An Improved Synthesis of 1,2,3,4-Tetrahydroisoquinolines *via* Intramolecular Cyclization of *N*-Acyl-*N*-(aryl)methyl-2-(phenylsulfinyl)ethylamine by Pummerer Reaction

Tatsumi SHINOHARA,[a] Jun TODA,[b] and Takehiro SANO*,[b]

Racing Chemistry Laboratories,[a] 4–37–6, Setagaya-ku, Tokyo 158, Japan and Showa College of Pharmaceutical Sciences,[b] 3–3165, Higashi-tamagawagakuen, Machida-shi, Tokyo 194, Japan.
Received October 31, 1996; accepted December 27, 1996

Pummerer reaction of the sulfoxides 5 of *N*-acyl-*N*-(aryl)methyl-2-(phenylthio)ethylamines (4) on treatment with trifluoroacetic anhydride (TFAA) effectively caused intramolecular cyclization under a mild condition to give *N*-acyl-4-phenylthio-1,2,3,4-tetrahydroisoquinolines (TIQs) (7). The reaction of the *N*-formyl sulfoxide 5c without a methoxy group in the benzene ring using a formyl group for *N*-protection is particularly efficient. Treatment of the *N*-formyl sulfoxide 5f with TFAA did not give any TIQ, but a sequential treatment using TFAA and $BF_3 \cdot Et_2O$ afforded *N*-formyl-4-phenylthio-TIQ (7f) in quantitative yield. The efficiency of this method of preparing TIQs was demonstrated in the synthesis of 1,4-dideuterio-TIQ (10D) and its *N*-methyl derivative (11D).

Key words Pummerer reaction; trifluoroacetic anhydride; boron trifluoride etherate; 1,2,3,4-tetrahydroisoquinoline; isoquinoline

Isoquinoline alkaloids, which are widely distributed in the plant and animal kingdoms, have received much attention because of their important biological activities.[1] For example, 1,2,3,4-tetrahydroisoquinolines (TIQs) such as **10b** and **11b** present in mammalian brain are known to induce Parkinson's disease.[2] Although there are well-known methods of preparing isoquinolines[3] such as the Pictet–Spengler reaction, Bischler–Napieralski reaction and Pomeranz–Fritsch synthesis, it is still difficult to synthesize isoquinolines which lack electron-donating groups in the benzene ring. Recently, Takano *et al.*[4] developed a route to TIQs which utilized a sulfoxide-mediated electrophilic cyclization reaction (Pummerer reaction).[5] This route is very attractive for preparing substrates to use in biological studies since isotope-labeling at the C-4 position is possible by reductive elimination of the phenylthio group. In this paper we describe an improvement and extention of Takano's TIQ synthesis.

Results and Discussion

N-Acyl sulfoxides **5** were prepared from aromatic aldehydes **1** and 2-phenythioethylamine (**2**)[6] according to the known method[4] with some modifications. Condensation of **1** with **2** in EtOH in the presence of acetic acid followed by sodium borohydride reduction of the resulting imine gave *N*-(aryl)methyl-2-(phenylthio)ethylamines **3** in good yields. The free amines **3** were protected by acetylation, benzyloxycarbonylation, or formylation, and the resulting *N*-acyl derivatives **4** were oxidized with sodium metaperiodate in aqueous methanol to give the sulfoxides **5** in good yields. In most cases, the sulfones **6** were also generated as a by-product in yields of a few percent. The products were well characterized by MS, IR, and ^{1}H-NMR spectral data (see Experimental).

Our preliminary experiments revealed that the intramolecular cyclization of **5** by Pummerer reaction proceeded under a very mild condition in contrast with Takano's condition.[4] For example, the *N*-acetyl sulfoxide **5a**, on treatment with trifluoroacetic anhydride (TFAA) in benzene at room temperature for 18 h, gave *N*-acetyl-4-phenylthio-TIQ (**5a**) in 68% yield. The yield was similar to that reported by Takano *et al.*[4] This cyclization is markedly affected by the solvents used. *N*-Benzyloxycarbonyl sulfoxide **5b**, on treatment with TFAA in benzene at room temperature, gave *N*-benzyloxycarbonyl-4-phenylthio-TIQ (**7b**) in 64% yield. However, the reaction of **5b** in CH_2Cl_2 gave only a complex mixture of uncharacterizable products. On the other hand, the treatment in Et_2O or tetrahydrofuran (THF) caused the expected ring closure to give **7b**, though in lesser yields (49% in Et_2O and 42% in THF). Benzene seems to be the most suitable solvent for this reaction. Next, we found that suitable selection of the *N*-protecting group is critical for this intramolecular cyclization. The *N*-formyl sulfoxide **5c**, on treatment with TFAA in benzene for 20 h at room temperature, gave *N*-formyl-4-phenylthio-TIQ (**7c**) in 97% yield. The results are summarized in Table 1. The *N*-acyl-4-phenylthio-TIQs **7** were isolated in a pure form by flash chromatography over SiO_2 and fully characterized by MS, IR, and NMR examinations (see Experimental), although they gradually deteriorated on storage even in a refrigerator.

Next, we applied this reaction to the sulfoxides **5d—f** which lack the methoxy group in the benzene ring. Contrary to our expectation, the results were very disappointing (Chart 2). For example, reaction of the *N*-acetyl sulfoxide **5d** with TFAA in benzene at room temperature did not give the expected product, but an oxazepine **14** in 21% yield. The oxazepine structure of **14** was readily deduced from the ^{1}H- and ^{13}C-NMR spectral data together with the mass spectrum, which indicated the presence of benzyl, SPh, and trifluoromethyl moieties, but the absence of an acetyl methyl group. The formation of **14** can be rationalized in terms of dehydrative intramolecular ring closure between the acetyl methyl and the trifluoroacetyl carbonyl in the intermediary trifluoroacetate **12**.

The reaction of the *N*-benzyloxycarbonyl sulfoxide **5e**

* To whom correspondence should be addressed.

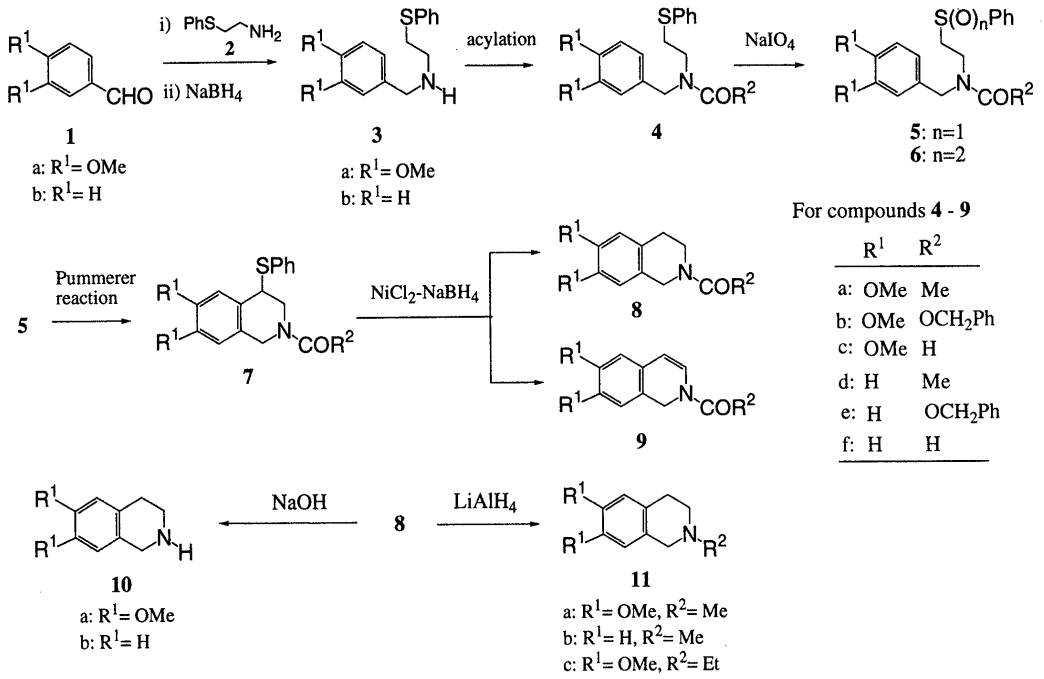

Chart 1

Table 1. Pummerer Reaction of *N*-Acyl Sulfoxides **5**

Run	Sulfoxides (**5**)		Conditions				Yield (%)	
		N-Acyl	Reagent[a]	Solvent	Time (h)	Temp.	PhSTIQ (**7**)	Others
1	**5a**	COMe	A	Benzene	18	r.t.	(**7a**) 68	—
2	**5b**	$COOCH_2Ph$	A	Benzene	3	r.t.	(**7b**) 56	—
3	**5b**	$COOCH_2Ph$	A	Benzene	16	r.t.	(**7b**) 64	—
4	**5b**	$COOCH_2Ph$	A	CH_2Cl_2	3	r.t.	—[b]	—
5	**5b**	$COOCH_2Ph$	A	Et_2O	3	r.t.	(**7b**) 49	—
6	**5b**	$COOCH_2Ph$	A	THF	3	r.t.	(**7b**) 42	—
7	**5c**	CHO	A	Benzene	20	r.t.	(**7c**) 97	—
8	**5d**	COMe	A	Benzene	18	r.t.	—	(**14**) 21
9	**5e**	$COOCH_2Ph$	A	Benzene	16	r.t.	—	(**15**) 62
10	**5f**	CHO	A	Benzene	18	r.t.	—[b]	—
11	**5f**	CHO	B	Benzene	2.5	r.t.	(**7f**) 99	—
12	**5d**	COMe	B	Benzene	3	r.t.	(**7d**) 2	—
13	**5e**	$COOCH_2Ph$	B	Benzene	3	r.t.	(**7e**) 15	(**15**) 67
14	**5D**	CHO	B	Benzene	3	r.t.	(**7D**) 98	—

a) A: TFAA only. B: TFAA–$BF_3 \cdot Et_2O$. *b*) An intractable mixture. r.t. = room temp.

under a similar condition gave an oxazolidine **15** in 62% yield, but no TIQ. The product **15** should be formed by the attack of benzyloxycarbonyl oxygen on the sulfenium cation **13**.

