79%) as a pale yellow oil. IR (film): 3311, 1596. <sup>1</sup>H-NMR: 1.82 (2H, quintet, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 2.75 (2H, t, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 2.99 (2H, t, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh) 3.71 (2H, s, -NHCH<sub>2</sub>Ar), 3.78 (6H, s, OMex2), 6.3-6.5 (3H, m, ArH), 7.1-7.4 (5H, m, SPh). <sup>13</sup>C-NMR: 29.4 (t), 31.4 (t), 47.9 (t), 53.9 (t), 55.2 (qx2), 98.9 (d), 105.8 (d), 125.7 (dx2), 128.8 (dx2), 129.0 (dx2), 136.5 (s), 142.8 (s), 160.8 (s). 160.9 (s). LRMS *m/z*: 317 (M<sup>+</sup>).

***N*-(2,5-Dimethoxyphenyl)methyl-(3-phenylsulfanyl)propylamine (3c):** From 2,5-dimethoxybenzaldehyde (**2c**) (1.19 g, 7.2 mmol) and 3-phenylsulfanylamine (1.2g, 7.2 mmol); column chromatography with ethyl acetate gave **3c** (1.90 g, 92%) as a yellow oil. IR (film): 3320, 1586.

$^1\text{H}$ -NMR: 1.83 (2H, quintet,  $J=7$  Hz,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ), 2.72 (2H, t,  $J=7$  Hz,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ), 2.99 (2H, t,  $J=7$  Hz,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ) 3.74 (2H, s,  $-\text{NHCH}_2\text{Ar}$ ), 3.76 (3H, s, OMe), 3.77 (3H, s, OMe), 6.7-7.4 (8H, m, ArH and SPh),  $^{13}\text{C}$ -NMR: 29.4 (t), 31.3 (t), 47.7 (t), 49.0 (t), 55.5 (q), 55.6 (q), 111.0 (d), 112.0 (d), 115.8 (d), 125.6 (d), 128.7 (dx2), 128.9 (dx2), 129.5 (s), 136.6 (s), 151.7 (s), 153.3 (s). LRMS  $m/z$ : 317 ( $\text{M}^+$ ).

***N*-(3-Methoxyphenyl)methyl-(3-phenylsulfanyl)propylamine (3d):** From 3-methoxybenzaldehyde (**2d**) (0.980 g, 7.2 mmol) and 3-phenylsulfanylamine (1.2g, 7.2 mmol); column chromatography with  $\text{CHCl}_3$  gave **3d** (1.736 g, 84%) as yellow oil. IR (film): 1585.  $^1\text{H}$ -NMR: 1.83 (2H, quintet,  $J=7$  Hz,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ), 2.75 (2H, t,  $J=7$  Hz,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ), 2.99 (2H, t,  $J=7$  Hz,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ) 3.75 (2H, s,  $-\text{NHCH}_2\text{Ar}$ ), 3.80 (3H, s, OMe), 6.7-7.4 (9H, m, ArH and SPh),  $^{13}\text{C}$ -NMR: 29.5 (t), 31.5 (t), 48.0 (t), 53.8 (t), 55.1 (q), 112.4 (d), 113.5 (d), 120.3 (d), 125.9 (d), 128.8 (dx2), 129.1 (dx2), 129.3 (d), 136.6 (s), 141.9 (s), 159.7 (s). LRMS  $m/z$ : 287 ( $\text{M}^+$ ).

***N*-(4-Methoxyphenyl)methyl-(3-phenylsulfanyl)propylamine (3e):** From 4-methoxybenzaldehyde (**2e**) (0.980 g, 7.2 mmol) and 3-phenylsulfanylamine (1.2g, 7.2 mmol); column chromatography with  $\text{CHCl}_3$  gave **3e** (1.488 g, 72%) as a yellow oil. IR (film): 1587.  $^1\text{H}$ -NMR: 1.82 (2H, quintet,  $J=7$  Hz,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ), 2.74 (2H, t,  $J=7$  Hz,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ), 2.99 (2H, t,  $J=7$  Hz,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ) 3.70 (2H, s,  $-\text{NHCH}_2\text{Ar}$ ), 3.79 (3H, s, OMe), 7.1-7.4 (9H, m, ArH and SPh),  $^{13}\text{C}$ -NMR: 29.4 (t), 31.5 (t), 47.8 (t), 53.2 (t), 55.2 (q), 113.7 (dx2), 125.8 (d), 128.8 (dx2), 129.1 (dx2), 129.2 (dx2), 132.3 (s), 136.6 (s), 158.6 (s). LRMS  $m/z$ : 287 ( $\text{M}^+$  )

***N*-(2-Methoxyphenyl)methyl-(3-phenylsulfanyl)propylamine (3f):** From 2-methoxybenzaldehyde (**2f**) (0.980 g, 7.2 mmol) and 3-phenylsulfanylamine (1.2g, 7.2 mmol); column chromatography with  $\text{CHCl}_3$  gave **4f** (1.570 g, 76%) as a yellow oil. IR (film): 1610.  $^1\text{H}$ -NMR: 1.83 (2H, quintet,  $J=7$  Hz,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ), 2.72 (2H, t,  $J=7$  Hz,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ), 2.98 (2H, t,  $J=7$  Hz,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ) 3.77 (2H, s,  $-\text{NHCH}_2\text{Ar}$ ), 3.82 (3H, s, OMe), 6.8-7.0 (2H, m, ArH), 7.1-7.4 (7H, m,

ArH and SPh),  $^{13}\text{C}$ -NMR: 29.5 (t), 31.5 (t), 47.9 (t), 49.1 (t), 55.2 (q), 110.2 (d), 120.3 (d), 125.7 (d), 128.1 (d), 128.3 (d), 128.7 (dx2), 129.0 (dx2), 129.7 (d), 136.7 (s), 157.6 (s). LRMS  $m/z$ : 287 ( $\text{M}^+$ ).