On the other hand, when the *N*-formyl sulfoxide **5f** was treated with TFAA in benzene for 30 min at room temperature, a less polar product appeared on TLC as a single spot. However, this product was found to decompose rapidly and completely during working-up procedures to give only an intractable mixture. We assumed that the product may be a *β*-phenylthio-enamine **16**, which should be very labile to air oxidation and hydrolysis. The results are shown in Table 1.

The desired intramolecular cyclization of the *N*-formyl sulfoxide **5f** was achieved by using TFAA and $BF_3 \cdot Et_2O$. A solution of **5f** in benzene was treated with TFAA for 30 min at room temperature, then $BF_3 \cdot Et_2O$ was added and the mixture was allowed to react for a further 2 h, giving *N*-formyl-4-phenylthio-TIQ (**7f**) in 99% yield. The use of the formyl group for *N*-protection ($R^1 = H$) seems to be essential for this cyclization, since other *N*-acyl derivatives **5d** and **5e** gave poor results; **5d** gave *N*-acetyl-4-phenylthio-TIQ (**7d**) in only 2% yield, and **5e** gave *N*-benzyloxycarbonyl-4-phenylthio-TIQ (**7e**) in 15% yield, together with **15** (67%).

Reductive removal of the phenylthio group of **7** readily proceeded on treatment with $NiCl_2$–$NaBH_4$[7] in MeOH–THF to give *N*-acyl-TIQs **8** in good yields, though 1,2-dihydroisoquinolines **9** were produced as a by-product in some cases. Deprotection of the *N*-acyl group was readily achieved by conventional methods. Alkaline hydrolysis of **8** gave TIQs **10**. Reduction of **8** with $LiAlH_4$ gave *N*-alkyl-TIQs **11** in good yields. The results are indicated in Table 2.

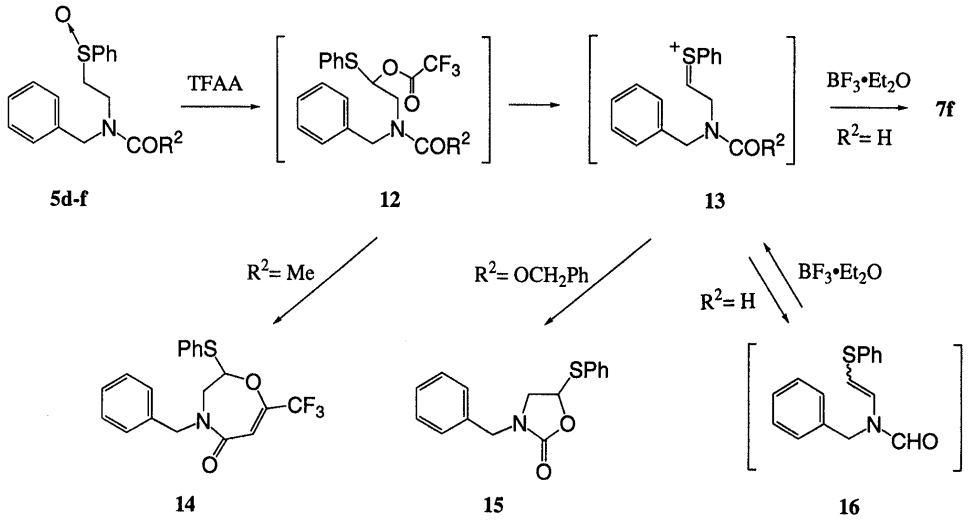

Chart 2

Table 2. Preparation of TIQs **10** and *N*-Alkyl-TIQs **11**

Reduction of **7**[a]				Hydrolysis of **8**[b]			Reduction of **8**[c]	
		Yield (%)				Yield (%)		Yield (%)
	N-Acyl	**8**	**9**		*N*-Acyl	**10**		**11**
7a	COMe	(**8a**) 76	—	**8a**	COMe	(**10a**) 78	**8a**	(**11c**) 88
7b	$COOCH_2Ph$	(**8b**) 59	(**9b**) 5	**8b**	$COOCH_2Ph$	(**10a**) 89	**8b**	(**11a**) 95
7c	CHO	(**8c**) 74	—	**8c**	CHO	(**10a**) 100	**8c**	(**11a**) 87
7f	CHO	(**8f**) 71	—	**8f**	CHO	(**10b**) 96	**8f**	(**11b**) 91
7D[d]	CHO	(**8D**) 86	(**9D**) 2	**8D**	CHO	(**10D**) 92	**8D**	(**11D**) 90

a) $NaBH_4$–$NiCl_2$. *b*) NaOH. *c*) $LiAlH_4$. *d*) $NaBD_4$–$NiCl_2$.

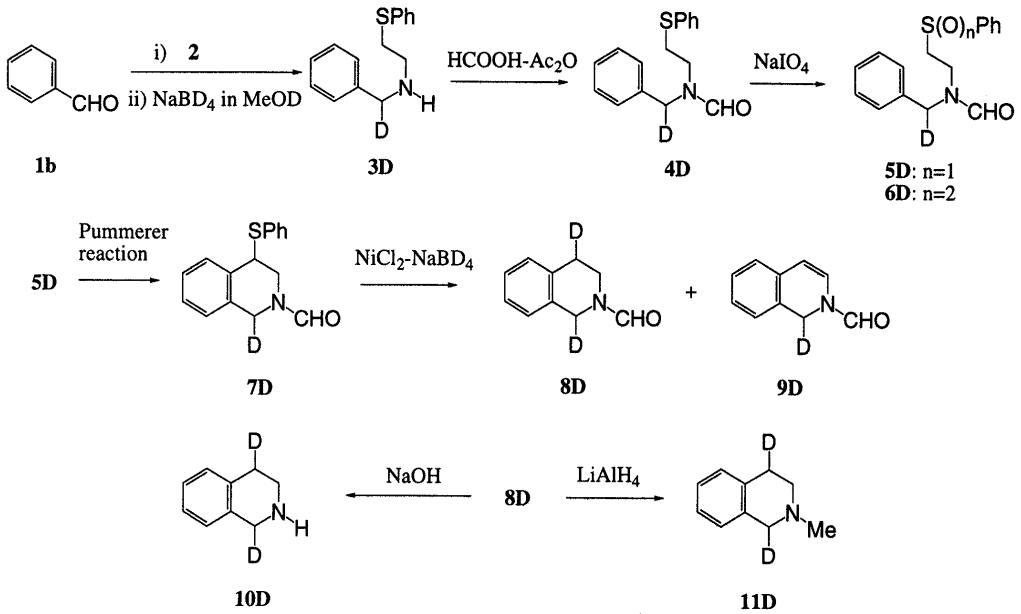

Chart 3

This method was applied to the synthesis of deuterium-labeled derivatives of **10b** and **11b**, which were identified as inducers of Parkinson's disease.[2] The 1-deuterio-*N*-formyl sulfoxide **5D**, on treatment with TFAA and BF_3·Et_2O, gave *N*-formyl-1-deuterio-4-phenylthio-TIQ (**7D**) in 98% yield. Reductive desulfurization of **7D** with $NiCl_2$-$NaBD_4$[7] gave *N*-formyl-1,4-dideuterio-TIQ (**8D**) in 86% yield. Hydrolysis and reduction of **8D** gave 1,4-dideuterio-TIQ (**10D**) and *N*-methyl-TIQ (**11D**), respectively. Incorporation of deuterium into the C-4 position is practically complete as revealed by the mass and ^{1}H-NMR spectra, although the compound is a diastereomeric mixture with respect to the stereochemistry of deuterium at C-1 and C-4.

In summary, the Pummerer reaction of the sulfoxides **5** of *N*-acyl-*N*-(aryl)methyl-2-(phenythio)ethylamines (**4**) resulted in intramolecular carbon–carbon bond formation under very mild conditions to produce 4-phenylthio-TIQs (**7**). The reaction using formamide as an *N*-protecting group gives an excellent result. The route produced 6,7-dimethoxy-TIQ (**10a**) in 62% overall yield from **1a**. In particular, it was proved that Pummerer reaction under a modified condition using TFAA and $BF_3 \cdot Et_2O$ is applicable to the synthesis of TIQ derivatives which lack an electron-donating group in the benzene ring, when the formamide was used for *N*-protection. Thus, TIQ (**10b**) and its 1,4-dideuterio-TIQ (**10D**) were synthesized from benzaldehyde **1b** in 57 and 60% overall yields, respectively. The deuterio-TIQs should be of great value for metabolic studies.

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^{-1}. NMR spectra were measured on a JEOL JNM-EX 90 (^1H, 90 MHz) or a JEOL JNM-A 500 (^1H, 500 MHz; ^{13}C, 125 MHz) spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard at room temperature or at 80 °C, and the chemical shifts are given in δ values. Unless otherwise noted, spectral data measured at 90 MHz at room temperature are shown. The following abbreviations are used; s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, m = multiplet, and br = broad. Low resolution MS (LRMS) and high resolution MS (HRMS) were taken on a JEOL JMS-AX 505H spectrometer at 70 eV (electron impact MS (EIMS)) or at 270 eV (chemical ionization MS (CIMS), reactant gas: iso-butane) using direct or GC/MS inlet systems. Thin-layer chromatography (TLC) was performed on Merck precoated Silica gel 60 F_{254} 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_2SO_4, and concentrated *in vacuo* to dryness. The known TIQs were also characterized by MS, IR, and ^1H-NMR examinations. The ^1H-NMR spectra indicated that all *N*-acetyl- (**4a**, **4d**, **5a**, and **5d**), and *N*-formyl derivatives (**4c**, **4f**, **5c**, and **5f**) and also *N*-acetyl- (**7a**, **7d**, and **8a**), and *N*-formyl-TIQs (**7c**, **7f**, **8c** and **8f**) are present in $CDCl_3$ as a mixture of two rotational isomers of the N–CO bond.[8]

General Procedure for the Preparation of Sulfoxides (5) Preparation of *N*-(Aryl)methyl-2-(phenylthio)ethylamines (**3a, b**): A solution of **1a** or **1b** (5 g), 2-phenylthioethylamine (**2**)[6] (1.5 molar eq), and acetic acid (1.5 molar eq) in EtOH (100 ml) was refluxed for 18—20 h under an Ar atmosphere. The reaction mixture was concentrated *in vacuo*, then the residue was dissolved in MeOH (100 ml). To this solution, $NaBH_4$ (1 molar eq) was added in small portions under ice-cooling. The reaction mixture was stirred at room temperature for 1 h, concentrated *in vacuo*, diluted with water, and extracted with $CHCl_3$. The crude product was dissolved in Et_2O (*ca.* 300 ml) and extracted with 10% HCl–H_2O. The aqueous layer was basified with 10% NaOH–H_2O, and extracted with $CHCl_3$. The products (**3a** and **3b**) were purified by column chromatography.

N-(3,4-Dimethoxyphenyl)methyl-2-(phenylthio)ethylamine (**3a**): Eluent for column chromatography: AcOEt. Yield: 92%. Pale yellow oil. IR: 1593, 1516, 1265. ^1H-NMR: 2.77—2.93 (2H, m, $-SCH_2-$), 3.02—3.18 (2H, m, $-CH_2NH-$), 3.73, (1H, s, $ArCH_2N=$), 3.86, 3.87 (each 3H, s, $2\times-OCH_3$), 6.80, 6.81, 6.86 (each 1H, s, Ar-H), 7.20—7.35 (5H, m, Ar-H). EIMS *m/z*: 303 (M^+), 151 (base peak). HRMS: Calcd for $C_{17}H_{21}NO_2S$: 303.1293. Found: 303.1314.

N-Benzyl-2-(phenylthio)ethylamine (**3b**): Eluent for column chromatography: AcOEt–*n*-hexane (2 : 1). Yield: 94%. Colorless oil. IR: 1591, 1516, 1265. ^1H-NMR: 2.75—2.90 (2H, m, $-SCH_2-$), 2.95—3.15 (2H, m, $-CH_2NH-$), 3.76 (2H, s, $ArCH_2N=$), 7.10—7.30 (10H, m, Ar-H). EIMS *m/z*: 243 (M^+), 91 (base peak). HRMS: Calcd for $C_{15}H_{17}NS$: 243.1082. Found: 243.1046.

Acetylation of **3a** and **3b**:A solution of **3a** (1.5 g) or **3b** (1.9 g), and acetic anhydride (5 ml) in dry pyridine (10 ml) was stirred at room temperature for 16 h. The reaction mixture was poured into ice-water, extracted with CH_2Cl_2, and washed with 5% HCl–H_2O, 5% NaOH–H_2O, and brine. The products (**4a** and **4d**) were purified by column chromatography.

N-Acetyl-*N*-(3,4-dimethoxyphenyl)methyl-2-(phenylthio)ethylamine (**4a**): Eluent for column chromatography: AcOEt. Yield: 96%. Pale yellow gum. IR: 1647, 1518, 1417, 1265. ^1H-NMR: 2.05, 2.11 (total 3H, each s, $-COCH_3$), 2.85—3.20 (2H, m, $-SCH_2-$), 3.30—3.70 (2H, m, $-CH_2N=$), 3.83, 3.86 (each 3H, s, $2\times-OCH_3$), 4.47 (2H, s, $ArCH_2N=$), 6.59—6.80 (3H, m, Ar-H), 7.10—7.40 (5H, m, Ar-H). EIMS *m/z*: 345 (M^+), 151 (base peak). HRMS : Calcd for $C_{19}H_{23}NO_3S$: 345.1399. Found: 345.1358.

N-Acetyl-*N*-benzyl-2-(phenylthio)ethylamine (**4d**): Eluent for column chromatography: CH_2Cl_2. Yield: 89%. Colorless gum. IR: 1649, 1439, 1421. ^1H-NMR: 2.05, 2.07 (total 3H, each s, $-COCH_3$), 2.85—3.20 (2H, m, $-SCH_2-$), 3.30—3.65 (2H, m, $-CH_2N=$), 4.51, 4.55 (total 2H, each s, $ArCH_2N=$), 7.05—7.40 (10H, br m, Ar-H). EIMS *m/z*: 285 (M^+), 136 (base peak). HRMS: Calcd for $C_{17}H_{19}NOS$: 285.1188. Found: 285.1156.

Benzyloxycarbonylation of **3a** and **3b**: A solution of benzyl chloroformate (1.1 molar eq) in dry benzene (20 ml) was added dropwise to a solution of **3a** (5 g) or **3b** (10 g), and triethylamine (1.5 molar eq) in dry benzene (80 ml) and the mixture was stirred at room temperature for 2 h. After removal of precipitates by filtration, the filtrate was extracted with benzene. The products (**4a** and **4e**) were purified by column chromatography.

N-Benzyloxycarbonyl-*N*-(3,4-dimethoxyphenyl)methyl-2-(phenylthio)-ethylamine (**4a**): Eluent for column chromatography: CH_2Cl_2. Yield: 89%. Pale yellow oil. IR: 1694, 1518, 1417, 1265. ^1H-NMR: 2.80—3.20 (2H, br m, $-SCH_2-$), 3.30—3.55 (2H, br m, $-CH_2N=$), 3.60—3.80 (3H, br m, $-OCH_3$), 3.85 (3H, s, $-OCH_3$), 4.43 (2H, s, $ArCH_2N=$), 5.19 (2H, s, OCH_2Ar), 6.60—6.80 (3H, br s, Ar-H), 7.18 (5H, s, Ar-H), 7.34 (5H, s, Ar-H). EIMS *m/z*: 437 (M^+), 151 (base peak). HRMS: Calcd for $C_{25}H_{27}NO_4S$: 437.1662. Found: 437.1620.

N-Benzyloxycarbonyl-*N*-benzyl-2-(phenylthio)ethylamine (**4e**): Eluent for column chromatography: CH_2Cl_2. Yield: 85%. Colorless oil. IR: 1702, 1584, 1421, 1232. ^1H-NMR: 2.90—3.20 (2H, br m, $-SCH_2-$), 3.30—3.60 (2H, br m, $-CH_2N=$), 4.51 (2H, s, $ArCH_2N=$), 5.19 (2H, s, $-OCH_2Ar$), 7.10—7.40 (15H, m, Ar-H). EIMS *m/z*: 377 (M^+), 91 (base peak). HRMS: Calcd for $C_{23}H_{23}NO_2S$: 377.1450. Found: 377.1439.

Formylation of 3a and 3b A mixture of **3a, b** (each 1 g), 98—100% formic acid (40 molar eq) and acetic anhydride (10 molar eq) was heated at 70 °C for 1 h, then concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The products (**4c** and **4f**) were purified by column chromatography.

N-Formyl-*N*-(3,4-dimethoxyphenyl)methyl-2-(phenylthio)ethylamine (**4c**): Eluent for column chromatography: AcOEt–*n*-hexane (3 : 1). Yield: 98%. Colorless gum. IR: 1669, 1593, 1518, 1265. ^1H-NMR: 2.90—3.18 (2H, m, $-SCH_2-$), 3.25—3.55 (2H, m, $-CH_2N=$), 3.82, 3.83, 3.86, 3.87 (total 6H, each s, $2\times-OCH_3$), 4.35, 4.44 (total 2H, each s, $ArCH_2N=$), 6.60—6.90 (3H, m, Ar-H), 7.10—7.40 (5H, m, Ar-H), 8.11, 8.28 (total 1H, each s, =N–CHO). EIMS *m/z*: 331 (M^+), 195 (base peak). HRMS: Calcd for $C_{18}H_{21}NO_3S$: 331.1242. Found: 331.1312.