***N*-(3-phenylsulfanyl)propylbenzylamine (3g):** From benzaldehyde (**2g**) (0.763 g, 7.2 mmol) and 3-phenylsulfanylamine (1.2g, 7.2 mmol); column chromatography with  $\text{CHCl}_3$  gave **3g** (1.091 g, 59 %) as a yellow oil. IR (film): 1583, 1481.  $^1\text{H}$ -NMR: 1.84 (2H, quintet,  $J=7$  Hz,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ), 2.76 (2H, t,  $J=7$  Hz,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ), 3.00 (2H, t,  $J=7$  Hz,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ) 3.77 (2H, s,  $-\text{NHCH}_2\text{Ar}$ ), 7.0-7.5 (10H, m, Ph and SPh),  $^{13}\text{C}$ -NMR: 29.4 (t), 31.4(t), 47.9 (t), 53.8 (t), 125.7 (d), 126.8 (d), 128.0 (dx2), 128.3 (dx2), 128.7 (dx2), 129.0 (dx2), 136.6 (s), 140.2 (s). LRMS  $m/z$ : 257 ( $\text{M}^+$ ).

**Formylation of 3. Typical Procedure.** The mixture of formic acid (13.8 g, 0.3 mol) and acetic anhydride (10.2 g, 0.1 mol) was added at rt to **3a** (3.17 g, 10 mmol) and the mixture was heated at 70 °C for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was extracted with  $\text{CHCl}_3$ . After removal of the solvent, the residue was chromatographed with hexane-ethyl acetate (1:2) to give **4a** (3.45 g, quant.) as a yellow gum.

***N*-(3,4-Dimethoxyphenyl)methyl-*N*-[(3-phenylsulfanyl)propyl]fromamide (4a)** IR (film): 1669, 1593.  $^1\text{H}$ -NMR: 1.7-1.9 ( total 2H, m,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ), 2.8-3.0 (total 2H, m,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ), 3.2-3.4 (total 2H, m,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ), 3.84, 3.85, 3.86, 3.88 (total 6H, each s, OMe), 4.30, 4.44 (total 2H, each s,  $-\text{NHCH}_2\text{Ar}$ ), 6.7-6.8 (total 3H, m, ArH), 7.2-7.4 (total 5H, m, SPh), 8.19, 8.28 (total 1H, each s, CHO). LRMS  $m/z$ : 345 ( $\text{M}^+$ ). HRMS  $m/z$  ( $\text{M}^+$ ): Calcd for  $\text{C}_{19}\text{H}_{23}\text{NO}_3\text{S}$ : 345.1398. Found: 345.1398

***N*-(3,5-Dimethoxyphenyl)methyl-*N*-[(3-phenylsulfanyl)propyl]fromamide (4b)** From **3b** (3.17 g, 10 mmol); column chromatography with hexane-ethyl acetate (2:1) gave **4b** (3.45g, quant.) as a yellow gum. IR (film): 1671, 1599.  $^1\text{H}$ -NMR: 1.7-1.9 (total 2H, m,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ), 2.8-2.9 (total 2H, m,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ) 3.2-3.5 (total 2H, m,  $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SPh}$ ), 3.76, 3.77, 3.79, 3.84 (total 6H, each s, OMe), 4.28, 4.43 (total 2H, each s,  $-\text{NHCH}_2\text{Ar}$ ), 6.3-6.4 (total 3H, m, ArH), 7.2-7.4 (total 5H, m, SPh), 8.19, 8.25 (total 1H, each s, CHO). LRMS  $m/z$ : 345 ( $\text{M}^+$ ). HRMS  $m/z$  ( $\text{M}^+$ ): Calcd for  $\text{C}_{19}\text{H}_{23}\text{NO}_3\text{S}$ :

345.1399. Found:345.1423.

***N*-(2,5-Dimethoxyphenyl)methyl-*N*-[(3-phenylsulfanyl)propyl]formamide (4c)** From **3c** (3.17 g, 10 mmol); column chromatography with hexane-ethyl acetate (2:1) gave **4c** (3.04g, 88%) as a yellow gum. IR (film): 1671, 1590. <sup>1</sup>H-NMR: 1.8-1.9 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 2.85 (2H, t, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.2-3.4 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.73, 3.76 (total 6H, each s, OMe), 4.32, 4.53 (total 2H, each s, -NHCH<sub>2</sub>Ar), 6.7-6.8 (total 3H, m, ArH), 7.2-7.3 (total 5H, m, SPh), 8.18, 8.26 (total 1H, each s, CHO). LRMS *m/z*: 345 (M<sup>+</sup>). HRMS *m/z* (M<sup>+</sup>): Calcd for C<sub>19</sub>H<sub>23</sub>NO<sub>3</sub>S: 345.1399. Found:345.1434.

***N*-(3-Methoxyphenyl)methyl-*N*-[(3-phenylsulfanyl)propyl]formamide (4d)** From **3d** (2.87 g, 10 mmol); column chromatography with hexane-ethyl acetate (2:1) gave **4d** (2.96g, 94%) as a yellow gum. IR (film): 1678, 1601. <sup>1</sup>H-NMR: 1.80 (2H, quintet, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 2.83, 2.86 (total 2H, each t, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.28, 3.36 (total 2H, each t, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.78, 3.79 (total 3H, each s, OMe), 4.32, 4.47 (total 2H, each s, -NHCH<sub>2</sub>Ar), 6.7-7.4 (total 9H, m, ArH and SPh), 8.20, 8.27 (total 1H, each s, CHO). LRMS *m/z*: 315 (M<sup>+</sup>). HRMS *m/z* (M<sup>+</sup>): Calcd for C<sub>18</sub>H<sub>21</sub>NO<sub>2</sub>S: 315.1290. Found: 315.1288.

***N*-(4-Methoxyphenyl)methyl-*N*-[(3-phenylsulfanyl)propyl]formamide (4e)** From **3e** (2.87 g, 10 mmol); column chromatography with hexane-ethyl acetate (2:1) gave **4e** (2.80 g, 89%) as colorless plates recrystallized from CHCl<sub>3</sub>-Et<sub>2</sub>O, mp 175-178°C. IR: 1672. <sup>1</sup>H-NMR: 1.79 (2H, quintet, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 2.85, 2.85 (total 2H, each t, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.27, 3.34 (total 2H, each t, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.79, 3.80 (total 3H, each s, OMe), 4.29, 4.43 (total 2H, each s, -NHCH<sub>2</sub>Ar), 6.8-7.4 (total 9H, m, ArH and SPh), 8.18, 8.27 (total 1H, each s, CHO). LRMS *m/z*: 315 (M<sup>+</sup>). *Anal.* Calcd for C<sub>18</sub>H<sub>21</sub>NO<sub>2</sub>S: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.53; H, 6.76; N, 4.25.

***N*-(2-Methoxyphenyl)methyl-*N*-[(3-phenylsulfanyl)propyl]formamide (4f)** From **3f** (2.87 g, 10 mmol); column chromatography with hexane-ethyl acetate (2:1) gave **4f** (2.94g, 90%) as a yellow gum.

IR (film): 1670. <sup>1</sup>H-NMR: 1.7-2.0 (2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 2.85 (2H, t, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.29, 3.34 (total 2H, each t, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.80 (3H, each s, OMe), 4.35, 4.56 (total 2H, each s, -NHCH<sub>2</sub>Ar), 6.8-7.5 (total 9H, m, ArH and SPh), 8.18, 8.27 (total 1H, each s, CHO). LRMS *m/z*: 315 (*M*<sup>+</sup>). HRMS *m/z* (*M*<sup>+</sup>): Calcd for C<sub>18</sub>H<sub>21</sub>NO<sub>2</sub>S: 315.1290. Found: 315.1279.

***N*-Benzyl-*N*-[(3-phenylsulfonyl)propyl]formamide (4g)** From **3g** (2.57 g, 10 mmol); column chromatography with hexane-ethyl acetate (2:1) gave **4g** (2.565g, 90%) as a yellow gum. IR (film): 1672. <sup>1</sup>H-NMR: 1.79 (2H, quintet, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 2.83, 2.86 (total 2H, each t, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.29, 3.36 (total 2H, each t, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 4.35, 4.50 (total 2H, each s, -NHCH<sub>2</sub>Ar), 7.1-7.5 (10H, m, Ph and SPh), 8.20, 8.28 (total 1H, each s, CHO). LRMS *m/z*: 285 (*M*<sup>+</sup>). HRMS *m/z* (*M*<sup>+</sup>): Calcd for C<sub>17</sub>H<sub>19</sub>NOS: 285.1184. Found: 285.1177

**Oxidation of 4a with NaIO<sub>4</sub>. Typical Procedure.** NaIO<sub>4</sub> (6.42g, 30 mmol) in H<sub>2</sub>O (35 mL) was added to a solution of **4a** (6.9g, 20 mmol) in MeOH (70 mL) and stirred at rt for 5 h. After removal of inorganic precipitates by filtration, the filtrate was concentrated *in vacuo*. The residue was extracted with CHCl<sub>3</sub>. The product was purified by column chromatography with ethyl acetate to give **5a** (6.137 g, 84%) as a yellow gum.

***N*-(3,4-Dimethoxyphenyl)methyl-*N*-[(3-phenylsulfonyl)propyl]formamide (5a)** IR (film): 1666, 1025. <sup>1</sup>H-NMR: 1.8-2.1 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 2.5-2.8 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.1-3.5 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.86, 3.87, 4.22 (total 6H, each s, OMe), 4.31, 4.41 (total 2H, each s, -NHCH<sub>2</sub>Ar), 6.6-6.9 (total 3H, m, ArH), 7.4-7.6 (total 5H, m, SPh), 8.14, 8.28 (total 1H, each s, CHO). LRMS *m/z*: 361 (*M*<sup>+</sup>).

***N*-(3,5-Dimethoxyphenyl)methyl-*N*-[(3-phenylsulfonyl)propyl]formamide (5b)** From **4b** (3.45 g, 10 mmol); column chromatography with ethyl acetate gave **5b** (3.1g, 86%) as a yellow gum. IR (film): 1668, 1047. <sup>1</sup>H-NMR: 1.8-2.1 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 2.5-2.9 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.2-3.5 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.76, 3.78 (total 6H, each s, OMe), 4.2-4.5 (total 2H, m,

-NHCH<sub>2</sub>Ar), 6.2-6.4 (total 3H, m, ArH), 7.4-7.7 (total 5H, m, SPh), 8.15, 8.25 (total 1H, each s, CHO).  
LRMS *m/z*: 361 (M<sup>+</sup>).