N-Benzyl-*N*-formyl-2-(phenylthio)ethylamine (**4f**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 97%. Colorless oil. IR: 1673, 1584, 1439, 1398. ^1H-NMR: 2.85—3.10 (2H, m, $-SCH_2-$), 3.25—3.55 (2H, m, $-CH_2N=$), 4.41, 4.50 (total 2H, each s, $ArCH_2N=$), 7.05—7.45 (10H, m, Ar-H), 8.13, 8.28 (total 1H, each s, =N–CHO). EIMS *m/z*: 271 (M^+), 136 (base peak). HRMS: Calcd for $C_{16}H_{17}NOS$: 271.1031. Found: 271.1015.

Oxidation of 4a—f with $NaIO_4$ A solution of sodium metaperiodate (1.5 molar eq) in H_2O (10 ml) was added to a solution of **4a—f** (each 2 g) in MeOH (80 ml), and the mixture was stirred at room temperature for 15—20 h. After removal of precipitated inorganic materials by filtration, the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$. The products (**5a—f**) and the by-products (**6a—f**) were separated by column chromatography.

N-Acetyl-*N*-(3,4-dimethoxyphenyl)methyl-2-(phenylsulfinyl)ethylamine (**5a**): Eluent for column chromatography: AcOEt–MeOH (95 : 5). Yield: 93%. Colorless gum. IR: 1649, 1518, 1417, 1265, 1029. ^1H-NMR: 2.11, 2.15 (total 3H, each s, $-COCH_3$), 2.60—3.90 (total 4H, m, $-SOCH_2CH_2N=$), 3.85, 3.87 (total 6H, each s, $2\times-OCH_3$), 4.46, 4.55

(total 2H, each s, $ArCH_2N=$), 6.65—6.90 (3H, m, Ar-H), 7.45—7.65 (5H, m, Ar-H). CIMS *m/z*: 362 (MH^+, base peak).

N-Acetyl-*N*-(3,4-dimethoxyphenyl)methyl-2-(phenylsulfonyl)ethylamine (**6a**): Eluent for column chromatography: AcOEt–MeOH (95 : 5). Yield: 3.2%. Colorless gum. IR: 1649, 1518, 1419, 1265. ^{1}H-NMR: 2.07 (3H, s, $-COCH_3$), 3.05—3.50, 3.55—3.80 (each 2H, m, $-SO_2CH_2CH_2N=$), 3.84, 3.87, 3.88 (total 6H, each s, $2\times-OCH_3$), 4.43, 4.52 (total 2H, each s, $ArCH_2N=$), 6.60—6.90 (3H, m, Ar-H), 7.50—7.95 (5H, m, Ar-H). EIMS *m/z*: 377 (M^+), 334 (base peak). HRMS: Calcd for $C_{19}H_{23}NO_5S$: 377.1297. Found: 377.1271.

N-Benzyloxycarbonyl-*N*-(3,4-dimethoxyphenyl)methyl-2-(phenylsulfinyl)ethylamine (**5b**): Eluent for column chromatography: $CHCl_3$. Yield: 93%. Colorless gum. IR: 1700, 1518, 1417, 1267, 1044. ^{1}H-NMR: 2.70—3.20, 3.50—3.75 (each 2H, br m, $-SOCH_2CH_2N=$), 3.75 (3H, br s, $-OCH_3$), 3.86 (3H, s, $-OCH_3$), 4.33, 4.59 (each 1H, d, $J=15$ Hz, $ArCH_2N=$), 5.17 (2H, s, $-OCH_2Ar$), 6.77 (3H, s, Ar-H), 7.34 (5H, s, Ar-H), 7.48 (5H, br s, Ar-H). CIMS *m/z*: 454 (MH^+, base peak).

N-Benzyloxycarbonyl-*N*-(3,4-dimethoxyphenyl)methyl-2-(phenylsulfonyl)ethylamine (**6b**): Eluent for column chromatography: $CHCl_3$. Yield: 1.8%. Colorless gum. IR: 1702, 1593, 1518, 1145. ^{1}H-NMR: 3.00—3.70 (4H, br, $-SO_2CH_2CH_2N=$), 3.75 (3H, br s, $-OCH_3$), 3.86 (3H, s, $-OCH_3$), 4.40 (2H, s, $ArCH_2N=$), 5.11 (2H, s, $-OCH_2Ar$), 6.74 (3H, br s, Ar-H), 7.32 (5H, m, Ar-H), 7.50—7.90 (5H, m, Ar-H). EIMS *m/z*: 469 (M^+), 335 (base peak). HRMS: Calcd for $C_{25}H_{27}NO_6S$: 469.1587. Found: 469.1536.

N-Formyl-*N*-(3,4-dimethoxyphenyl)methyl-2-(phenylsulfinyl)ethylamine (**5c**): Eluent for column chromatography: AcOEt–MeOH (95 : 5). Yield: 96%. Colorless gum. IR: 1671, 1518, 1265, 1042. ^{1}H-NMR: 2.70—3.80 (4H, m, $-SOCH_2CH_2N=$), 3.85, 3.87, 3.88 (total 6H, each s, $2\times-OCH_3$), 4.30—4.60 (2H, m, $ArCH_2N=$), 6.70—6.85 (3H, m, Ar-H), 7.45—7.60 (5H, m, Ar-H), 8.24, 8.28 (total 1H, each s, =N–CHO). CIMS *m/z*: 348 (MH^+), 332 (base peak).

N-Formyl-*N*-(3,4-dimethoxyphenyl)methyl-2-(phenylsulfonyl)ethylamine (**6c**): Eluent for column chromatography: AcOEt–MeOH (95 : 5). Yield: 2.3%. Colorless gum. IR: 1671, 1518, 1265, 1151, 1027. ^{1}H-NMR: 3.15—3.40, 3.50—3.70 (each 2H, m, $-SO_2CH_2CH_2N=$), 3.83, 3.86, 3.87, 3.89 (total 6H, each s, $2\times-OCH_3$), 4.35, 4.10 (total 2H, each s, $ArCH_2N=$), 6.65—6.90 (3H, m, Ar-H), 7.45—7.95 (5H, m, Ar-H), 8.16, 8.21 (total 1H, each s, =N–CHO). EIMS *m/z*: 363 (M^+), 334 (base peak). HRMS: Calcd for $C_{18}H_{21}O_5S$: 363.1141. Found: 363.1163.

N-Acetyl-*N*-benzyl-2-(phenylsulfinyl)ethylamine (**5d**): Eluent for column chromatography: AcOEt. Yield: 88%. Colorless gum. IR: 1649, 1479, 1444, 1044. ^{1}H-NMR: 2.09, 2.17 (total 3H, each s, $-COCH_3$), 2.60—3.30, 3.30—3.90 (each 2H, m, $-SOCH_2CH_2N=$), 4.53, 4.60 (total 2H, each s, $ArCH_2N=$), 7.10—7.70 (10H, Ar-H), CIMS *m/z*: 302 (MH^+, base peak).

N-Acetyl-*N*-benzyl-2-(phenylsulfonyl)ethylamine (**6d**): Eluent for column chromatography: AcOEt. Yield: 4.1%. Colorless gum. IR: 1649, 1448, 1305, 1151. ^{1}H-NMR: 2.05, 2.10 (total 3H, each s, $-COCH_3$), 3.10—3.50, 3.55—3.80 (each 2H, m, $-SO_2CH_2CH_2N=$), 4.48, 4.58 (total 2H, each s, $ArCH_2N=$), 7.10—7.95 (10H, m, Ar-H). EIMS *m/z*: 317 (M^+), 274 (base peak). CIMS *m/z*: 318 (MH^+, base peak).

N-Benzyloxycarbonyl-*N*-benzyl-2-(phenylsulfinyl)ethylamine (**5e**): Eluent for column chromatography: Benzene–AcOEt (3 : 1). Yield: 94%. Colorless gum. IR: 1702, 1423, 1234, 1046. ^{1}H-NMR: 2.70—3.20, 3.62 (each 2H, br m and t, $J=7$ Hz, $-SOCH_2CH_2N=$), 4.40, 4.65 (each 1H, d, $J=15$ Hz, $ArCH_2N=$), 5.16 (2H, s, $-OCH_2Ar$), 7.10—7.70 (15H, m, Ar-H). CIMS *m/z*: 394 (MH^+, base peak).

N-Benzyloxycarbonyl-*N*-benzyl-2-(phenylsulfonyl)ethylamine (**6e**): Eluent for column chromatography: benzene–AcOEt (3 : 1). Yield: 4.2%. Colorless gum. IR: 1702, 1475, 1307, 1149. ^{1}H-NMR: 3.00—3.70 (4H, br m, $-SO_2CH_2CH_2N=$), 4.46 (2H, s, $ArCH_2N=$), 5.10 (2H, s, $-OCH_2Ar$), 7.00—8.00 (15H, m, Ar-H). EIMS *m/z*: 274 (base peak). CIMS *m/z*: 410 (MH^+, base peak).