***N*-(2,5-Dimethoxyphenyl)methyl-*N*-[(3-phenylsulfinyl)propyl]fromamide (5c)** From **4c** (3.45 g, 10 mmol); column chromatography with ethyl acetate gave **5c** (3.45g, 95%) as a yellow gum. IR (film): 1669, 1048. <sup>1</sup>H-NMR: 1.8-2.0 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 2.6-2.8 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.2-3.5 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.73, 3.76 (total 6H, each s, OMe), 4.32, 4.50 (total 2H, each s, -NHCH<sub>2</sub>Ar), 6.7-6.8 (total 3H, m, ArH), 7.4-7.6 (total 5H, m, SPh), 8.11, 8.25 (total 1H, each s, CHO).  
LRMS *m/z*: 361 (M<sup>+</sup>).

***N*-(3-Methoxyphenyl)methyl-*N*-[(3-phenylsulfinyl)propyl]fromamide (5d)** From **4d** (6.3 g, 20 mmol); column chromatography with ethyl acetate gave **5d** (4.965, 75%) as a yellow gum. IR (film): 1664, 1045. <sup>1</sup>H-NMR: 1.7-2.3 (2H, quintet, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 2.5-2.9 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.1-3.5 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.78, 3.80 (total 3H, each s, OMe), 4.2-4.6 (total 2H, m, -NHCH<sub>2</sub>Ar), 6.7-7.8 (total 9H, m, ArH and SPh), 8.15, 8.27 (total 1H, each s, CHO).  
LRMS *m/z*: 315 (M<sup>+</sup>-16).

***N*-(4-Methoxyphenyl)methyl-*N*-[(3-phenylsulfinyl)propyl]fromamide (5e)** From **4e** (6.3 g, 20 mmol); column chromatography with ethyl acetate gave **5e** (5.43 g, 82%) as a colorless gum. IR: 1664, 1033. <sup>1</sup>H-NMR: 1.7-2.0 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 2.6-2.9 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.2-3.4 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.79, 3.81 (total 3H, each s, OMe), 4.2-4.6 (total 2H, m, -NHCH<sub>2</sub>Ar), 6.7-7.4 (total 9H, m, ArH and SPh), 8.13, 8.27 (total 1H, each s, CHO).  
LRMS *m/z*: 286 (M<sup>+</sup>-45).

***N*-(2-Methoxyphenyl)methyl-*N*-[(3-phenylsulfinyl)propyl]fromamide (5f)** From **4f** (6.3 g, 20 mmol); column chromatography with ethyl acetate gave **5f** (4.90g, 74%) as a yellow gum. IR (film): 1664, 1045. <sup>1</sup>H-NMR: 1.7-2.1 (2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 2.6-2.9 (2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.0-3.5 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.81 (3H, s, OMe), 4.35, 4.51 (total 2H, each s, -NHCH<sub>2</sub>Ar), 6.8-7.7

(total 9H, m, ArH and SPh), 8.12, 8.27 (total 1H, each s, CHO). LRMS  $m/z$ : 286 ( $M^+$ -45).

***N*-Benzyl-*N*-[(3-phenylsulfinyl)propyl]formamide (5g)** From **4g** (7.5 g, 26.3 mmol); column chromatography with ethyl acetate gave **5g** (6.71g, 85%) as a colorless gum. IR (film): 1670, 1045.  $^1\text{H-NMR}$ : 1.7-2.0 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 2.4-3.0 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 3.1-3.5 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SPh), 4.2-4.5 (total 2H, m, -NHCH<sub>2</sub>Ar), 7.1-7.7 (total 10H, m, Ph and SPh), 8.16, 8.28 (total 1H, each s, CHO). LRMS  $m/z$ : 256 ( $M^+$ -45).

#### **Pummerer Reaction of 5a. Typical Procedure.**

i) Method A. TFAA (1.586 g, 7.55 mmol) was added to a solution of **5a** (500 mg, 1.51 mmol) in benzene (50 mL) at rt, and the mixture was stirred for 4 h under an argon atmosphere. After removal of the solvent *in vacuo*, the product was purified by column chromatography with ethyl acetate-hexane (1:4) to give **6a** (260 mg, 56%) and **7a** (146 mg, 31%).

ii) Method B. TFAA (582 mg, 2.8 mmol) was added to a solution of **5a** (200 mg, 0.55 mmol) in benzene (20 mL) at rt, and the mixture was stirred for 30 min under an argon atmosphere. To this solution BF<sub>3</sub>•Et<sub>2</sub>O (394 mg, 2.8 mmol) was added, and the mixture was stirred at rt for 45 min. After removal of the solvent *in vacuo*, the residue was treated with 5% NaHCO<sub>3</sub> and extracted with CHCl<sub>3</sub>. The residual oil was purified by column chromatography with ethyl acetate to give **6a** (125 mg, 66%) and **4a** (9 mg, 5%).

**2-Formyl-7,8-dimethoxy-5-phenylsulfonyl-2,3,4,5-tetrahydro-1H-2-benzazepine (6a)** Colorless gum. IR(film): 1668.  $^1\text{H-NMR}$ : 2.0-2.3 (total 2H, m, 4-H), 3.67, 3.88 (total 6H, each s, OMe), 3.4-5.1 (total 5H, m, 1-H, 3-H, 5-H), 6.41, 6.44, 6.69, 6.89 (total 2H, each s, ArH), 7.2-7.3 (total 5H, m, SPh), 8.05, 8.15 (total 1H, each s, CHO). LRMS  $m/z$ : 343 ( $M^+$ ). HRMS  $m/z$  ( $M^+$ ): Calcd for C<sub>19</sub>H<sub>21</sub>NO<sub>3</sub>S: 343.1240. Found: 343.1227.