N-Benzyl-*N*-formyl-2-(phenylsulfinyl)ethylamine (**5f**): Eluent for column chromatography: AcOEt. Yield: 93%. Colorless gum. IR: 1671, 1444, 1041. ^{1}H-NMR: 2.60—3.35, 3.35—4.00 (each 2H, m, $-SOCH_2CH_2N=$), 4.48, 4.56 (total 2H, each s, $ArCH_2N=$), 7.10—7.70 (10H, m, Ar-H), 8.26, 8.28 (total 1H, each s, =N–CHO). CIMS *m/z*: 288 (MH^+, base peak).

N-Benzyl-*N*-formyl-2-(phenylsulfonyl)ethylamine (**6f**): Eluent for column chromatography: AcOEt. Yield: 1.6%. Colorless gum. IR: 1667, 1307, 1152, 1087. ^{1}H-NMR: 3.05—3.40, 3.48—3.70 (each 2H, m, $-SO_2CH_2CH_2N=$), 4.39, 4.46 (total 2H, each s, $ArCH_2N=$), 7.10—8.00 (10H, m, Ar-H), 8.18, 8.21 (total 1H, each s, =N–CHO. EIMS *m/z*: 303 (M^+), 274 (base peak). HRMS: Calcd for $C_{16}H_{17}NO_3S$: 303.0929. Found: 303.0965.

General Procedure for the Pummerer Cyclization of Sulfoxides 5

Method A: TFAA (5 molar eq) was added to a solution of a sulfoxide **5a—f** (each 500 mg) in appropriate solvents (40 ml) at room temperature, and the mixture was stirred for several hours. The reaction mixture was concentrated *in vacuo*, and the products (**7a—c**, **14** and **15**) were purified by column chromatography.

Method B: TFAA (5 molar eq) was added to a solution of a sulfoxide **5d—f** (500 mg) in dry benzene (40 ml) at room temperature, and the mixture was stirred for 0.5—1 h. $BF_3\cdot Et_2O$ (3 molar eq) was added and stirring was continued at the same temperature for 2 h. The reaction mixture was washed with 5% NaOH–H_2O. The products (**7e, f**, and **15**) were purified by column chromatography. The reaction conditions and yields are summarized in Table 1.

1,2,3,4-Tetrahydro-2-acetyl-6,7-dimethoxy-4-phenylthioisoquinoline (**7a**): Eluent for column chromatography: AcOEt–benzene (1 : 1). Colorless needles, mp 139—141 °C (from AcOEt–*n*-hexane). IR: 1636, 1520, 1450, 1265, 1226, 1125. ^{1}H-NMR (500 MHz, room temp): 2.04, 2.13 (total 3H, each s, $-COCH_3$), 3.46, 3.68, 3.97, 4.50 (total 2H, each dd, $J=3.5$, 13.5 Hz, $-CH_2N=$), 3.82, 3.85, 3.86, 3.87 (total 6H, each s, $2\times-OCH_3$), 4.32, 4.53 (total 1H, each t, $J=3$ Hz, $-SCH=$), 4.29, 4.47, 4.61, 5.08 (total 2H, each d, $J=16.5$ Hz, $ArCH_2N=$), 6.56, 6.60, 6.76, 6.85 (total 2H, each s, Ar-H), 7.26—7.53 (5H, m, Ar-H). ^{13}C-NMR (500 MHz, room temp.): 21.3, 21.9 (total 1C, q, =NCO–), 43.3, 43.6 (total 1C, t, C1 or C3), 46.8, 47.1 (total 1C, d, C4), 47.4, 47.7 (total 1C, t, C1 or C3), 55.9 (1C, q, OCH_3), 56.0 (1C, q, OCH_3), 108.3, 108.9 (total 1C, d, C5 or C8), 111.6, 111.9 (total 1C, d, C5 or C8), 124.3, 124.7 (total 1C, s, C4a or C8a), 125.9, 126.2 (total 1C, s, C4a or C8a), 127.5, 128.0 (total 1C, d, Ar), 128.9, 131.5 (total 2C, d, Ar), 129.3, 134.1 (total 2C, d, Ar), 133.8, 134.7 (total 1C, s, Ar), 147.7, 148.0 (total 1C, s, C6 or C7), 148.8, 149.0 (total 1C, s, C6 or C7), 169.9, 170.2 (total 1C, s, –CO–). EIMS *m/z*: 343 (M^+), 192 (base peak). CIMS *m/z*: 344 (MH^+), 234 (base peak). *Anal.* Calcd for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08. Found: C, 66.53; H, 6.28; N, 4.02.

1,2,3,4-Tetrahydro-2-benzyloxycarbonyl-6,7-dimethoxy-4-phenylthioisoquinoline (**7b**): Eluent for column chromatography: *n*-hexane–AcOEt (2 : 1). Pale yellow gum. IR: 1702, 1518, 1255, 1224. ^{1}H-NMR: 3.83, 3.85 (each 3H, s, $2\times-OCH_3$), 3.40—5.10 (m, $-SCHCH_2N=$, $ArCH_2N=$), 5.18 (2H, br s, $-OCH_2Ar$), 6.56, 6.81 (each 1H, br s, Ar-H), 7.10—7.60 (10H, br s, Ar-H). ^{1}H-NMR (500 MHz, 80 °C): 3.36 (1H, dd, $J=3$, 13.5 Hz, =CHN=), 4.13 (1H, dd, $J=4$, 13.5 Hz, =CHN=), 3.79, 3.83 (each 3H, each s, $2\times-OCH_3$), 4.32 (1H, t, $J=4$ Hz, $-SCH=$), 4.42, 4.72 (each 1H, each d, $J=16.5$ Hz, $ArCH_2N=$), 5.16, 5.19 (each 1H, each d, $J=12.5$ Hz, $-OCH_2Ar$), 6.56, 6.83 (each 1H, each s, Ar-H), 7.15—7.40 (10H, m, Ar-H). ^{13}C-NMR (500 MHz, room temp.): 45.1 (2C, t, C1 and C3), 46.8, 47.3 (total 1C, d, C4), 55.7 (2C, q, $2\times OCH_3$), 67.1 (1C, t, $-OCH_2-$), 108.3, 108.5 total 1C, d, C5 or C8), 111.8 (1C, d, C5 or C8), 124.7, 125.2 (total 1C, s, C4a or C8a), 125.3, 125.6 (total 1C, s, C4a or C8a), 127.3 (1C, d, Ar), 127.8 (3C, d, Ar), 128.3(1C, d, Ar), 128.8 (3C, d, Ar), 132.5 (1C, d, Ar), 133.9 (1C, d, Ar), 133.8, 134.4 (total 1C, s, Ar), 136.2, 136.5 (total 1C, s, Ar), 147.5 (1C, s, C6 or C7), 148.6, 148.7 (total 1C, s, C6 or C7), 155.4, 155.5 (total 1C, s, =NCO–), EIMS *m/z*: 435 (M^+), 91 (base peak). CIMS *m/z*: 436 (MH^+), 326 (base peak).

1,2,3,4-Tetrahydro-2-formyl-6,7-dimethoxy-4-phenylthioisoquinoline (**7c**): Eluent for column chromatography: AcOEt–*n*-hexane (2 : 1). Colorless prism, mp 131—133 °C (from AcOEt–*n*-hexane). IR: 1665, 1518, 1441, 1265, 1116. ^{1}H-NMR: 3.84, 3.85 (each 3H, s, $2\times-OCH_3$), 3.30—4.70 (m, $-SCHCH_2N=$, $ArCH_2N=$), 4.17, 5.09 (each d, $J=17$ Hz, $ArCH_2N=$), 6.56, 6.59, 6.79, 6.88 (total 2H, each s, Ar-H), 7.20—7.60 (5H, m, Ar-H), 8.05, 8.33 (total 1H, each s, =N–CHO). ^{1}H-NMR (500 MHz, 80 °C): 3.63, 3.65, 3.69, 4.18 (total 2H, each dd, $J=3.5$, 13.5 Hz, $-CH_2N=$), 3.81, 3.82, 3.84, 3.85 (total 6H, each s, $2\times-OCH_3$), 4.34, 4.39 (total 1H, each t, $J=3.5$ Hz, $-SCH=$), 4.22, 4.40, 4.52, 4.99 (total 2H, each d, $J=17$ Hz, $ArCH_2N=$), 6.55, 6.59, 6.79, 6.91 (total 2H, each s, Ar-H), 7.25—7.55 (5H, m, Ar-H), 8.05, 8.29 (total 1H, each s, =N–CHO). ^{13}C-NMR (500 MHz, room temp.): 41.8, 41.9 (total 1C, t, C1 or C3), 46.8, 46.8 (total 1C, t, C1 or C3), 46.8 (1C, d, C4), 55.9 (2C, q, $2\times OCH_3$), 108.1, 108.8 (total 1C, d, C5 or C8), 112.1, 112.4 (total 1C, d, C5 or C8), 124.2, 124.5 (total 1C, s, C4a or C8a), 124.6, 125.6 (total 1C, s, C4a or C8a), 128.0, 128.2 (total 1C, d, Ar), 129.1, 129.3 (total 1C, d, Ar), 132.7 (2C, d, Ar), 133.7, 133.9 (total 1C, s, Ar),

134 (1C, d, Ar), 147.9, 148.1 (1C, s, C6 or C7), 148.9, 149.2 (1C, s, C6 or C7), 161.6, 162.2 (1C, s, –CO–). EIMS *m/z*: 329 (M^+), 220 (base peak). CIMS *m/z*: 330 (MH^+), 220 (base peak). *Anal.* Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.77; H, 5.92; N, 4.03.

2,3-Dihydro-4-benzyl-2-phenylthio-7-trifluoromethyl-1,4-oxazepin-5-one (**14**): Eluent for column chromatography: $CHCl_3$. Colorless gum. IR: 1638, 1576, 1427, 1191, 1149. ^{1}H-NMR (500 MHz, room temp.): 3.66 (1H, dd, J=8.5, 12.5 Hz, =CHN=), 4.09 (1H, dd, J=9.5, 12.5 Hz, =CHN=), 4.42 (2H, s, $ArCH_2N$=), 6.07 (1H, dd, J=8.5, 9.5 Hz, –SCH=), 7.22—7.48 (11H, m, olefinic-1H and Ar-H). ^{13}C-NMR: 52.5 (1C, t, C3), 53.5 (1C, t, $ArCH_2N$=), 88.5 (1C, d, C2), 116.8 (1C, q, J=291 Hz, $-CF_3$), 128.7 (3C, d, Ar), 129.3 (1c, d, Ar), 129.6 (1C, d, Ar), 129.7 (2C, d, Ar), 129.8 (3C, d, Ar), 131.4 (1C, s, Ar), 133.1 (2C, d, Ar), 172.5 (1C, s, C5, –CO–), 172.3 (1C, q, J=35 Hz, C6, =$\underline{C}CF_3$). EIMS *m/z*: 379 (M^+), 136 (base peak). CIMS *m/z*: 380 (MH^+, base peak).

2-Phenylthio-4-benzyl-1,4-oxazolin-5-one (**15**): Eluent for column chromatography: $CHCl_3$. Colorless needles, mp 53—55 °C (from Et_2O–*n*-hexane). IR: 1760, 1493, 1437, 1253. ^{1}H-NMR (500 MHz, room temp.): 3.27 (1H, dd, J=5.5, 10 Hz, =CHN=), 3.75 (1H, dd, J=9, 10 Hz, =CHN=), 4.32 (1H, d, J=15 Hz, $ArCH_2N$=), 5.73 (1H, dd, J=5.5, 9 Hz, –SCH=), 7.13—7.56 (10H, m, Ar-H). ^{13}C-NMR (500 MHz, room temp.): 48.0 (1C, t, $ArCH_2N$=), 49.3 (1C, t, C3), 79.9 (1C, d, C2), 127.9 (2C, d, Ar), 128.0 (1C, d, Ar), 128.8 (2C, d, Ar), 128.9 (1C, d, Ar), 129.3 (2C, d, Ar), 130.6 (1C, s, Ar), 133.5 (2C, d, Ar), 135.1 (1C, s, Ar), 156.63 (1C, s, C5, –CO–). EIMS *m/z*: 285 (M^+), 91 (base peak). HRMS: Calcd for $C_{16}H_{15}NO_2S$: 285.0824. Found: 285.0890.

1,2,3,4-Tetrahydro-2-acetyl-4-phenylthioisoquinoline (**7d**): Eluent for column chromatography: *n*-hexane–AcOEt (2:1). Colorless gum. IR: 1649, 1584, 1439, 1272, 1238. ^{1}H-NMR (500 MHz, room temp.): 2.02, 2.19 (total 3H, each s, $-COCH_3$), 3.45, 3.68, 3.96, 4.51 (total 2H, each dd, J=3, 13.5 Hz, $-CH_2N$=), 4.38, 4.59 (total 1H, each t, J=3 Hz, –SCH=), 4.39, 4.59, 4.69, 5.12 (total 2H, each d, J=17 Hz), 7.08—7.54 (9H, m, Ar-H). ^{13}C-NMR (500 MHz, room temp.): 21.3, 21.9 (total 1C, q, $-CH_3$), 21.3, 21.9 (total 1C, t, C1 or C3), 43.2, 44.0 (total 1C, d, C4), 47.5, 47.7 (total 1C, t, C1 or C3), 126.0, 126.6 (total 1C, d, Ar), 126.8, 127.0 (total 1C, d, Ar), 127.5, 127.7 (total 1C, d, Ar), 128.0, 128.1 (total 1C, d, Ar), 128.9, 129.3 (total 1C, d, Ar), 129.2, 129.7 (total 1C, d, Ar), 131.6 (2C, d, Ar), 132.6 (1C, s, Ar), 133.5, 133.6 (total 1C, s, Ar), 134.1 (1C, d, Ar), 134.2, 134.5 (total 1C, Ar), 169.9, 170.2 (total 1C, s, –CO–). EIMS *m/z*: 283 (M^+), 132 (base peak). CIMS *m/z*: 284 (M^+, base peak).

1,2,3,4-Tetrahydro-2-benzyloxycarbonyl-4-phenylthioisoquinoline (**7e**): Eluent for column chromatography: $CHCl_3$. Pale yellow gum. IR: 1702, 1584, 1433, 1232. ^{1}H-NMR: 3.56 (1H, dd, J=3, 13 Hz, $-CH_2N$=), 4.10—4.50 (m, –SCHCH_2N=, $ArCH_2N$=), 4.47, 4.90 (each d, J=17.5 Hz, $ArCH_2N$=), 5.20 (2H, s, $-OCH_2Ar$), 7.00—7.60 (14H, br m, Ar-H). ^{1}H-NMR (500 MHz, 80 °C): 3.64 (1H, dd, J=3.5, 13.5 Hz, =CHN=), 4.15 (1H, dd, J=4, 13.5 Hz, =CHN=), 4.38 (1H, t, J=4 Hz, –SCH=), 4.51, 4.80 (each 1H, each d, J=16.5 Hz, $ArCH_2N$=), 5.16, 5.20 (each 1H, each d, J=12.5 Hz, $-OCH_2Ar$), 7.05—7.45 (14H, m, Ar-H). ^{13}C-NMR (500 MHz, room temp.): 45.3, 45.6 (total 1C, t, C1 or C3), 47.4, 47.8 (total 1C, d, C4), 67.4 (1C, t, $-OCH_2$–), 126.3, 126.5 (total 1C, d, Ar), 126.7 (1C, d, Ar), 127.6, 127.7 (total 1C, d, Ar), 127.8, 128.1 (total 1C, d, Ar), 128.0 (2C, d, Ar), 128.5 (2C, d, Ar), 129.0 (3C, d, Ar), 129.6, 129.8 (total 1C, d, Ar), 132.9 (1C, d, Ar), 133.1, 133.2 (total 1C, s, Ar), 133.6, 133.8 (total 1C, s, Ar), 133.9, 134.4 (total 1C, s, Ar), 134.2 (1C, d, Ar), 136.5, 136.7 (total 1C, s, Ar), 155.6, 155.8 (1C, s, –CO–). EIMS *m/z*: 375 (M^+), 91 (base peak). CIMS *m/z*: 376 (MH^+, base peak).

1,2,3,4-Tetrahydro-2-formyl-4-phenylthioisoquinoline (**7f**): Eluent for column chromatography: benzene–AcOEt (2:1). Colorless gum. IR: 1671, 1582, 1481, 1437. ^{1}H-NMR: 3.67 (d, J=3 Hz, $-CH_2N$=), 3.40—4.70 (m, –SCHCH_2N=, $ArCH_2N$=), 4.26, 5.16 (each d, J=17.5 Hz, $ArCH_2N$=), 7.10—7.70 (9H, m, Ar-H), 8.05, 9.34 (total 1H, each s, =N–CHO). ^{1}H-NMR (500 MHz, 80 °C): 3.64, 3.66, 3.71, 4.21 (total 2H, each dd, J=3.5, 13.5 Hz, $-CH_2N$=), 4.40, 4.46 (total 1H, each t, J=3.5 Hz, –SCH=), 4.30, 4.48, 4.61, 5.06 (total 2H, each d, J=17 Hz, $ArCH_2N$=), 7.05—7.55 (9H, m, Ar-H), 8.06, 8.30 (total 1H, each s, =N–CHO). ^{13}C-NMR (500 MHz, room temp.): 41.8, 42.1 (total 1C, t, C1 or C3), 46.6, 47.0 (total 1C, t, C1 or C3), 47.1 (1C, d, C4), 125.9, 126.7 (total 1C, d, Ar), 126.9, 127.3 (total 1C, d, Ar), 127.9, 128.1 (total 1C, d, Ar), 128.2, 128.3 (total 1C, d, Ar), 129.1, 129.3 (total 2C, d, Ar), 130.0, 130.4 (total 1C, d, Ar), 132.3, 132.4 (total 1C, s, Ar), 132.5, 133.6 (total 1C, s, Ar), 132.9, 134.2 (total 2C, s, Ar), 133.6, 133.7 (total 1C, s, Ar), 161.6, 162.3 (total 1C, s, –CO–). EIMS *m/z*: 269 (M^+), 159 (base peak). CIMS *m/z*: 270 (MH^+, base peak).