***N*-[(3,5-Dimethoxyphenyl)methyl]-*N*-[(3-phenylsulfonyl)-2-propenyl]formamide (7a):** Yellow gum. IR (film): 1671.  $^1\text{H-NMR}$ : 3.80, 3.83, 3.84, 3.86, 3.87 (total 6H, each s, OMe), 3.7-4.2 (total 2H, m, -CH<sub>2</sub>CH=), 4.33, 4.41, 4.46 (total 2H, each s, -CH<sub>2</sub>Ar), 5.4-5.8 (total 1H, m, -CH=CH-), 6.1-6.6 (total 1H,

m, -CH=CH=), 6.6-6.9 (total 3H, m, -ArH), 7.2-7.5 (total 5H, m, SPh), 8.20, 8.26, 8.30, 8.32 (total 1H, each s, CHO). LRMS  $m/z$ : 343 ( $M^+$ ). HRMS  $m/z$  ( $M^+$ ): Calcd for  $C_{19}H_{21}NO_3S$ : 343.1239. Found: 343.1223.

#### **Pummerer Reaction of 5b.**

i) Method A. **5b** (100 mg, 0.28 mmol) gave **6b** (12 mg, 13%).

ii) Method B. **5b** (1g, 2.8 mmol) gave **6b** (578 mg, 61%).

**2-Formyl-6,8-dimethoxy-5-phenylsulfanyl-2,3,4,5-tetrahydro-1H-2-benzazepine (6b)** Pale yellow gum. IR(film): 1671, 1604.  $^1H$ -NMR: 1.8-2.2 (total 2H, m, 4-H), 3.64, 3.80 (total 6H, each s, OMe), 3.8-5.1 (total 4H, m, 1-H, 3-H), 5.4-5.5 (total 1H, m, 5-H), 6.28, 6.31 (total 1H, each s, 7-H), 6.53-6.55 (total 1H, each s, 9-H), 7.2-7.5 (total 5H, m, SPh), 8.04, 8.13 (total 1H, each s, CHO). LRMS  $m/z$ : 343 ( $M^+$ ).

#### **Pummerer Reaction of 5c.**

Method B. **5c** (500 mg, 1.4 mmol) gave **6c** (214mg, 45%).

**2-Formyl-6,9-dimethoxy-5-phenylsulfanyl-2,3,4,5-tetrahydro-1H-2-benzazepine (6c)** Pale yellow gum. IR(film): 1668, 1593.  $^1H$ -NMR: 3.5-4.3 (total 4H, m, 3-H, 4-H), 3.62, 3.64, 3.80, 3.86 (total 6H, each s, OMe), 4.53, 4.71 (total 1H, each s, 1-H), 5.10, 5.27 (total 1H, each bs, 1-H), 5.4-5.5 (total 1H, m, 5-H), 6.7-6.8 (total 2H, m, 7-H and 8-H), 7.2-7.5 (total 5H, m, SPh), 8.07, 8.11 (total 1H, each s, CHO). LRMS  $m/z$ : 343 ( $M^+$ ). HRMS  $m/z$  ( $M^+$ ): Calcd for  $C_{19}H_{21}NO_3S$ : 343.1242. Found: 343.1288.

#### **Pummerer Reaction of 5d.**

i) Method A. **5d** (125 mg, 0.38 mmol) gave **6d** (15 mg, 13%).

ii) Method B. **5d** (3 g, 9.06 mmol) gave **6d** (2.2 g, 78%).

**2-Formyl-8-methoxy-5-phenylsulfanyl-2,3,4,5-tetrahydro-1H-2-benzazepine (6d)** Pale yellow gum. IR(film): 1670.  $^1H$ -NMR: 2.0-2.3 (total 2H, m, 4-H), 3.5-3.9 (total 1H, m, 5-H), 3.78 (3H, s, OMe), 4.3-5.1 (total 4H, m, 1-H, 3-H), 6.5-6.9 (total 3H, m, ArH), 7.2-7.4 (total 5H, m, SPh), 8.04, 8.13 (total 1H, each s, CHO). LRMS  $m/z$ : 313 ( $M^+$ ). HRMS  $m/z$  ( $M^+$ ): Calcd for  $C_{18}H_{19}NO_2S$ : 313.1133. Found: 313.1101.

### Pummerer Reaction of 5e.

Method B. **5e** (500 mg, 1.51 mmol) gave **8e** (68 mg, 21%).

**N-(4-Methoxyphenyl)methyl-N-[3,3-di(phenylsulfanyl)propyl]formamide (8e)** Yellow gum. IR (film): 1670, 1512. <sup>1</sup>H-NMR: 1.97 (2H, brq, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH(SPh)<sub>2</sub>), 3.2-3.6 (total 2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH(SPh)<sub>2</sub>), 3.79, 3.80 (total 3H, each s, OMe), 4.1-4.4 (total 3H, m, -NHCH<sub>2</sub>Ar and -CH(SPh)<sub>2</sub>), 6.7-7.6 (total 14H, m, ArH and SPhx2), 8.16, 8.23 (total 1H. each s, CHO). LRMS *m/z*: 423 (M<sup>+</sup>).

### Pummerer Reaction of 5f.

Method B. **5f** (500 mg, 1.51 mmol) gave **8f** (107 mg, 33%).