Reductive Desulfurization of 2-Acyl-4-phenylthio-TIQs (7) $NaBH_4$ (10.5 molar eq) was added in small portions to a stirred solution of one of **7a**—**c** and **7e, f** (each 400 mg) with $NiCl_2 \cdot 6H_2O$ (3.5 molar eq) in MeOH–THF (3:1) (40 ml) under ice-cooling. After the addition, stirring was continued at room temperature for 30 min. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was suspended in water, acidified with 5% HCl–H_2O, and extracted with $CHCl_3$. The products (**8a, b, 8e, f** and **9b**) were isolated by column chromatography and the product (**8c**) was purified by recrystallization.

1,2,3,4-Tetrahydro-2-acetyl-6,7-dimethoxyisoquinoline (**8a**): Eluent for column chromatography: AcOEt. Yield: 76%. Colorless prism, mp 105—107 °C (from AcOEt–*n*-hexane) (lit.,[9] mp 94—95 °C).

1,2,3,4-Tetrahydro-2-benzyloxycarbonyl-6,7-dimethoxyisoquinoline (**8b**): Eluent for column chromatography: *n*-hexane–AcOEt (2:1). Yield: 59%. Colorless gum. IR: 1702, 1613, 1520, 1226. ^{1}H-NMR: 2.77 (2H, t, J=6 Hz, $ArCH_2$–), 3.12 (2H, t, J=6 Hz, $-CH_2N$=), 3.84, 3.85 (each 3H, each s, 2×$-OCH_3$), 4.57 (2H, s, $ArCH_2N$=), 5.18 (2H, s, $-OCH_2Ar$), 6.85, 6.61 (each 1H, each s, Ar-H), 7.36 (5H, s, Ar-H). EIMS *m/z*: 327 (M^+), 236 (base peak). HRMS: Calcd for $C_{19}H_{21}NO_4$: 327.1470. Found: 327.1440.

1,2-Dihydro-2-benzyloxycarbonyl-6,7-dimethoxyisoquinoline (**9b**): This compound was obtained during desulfurization of **7b** as a by-product. Eluent for column chromatography: *n*-hexane–AcOEt (2:1). Yield: 4.7%. Colorless gum. IR: 1711, 1640, 1520, 1348, 1226. ^{1}H-NMR: 3.85 (6H, s, 2×$-OCH_3$), 4.82 (2H, s, $ArCH_2N$=), 5.23 (2H, s, $-OCH_2Ar$), 5.67 (1H, d, J=7.5 Hz, ArCH=), 6.55, 6.59 (each 1H, s, Ar-H), 6.82 (1H, d, J=7.5 Hz, =CHN=), 7.37 (5H, s, Ar-H). EIMS *m/z*: 325 (M^+), 91 (base peak). HRMS: Calcd for $C_{19}H_{19}NO_4$: 325.1314. Found: 325.1351.

1,2,3,4-Tetrahydro-2-formyl-6,7-dimethoxyisoquinoline (**8c**): Eluent for column chromatography: AcOEt. Yield: 74%. Colorless needles, mp 128—131 °C (from AcOEt), (lit.,[10] mp 129—130 °C).

1,2,3,4-Tetrahydro-2-benzyloxycarbonylisoquinoline (**8e**): Eluent for column chromatography: *n*-hexane–AcOEt (3:1). Yield: 57%. Colorless oil. IR: 1702, 1431, 1228. ^{1}H-NMR: 2.84 (2H, t, J=6 Hz, $ArCH_2$–), 3.73 (2H, t, J=6 Hz, $-CH_2N$=), 4.65 (2H, s, $ArCH_2N$=), 5.18 (2H, s, $-OCH_2Ar$), 7.14 (4H, s, Ar-H), 7.36 (5H, s, Ar-H). EIMS *m/z*: 267 (M^+), 176 (base peak). CIMS *m/z*: 268 (MH^+, base peak).

1,2,3,4-Tetrahydro-2-formylisoquinoline (**8f**): Eluent for column chromatography: AcOEt. Yield: 71%. Colorless oil.[10]

Hydrolysis of 2-Acyl-TIQs (8) A 10% NaOH solution (2 ml) was added to a solution of one of the 2-acyl-TIQs **8a—c and 8e, f** (each 200 mg) in EtOH (10 ml), and the mixture was stirred at room temperature for 3—4 h (for **8c** and **8f**) or refluxed for 16—18 h (for **8a, b** and **8e**). The reaction mixture was concentrated *in vacuo*, and the residue was diluted with water, then extracted with $CHCl_3$. The products (**10a** and **10b**) were purified by column chromatography. The yields are shown in Table 2.

1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinoline (**10a**): Eluent for column chromatography: $CHCl_3$–MeOH (8:2). Colorless gum, mp 268—270 °C (HCl salt) (lit.[11], mp 262 °C; lit.[12], mp 255—256 °C; lit.[13] mp 248 °C, HCl salt).

1,2,3,4-Tetrahydroisoquinoline (**10b**): Eluent for column chromatography: $CHCL_3$–MeOH (8:2). Pale yellow oil, mp 203—207 °C (HCl salt) (lit.,[11] mp 196—197 °C; lit.[14], mp 195—197 °C, HCl salt).

$LiAlH_4$ Reduction of 2-Acyl-TIQs (8) $LiAlH_4$ (2 molar eq) was added to a solution of one of **8a—c** and **8e, f** (each 300 mg) in dry THF (20 ml) under ice-cooling, and refluxed for 1—2 h. Et_2O, saturated with water, was added to the reaction mixture and insoluble material was filtered off. The product was purified by column chromatography to give **11a—c**. Yields are shown in Table 2.

1,2,3,4-Tetrahydro-2-methyl-6,7-dimethoxyisoquinoline (**11a**): Eluent for column chromatography: $CHCl_3$–MeOH (95:5). Colorless oil, mp 215—223 °C (HCl salt) (lit.[13], 210 °C, HCl salt).

1,2,3,4-Tetrahydro-2-methylisoquinoline (**11b**): Eluent for column chromatography: $CHCl_3$–MeOH (95:5). Colorless oil, mp 217—229 °C (HCl salt) (lit.[15], mp 227 °C, HCl salt).

1,2,3,4-Tetrahydro-2-ethyl-6,7-dimethoxyisoquinoline (**11c**): Eluent for column chromatography: $CHCl_3$–MeOH (95:5). Colorless oil, mp 235—245 °C (HCl salt) (lit.[15], mp 246 °C, HCl salt).

***N*-(Phenyl)-[$^2H_1$]-methyl-2-(phenylthio)ethylamine (3D)** A solution of **1b** (3 g, 28.30 mmol), 2-phenylthioethylamine (**2**)[6] (6.5 g, 42.48 mmol)

and acetic acid (2.6 g, 43.33 mmol) in EtOD (25 ml) was refluxed for 20 h under an Ar atmosphere. The reaction mixture was concentrated *in vacuo*. The residue was taken up in MeOD (25 ml), then $NaBD_4$ (1.2 g, 21.71 mmol) was added in small portions under ice-cooling, and the mixture was stirred at room temperature for 1 h. It was worked up as described above, and purified by column chromatography (AcOEt : *n*-hexane = 2 : 1) to give **3D** (6.12 g, 89%), as a pale yellow oil. IR: 1584, 1481, 1439. ^{1}H-NMR: 2.75—2.95 (2H, m, $-SCH_2-$), 3.00—3.20 (2H, m, $-CH_2N=$), 3.77 (1H, t, J = 2 Hz, ArCHDN=), 7.15—7.35 (10H, m, Ar-H). EIMS *m/z*: 244 (M^+), 92 (base peak). HRMS: Calcd for $C_{15}H_{16}DNS$: 244.1141. Found: 244.1120.

***N*-Formyl-*N*-(phenyl)-[$^2H_1$]-methyl-2-(phenylthio)ethylamine (4D)** A mixture of **3D** (5 g, 20.49 mmol), 98—100% formic acid (28.2 g, 600—613 mmol) and acetic anhydride (20.9 g, 205 mmol) was heated at 70 °C for 1 h. The reaction mixture was worked up as described above, and purified by column chromatography (AcOEt : *n*-hexane = 1 : 1) to give **4D** (5.37 g, 96%), as a colorless gum. IR: 1671, 1584, 1425, 1282. ^{1}H-NMR: 2.82—3.10 (2H, m, $-SCH_2-$), 3.25—3.55 (2H, m, $-CH_2N=$), 4.40, 4.48 (total 1H, each br m, ArCHDN=), 7.05—7.40 (10H, m, Ar-H), 8.13, 8.28 (total 1H, each s, =N–CHO). EIMS *m/z*: 272 (M^+), 136 (base peak). HRMS: Calcd for $C_{16}H_{16}DNOS$: 272.1093. Found: 272.1148.

***N*-Formyl-*N*-(phenyl)-[$^2H_1$]-methyl-2-(phenylsulfinyl)ethylamine (5D)** A solution of sodium metaperiodate (5.9 g, 27.58 mmol) in water (40 ml) was added to a solution of **4D** (5 g, 18.38 mmol) in MeOH (200 ml). The reaction mixture was stirred at room temperature for 16 h, then worked up as described above, and the residue was purified by column chromatography (AcOEt) to give **5D** (4.76 g, 90%), as a colorless gum, and *N*-formyl-*N*-(phenyl)-[$^2H_1$]-methyl-2-(phenylsulfonyl)ethylamine **6D** (0.39 g, 7%), as a colorless gum. **5D**: IR: 1671, 1446, 1282, 1044. ^{1}H-NMR: 2.60—3.35, 3.40—4.00 (each 2H, m, $-SOCH_2CH_2N=$), 4.49, 4.59 (total 1H, each br m, ArCHDN=), 7.10—7.40, 7.40—7.60 (each 5H, m, Ar-H), 8.26, 8.28 (total 1H, each s, =N–CHO). CIMS *m/z*: 289 (MH^+, base peak). **6D**: IR: 1671, 1448, 1307, 1152. ^{1}H-NMR: 3.10—3.40, 3.45—3.70 (each 2H, m, $-SO_2CH_2CH_2N=$), 4.37, 4.45 (total 1H, each br s, ArCHDN=), 7.10—7.90 (10H, m, Ar-H), 8.17, 8.21 (total 1H, each s, =N–CHO). EIMS *m/z*: 304 (M^+), 275 (base peak). HRMS: Calcd for $C_{16}H_{16}DNO_3S$: 304. 0991. Found: 304.0948.

1,2,3,4-Tetrahydro-4-phenylthio-[1-$^2H_1$]-isoquinoline (7D) TFAA (7.33 g, 34.76 mmol) was added to a solution of **5D** (2 g, 6.94 mmol) in dry benzene (50 ml) at room temperature. The reaction mixture was stirred for 1 h, then $BF_3 \cdot Et_2O$ (3 g, 21.14 mmol) was added, and the whole was further stirred at the same temperature for 2 h. It was worked up as described above, and purified by column chromatography (AcOEt : *n*-hexane = 1 : 1) to give **7D** (1.83 g, 98%), as a colorless gum. IR: 1667, 1582, 1437. ^{1}H-NMR (500 MHz, room temp.): 3.50, 3.52, 3.65, 3.69, 4.29, 4.31 (total 2H, each dd, J = 3.5, 13.5 Hz, $-CH_2N=$), 4.41, 4.51 (total 1H, each t, J = 3.5 Hz, –SCH=), 4.25, 4.50, 4.63, 5.13 (total 2H, each s, ArCHDN=), 7.10—7.60 (9H, m, Ar-H), 8.05, 8.34 (total 1H, each s, =N–CHO). EIMS *m/z*: 270 (M^+), 160 (base peak). HRMS: Calcd for $C_{16}H_{14}DNOS$: 270.0936. Found: 270.0913.

1,2,3,4-Tetrahydro-2-formyl-[1,4-$^2H_2$]-isoquinoline (8D) $NaBD_4$ (3.25 g, 77.75 mmol) was added in small portions to a stirred solution of **7D** (2 g, 7.41 mmol) and $NiCl_2 \cdot 6H_2O$ (6.16 g, 25.92 mmol) in MeOD–THF (3 : 1) (120 ml) under ice-cooling. After the addition, stirring was continued at room temperature for 30 min. The reaction mixture was worked up as described above, and purified by column chromatography to give **8D** (1.04 g, 86%), as a colorless oil, and 1,2-dihydro-2-formyl-[1-$^2H_1$]-isoquinoline **9D** (23 mg, 1.94%), as a colorless oil. **8D**: IR: 1669, 1437, 1400. ^{1}H-NMR: 2.75—3.00 (1H, br m, ArCHD–), 3.55—3.85 (2H, m, $-CH_2N=$), 4.51, 4.64 (total 1H, each t, J = 2.5 Hz, ArCHDN=), 7.00—7.30 (4H, m, Ar-H), 8.19, 8.24 (total 1H, each s, =N–CHO). EIMS *m/z*: 163 (M^+, base peak). HRMS: Calcd for $C_{10}H_9D_2NO$: 163.0966. Found: 163.0962. **9D**: IR: 1686, 1634, 1574. ^{1}H-NMR: 4.71, 4.89 (total 1H, t, J = 2.5 Hz, ArCHDN=), 5.82, 6.07 (total 1H, d, J = 8 Hz and dd, –CH=N=), 6.57 (0.75H, d, J = 8 Hz, ArCH=), 6.95—7.85 (4.25H, m, Ar-H and ArCH=), 8.18, 8.31 (total 1H, each s, =N–CHO). EIMS *m/z*: 160 (M^+), 131 (base peak). HRMS: Calcd for $C_{10}H_8DNO$: 160.0747. Found: 160.0700.

1,2,3,4-Tetrahydro-[1,4-$^2H_2$]-isoquinoline (10D) A 10% NaOH solution (4 ml) was added to a solution of **8D** (410 mg, 2.52 mmol) in EtOH (10 ml), and the mixture was stirred at room temperature for 4 h. It was worked up as described above, and purified by column chromatography ($CHCl_3$: MeOH = 8 : 2) to give **10D** (312 mg, 92%), as a pale yellow oil, mp 200—203 °C (HCl salt). IR: 3300, 1493, 1454. ^{1}H-NMR: 2.60—2.90 (1H, br m, ArCHD–), 3.00—3.20 (2H, m, $-CH_2N=$), 3.97 (1H, br t, J = 1.5 Hz, ArCHDN=), 6.95—7.20 (4H, m, Ar-H). EIMS *m/z*: 135 (M^+), 106 (base peak). HRMS: Calcd for $C_9H_9D_2N$: 135.1017. Found: 135.0997.

1,2,3,4-Tetrahydro-2-methyl-[1,4-$^2H_2$]-isoquinoline (11D) $LiAlH_4$ (196 mg, 5.16 mmol) was added to a solution of **8D** (420 mg, 2.58 mmol) in dry THF (20 ml) under ice-cooling. The reaction mixture was refluxed for 1 h, then worked up as described above, and the residue was purified by column chromatography to give **11D** (346 mg, 90%), as a pale yellow oil. IR: 1497, 1456. ^{1}H-NMR: 2.45 (3H, s, $=N-CH_3$), 2.55—3.00 (3H, m, $ArCHDCH_2N=$), 3.54 (1H, br t, J = 1.5 Hz, ArCHDN=), 6.95—7.15 (4H, m, Ar-H). EIMS *m/z*: 149 (M^+), 148 (base peak). HRMS: Calcd for $C_{10}H_{11}ND_2$: 149.1172. Found: 149.1164.

References

1) Lundstorom J., "The Alkaloids," Vol. 21, ed. by Brossi A., Academic Press, New York, 1983, pp. 255—327; Collins M. A., *ibid.*, pp. 329—358; Brossi A., "The Alkaloids," Vol. 43, ed. by Cordell G. A., Academic Press, San Diego, 1993, pp. 119—183.
2) Ohta S., Kohno M., Makino Y., Tachikawa O., Hirobe M., *Biomed. Res.*, **8**, 453—456 (1987); Niwa T., Takeda N., Kaneda N., Hashizume Y., Nagatsu T., *Biochem. Biophys. Res. Commun.*, **144**, 1084—1089 (1987).
3) A recent review of syntheses of isoquinolines: Rozwadowska M. D., *Heterocycles*, **39**, 903—931 (1994).
4) Takano S., Iida H., Inomata K., Ogasawara K., *Heterocycles*, **35**, 47—52 (1993).
5) For sulfoxide-mediated cyclization reaction : Trost B. M., "Comprehensive Organic Synthesis," Vol. 7, ed. by I. Fleming, Pergamon Press, Oxford, 1991, pp. 193—216; Tamura Y., Uenishi J., Maeda H., Choi H., Ishibashi H., *Synthesis*, **1981**, 534-537; Ishibashi H., Harada S., Okada M., Somekawa M., Kido M., Ikeda M., *Chem. Pharm. Bull.*, **37**, 939—943 (1989); Lee A. W. M., Chan W. H., Chan E. T. T., *J. Chem. Soc., Perkin Trans. 1*, **1992**, 309—310; Ishibashi H., Takagaki K., Imada N., Ikeda M., *SYNLETT*, **1994**, 49—50.
6) Cortese F., *J. Am. Chem. Soc.*, **58**, 191—192 (1936).
7) Back T. G., Baron D. L., Yang K., *J. Org Chem.*, **58**, 2407—2413 (1993).
8) Dalton D. R., Ramey K. C., Gisler H. J., Jr., Lendvay L. J., Abraham A., *J. Am. Chem. Soc.*, **91**, 6367—6371 (1969).
9) Venkov A. P., Lukanov L. K., *Synthesis*, **1989**, 59—61.
10) Lukanov L. K., Venkov A. P., Mollov N. M., *Synthesis*, **1987**, 1031—1032.
11) Forsyth R., Kelly C. I., Pyman F. L., *J. Chem. Soc.*, **127**, 1659—1667 (1925).
12) Ruchirawat S., Chaisupakitsin M., Patranuwatana N., Chshaw J. L., Davis V. E., *Synth. Commun.*, **14**, 1221—1228 (1984).
13) Mata R., McLaughlin J. L., *Phytochemistry*, **19**, 673—678 (1980).
14) Kondo H., Ochiai H., *J. Pharm. Soc. Jpn.*, **495**, 313—319 (1923).
15) Buck J. S., Ide W. S., *J. Am. Chem. Soc.*, **60**, 2101—2103 (1938).