**N-(2-Methoxyphenyl)methyl-N-[3,3-di(phenylsulfanyl)propyl]fromamide (8f)** IR (film): 1670. <sup>1</sup>H-NMR: 1.6-2.2 (2H, m, -NHCH<sub>2</sub>CH<sub>2</sub>CH(SPh)<sub>2</sub>), 3.44 (2H, brq, *J*=7 Hz, -NHCH<sub>2</sub>CH<sub>2</sub>CH(SPh)<sub>2</sub>), 3.76, 3.79 (total 3H, each s, OMe), 4.1-4.7 (total 3H, m, -NHCH<sub>2</sub>Ar and -CH(SPh)<sub>2</sub>), 6.8-7.6 (total 14H, m, ArH and SPhx2), 8.16, 8.24 (total 1H. each s, CHO). LRMS *m/z*: 423 (M<sup>+</sup>).

**Reductive Desulfurization of 6. Typical Procedure.** To a stirred suspension of **6a** (1.81 g, 5.3 mmol) and NiCl<sub>2</sub>•6H<sub>2</sub>O (4.40g, 18.5 mmol) in MeOH-THF (3:1, 80 mL) was added NaBH<sub>4</sub> (2.11 g, 55.5mmol) by portions at 0°C. After the addition completed, stirring was continued for 20 min. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The products were purified by column chromatography with ethyl acetate-hexane (1:1) and recrystallized from ethyl acetate-Et<sub>2</sub>O to give **9a** (998 mg, 80%) as colorless prisms, mp 130-132 °C.

**2-Formyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (9a).** IR: 1666, 1604. <sup>1</sup>H-NMR: 1.7-1.9 (total 2H, m, 4-H), 2.8-3.0 (total 2H, m, 5-H), 3.5-3.8 (total 2H, m, 3-H), 3.83, 3.84 (total 6H, each s, OMe), 4.36, 4.46 (total 2H, each s, 1-H), 6.66, 6.89 (total 2H, each s, ArH), 7.98, 8.12 (total 1H, each s, CHO), LRMS *m/z*: 235 (M<sup>+</sup>). HRMS *m/z* (M<sup>+</sup>): Calcd for C<sub>13</sub>H<sub>17</sub>NO<sub>3</sub>: 235.1209. Found: 235.1208.

**2-Formyl-6,8-dimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (9b).** From **6b** (578 mg, 1.7 mmol); column chromatography with ethyl acetate-hexane (1:1) gave **9b** (297 mg, 75%) as colorless prisms

recrystallized from ethyl acetate-Et<sub>2</sub>O, mp 83-85 °C. IR: 1664. <sup>1</sup>H-NMR: 1.6-1.9 (total 2H, m, 4-H), 2.9-3.2 (total 2H, m, 5-H), 3.5-3.7 (total 2H, m, 3-H), 3.77, 3.78, 3.80 (total 6H, each s, OMe), 4.38, 4.50 (total 2H, each s, 1-H), 6.3-6.6 (total 2H, m, ArH), 8.00, 8.13 (total 1H, each s, CHO), LRMS *m/z*: 235 (M<sup>+</sup>).

**2-Formyl-6,9-dimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (9c).** From **6c** (963 mg, 2.8 mmol); column chromatography with ethyl acetate-hexane (1:1) gave **9c** (338 mg, 53%) as pale yellow prisms recrystallized from ethyl acetate-Et<sub>2</sub>O, mp 83-88 °C. IR: 1670, 1596. <sup>1</sup>H-NMR: 1.7-1.9 (total 2H, m, 4-H), 2.9-3.1 (total 2H, m, 5-H), 3.4-3.63 (total 2H, m, 3-H), 3.76, 3.80, 3.84 (total 6H, each s, OMe), 4.59, 4.73 (total 2H, each s, 1-H), 6.7 (total 2H, m, ArH), 8.02, 8.12 (total 1H, each s, CHO), LRMS *m/z*: 235 (M<sup>+</sup>). HRMS *m/z* (M<sup>+</sup>): Calcd for C<sub>13</sub>H<sub>17</sub>NO<sub>3</sub>: 235.1206. Found: 235.1298.

**2-Formyl-8-methoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (9d).** From **6d** (2 g, 6.39 mmol); column chromatography with ethyl acetate-hexane (1:1) gave **9d** (935 mg, 71%) as a pale yellow gum. IR (film): 1670. <sup>1</sup>H-NMR: 1.6-2.0 (2H, m, 4-H), 2.92 (2H, t, *J*=6 Hz, 5-H), 3.5-4.0 (total 2H, m, 3-H), 3.78 (3H, s, OMe), 4.59, 4.73 (total 2H, each s, 1-H), 6.7 (3H, m, ArH), 8.02, 8.12 (total 1H, each s, CHO), LRMS *m/z*: 205 (M<sup>+</sup>). HRMS *m/z* (M<sup>+</sup>): Calcd for C<sub>12</sub>H<sub>15</sub>NO<sub>2</sub>: 205.1103. Found: 205.1121.

**Hydrolysis of 9a. Typical Procedure.** A solution of **9a** (300 mg, 1.3 mmol) in EtOH (5 mL) and 10% NaOH (5 mL) was refluxed for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was extracted with CHCl<sub>3</sub>. The product was purified by column chromatography with ethyl acetate to give **10a** (259 mg, 98%) as a pale yellow gum.<sup>11</sup>

**7,8-Dimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (10a).**<sup>9,10</sup> IR (film): 1606. <sup>1</sup>H-NMR: 1.6-1.9 (2H, m, 4-H), 2.8-3.0 (2H, m, 5-H), 3.1-3.3 (2H, m, 3-H), 3.85 (3H, s, OMe), 3.86 (3H, s, OMe), 3.88 (2H, s, 1-H), 6.68 (1H, s, ArH), 6.70 (1H, s, ArH). <sup>13</sup>C-NMR: 30.3 (t), 34.9 (t), 52.8 (t), 53.9 (t), 55.1 (qx2), 111.9 (d), 112.7 (d), 134.3 (s), 134.5 (s), 145.7 (s), 146.4 (s). LRMS *m/z*: 207 (M). HRMS *m/z* (M<sup>+</sup>): Calcd for C<sub>12</sub>H<sub>17</sub>NO<sub>2</sub>: 207.1260. Found: 207.1290.

**6,8-Dimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (10b).** From **9b** (297 mg, 1.3 mmol); column

chromatography with ethyl acetate gave **10b** (169 mg, 65%) as colorless prisms recrystallized from ethyl acetate-hexane, mp 68-70 °C. IR: 1587. <sup>1</sup>H-NMR: 1.5-1.8 (2H, m, 4-H), 2.8-3.0 (2H, m, 5-H), 3.1-3.2 (2H, m, 3-H), 3.78 (6H, s, OMe), 3.88 (2H, s, 1-H), 6.31 (1H, d, *J*=2 Hz, ArH), 6.36(1H, d, *J*=2 Hz, ArH). <sup>13</sup>C-NMR: 24.5 (t), 30.4 (t), 53.6 (t), 55.2 (t), 55.3 (q), 55.8 (q), 97.2 (d), 105.3 (d), 123.3 (s), 145.1 (s), 157.6 (s), 158.1 (s). LRMS *m/z*: 207 (*M*<sup>+</sup>). HRMS *m/z* (*M*<sup>+</sup>): Calcd for C<sub>12</sub>H<sub>17</sub>NO<sub>2</sub>: 207.1256. Found: 207.1238.

**6,9-Dimethoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepine (10c).** From **9c** (100 mg, 0.43 mmol); column chromatography with ethyl acetate gave **10c** (82 mg, 85%) as colorless prisms recrystallized from ethyl acetate-hexane, mp 58-60 °C. IR: 1594. <sup>1</sup>H-NMR: 1.6-1.7 (2H, m, 4-H), 3.0 (2H, m, 5-H), 3.2 (2H, m, 3-H), 3.75 (6H, s, OMe), 4.07 (2H, s, 1-H), 6.66 (1H, d, *J*=9 Hz, ArH), 6.70 (1H, d, *J*=9 Hz, ArH). <sup>13</sup>C-NMR: 25.3 (t), 29.3 (t), 44.6 (t), 53.4 (t), 56.3 (q), 56.6 (q), 109.2 (d), 110.6 (d), 132.2 (s), 133.5 (s), 150.7 (s), 150.9 (s). LRMS *m/z*: 207 (*M*<sup>+</sup>). HRMS *m/z* (*M*<sup>+</sup>): Calcd for C<sub>12</sub>H<sub>17</sub>NO<sub>2</sub>: 207.1258. Found: 207.1253

**8-Methoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepine (10d).** From **9d** (300 mg, 1.46 mmol); column chromatography with ethyl acetate gave **10d** (240 mg, 93%) as colorless needles recrystallized from ethyl acetate-hexane, mp 39-41 °C. IR: 1610. <sup>1</sup>H-NMR: 1.68 (2H, m, 4-H), 2.89 (2H, t, *J*=5 Hz, 5-H), 3.19 (2H, t, *J*=5 Hz, 3-H), 3.77 (3H, s, OMe), 3.88 (2H, s, 1-H), 6.5-7.2 (3H, m, ArH). <sup>13</sup>C-NMR: 31.1 (t), 35.1 (t), 53.4 (t), 55.1 (t), 55.1 (q), 111.2 (d), 114.4 (d), 130.0 (d), 134.8 (s), 143.8 (s), 157.7 (s). LRMS *m/z*: 178 (*M*<sup>+</sup>).

**Reduction of 9a with LiAlH<sub>4</sub>. Typical Procedure.** LiAlH<sub>4</sub> (97 mg, 2.6 mmol) was added to the solution of **9a** (300 mg, 1.3 mmol) in dry THF (15 mL) under ice-cooling, and the mixture was refluxed for 1 h. Et<sub>2</sub>O saturated with water was added to the reaction mixture, and insoluble material was filtered off. The filtrate was concentrated *in vacuo* and the residue was extracted with CHCl<sub>3</sub>. The product was purified by column chromatography with ethyl acetate to give **11a** (258 mg, 91%) as a pale yellow gum.

**7,8-Dimethoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (11a).** IR(film): 1606. <sup>1</sup>H-NMR:

1.6-1.9 (2H, m, 4-H), 2.32 (3H, s, NMe), 2.7-3.0 (4H, m, 5-H and 3-H), 3.49 (2H, s, 1-H), 3.83 (6H, s, OMe), 6.67 (1H, s, ArH), 6.68 (1H, s, ArH).  $^{13}\text{C}$ -NMR: 25.7 (t), 34.7 (t), 43.2 (q), 55.3 (q), 55.4 (q), 60.8 (t), 61.4 (t), 112.4 (d), 113.4 (d), 130.7 (s), 134.6 (s), 146.0 (s), 146.9 (s). LRMS  $m/z$ : 221 ( $\text{M}^+$ ). HRMS  $m/z$  ( $\text{M}^+$ ): Calcd for  $\text{C}_{13}\text{H}_{19}\text{NO}_2$ : 221.1414. Found: 221.1399.

**6,8-Dimethoxy-2-methyl-2,3,4,5-tetrahydro-1H-2-benzazepine (11b).** From **9b** (256 mg, 1.3 mmol); column chromatography with ethyl acetate gave **11b** (240 mg, 99%) as a colorless gum. IR(film): 1606.  $^1\text{H}$ -NMR: 1.6-1.8 (2H, m, 4-H), 2.31 (3H, s, NMe), 2.8-3.0 (4H, m, 3-H and 5-H), 3.75 (2H, s, 1-H), 3.777 (3H, s, OMe), 3.782 (3H, s, OMe), 6.33 (1H, d,  $J=2$  Hz, ArH), 6.36 (1H, d,  $J=2$  Hz, ArH).  $^{13}\text{C}$ -NMR: 24.3 (t), 25.5 (t), 43.5 (q), 55.3 (q), 55.8 (q), 61.4 (t), 62.3 (t), 97.4 (d), 106.7 (d), 123.4 (s), 141.6 (s), 157.2 (s), 158.1 (s). LRMS  $m/z$ : 221 ( $\text{M}^+$ ). HRMS  $m/z$  ( $\text{M}^+$ ): Calcd for  $\text{C}_{13}\text{H}_{19}\text{NO}_2$ : 221.1416. Found: 221.1454.

**6,8-Dimethoxy-2-methyl-2,3,4,5-tetrahydro-1H-2-benzazepine (11c).** From **9c** (500 mg, 2.1 mmol); column chromatography with ethyl acetate gave **11c** (435 mg, 93%) as a colorless gum. IR(film): 1594.  $^1\text{H}$ -NMR: 1.6-1.7 (2H, m, 4-H), 2.27 (3H, s, NMe), 2.8-2.9 (4H, m, 3-H and 5-H), 3.657 (3H, s, OMe), 3.664 (3H, s, OMe), 3.79 (2H, s, 1-H), 6.54 (1H, d,  $J=9$  Hz, ArH), 6.66 (1H, d,  $J=9$  Hz, ArH).  $^{13}\text{C}$ -NMR: 24.8 (t), 25.9 (t), 44.9 (q), 52.0 (t), 56.1 (q), 56.5 (q), 61.9 (t), 108.8 (d), 110.5 (d), 129.2 (s), 133.5 (s), 150.5 (s), 151.4 (s). LRMS  $m/z$ : 221 ( $\text{M}^+$ ).

**8-Methoxy-2-methyl-2,3,4,5-tetrahydro-1H-2-benzazepine (11d).** From **9d** (100 mg, 0.49 mmol); column chromatography with ethyl acetate gave **11d** (87 mg, 94%) as a colorless gum. IR (film): 1608.  $^1\text{H}$ -NMR: 1.5-1.8 (2H, m, 4-H), 2.21 (3H, s, NMe), 2.72 (2H, t,  $J=6$  Hz, 5-H), 2.90 (2H, t,  $J=6$  Hz, 3-H), 3.65 (2H, s, 1-H), 3.67 (3H, s, OMe), 6.4-7.0 (3H, m, ArH).  $^{13}\text{C}$ -NMR: 25.8 (t), 34.7 (t), 43.0 (q), 55.1 (q), 61.1 (t), 62.1 (t), 111.5 (d), 115.8 (d), 129.5 (d), 134.8 (s), 140.1 (s), 157.7 (s). LRMS  $m/z$ : 191 ( $\text{M}^+$ ).

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## REFERENCES

1. M. Kennedy and M. McKervey, "Comprehensive Organic Chemistry," Vol. 7, ed. by B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, pp 193-216.
2. A. Padwa, D. E. Jr. Gunn, and H. Osterhout, *Synthesis*, **1997**, 1353.
3. (a) T. Shinohara, J. Toda, and T. Sano, *Chem. Pharm. Bull.* 1997, **45**, 813. (b) T. Shinohara, A. Takeda, J. Toda, Y. Ueda, M. Kohno, and T. Sano, *ibid.* 1998, **46**, 918. (c) T. Shinohara, A. Takeda, J. Toda, N. Terasawa, and T. Sano, *Heterocycles*, 1997, **46**, 555. (d) T. Shinohara, A. Takeda, J. Toda, and T. Sano, *Chem. Pharm. Bull.* 1998, **46**, 430.
4. J. Toda, M. Sakagami, and T. Sano, *Chem. Pharm. Bull.*, 1999, **47**, 1269.
5. (a) H. Ishibashi, S. Harada, K. Sato, M. Ikeda, S. Akai, and Y. Tamura, *Chem. Pharm. Bull.*, 1985, **33**, 5278. (b) H. Ishibashi, K. Sato, and M. Ikeda, *J. Chem. Soc., Perkin Trans. I*, **1985**, 605. (c) J. Toda, Y. Niimura, K. Takeda, T. Sano, and Y. Tsuda, *Chem. Pharm. Bull.*, 1998, **46**, 906. (d) J. Toda, Y. Niimura, T. Sano, and Y. Tsuda, *Heterocycles*, 1998, **48**, 1599.
6. T. Shinohara, A. Takeda, J. Toda, and T. Sano, *Heterocycles*, 1998, **48**, 981.
7. J. Toda, M. Sakagami, Y. Goan, M. Simakata, T. Saitoh, Y. Horiguchi, and T. Sano, *Chem. Pharm. Bull.*, 2000, in press.
8. J. Toda, T. Ichikawa, T. Saitoh, Y. Horiguchi, and T. Sano, *Heterocycles*, 2000, **53**, 2009.
9. C. J. W. Walpole, S. Bevan, G. Bovermann, J. J. Boelsterli, R. Brecenridge, J. W. Davies, G. A. Hughes, I. James, L. Oberer, J. Winter, and R. Wrigglesworth, *J. Med. Chem.*, 1994, **37**, 1942.
10. D. A. Alonso, A. Costa, B. Mancheno, and C. Najera, *Tetrahedron*, 1997, **53**, 4791.
11. The physical data were not described in reference 9 and 10.